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Optimizing the Use of Geriatric Livers for Transplantation in the Eurotransplant Region

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Acceptance criteria for liver allografts are ever more expanding because of a persisting wait-list mortality. Older livers are therefore offered and used more frequently for transplantation. This study aims to analyze the use and longterm outcome of these transplantations. Data were included on 17,811 first liver transplantations (LTs) and information on livers that were reported for allocation but not transplanted from 2000 to 2015 in the Eurotransplant (ET) region. Graft survival was defined as the period between transplantation and date of retransplantation or date of recipient death. In the study period, 2394 (13%) transplantations were performed with livers ≥70 years old. Graft survival was 74%, 57%, and 41% at 1-, 5-, and 10-year follow-up, respectively. A history of diabetes mellitus in the donor (hazard ratio [HR], 1.3; $P = 0.01$) and positive hepatitis C virus antibody in the recipient (HR, 1.5; $P < 0.001$) are specific risk factors for transplantations with livers ≥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 LTs in the ET 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.

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SEE EDITORIAL ON PAGE 205

The number of patients registered for a liver transplantation (LT) in the Eurotransplant (ET) region exceeds the number of available liver allografts. In 2016, 2258 patients were registered for a LT, and 1567 transplantations were performed. Wait-list mortality is therefore a serious issue: Over 500 patients died in 2016 while waiting and over 1700 patients were still on the waiting list at the year's 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 wait-list mortality.

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BAR, Balance of Risk score; BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; CNS, central nervous system; CT, computed tomography; CVA, cerebrovascular accident; DCD, donation after circulatory death; df, degrees of freedom; DM, diabetes mellitus; DRI, donor risk index; DRM, donor-to-recipient model; ET, Eurotransplant; GGT, gamma-glutamyltransferase; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HCVAb, hepatitis C virus antibody; HR, hazard ratio; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; psplines, penalized smoothing splines; sRRI, simplified recipient risk index.

However, they are likely to negatively affect posttransplantation outcomes because donor age is a well-known risk factor.[3] For example, it has been included as an important risk factor in several outcome models, like the donor risk index (DRI),[4] ET-DRI,[5] and BAR score.[6] The latter uses a cutoff for older donors of 40 years old,[6] whereas the DRI and ET-DRI have donor age categorized into 5 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 (HR) 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 posttransplantation outcome is yet unclear, especially when transplanting livers from donors ≥70 years.

The demographical transition in Western countries with aging populations and promising posttransplantation results[7-9] indicates 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.[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 outcomes after LT in the ET region. Second, an evaluation of the current and potential use of liver allografts from donors of 70 years and older is performed.

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Patients and Methods

DESIGN

All first LTs performed in adult recipients (≥18 years) with liver allografts from deceased donors from January 1, 2000 until December 31, 2015 in the ET region were included. Follow-up data were obtained from the ET Network Information System and ET Liver Registry up to March 2017. Also, data were obtained on the reported but nontransplanted liver allografts from donors of 70 years and older within the study period. The study protocol was approved by the ET Liver Intestine Advisory Committee, and no ethical statement was required according to European guidelines and Dutch law because 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 measure. Graft survival was defined as the period between the date of transplantation and date of retransplantation or date of recipient death, whichever occurred first (nondeath censored graft survival). Patient survival at 1, 5, and 10 years was considered a secondary outcome and was defined as the time between the date of transplantation and the 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 nontransplanted livers.

PREFERRED RECIPIENTS

Preferred and nonpreferred 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 years, body mass index (BMI) <35 kg/m^2, an indication other than hepatocellular carcinoma (HCC) or hepatitis C virus (HCV), and a cold ischemia time (CIT) <8 hours. In our study, we only considered recipients with an age >45 years, BMI <35 kg/m^2, an indication other than HCV, and a CIT <8 hours as preferred recipients. Retransplantations 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 a separate variable or as a category in the etiology of the liver disease variable.

TRANSPLANT CENTERS

Transplant centers were first categorized by the median number of LTs 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 with 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 (CI).[12]

DATA ANALYSIS

Clinical characteristics were summarized by median and 25% and 75% interquartile range (IQR) or by n (%) for continuous and categorical factors, respectively. Factors between groups were compared using Kruskal-Wallis (continuous) and chi-square tests (categorical). Missing values were imputed with the median value for gamma-glutamyltransferase (GGT; 34 U/L, 2%), aspartate aminotransferase (ASAT; 41 U/L, 1%), alanine aminotransferase (ALAT; 29 U/L, 1%), and bilirubin (9.4 μmol/L, 3%). Missing CITs (37%) were imputed based on 3 factors: allocation (local, regional, and extraregional), 3 years' nondeath-censored graft survival, and CITs in a 5-fold database by multiple imputation using chained equations. 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 hepatitis C virus antibody (HCVAb), hepatitis B core antibody (HBcAb), and recipient HCVAb were considered negative when missing (1%, 1%, and 24%, respectively) or not tested (0%, 2%, and 8%, respectively). The 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 Model for End-Stage Liver Disease (MELD) score. MELD score was only known for recipients that were listed in the time period after December 16, 2006 because then MELD score was implemented in ET.

STATISTICAL ANALYSIS

Posttransplantation outcomes at 10 years were analyzed with Kaplan-Meier analysis and by log-rank test. Results were stratified for 4 donor age categories (<60, 60-69, 70-79, and ≥80 years). 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 (DRM). Then, the effect of donor age on outcome was analyzed in preferred and nonpreferred recipients. Within both patient categories, outcome was stratified by 2 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 LTs with livers ≥70 years old in a Kaplan-Meier analysis, and then, according to their relative performance on graft survival at 5-year follow-up in a funnel-plot analysis. Centers with few such transplantations were excluded for this analysis (<10 LTs). To analyze the utilization rate, livers from donors ≥70 years old that were reported to ET were compared by transplantation status (yes/no).

A *P* value of <0.05 was considered statistically significant, and all analyses were performed with SPSS, version 24.0 (IBM, 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 ET region. Mean follow-up period was 6.3 years. Median donor age

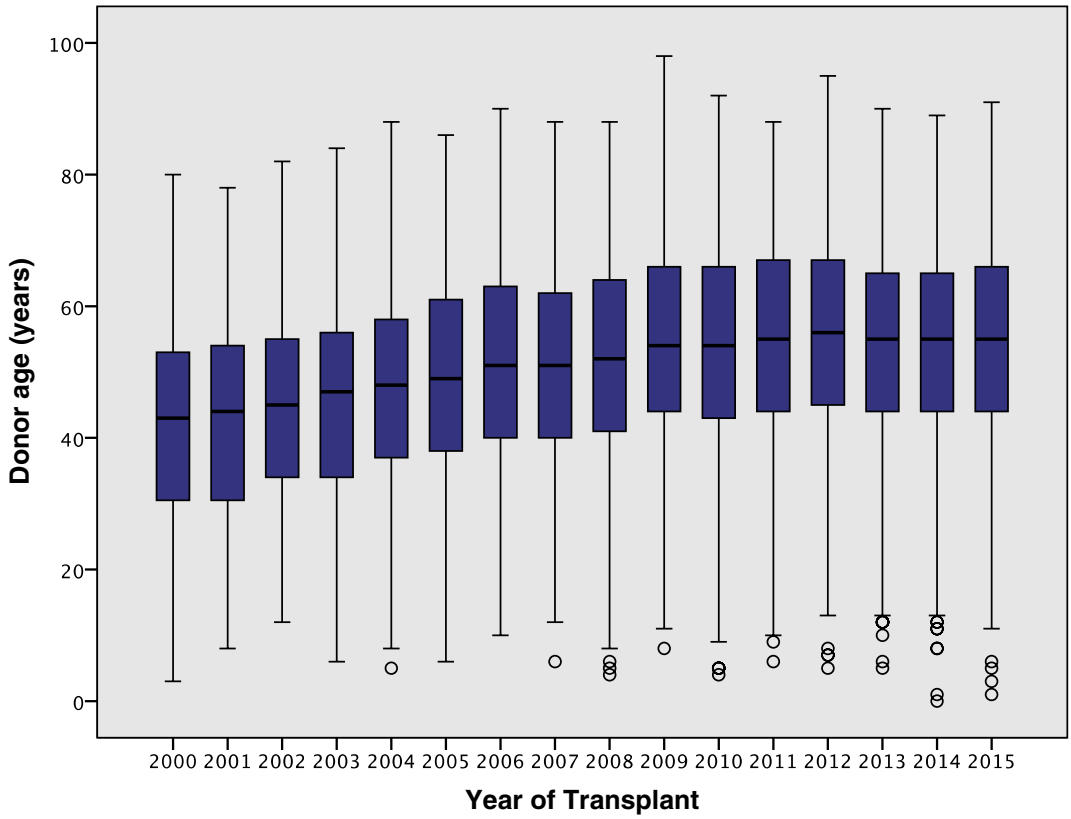

FIG. 1. Trends in donor age. Median donor age increased from 42 to 55 years old from 2000-2015.

of all transplanted livers was 51 years old (maximum 98 years) and increased from 42 to 55 years (Fig. 1). Nearly half of all transplanted livers were allocated extraregionally (45%) and 23% 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 years, and median laboratory 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%, and 55% after 1, 5, and 10 years, respectively.

OUTCOME BY DONOR AGE GROUPS

Of all transplantations, 15,147 (85%) were performed with donors <70 years old and 2014 (11%), 369 (2%), and 11 (0.06%) transplantations were performed with livers from septuagenarian, octogenarian, and nonagenarian donors, respectively (Fig. 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, whereas trauma was more frequent in younger donors. DM had a higher prevalence in livers ≥70 years old (16% versus 5%; $P < 0.001$) in contrast to cardiac arrest (4% versus 13%; $P < 0.001$). Furthermore, CITs were longer in transplanted livers <70 years old (8.9 versus 8.7, $P < 0.001$). The ET-DRI—as a measurement of donor quality—was significantly different in both groups (1.7 versus 2.4; $P < 0.001$), but no significant difference was shown with the factor donor age set at reference (1.4 versus 1.4; $P = 0.31$).

Patients transplanted with a liver ≥70 years old were older as compared with recipients of livers from donors <70 years old (58 versus 54 years old; $P < 0.001$). The recipients of older livers did also have a lower median

TABLE 1. Demographics of All Livers Used for First Liver–Only Transplantations in 2000-2015

	Value (n = 17,811)
Donor factor	
Age, years	51 (40-63)
Height, cm	175 (166-180)
Weight, kg	75 (68-85)
BMI, kg/m^2	25 (23-28)
Sex, male	9713 (55)
HCVAb (positive)	138 (1)
HBcAb (positive)	1001 (6)
Cause of death	
Anoxia	1421 (8)
Circulational	556 (3)
CNS tumor	104 (1)
CVA/stroke	10,659 (60)
Head trauma	4186 (24)
Other	885 (5)
DCD	744 (4)
Split liver	641 (4)
CT present	1725 (10)
Ultrasound abdomen present	13,316 (75)
Cardiac arrest (yes)	2098 (12)
Hypotensive period (yes)	3131 (18)
Diabetes (yes)	1203 (7)
Latest laboratory 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	10,350 (58)
Hungary*	240 (1)
The Netherlands	1593 (9)
Belgium	2694 (15)
Croatia†	803 (5)
Slovenia‡	334 (2)
Austria	1751 (10)
Luxemburg	46 (<1)
Transplant factor	
Allocation	
Local	5121 (29)
Regional	4614 (26)
Extraregional	8076 (45)
Rescue allocation (yes)	4011 (23)
CIT, 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)

NOTE: Data are given as n (%) or median (IQR).
*Joined ET in May 2013.
†Joined ET in May 2007.
‡Joined ET in January 2000.

TABLE 2. Demographics of All Recipients Receiving a First Liver–Only Transplantation in 2000-2015

Recipient factor	Value (n = 17,811)
Age, years	54 (47-61)
Height, cm	173 (167-180)
Weight, kg	77 (67-88)
BMI, kg/m^2	25 (23-29)
Laboratory MELD	16 (11-27)
Match MELD*	23 (16-31)
Sex, male	11,796 (66)
HCVAb (positive)	3474 (19)
Primary disease on waiting list	
Metabolic	612 (3)
Acute	1496 (8)
Cholestatic	2018 (11)
Alcoholic	4102 (23)
Malignant	3138 (18)
HBV	603 (3)
HCV	1516 (9)
Other cirrhosis	3334 (19)
Other/unknown	992 (6)
Laboratory MELD category	
<15	5059 (28)
15-25	3688 (21)
26-34	1851 (10)
35+	1698 (10)
Missing	5515 (31)
Country of transplantation	
Germany	10,651 (60)
Hungary†	170 (1)
The Netherlands	1434 (8)
Belgium	2756 (15)
Croatia‡	787 (4)
Slovenia§	243 (1)
Austria	1770 (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)

NOTE: Data are given as n (%) or median (IQR).
*Match MELD values are either the exceptional or laboratory MELD score used for matching.
†Joined ET in May 2013.
‡Joined ET in May 2007.
§Joined ET in January 2000.
‖Calculated for patients listed after MELD implementation, December 2006 (n = 12,296).

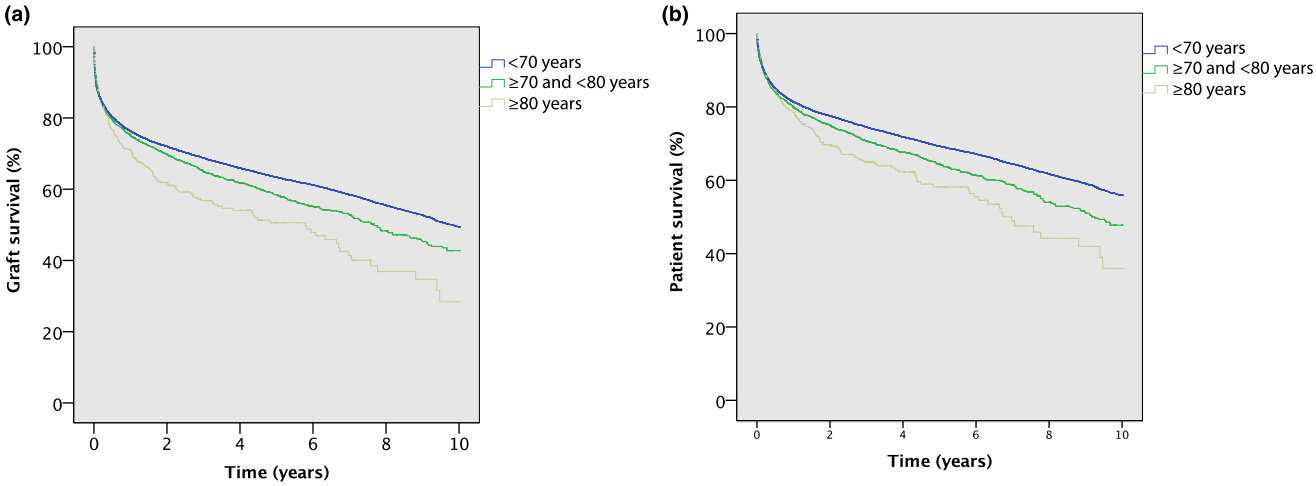

FIG. 2. Kaplan-Meier analysis of survival by donor age category (n = 17,811).

TABLE 3. Graft and Patient Survival Rates

	1 Year	5 Years	10 Years
Graft survival			
<70 years (n = 15,147)			
Survival	76%	63%	50%
Number of events	3527	4989	5722
Number at risk	10,775	5296	1680
70-79 years (n = 2014)			
Survival	75%	58%	43%
Number of events	483	707	782
Number at risk	1358	507	99
≥80 years (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			
<70 years (n = 15,147)			
Survival	81%	69%	56%
Number of events	2763	4124	4837
Number at risk	11,480	5818	1900
70-79 years (n = 2014)			
Survival	80%	64%	48%
Number of events	388	595	673
Number at risk	1436	556	110
≥80 years (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

laboratory MELD score (16 versus 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% versus 17%) and alcoholic liver cirrhosis (30% versus 22%).

When analyzing graft survival, significant differences were observed across donor age categories (<70, 70-79, and ≥80 years) at 5-year ($P \leq 0.001$) and 10-year follow-up ($P \leq 0.001$; Fig. 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 ($P \leq 0.001$) and 10-year follow-up ($P \leq 0.001$; Fig. 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 5 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 of <45 years old ($P = 0.01$),

TABLE 4. Characteristics of All Transplantations in 2000-2015 Per Donor Age Category

	<70 Years (n = 15,417)	≥70 Years (n = 2394)	*P* Value	70-79 Years (n = 2014)	80-89 Years (n = 369)	≥90 Years (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, kg/m^2	25 (23-28)	26 (24-28)	<0.001	26 (24-28)	26 (24-28)	24 (22-26)
Sex, male	8649 (56)	1064 (44)	<0.001	927 (46)	136 (37)	1 (9)
HCVAb (positive)	131 (1)	7 (<1)	0.004	7 (0)	0 (0)	0 (0)
HBcAb (positive)	800 (5)	201 (8)	<0.001	159 (8)	42 (11)	0 (0)
Cause of death			<0.001			
Anoxia	1317 (9)	104 (4)		90 (4)	14 (4)	0 (0)
Circulational	511 (3)	45 (2)		41 (2)	4 (1)	0 (0)
CNS tumor	102 (1)	2 (<1)		2 (0)	0 (0)	0 (0)
CVA/stroke	8817 (57)	1842 (77)		1555 (77)	278 (75)	9 (82)
Trauma	3843 (25)	343 (14)		273 (14)	68 (18)	2 (18)
Other	827 (5)	58 (2)		53 (3)	5 (1)	0 (0)
DCD	717 (5)	27 (1)	<0.001	26 (1)	1 (<1)	0 (0)
Split liver	641 (4)	0 (0)	<0.001	0 (0)	0 (0)	0 (0)
Imaging						
CT abdomen result present	1501 (10)	224 (9)	0.56	190 (9)	33 (9)	1 (9)
Ultrasound abdomen present	11,200 (73)	2216 (93)	<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	1998 (13)	100 (4)	<0.001	88 (4)	12 (3)	0 (0)
Hypotensive periods	2871 (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	4382 (28)	739 (31)		633 (31)	100 (27)	6 (55)
Regional	3953 (26)	661 (28)		550 (27)	108 (29)	3 (27)
Extraregional	7082 (46)	994 (42)		831 (41)	161 (44)	2 (18)
Rescue (yes)	3162 (21)	849 (35)	<0.001	678 (34)	204 (55)	6 (55)
CIT, 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)
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)
Transplantation period			<0.001			
2000-2003	3287 (21)	109 (5)		96 (5)	13 (4)	0 (0)
2004-2006	2631 (17)	293 (12)		256 (13)	36 (10)	1 (9)
2007-2009	3168 (21)	508 (21)		424 (21)	82 (22)	2 (18)
2010-2012	3218 (21)	798 (33)		662 (33)	133 (36)	3 (27)
2013-2015	3113 (20)	686 (29)		576 (29)	105 (28)	5 (46)

TABLE 4. *Continued*

	<70 Years (n = 15,417)	≥70 Years (n = 2394)	*P* Value	70-79 Years (n = 2014)	80-89 Years (n = 369)	≥90 Years (n = 11)
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, kg/m^2	25 (23-29)	26 (23-29)	<0.001	26 (23-29)	26 (23-29)	27 (25-28)
Laboratory 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)	1612 (67)	0.22	1358 (67)	249 (67)	5 (45)
HCVAb	2164 (14)	310 (13)	0.15	258 (13)	51 (14)	1 (9)
Primary disease on waiting list			<0.001			
Metabolic	555 (4)	57 (2)		47 (2)	10 (3)	0 (0)
Acute	1395 (9)	101 (4)		89 (4)	12 (3)	0 (0)
Cholestatic	1795 (12)	223 (9)		192 (10)	30 (8)	1 (9)
Alcoholic	3389 (22)	713 (30)		584 (29)	125 (34)	4 (36)
Malignant	2573 (17)	565 (24)		472 (23)	89 (24)	4 (36)
HBV	504 (3)	99 (4)		83 (4)	16 (4)	0 (0)
HCV	1331 (9)	185 (8)		151 (7)	33 (9)	1 (9)
Other cirrhosis	2956 (19)	378 (16)		329 (16)	48 (13)	1 (9)
Other/unknown	919 (6)	73 (3)		67 (3)	6 (2)	0 (0)
Laboratory MELD category			<0.001			
<15	4130 (27)	929 (39)		765 (38)	160 (43)	4 (36)
15-25	3008 (20)	680 (28)		556 (28)	120 (33)	4 (36)
26-34	1581 (10)	270 (11)		238 (12)	30 (8)	2 (18)
≥35	1504 (10)	194 (8)		175 (9)	18 (5)	1 (9)
Missing (pre-MELD era)	5194 (34)	321 (13)		280 (14)	41 (11)	Not available
Match MELD category*			<0.001			
<15	2259 (15)	415 (17)		344 (17)	68 (18)	3 (27)
15-25	3266 (21)	707 (30)		582 (29)	120 (33)	5 (46)
26-34	3065 (20)	739 (31)		615 (31)	122 (33)	2 (18)
≥35	1633 (11)	212 (9)		193 (10)	18 (5)	1 (9)
Missing (pre-MELD era)	5194 (34)	321 (13)		280 (14)	41 (11)	0 (0)
MELD present, n	10,223	2073		1734	328	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)

NOTE: Data are given as n (%) or median (IQR).
*Match MELD values are either the exceptional or laboratory MELD score used for matching.
†sRRI and DRM are calculated for all recipients after MELD implementation in December 2006.

MELD score category ($P < 0.001$), and HCVAb status of the recipient ($P < 0.001$; Fig. 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 years old, n = 217; 45-55 years old, n = 650; 55-65 years old, n = 1120; >65 years old, n = 407), inferior survival was observed in recipients <45 years old with a survival rate of 54% as compared with 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 ($P < 0.69$; Supporting Fig. 1). No clear cutoff 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 Fig. 3. It shows a stable risk up to a

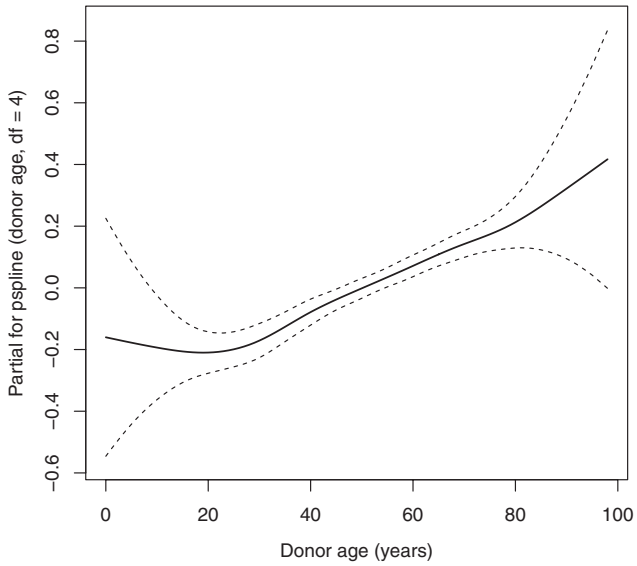

FIG. 3. The adjusted risk of donor age on graft survival (n = 12,296). Donor age has a linear, increasing risk for graft survival from 25 years old up to 80 years old, that shows no signs of decreasing over 80 years old.

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 = 2073)

	Wald	HR	95% CI	p–Value
Donor				
Age, years		1.02	1.003-1.036	0.02
Medical history,				
DM (yes)		1.30	1.047-1.500	0.01
Transplant				
Cold ischemia time (continuos hours)		1.04	1.019-1.071	0.001
Rescue_R (yes)		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		Reference		Reference
≥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 (positive)		1.5	1.229-1.801	<0.001

NOTE: 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, and etiology of disease.

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 95% CI increases because of limited numbers.

OUTCOME IN PREFERRED AND NONPREFERRED RECIPIENTS

Transplantations were then divided into 2 groups of preferred and nonpreferred recipients as described by Segev et al.[11] (Fig. 4). According to these criteria (recipient age >45 years old, recipient BMI <35 kg/m^2, etiology of liver diseases other than HCV cirrhosis, and CIT <8 hours), 4576 (26%) and 13,235 (74%) patients were identified as preferred and nonpreferred recipients, respectively. A similar distribution of laboratory MELD score was present in both groups (Supporting Fig. 2).

In preferred recipients, there was only a minor, nonstatistically significant difference in graft survival between recipients who underwent transplantation with a liver younger than 70 or older than 70 years old (HR, 1.1; 95% CI, 0.92-1.23; $P = 0.40$; Fig. 4A). In nonpreferred recipients on the contrary, a donor age over 70 years old had a significant impact on graft survival (HR, 1.2; 95% CI, 1.14-1.35; $P < 0.001$; Fig. 4B). An even more distinctive difference between preferred and nonpreferred 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; 95% CI, 0.96-1.37; $P = 0.13$; Fig. 4C), whereas it had a major impact in nonpreferred recipients (HR, 1.5; 95% CI, 1.39-1.71; $P < 0.001$; Fig. 4). Similar results were observed for patient survival at 5 years (Supporting Fig. 3A-D).

CENTER ANALYSIS

No difference in outcome of transplantations with livers ≥70 years old (n = 2394) was observed when centers were stratified according to the number of transplanted with livers ≥70 years old (≤70 or >70 transplantations; $P = 0.781$) or by proportion of livers >70 years old (≤12% or >12%; $P = 0.395$; Supporting Fig. 4A,B) in the study period. High proportion centers tended to transplant younger donors (54 years old versus 49 years old; $P < 0.001$), but no (clinical) significant differences

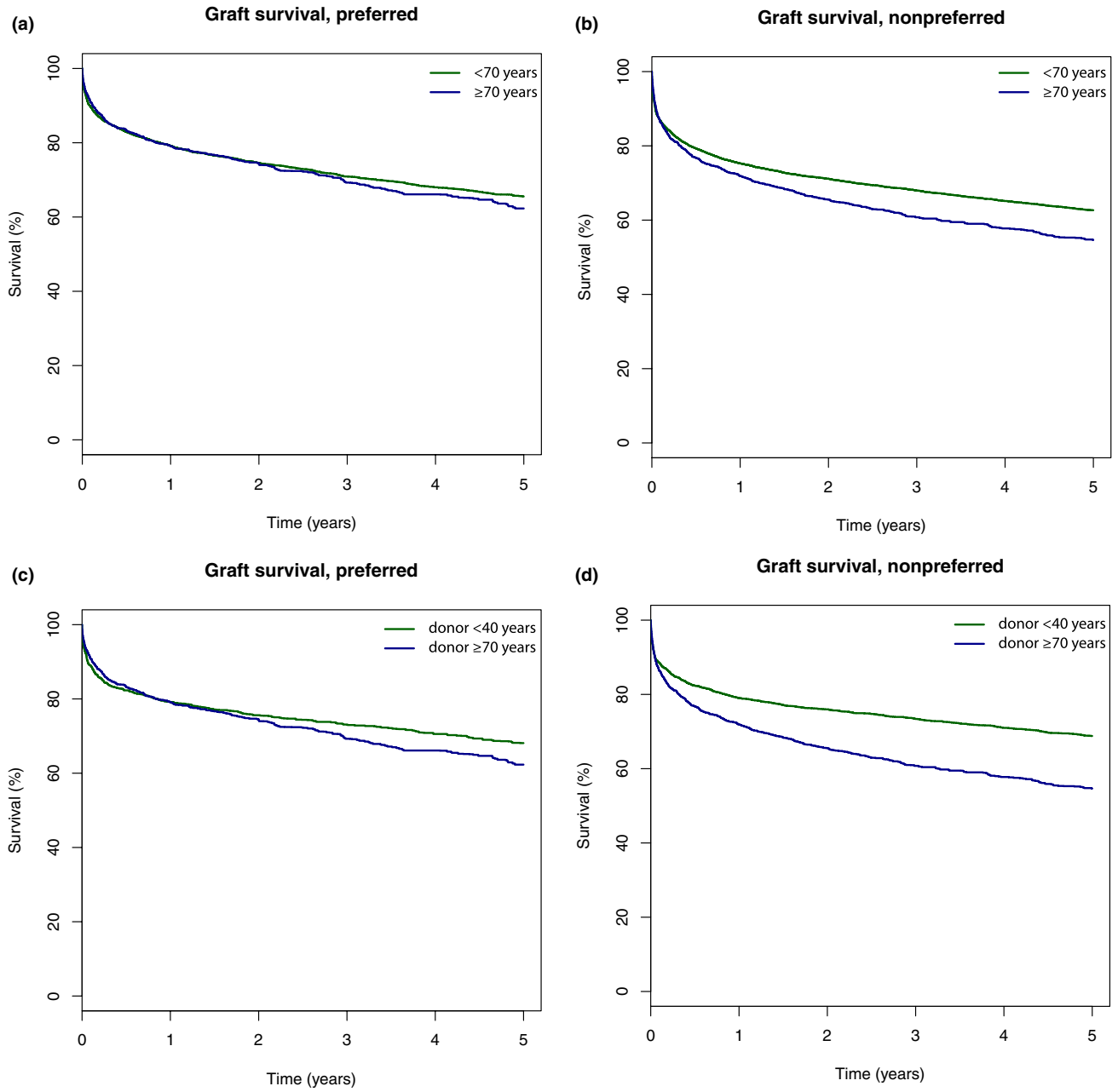

FIG. 4. Graft survival in preferred recipients versus nonpreferred recipients. (A) In preferred recipients, no statistical significant difference can be observed in graft survival whether transplanted with a liver below or over 70 years old (HR 1.1; CI 0.92-1.23, $P = 0.40$). In nonpreferred recipients, this difference in outcome is statistically significant (B) whether transplanted with a liver below or over 70 years old (HR 1.2; CI 1.14-1.35, $P < 0.001$). 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 1.2; CI 0.96-1.37, $P = 0.13$) while a statistically significant difference was observed in nonpreferred recipients (D) (HR 1.5; CI 1.39-1.71, $P < 0.001$).

in median laboratory MELD score (17 versus 16; $P < 0.001$) or CIT (8.8 hours versus 8.9 hours; $P = 0.96$) were observed as compared with low proportion centers.

When centers were categorized according to outcome of transplantations with livers ≥70 years old, 6 centers (n = 570 LTs) had significantly "better than expected" graft survival at 5-year follow-up, whereas 8 (n = 649 LTs) and 20 transplantation centers (n = 1160 LTs), respectively, had "worse than expected" or "as expected" outcome (Supporting

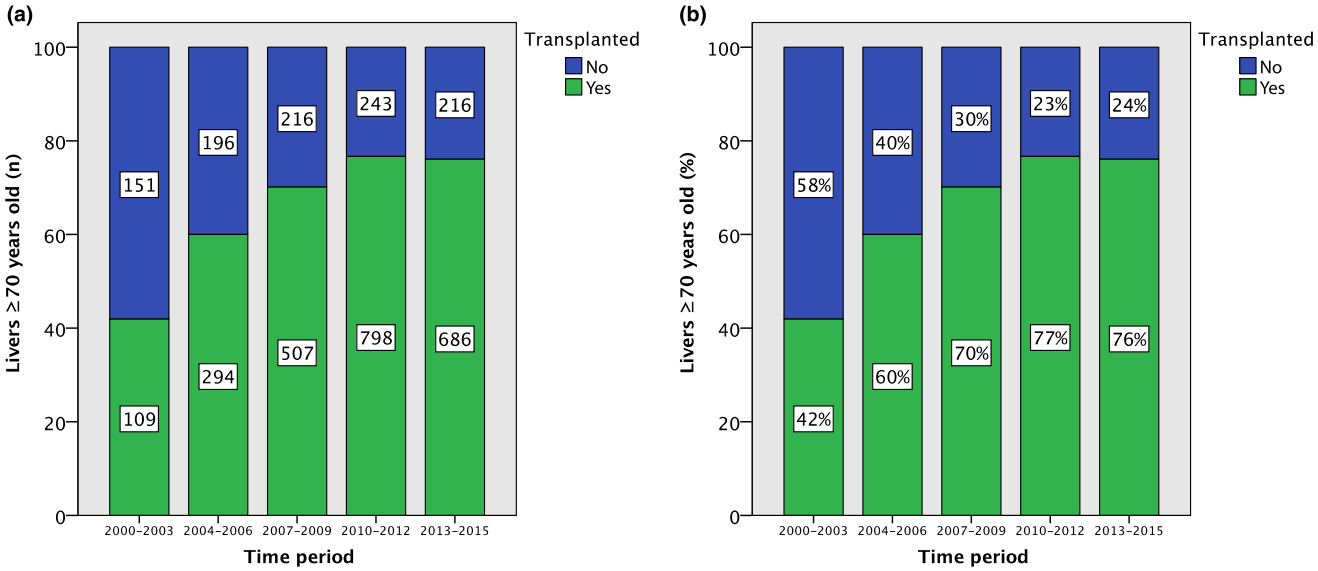

FIG. 5. Utilization of livers ≥70 years old. Number of livers ≥70 years old reported to ET by transplantation status (numbers). Number of livers ≥70 years old reported to ET by transplantation status (relative %).

Fig. 4C). Characteristics of these groups are shown in Supporting Table 2. 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, 1022 out of 3416 (30%) livers were not transplanted. Characteristics of transplanted versus nontransplanted liver allografts are shown in Supporting Table 1. Most notably, hepatitis B virus (HBV) and HCV were more often observed in nontransplanted livers with rates for HBV of 12% versus 8% ($P \leq 0.001$), and HCV of 3% versus 0% ($P \leq 0.001$), respectively. Also, diabetes was more often present in donors of nontransplanted livers (23% versus 16%; $P \leq 0.001$), and laboratory values (GGT, transaminases, and bilirubin) were significantly higher in donors of nontransplanted livers. The utilization rate increased from 42% in 2000-2003 to 77% in 2010-2012 and stabilized at 76% in 2013-2015 (Fig. 5). Of all 1022 nontransplanted livers, 374 (37%) were procured. The proportion of nontransplanted 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 the 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.

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 HCV in the recipient should therefore be avoided when transplanting older livers. With an adequate selection, wait-list 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 aging of transplanted livers is distinctive; the median donor age increased

TABLE 6. Reasons for Discarding Older Livers

	Value (n = 374)
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) CIT	24 (6)
Other‡	4 (1)
No information available	69 (18)

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

from 43 to 55 years in only 15 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 outcomes could potentially be improved by optimizing our patient selection. This is 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 aging rapidly, and the higher acceptance rate is likely because of the persisting shortage that was also observed in this study (Fig. 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 arises as to 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 up to 80 years old. The risk of livers from donors of 80 years may increase nonlinearly 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.[8] 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.[8,16,17] 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.[18] Considering the recipient selection criteria that were used by Segev et al.,[11] we could confirm CIT, HCV, and a recipient age <45 years, but not recipient BMI (continuous or with a BMI of 35 kg/m^2 as a cutoff). Yet, we have confirmed their findings that in "preferred patients" donor age has no significant effect as compared with "nonpreferred 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[7,8,19-21] with lower laboratory MELD scores[22,23] who more often suffer from malignant disease.[7,20,21] 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, had diabetes less often, and underwent transplantation in recipients with lower laboratory MELD scores. We have therefore adjusted outcomes 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[24] because information on biopsies was insufficiently available. We considered graft survival a primary outcome because information on biliary complications or early bile production was not available in the ET database. This is a potential limitation because some studies found suggestions for more biliary complications in transplantations with livers from elderly donors.[3,17,25-27] However, biliary

complications will likely also affect graft survival in the long run.

OUTCOMES IN OTHER STUDIES

The presented results of outcomes 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% to 90%[7,9,28-33] and 5-year patient survival rates from 50% to 80%.[7,20,28-30,34] The sometimes very promising outcomes[7-9,31,32] are apparently contradicting to the higher intrinsic risk of older donors.[10,35] These results are therefore likely to be explained by the frequent single-center design, relatively small numbers of included transplantations, different aging patterns in other countries,[36] 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,[7-9,20,23,27,29] more often have pretransplant biopsies,[8,16,20,22,29,37] have a lower incidence of cardiac arrest,[7,8,20-23,27] and are more frequently regionally procured.[8,22,23] 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 and 2015. In the overall study period, the 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 livers that were used for retransplantations were included (data not shown). These rates are very high in comparison to other studies who report usage rates of approximately 60%[38] and 52%-63% for liver donors ≥70 years and ≥80 years old, respectively.[7,16,38] It does, however, correspond with usage in the United States where 74% of livers of 70 years and older are used for transplantation.[10] Although the United States 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 with the United States. By using the same inclusion criteria as Halazun et al.,[10] in ET 2625 out of 21,644 (12%) transplantations in adults were performed with donors from 70 years and older as compared with 4.3% in the United States (data from ET).

IMPLICATIONS

Outcomes of geriatric LT in ET 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 because we have confirmed good outcomes of older livers in preferred recipients as defined by Segev et al.[11] It is interesting that posttransplantation outcomes in these preferred recipients are not significantly affected by older donor age. Although not fully understood, the factors recipient age >45 years, BMI <35 kg/m^2, and CIT <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 CIT, 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.[39] Second, we should strive to improve the number of older donors who 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 ET 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%) LT 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 nontransplanted livers, we suggest avoiding an age limit to report potential donors. Because of this, otherwise transplantable older donor livers will not be missed.

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 an 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 wait-list mortality safely.

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