ORIGINAL ARTICLE

Association between donor age and risk of graft failure after liver transplantation: an analysis of the Eurotransplant database

Sebastian Pratschke[1], Andreas Bender[2], Florian Boesch[1], Joachim Andrassy[1], Marieke van Rosmalen[3], Undine Samuel[3], Xavier Rogiers[4], Bruno Meiser[5], Helmut Küchenhoff[2], David Driesslein[2], Jens Werner[1], Markus Guba[1,*] & Martin K. Angele[1,*] for the Eurotransplant Liver and Intestine Advisory Committee (ELIAC)

1 Department of General, Visceral, Vascular and Transplantation Surgery, Hospital of the LMU Munich, Munich, Germany
2 Statistical Consulting Unit StaBLab, Department of Statistics, Ludwig-Maximilians University, Munich, Germany
3 Eurotransplant International Foundation, Leiden, The Netherlands
4 Transplantatiecentrum, Universitair Ziekenhuis Gent, Gent, Belgium
5 Transplant Center, Hospital of the LMU Munich, Munich, Germany

Correspondence
Martin K. Angele MD, Department of General, Visceral, Vascular and Transplantation Surgery, Hospital of the University of Munich, Marchioninistr. 15, 81377 Munich, Germany.
Tel.: +49 89 4400 72781;
fax: +49 89 78893;
e-mail: martin.angele@med.uni-muenchen.de

*Both authors contributed equally to the manuscript.

SUMMARY

Grafts from elderly donors are increasingly used for liver transplantation. As of yet there is no published systematic data to guide the use of specific age cutoffs the effect of elderly donors on patient outcomes must be clarified. This study analyzed the Eurotransplant database (01/01/2000–31/07/2014; $N = 26\ 294$) out of whom 8341 liver transplantations were filtered to identify for this analysis. 2162 of the grafts came from donors >60 including 203 from octogenarians ≥80 years. Primary outcome was the risk of graft failure according to donor age using a confounder adjusted Cox-Regression model with frailty terms (or random effects). The proportion of elderly grafts increased during the study period [i.e., octogenarians 0.1% ($n = 1$) in 2000 to 3.4% ($n = 45$) in 2013]. Kaplan–Meier and Cox-analyses revealed a reduced survival and a higher risk for graft failure with increasing donor age. Although the age effect was allowed to vary non-linearly, a linear association hazard ratio (HR = 1.1 for a 10 year increase in donor age) was evident. The linearity of the association suggests that there is no particular age at which the effect increases more rapidly, providing no evidence for a cutoff age. In clinical practice, the combination of high donor age with HU-transplantations, hepatitis C, high MELD-scores and long cold ischemic time should be avoided.

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Key words
donor age, clinical liver transplantation, cox regression model, cutoff age, frailty terms, graft failure

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Introduction

The impact of donor age on liver transplantation is the subject of much debate. Because of the growing number of elderly donors, numerous studies have tried to examine the effects of donor age and to define potential limits of organ acceptance. However, conclusive and methodologically sound multivariate analyses of the effects of donor age in liver transplantation are lacking. The question whether there is a chronological age after which grafts from elderly donors should be excluded from transplantation has yet to be answered. Previous monocentric studies have suggested that

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livers from elderly donors can be safely used for transplantation. In these analyses, arbitrary cutoffs were utilized which vary between 55 and 80 years [1–3]. Based on these data, a donor age of 65 years is currently considered an extended donor criterion (EDC) by Eurotransplant [4]. However, demographic changes in industrialized countries [5] and the increasing shortage of donor organs [6] have led to a growing acceptance of grafts from extended criteria donors. Elderly donors who would have previously been rejected are increasingly considered to fill the gap between the supply of and the demand for donor organs [7].

Therefore, the aim of the present study was to clarify the following questions: (i) Is there an age limit for organ donors in liver transplantation that is an absolute contraindication to organ donation? and (ii) should chronological age be used to define EDC-organs, and if so which age cutoff is most clinically relevant?

This study was initialized in cooperation with Eurotransplant and addresses these questions using a multivariate model adjusted for multiple confounders within a large multicenter patient collective. A special focus of our study was the outcome of liver grafts from very elderly donors (i.e., octogenarians ≥80 years). In this respect, advanced statistical models allow the analysis of numeric variables without categorizing which appears to be more suitable to identify donor age-associated risks [8].

Moreover, a variety of clinical situations was modeled using predicted graft survival probabilities for different diagnoses, labMELD-Scores and donor ages at different time points after liver transplantation.

Methods

Study overview

This retrospective cohort study incorporated all liver transplantations performed with donors registered in the Eurotransplant allocation area (observation period 1/1/2000 until 31/7/2014; $N = 26\,294$ liver donors). All data analyzed (i.e., age, sex, graft function, laboratory values, etc.) was provided by Eurotransplant International Foundation which covers the transnational organ allocation within Austria, Belgium, Croatia, Germany, Hungary, Luxemburg, the Netherlands and Slovenia with a population of 135 million inhabitants.

Patients

Descriptive analyses were performed utilizing the complete raw data set. For multivariate analyses, 8341 of the available observations remained eligible for analysis after applying the inclusion and exclusion criteria (see below, for further details see Appendix S1).

Inclusion criteria

Main inclusion criteria were first liver transplantation, adult liver transplantation (recipient ≥16 years), donor age ≥16 years, whole liver transplantation and transplantation after 2005 (introduction of a MELD-score based allocation by Eurotransplant).

Exclusion criteria

Most exclusions were because of recipients or donors younger than 16 years, donation after circulatory death and missing values in important confounders, especially labMELD-Scores, that were not recorded until 2005 (see Appendix S1). Split liver transplantations were excluded as well as death at time 0 and observations with implausible values. Retransplantations were also excluded.

Data collection

Confounders in organ donors

An extensive search for medically plausible and available confounders was performed, generating the following variables (as reported in the Eurotransplant donor report): BMI, sex, age, γGT, ALT, AST, admission to ICU (days before transplant) and cold ischemia time (CIT). Causes of death in donors were captured and categorized as follows: Intracranial bleeding (ICB), hypoxic brain damage (hypoxia), trauma, others.

Confounders in organ recipients

In organ recipients, the following confounders were included: BMI, sex, age, diagnosis, labMELD (last labMELD reported to Eurotransplant before transplantation), transplantation center, perfusion fluid, allocation mode (high-urgency vs. non high-urgency). Diagnoses leading to liver transplantation were categorized as follows: acute liver failure, alcohol induced cirrhosis (AIC), biliary diseases, malignancy [i.e., hepatocellular carcinoma (HCC)], hepatitis C (HCV), viral hepatitis (HBV, HDV, HEV), metabolic diseases, other cirrhosis and others.

Statistical analysis

Primary endpoint of the study was graft failure. Graft failure was inferred from secondary variables. The most

reliable variable in that regard was retransplantation, thus when retransplantation data were given, we used this date to calculate the time until graft failure. When death from liver failure was given without prior retransplantation, we used the time-point of death as time until graft failure. If the last observation was a routine follow-up and no retransplantation or death occurred, we considered the patient/graft as censored and calculated the censoring time based on the data of the last follow-up. If neither of the variables was given, the observation was administratively censored at 2013-12-31. The censoring time was then obtained by the time from transplantation date until the end of the follow-up period. The exact calculations are given in the supplementary R-code (https://github.com/adibender/liver; data could not be shared, however, because of Eurotransplant policy). In the initial, descriptive analysis of the data, categorical variables were described by frequency (%) and continuous variables as mean ± SD, grouped by different categories of donor age [≥16 (A), elderly 65 < 80 (B), very elderly ≥80 years (C)], respectively. As this categorization has no substantive or empirical justification and categorization most often leads to loss of information, we estimated the effect of donor age utilizing a Cox Regression model (with frailty) non-linearly, simultaneously adjusting for the confounders listed above.

Modeling

The Cox regression model [9] with frailty terms was used to model the association between the aforementioned confounders, donor age, and graft failure. All variables identified as potential confounders were included in the model and no variable selection was performed. All continuous variables were allowed to vary non-linearly (using P-Splines [10]). Categorical variables were included as reference-coded dummy variables. Additionally, we included a Gaussian frailty [11] term to account for the heterogeneity between different transplant centers. To account for improved graft survival because of potential medical progress, we also adjusted for the transplant year. The statistical programming language R was used for this analysis [32]. The full specification of the model can be found in the Appendix S1.

Results

Patients

Within the final study population ($N = 8341$), 2626 patients experienced an event (graft failure). Three hundred thirty-seven livers from octogenarian donors were transplanted of which 203 were eligible for analysis, 105 of which experienced an event. During the study period, there was an increase in octogenarian donors from 0.1% in 2000 ($n = 1$) to 3% in 2013 ($n = 44$). The portion of donors aged 65–80 also increased from 5.2% in 2000 ($n = 56$) to 20.2% ($n = 303$) in 2013.

Cox regression analysis

Results of the confounder adjusted Cox regression are summarized in Figures 1–3 and Table 1. Table 1 depicts estimated model coefficients for reference coded categorical variables.

On average (all other covariates being equal), female recipients (compared to males) have a decreased risk of graft failure [HR: 0.83, CI: (0.75,0.91)]. Compared to recipients with acute liver failure and non-high urgency, recipients diagnosed with acute liver failure and with high urgency [HR: 0.42, CI: (0.33,0.53)]. AIC [HR: 0.27, CI: (0.22,0.33)], HCV [HR: 0.49, CI: (0.39,0.62)] and the other diagnosis all have a decreased risk of graft failure.

Figure 1 depicts the potentially non-linear effect estimates for continuous confounders and shows that the risk increases for higher labMELD-Scores (especially for labMELD-Scores >25) as well as for increased procurement time (CIT) and recipient age. For recipients' BMI the risk decreases between BMIs of 15 and 25 and remains constant for the remainder.

The estimate of the donor age effect is depicted in Fig. 2: While the risk of graft failure increases for grafts from older donors (HR = 1.1 for a 10 year increase in donor age), the association is a linear function for any donor age without a specific point at which the risk increases more rapidly.

Graft survival

High donor age was associated with a decreased overall graft survival as shown by Kaplan–Meier analysis using categorized donor data (Fig. 4). The median organ survival following liver transplantation was also reduced after transplantation of grafts from elderly donors: (A): 2691; (B): 2250; (C): 1197 days.

The analysis of the raw data revealed that the retransplantation rate in patients receiving grafts from elderly donors was higher compared to grafts from younger donors: (C) 14.92%; (B) 11.41%; (A) 9.87%.

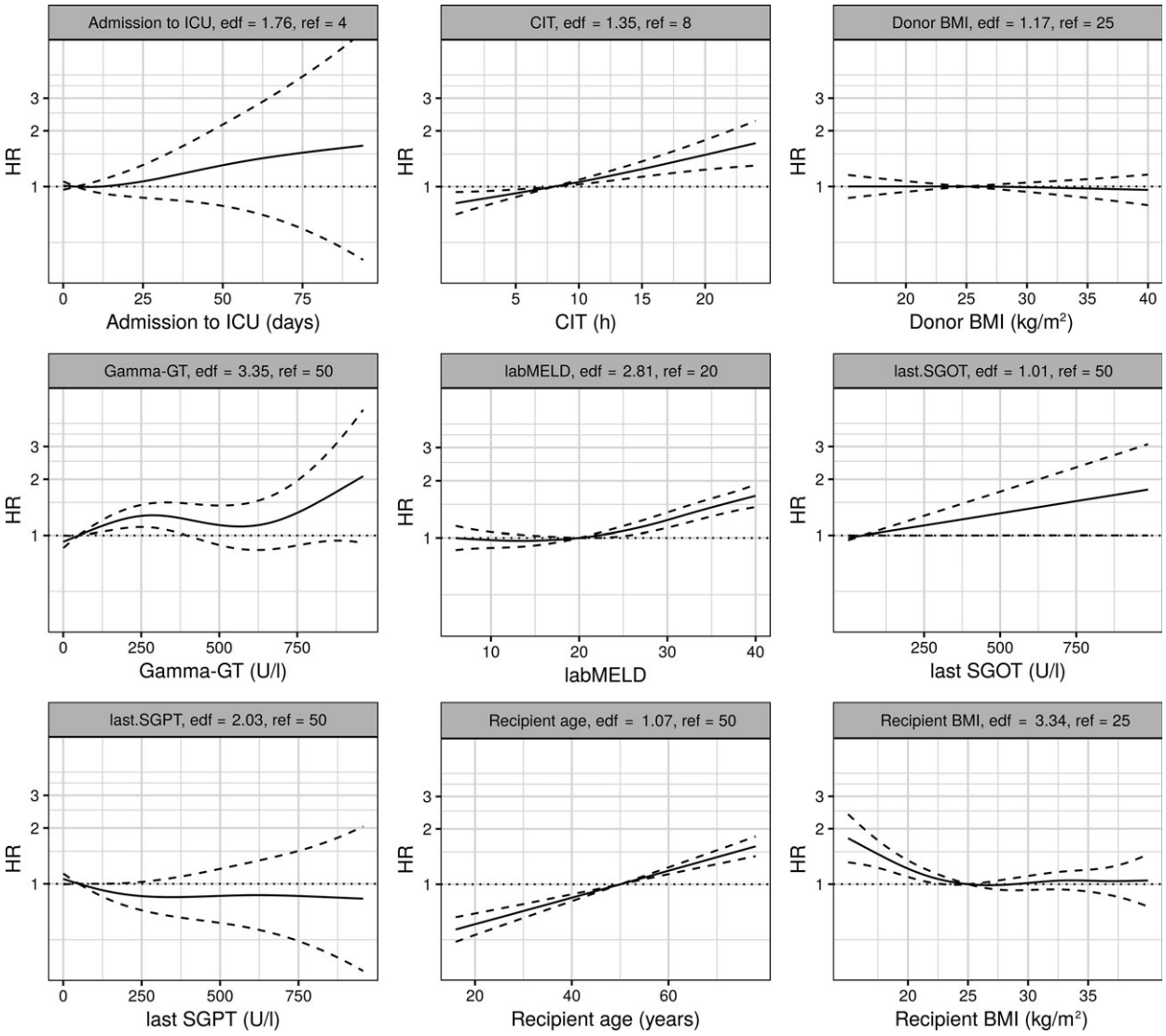

Figure 1 Confounder-adjusted Cox Regression analysis: estimated associations between continuous covariates and graft failure. Associations were allowed to vary non-linearly, but were estimated (almost) linearly in some cases. In the facet headers "edf" stands for "effective degrees of freedom", which is a measure for the smoothness of the estimated association (edf = 1 indicates a linear relationship w.r.t. the log-hazard). The displayed hazard ratios (HR) must be interpreted with respect to the reference value ("ref" in the facet headers). For example, HR = 1 for a recipient age of 50 (ref = 50) by definition, while a 60-year-old recipient has a HR of about 1.25 compared to a 50-year-old recipient.

Donor characteristics

Elderly donors exhibited lower aminotransferase levels [ALT: (A) (≥16 years): 62.3 ± 87.9 U/l, (B) (65 < 80 years): 38.7 ± 53.6 U/l, (C) (≥80 years): 29.3 ± 35.5 U/l; AST: (A) 78.9 ± 94.5 U/l, (B) 55.4 ± 62.0 U/l, (C) 46.4 ± 39.6 U/l; γGT (A) 86.0 ± 118.7 U/l, (B) 61.5 ± 84.9 U/l, (C) 54.2 ± 100.2 U/l and had shorter ICU stays (A) 4.8 ± 5.2, (B) 3.8 ± 4.7, (C) 3.1 ± 3.5 days] than younger donors. CIT was very similar for octogenarian donors and younger donors [(A) 8.6 ± 3.7, (B) 8.6 ± 3.6, (C) 8.2 ± 3.5 h]. The causes of donor death were also comparable for the groups (data not shown).

Recipients' characteristics

The recipients of livers from octogenarian donors were older than recipients of grafts from younger donors [(A) 52.5 ± 1.3, (B) 55.9 ± 9.2, (C) 57.0 ± 8.7 years] whereas the recipients' BMI did not differ between these groups. 29.8% of all octogenarian grafts (C) were transplanted into patients with alcoholic liver cirrhosis compared to 21.1% from the group of donors aged

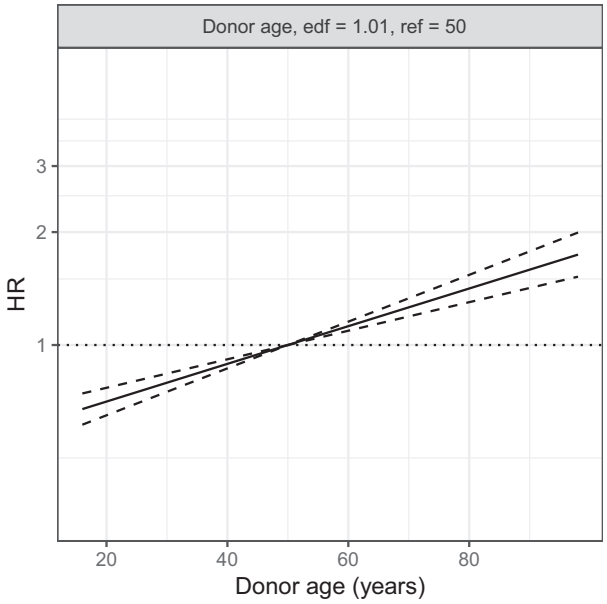

Figure 2 Hazard ratio of donor age, relative to a patient who received a graft from a 50-year-lod donor (everything else being equal).

<65 years (A) and 26.6% (B), respectively. Grafts from octogenarians were also more often transplanted into patients with a HCC: 19.9% from group (A) versus 22.6% from group (C). In contrast, octogenarian donors' grafts were used less in cases of acute graft failure [(A) 7.7%, (B) 4.4%, (C) 1.9%)] and in acute liver failure [(A) 12.1%, (B) 6.8%, (C) 2.8%], respectively. LabMELD-Scores were lower in recipients of elderly grafts: (A) 20.3 ± 10.7; (B) 18.9 ± 10.0; (C) 16.4 ± 8.7 [Median (A) 19; (B) 17; (C) 15].

Discussion

The utilization of EDC organs (i.e., grafts from elderly donors) has become routine in liver transplantation [12,13]. As organ donation rates are stagnant [6] and life expectancy is increasing [5], the number of elderly donors is even expected to rise. Today grafts from very elderly donors (i.e., octogenarians ≥80 years) are still rarely used in liver transplantation [14,15]: Within the study period, the proportion of grafts from octogenarian donors increased from 0.1% to 3.0%. In the Eurotransplant allocation area, a donor age older than 65 years is considered an EDC [4,16] and data suggest even higher donor ages to be suitable for transplantation [17]. The scientific rationale for such cutoff values, however, is weak and the limits of organ acceptance remain unclear. In this respect, previous studies evaluating the effect of donor age on outcome following liver transplantation display contradictory results and use arbitrary age-cutoffs [3,18,19]. Interestingly, most of these publications suggest that elderly donors can be safely transplanted if certain donor recipient matches are avoided (i.e., elderly donor and hepatitis C [20], long CIT [14], etc.).

Moreover, cardiovascular and metabolic comorbidities are more frequent in elderly patients. In this respect, numerous covariates and potential comorbidities may interfere with the association of donor age and outcome. Therefore, analyses of large databases considering relevant recipient as well as donor characteristics (i.e., cardiovascular disease, metabolic syndrome) are required.

The multivariate model including all other confounders revealed an association between donor age and the risk of graft failure (HR: 1.1 for a 10 year difference). Interestingly, the shape of the association was linear and not for example exponential with increasing age. For illustration, the incremental increase of risk is the same moving from donor age 20 to 21 as from ages 70 to 71 or from 80 to 81.

The present data therefore demonstrate that there is no evidence for a cutoff in donor age and that categories in liver donors cannot be applied to describe graft quality as demonstrated previously [1–3].

In a historic cohort of approximately 15 000 liver transplantations an age-cutoff of 55 years was published by Adam *et al.* [21]. Although this study demonstrated negative effects of an increased donor age on the outcome in liver transplantation a cutoff of 55 years does not reflect the present challenges in transplantation medicine.

Recently, risk scores in liver transplantation have been developed to analyze the effects of donor age systematically within multivariate models. Some of these models also analyze categorized data [22–24]. In contrast to a previous analysis [25] our model allows all continuous variables to vary non-linearly as demonstrated by the MELD-Score. Therefore, our data indicate the need for new risk scores for estimating an individual risk following liver transplantation using more complex statistical methods.

In a recent publication, Halazun *et al.* [26] claim that the use of elderly livers can be equivalent or even superior to younger donors in case of an optimal donor–recipient matching. It must be stated that this conclusion is drawn from a subgroup analysis of observational, univariate data which may incorporate a potential bias.

Therefore, our model was modified to provide information about donor age for purposes of graft allocation

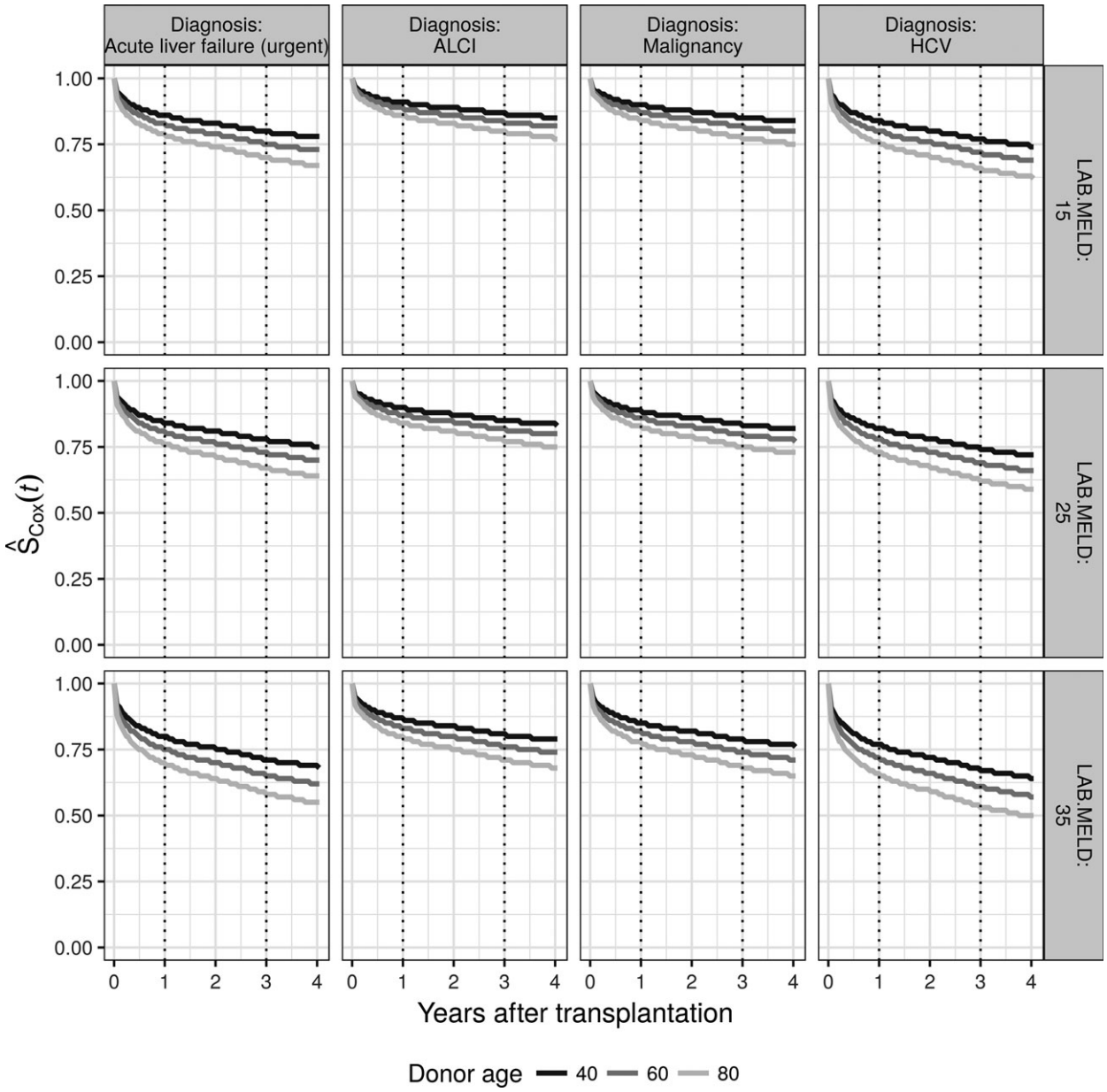

Figure 3 Model based, predicted graft survival curves for different diagnoses (acute liver failure, AIC, malignancy, HCV), labMELD Scores (15, 25, 35), and donor ages (40, 60, 80). All other variables are held constant across settings, using median values for continuous covariates and the modus for categorical variables.

despite the lack of an age cutoff: Fig. 3 illustrates differences in graft survival for different recipient diagnoses (acute liver failure, AIC, malignancy, HCV), labMELD-Scores (15, 25, 35), donor age (40, 60, 80 years), and various time points. In this respect, model-based, predicted graft survival probabilities for different scenarios were calculated (Table 2): For instance, giving a HCV patient with a labMELD of 35 a liver of an 80-year-old instead of a 60-year-old donor would decrease the survival probability of the graft after 360 days by 6%, while giving an 80-year-old instead of a 60-year-old graft to a patient with alcoholic cirrhosis (labMELD 35) would reduce the respective survival probability by only 3%. Note that this reflects the differences in hazards associated with different diagnoses rather than implying that the association of donor age and graft failure varies by diagnoses (which was not investigated). Nevertheless, this example illustrates, that graft survival is affected by multiple factors that should be considered with respect to graft allocation.

Table 1. Confounder-adjusted Cox Regression analysis: table of estimated hazard ratios (HR) for reference coded categorical covariates.

	Hazard ratio
Recipient sex: female	0.83 (0.75, 0.91)
Donor sex: female	0.98 (0.9, 1.06)
Recipient diagnosis: acute liver failure (urgent)	0.42 (0.33, 0.53)
Recipient diagnosis: ALCI	0.27 (0.22, 0.33)
Recipient diagnosis: BILE	0.36 (0.28, 0.46)
Recipient diagnosis: HCV	0.49 (0.39, 0.62)
Recipient diagnosis: malignancy	0.3 (0.24, 0.37)
Recipient diagnosis: metabolic	0.31 (0.23, 0.42)
Recipient diagnosis: other	0.4 (0.31, 0.52)
Recipient diagnosis: other cirrhosis	0.28 (0.23, 0.36)
Recipient diagnosis: viral hepatitis	0.29 (0.22, 0.38)
Donor cause of death: ICB	0.98 (0.89, 1.08)
Donor cause of death: other	1.12 (0.8, 1.56)
Donor cause of death: trauma	0.84 (0.6, 1.18)
Perfusion: (modified) UW	1.26 (0.88, 1.8)
Perfusion: none/other	1.15 (0.73, 1.81)
Transplant year: 2006	1.23 (0.88, 1.74)
Transplant year: 2007	1.17 (0.83, 1.65)
Transplant year: 2008	1.28 (0.91, 1.81)
Transplant year: 2009	1.16 (0.82, 1.64)
Transplant year: 2010	1.11 (0.78, 1.56)
Transplant year: 2011	1.12 (0.79, 1.58)
Transplant year: 2012	1.06 (0.74, 1.52)
Transplant year: 2013	1.11 (0.76, 1.6)

Respective 95% confidence intervals are given in brackets. The respective reference categories are given with an HR of 1.

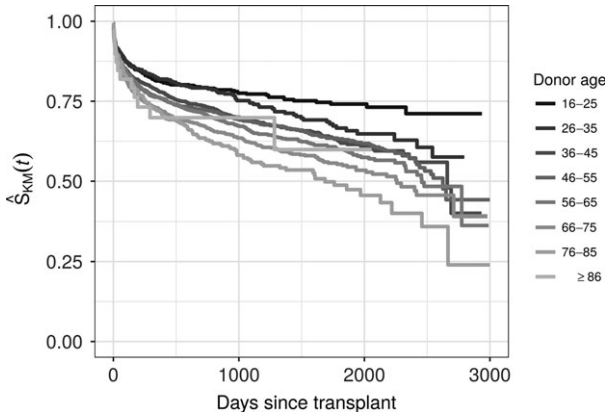

Figure 4 Kaplan–Meier estimates of the survival probability $\hat{S}_{KM}(t)$ at different time points of the follow-up, stratified by donor age categories.

With respect to donor characteristics, Gao *et al.* [27] recently demonstrated an improved outcome in recipients of elderly grafts and postulate that this is because of a reduced cold ischemic time over the last decades. Although this conclusion is drawn from univariate data, our results show an increased risk of graft failure in case of a prolonged cold ischemic time, too (Fig. 1). Therefore, improvements in transport and logistics must be achieved.

In general, considerations for an improved utilization of elderly grafts may already be used in practice as demonstrated by descriptive data using preliminary cut-offs: The portion of rescue allocations was 19.8% in all allocations. In this respect, elderly [65 < 80 years (B)] and very elderly [≥80 years (C)] grafts were utilized more frequently in rescue allocations [(A) 73.7 (B) 22.9% (C) 3.4%] as compared to primary allocations [(A) 76.2% (B) 12.9% (C) 0.9%] (data not shown). On the other hand, the descriptive data also demonstrate that the allocation of elderly grafts for acute health problems is still rare: Elderly grafts are rarely utilized for acute liver failure as shown by small numbers of transplantations for acute liver failure: (A) 12.1%; (B) 6.8%; (C) 2.8% (proportion in all transplants per age group). Furthermore, only six grafts from octogenarian donors were used for retransplantations. In case of high urgency transplantations the utilization of elderly donors could be an option even in young recipients. Unfortunately, grafts from very elderly donors (>80 years) were only used in four patients for HU transplantations. Therefore, no statement can be made on this important issue. In general, the descriptive data suggest a careful allocation of elderly grafts. Nevertheless, the present data could also promote an "old for old program" in liver transplantation which is supported by recent literature [28].

When interpreting our results, an increasing life expectancy must be taken into account. Current studies expect an average life expectancy of 100 years in babies born in industrialized countries today because of an improved healthcare [5]. Therefore, the relevance of an individual's chronological age as compared to its biological age will decrease. Especially, transplantation of grafts older than 80 years in young patients might create problems not known today, because the process of liver senescence is not fully understood. In this respect, attempts have been made to identify molecular markers of aging in the liver. Despite morphological changes according to age, that is, a reduction in size, age-associated deficits in liver function have not been described [29]. In particular, a diminished capacity of liver regeneration with age because of hepatocyte telomere-reduction and/or epigenetic silencing of E2F-regulated genes may be responsible for a decreased graft survival [30].

Table 2. Model based, predicted graft survival probabilities $\hat{S}_{Cox}(t)$ for different diagnoses (acute liver failure, AIC, malignancy, HCV), labMELD Scores (15, 25, 35), and donor ages (40, 60, 80) at time 90 (A), 360 (B), and 1080 days (C) after transplantation.

Donor age				
Recipient diagnosis	labMELD	40 survival	60 survival	80 survival
A				
Acute liver failure	15	0.91	0.89	0.86
	25	0.9	0.88	0.85
	35	0.87	0.84	0.8
AIC	15	0.94	0.93	0.91
	25	0.94	0.92	0.9
	35	0.92	0.9	0.87
Malignancy	15	0.94	0.92	0.9
	25	0.93	0.91	0.89
	35	0.91	0.88	0.86
HCV	15	0.9	0.87	0.84
	25	0.89	0.86	0.83
	35	0.85	0.82	0.78
B				
Acute liver failure	15	0.86	0.83	0.79
	25	0.84	0.81	0.76
	35	0.8	0.75	0.7
AIC	15	0.91	0.89	0.86
	25	0.9	0.87	0.84
	35	0.87	0.83	0.8
Malignancy	15	0.9	0.87	0.84
	25	0.89	0.86	0.83
	35	0.85	0.82	0.78
HCV	15	0.84	0.8	0.76
	25	0.82	0.78	0.73
	35	0.77	0.72	0.66
C				
Acute liver failure	15	0.80	0.75	0.70
	25	0.78	0.73	0.67
	35	0.71	0.66	0.59
AIC	15	0.87	0.84	0.80
	25	0.85	0.82	0.78
	35	0.81	0.76	0.71
Malignancy	15	0.85	0.82	0.78
	25	0.84	0.80	0.75
	35	0.79	0.74	0.69
HCV	15	0.77	0.72	0.66
	25	0.75	0.69	0.63
	35	0.68	0.61	0.54

All other variables are held constant across settings, using median values for continuous covariates and the modus for categorical variables.

Therefore, methods to detect the biological age of a graft from the donors' blood must be developed for estimating the age-associated risk of liver grafts.

In summary, the results of this study demonstrate an increased risk for organ failure associated with donor age. A specific cutoff as described in previous studies, however, cannot be defined given the present analysis, as the association between donor age and risk for graft failure was estimated as a linear function. Therefore, no graft can be rejected solely because of its age although there might be a theoretical acceptable risk threshold that physicians are willing to accept. Moreover, previous risk indices incorporating donor age must be reevaluated to improve outcomes and increase the pool of available donors. Acute liver failure, high MELD score, and a long cold ischemic time may represent situations in which advanced donor age may be particularly detrimental. In clinical practice, such considerations may be hindered by graft availability, transport and allocation logistics, ethical considerations [31] and other factors. Because of the growing life expectancy, the relevance of donor age may decline and new molecular markers reflecting a graft's biological age must be incorporated into the risk assessment in organ allocation.

Limitations

Using observational data alone can only establish associations, not causality, and such analyses can only account for confounders that are included in the analysis. Additionally, although, compared to other studies, the analysis considered a large number of elderly donors, the sample size was insufficient to investigate interactions between donor age and other confounders such as labMELD-Score and diagnosis or to perform conclusive subgroup analyses.

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Authorship

SP: Designed study, performed study, analyzed data, wrote paper. AB: Designed research, performed research, analyzed data, wrote paper. FB: Performed study , wrote paper. JA: wrote paper. MVR: collected data. US: collected data. XR: wrote paper. BM: wrote paper. HK: designed research, performed research, analyzed data. DD: analyzed data. JW: wrote paper. MG: wrote paper. MKA: designed study, wrote paper.

Conflict of interest

The first and the corresponding author (Sebastian Pratschke and Martin Angele) declare that they have no

financial interests, activities, relationships, and affiliations that potentially influence the submitted work.

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Data access, responsibility, and analysis

Sebastian Pratschke and Andreas Bender had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Data basis and statistical model.

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