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Retrospective Cohort Study

Influence of donor age on liver transplantation outcomes: A multivariate analysis and comparative study

Miran Bezjak, Ivan Stresec, Branislav Kocman, Stipislav Jadrijević, Tajana Filipec Kanizaj, Miro Antonijević, Bojana Dalbelo Bašić, Danko Mikulić

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Miran Bezjak, Branislav Kocman, Stipislav Jadrijević, Danko Mikulić, Department of Surgery, University Hospital Merkur, Zagreb 10000, Croatia

Ivan Stresec, Bojana Dalbelo Bašić, Department of Electronics, Microelectronics, Computer and Intelligent Systems, Faculty of Electrical Engineering and Computing, Zagreb 10000, Croatia

Tajana Filipec Kanizaj, Department of Gastroenterology, University Hospital Merkur, Zagreb 10000, Croatia

Miro Antonijević, Development of Software, Nanobit Ltd., Zagreb 10000, Croatia

Corresponding author: Danko Mikulić, FEBS, MD, PhD, Surgeon, Department of Surgery, University Hospital Merkur, Department of Surgery, University Hospital Merkur, 10000 Zagreb, Croatia. mikulicdanko@gmail.com

Abstract

BACKGROUND

The growing disparity between the rising demand for liver transplantation (LT) and the limited availability of donor organs has prompted a greater reliance on older liver grafts. Traditionally, utilizing livers from elderly donors has been associated with outcomes inferior to those achieved with grafts from younger donors. By accounting for additional risk factors, we hypothesize that the utilization of older liver grafts has a relatively minor impact on both patient survival and graft viability.

AIM

To evaluate the impact of donor age on LT outcomes using multivariate analysis and comparing young and elderly donor groups.

METHODS

In the period from April 2013 to December 2018, 656 adult liver transplants were performed at the University Hospital Merkur. Several multivariate Cox proportional hazards models were developed to independently assess the significance of donor age. Donor age was treated as a continuous variable. The approach involved univariate and multivariate analysis, including variable selection and assessment of interactions and transformations. Additionally, to exemplify the similarity of using young and old donor liver grafts, the group of 87 recipients of

elderly donor liver grafts (≥ 75 years) was compared to a group of 124 recipients of young liver grafts (≤ 45 years) from the dataset. Survival rates of the two groups were estimated using the Kaplan-Meier method and the log-rank test was used to test the differences between groups.

RESULTS

Using multivariate Cox analysis, we found no statistical significance in the role of donor age within the constructed models. Even when retained during the entire model development, the donor age's impact on survival remained insignificant and transformations and interactions yielded no substantial effects on survival. Consistent insignificance and low coefficient values suggest that donor age does not impact patient survival in our dataset. Notably, there was no statistical evidence that the five developed models did not adhere to the proportional hazards assumption. When comparing donor age groups, transplantation using elderly grafts showed similar early graft function, similar graft ($P = 0.92$), and patient survival rates ($P = 0.86$), and no significant difference in the incidence of postoperative complications.

CONCLUSION

Our center's experience indicates that donor age does not play a significant role in patient survival, with elderly livers performing comparably to younger grafts when accounting for other risk factors.

Key Words: Liver transplantation; Elderly donors; Survival analysis; Postoperative complications; Cox proportional hazard models

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Core Tip: Liver transplantation (LT) using elderly donor livers is traditionally expected to yield inferior results compared to transplantation using young donor grafts. We assessed the impact of donor age on LT outcomes through multivariate analysis and by comparing young and elderly donor groups. Results from our center show that donor age does not significantly affect patient survival. When adjusting for additional risk factors, elderly livers perform similarly to their younger counterparts. These findings challenge the conventional belief that older donor organs result in inferior outcomes, providing valuable insights for expanding the donor pool for liver transplants.

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INTRODUCTION

The disparity between available liver donors and the number of candidates on the waiting list is ever-increasing, leading to the constant evolution of strategies to overcome the problem of donor shortage[1]. Some of the more recent strategies include increased liver transplantation (LT) from donors after circulatory death, the use of machine perfusion, split LT, and living donor transplantation[2]. While the use of elderly donors is not a novel way of donor pool expansion, reports of increased incidence of short-term and long-term complications have stood in the way of the more widespread use of older livers for transplantation[3].

Historically, elderly grafts have been associated with increased graft loss and recipient mortality leading to cautious use of older livers[4,5]. Furthermore, the incidence of biliary and arterial complications appears to be increased in recipients of elderly grafts[6,7]. In recent years, we have witnessed general improvement in post-transplant mortality rates and decreased rates of liver graft loss. This is likely associated with advances in patient care, improved surgical techniques, and better matching between donors and recipients[8,9]. Despite these improvements in outcomes and numerous reports of similar graft and patient survival rates regardless of donor age, the use of elderly liver donors is still limited. In the United States, the percentage of elderly liver grafts used for transplantation is decreasing, with only 3.2% of grafts used in 2016 having been procured from donors over 70 years of age[4].

Increased cold ischemia times (CITs) have deleterious effects on graft and patient survival after LT[10]. Livers from older donors are likely to be less able to tolerate the effects of prolonged ischemia with inferior potential to recover and regenerate after ischemia-reperfusion injury[11].

We hypothesize that there is no significant impact of donor age on patient and graft survival and that the outcomes might be similar to those using younger grafts, provided that CITs are kept fairly short. In this retrospective study, we analyzed a prospectively collected dataset to assess the impact of donor age on patient and graft survival. Analysis was performed using the multivariate proportional hazards (Cox) model. Additionally, we stratified liver recipients into two

groups based on donor age (donors ≤ 45 years *vs* donors ≥ 75 years) and conducted a comparative analysis. CIT was kept short in both groups. Graft and patient survival were compared, together with complication rates and early biochemical markers of liver injury and function.

MATERIALS AND METHODS

Study design

In the period from April 2013 to December 2018, 656 adult liver transplants (≥ 18 years) were performed at the University Hospital Merkur, Zagreb. Clinical data encompassing information on recipients, donors, and grafts were collected. Alongside the observed donor age, a set of pre-transplantation variables with potential significance in the decision-making process of graft acceptance was compiled for data analysis. The data was analyzed using several multivariate proportional hazards models. To exemplify the similarity of outcomes when using old and young donor liver grafts, we separately compared two different donor groups. Within the collected cohort 87 liver transplants were performed using liver grafts from donors ≥ 75 years. They were compared to a group of 124 patients who received grafts from donors ≤ 45 years during the same period. Patients who underwent combined organ transplants were excluded from the study. Patients who underwent re-transplantation were not compared between the two groups but were included in the multivariate analysis. The endpoint of this study and the time of follow-up of the patients was the end of December 2019.

Donor parameters

The following donor parameters were obtained from the Eurotransplant donor info records: Age, gender, blood type, body mass index (BMI), sodium level, alanine transferase (ALT), gamma-glutamyl transferase (GGT), bilirubin, C-reactive protein (CRP). The information about whether the donor had recorded a pre-procurement cardiac arrest was also obtained. Donor cause of death was classified as anoxia, cerebrovascular accident, and other, and used to calculate the Eurotransplant Donor Risk Index (ET-DRI) according to Braat *et al*[12]. Upon arrival at the recipient center, all donor livers undergo a frozen section biopsy when the degree of steatosis is assessed and classified as mild ($< 30\%$), moderate ($30\%-60\%$), or severe ($> 60\%$). In addition to an assessment of steatosis, a detailed pathohistological analysis is performed to ensure an informed decision regarding the acceptance of an organ. CIT was also recorded. Donor and graft characteristics are presented in [Table 1](#).

Recipient parameters

The recipient data reviewed in the current analysis included: Recipient age, gender, blood type, BMI, indication for LT, urgency status before LT, intensive care unit (ICU) status before LT, date of transplantation, and laboratory Model for End - Stage Liver Disease (MELD) score[13].

Additionally, we calculated the Balance of Risk (BAR) score, which incorporates a combination of donor and recipient variables, including donor age, providing valuable insights into the intricate dynamics of transplantation outcomes[14, 15]. Recipient characteristics as well as BAR score are presented in [Table 2](#).

Outcome parameters

The primary outcome of this study, evaluated in the multivariate analysis, is overall graft survival, the period between LT and graft failure or death, whichever occurs first. The choice of this outcome parameter is a valuable metric for evaluating the success of LT. This is attributed to its consideration of both recipient survival and graft viability, which collectively carry tangible clinical importance[16,17]. Patient survival (the period between transplantation and death) and graft survival (the period between transplantation and graft failure or death) rates were separately assessed as secondary endpoints in the additional donor age group comparison (donors ≤ 45 years *vs* donors ≥ 75 years). The median follow-up was 629 d. Between the groups, early liver graft injury and function were assessed using postoperative values of aspartate aminotransferase (AST), ALT, bilirubin, and international normalized ratio (INR) on the first, third, and seventh postoperative days. Surgical complications were recorded and graded according to the Clavien-Dindo scheme[18]. In addition, all vascular and biliary complications were recorded separately.

Allocation policy

Since 2007, liver grafts in Croatia have been allocated according to the MELD system. However, whenever possible during the allocation process, the donor's liver is offered to the patient deemed most suitable for a particular graft. For instance, grafts from elderly donors are preferably allocated to hepatocellular carcinoma (HCC) patients, and patients with hepatitis C are preferably transplanted using grafts from younger donors to obtain better outcomes with appropriate matching.

Surgical procedure

All patients underwent whole liver cadaveric graft transplantation, procured from donation after brain death donors using aortic and portal flush with the University of Wisconsin solution. The institutional policy is to keep CIT as short as possible, especially for liver grafts procured from elderly donors. All LT procedures were performed using the piggyback technique.

Table 1 Donor and graft characteristics

Variable	Value (n = 656)
Male sex	389 (59.3)
Blood type	
0	238 (36.3)
A	267 (40.7)
B	111 (16.9)
AB	40 (6.1)
Pancreas offered (yes)	145 (22.1)
Cardiac arrest (yes)	93 (14.2)
Age (yr)	60 (48-70)
BMI (kg/m ²)	26.3 (24.4-28.4)
ET-DRI	1.72 (1.47-1.95)
Steatosis (%)	2 (0-10)
Na (mEq/L)	148 ± 9 (120-187)
ALT (U/L)	54.3 ± 79.6 (5-898)
GGT (U/L)	66.8 ± 99.8 (4-1129)
Bilirubin (mg/dL)	14 ± 12.6 (1-146)
CRP (mg/L)	162.6 ± 102.4 (1-621)
CIT (h)	7.11 ± 2.3 (1.22-13.87)

Data are presented as mean ± SD with ranges (min-max) or median with IQR (interquartile ranges) when the distribution is skewed for continuous variables. Categorical variables are presented as counts (%). BMI: Body mass index; Na: Sodium; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; CRP: C-reactive protein; ET-DRI: Eurotransplant Donor Risk Index; CIT: Cold ischemia time.

Statistics

The data were analyzed using the Python programming language version 3.8, with open-source libraries for statistics and visualization (sciPy, statsmodel, lifelines, matplotlib, seaborn)[19]. Several multivariate Cox proportional hazards models were developed using the model selection procedure laid out by Hosmer *et al*[20], in which the donor age was treated as a continuous variable. Multivariate models were developed on all 656 patients transplanted in the defined period of the study. In the first Cox model, the donor age variable was kept during all steps of the model development regardless of statistical significance. Four other models were developed, without special treatment of the donor age variable: (1) Using all variables; (2) without scores (MELD, BAR, and ET-DRI); (3) using all variables but without retransplanted patients; and (4) without scores and retransplanted patients. This was done to gain an objective insight into the impact of donor age on patient survival.

The first few steps of model development include univariate and multivariate analysis through Kaplan-Meier estimates, log-rank tests, Wald tests, and log partial likelihood tests. The only nonbinary categorical variable of diagnosis is treated as a single variable but modeled through 5 separate binary variables, one for each of the diagnoses other than alcoholic cirrhosis, which is the most common diagnosis in our dataset and is treated as the baseline case. After a loose univariate selection of variables, variables are added into a multivariate Cox model, subsequently removing any variables that become insignificant and have no potential confounding effect. This is concluded with an additional step of checking that all previously removed variables – including those removed in the univariate analysis – remain insignificant when added to the multivariate model. After these steps, we are left with a main effects model, which includes selected variables in their linear form (they, however, model the hazard with an exponential function). The main effects model is then potentially refined by checking the scales of continuous variables and checking for any medically relevant and statistically significant interactions.

Other than transformations, we also tested for interactions between variables. Interactions are included in the models as products between two variables and were tested only with variables present in the main effects model. The interactions we considered clinically relevant, and tested for are: recipient and donor age, recipient and donor sex; recipient age and CIT; CIT and steatosis; steatosis and MELD; steatosis and donor age; recipient age and recipient BMI; recipient and donor BMI; sodium levels and CIT. The interactions were tested only if both variables were already present in the main effects model. Additionally, all interaction pairs that included the diagnosis variable were also tested for.

As a final step, all models were verified to adhere to the proportional hazards assumption.

Table 2 Recipient characteristics

Variable	Value (n = 656)
Male sex	469 (71.5)
Blood type	
0	212 (32.3)
A	267 (40.7)
B	124 (18.9)
AB	53 (8.1)
Indication for LT	
Alcoholic liver cirrhosis	197 (30.03)
Cancer (HCC, CCC)	184 (28.05)
Cholestatic liver disease	53 (8.08)
Hepatitis C virus	41 (6.25)
Retransplantation	83 (12.65)
Miscellaneous	98 (14.94)
	<i>Median (IQR)</i>
Age (yr)	59 (52-64)
BMI (kg/m ²)	26 (23.9-29.4)
Days on the waiting list	25 (7-92)
Lab MELD	16 (11-21)
BAR	7 (4-10)

Data are presented as mean \pm SD with ranges (min-max) or median with IQR (interquartile ranges) when the distribution is skewed for continuous variables. Categorical variables are presented as counts (%). BMI: Body mass index; LT: Liver transplantation; HCC: Hepatocellular carcinoma; CCC: Cholangiocarcinoma; BAR: Balance of risk; MELD: Model for End-Stage Liver Disease.

In the selected older/younger groups (donors \leq 45 years *vs* donors \geq 75 years) survival rates were calculated by the Kaplan-Meier method using the log-rank test for the differences between the two groups. Categorical parameters, presented with counts and percentages were compared using the chi-square test or, if appropriate, Fischer's exact test. Continuous variables are presented as mean \pm SD with ranges (min-max) or median with interquartile ranges when the distribution is skewed. We tested the normality of distribution and accordingly compared the groups using the Mann-Whitney or *t*-test. *P* values $<$ 0.05 were considered statistically significant.

RESULTS

Donor age was not found as a statistically or practically significant variable in any of our univariate and multivariate analyses.

As previously mentioned, in the first Cox model, the donor age variable was kept during all steps of the model development regardless of statistical significance to try to gauge its effect. Before exploring transformations and interactions, in the linear main effects model, the coefficient and resulting hazard ratio (HR) of the donor age variable was insignificant and slightly above 1 (coef.: 0.027; HR: 1.028). Testing for transformations of the donor age and interactions with other variables showed no statistical significance or relevant effect on survival. Similarly, the remaining four models showed no significance or relevant effect of donor age. For all of the models, donor age was insignificant in the first step of development, meaning it was not added to the preliminary main effects model (*P* value of 0.91 for models with, and 0.69 for models without re-transplantation patients). After the main effects models were developed, trying to add the donor age back into the model once more yielded statistically insignificant changes and practically insignificant coefficients (*P* values ranged from 0.65 to 0.92, and HR were very close to 1, ranging from 0.99 to 1.01). For the development of the model 3, whose final model included interactions, we also added donor age to the final model, but it remained insignificant. Since donor age was found statistically insignificant in all steps of model development, and as a consequence, was not included in any of the final models. There was also no statistical evidence that the five developed models did not adhere to the proportional hazards assumption that would put into question the correctness of our modeling. We also considered the possibility that donor age is accounted for by other variables and that it could be a

Table 3 Cox proportional hazards model – all variables and metrics

Variable	Coefficient (95%CI)	Hazard ratio (95%CI)	P value
Donor pre-procurement cardiac arrest (yes)	0.400 (0.027, 0.774)	1.493 (1.028, 2.168)	0.035
Recipient age	0.031 (0.014, 0.049)	1.032 (1.014, 1.050)	< 0.001
Donor CRP	0.001 (0.000, 0.003)	1.001 (0.999, 1.003)	0.055
BAR score	0.031 (-0.001, 0.064)	1.032 (0.999, 1.066)	0.060
Indication for LT-cancer (HCC, CCC)	0.137 (-0.275, 0.548)	1.146 (0.760, 1.730)	0.515
Indication for LT-hepatitis C virus	1.029 (0.510, 1.548)	2.798 (1.665, 4.702)	< 0.001
Indication for LT-re-transplantation	0.593 (0.098, 1.087)	1.809 (1.103, 2.965)	0.019
Indication for LT-miscellaneous	0.307 (-0.190, 0.803)	1.359 (0.827, 2.233)	0.226
Indication for LT-cholestatic disease	-0.371 (-1.168, 0.426)	0.690 (0.311, 1.532)	0.362

The model had no significant transformations and interactions, and the final model is the (linear) main effects model. Donor age was eliminated as insignificant in all previous steps of development. CRP: C-reactive protein; BAR: Balance of Risk; LT: Liver transplantation; HCC: Hepatocellular carcinoma; CCC: Cholangiocarcinoma.

Table 4 Cox proportional hazards model – excluded metrics (Model for End-Stage Liver Disease, Balance of Risk, and Eurotransplant Donor Risk Index score)

Variable	Coefficient (95%CI)	Hazard ratio (95%CI)	P value
Donor pre-procurement cardiac arrest (yes)	0.401 (0.029, 0.774)	1.494 (1.029, 2.168)	0.035
Recipient age	0.034 (0.016, 0.051)	1.034 (1.016, 1.053)	< 0.001
Donor CRP	0.001 (0.000, 0.003)	1.001 (0.999, 1.003)	0.060
Indication for LT-cancer (HCC, CCC)	0.062 (-0.342, 0.465)	1.064 (0.711, 1.592)	0.764
indication for LT-hepatitis C virus	1.033 (0.515, 1.552)	2.811 (1.673, 4.722)	< 0.001
Indication for LT-re-transplantation	0.806 (0.367, 1.245)	2.240 (1.444, 3.474)	< 0.001
Indication for LT-miscellaneous	0.353 (-0.140, 0.845)	1.423 (0.870, 2.328)	0.160
Indication for LT-cholestatic disease	-0.346 (-1.144, 0.451)	0.707 (0.319, 1.570)	0.395

The final model did not include any transformations and interactions, as they were insignificant, and the final model is the (linear) main effects model. CRP: C-reactive protein; LT: Liver transplantation; HCC: Hepatocellular carcinoma; CCC: Cholangiocarcinoma.

relevant survival predictor in the absence of other predictors, but the univariate analysis and thorough model development procedure based on Hosmer *et al*[20], which tries to control for confounding and interaction, indicated otherwise. From multivariate analysis, therefore, we conclude that donor age does not play a significant role in the survival of patients captured by our data set. Several multivariate models highlighted the recipient's age, the presence of a pre-procurement cardiac arrest in the donor, and the donor's CRP levels as statistically significant variables. Moreover, hepatitis C virus-related cirrhosis was found as the most significant and impactful indication related to poor outcomes.

Coefficients and corresponding *P* values of the final models 1 and 2 can be seen in Tables 3 and 4. Model 2 development does not include the ET-DRI and BAR score, but results in very similar coefficients and *P* values, excluding the BAR score. Both models had no significant transformations of variables or interactions. As stated before, we tried adding the donor age variable to both of the models to further gauge its impact on survival. In both cases, the result was an insignificant coefficient with a very small, slightly negative value and a confidence interval including 0. Moreover, the inclusion of donor age leaves coefficients of other variables virtually unchanged, meaning that there is likely little confounding or collinearity. This, on its own, shows that donor age is highly unlikely to have a relevant impact on survival. In the context of comparing both models, it also suggests that the inclusion of the BAR score, a score that uses donor age as part of its calculation, does not in a relevant way capture the impact of donor age on survival. Similar results were observed in the two models that did not include re-transplantation patients: Model 3 had all the variables of model 1 with the addition of lab MELD, and had significant interactions between the diagnosis variable and recipient age and the diagnosis variable and lab MELD; model 4 was the same as model 1, with minor coefficient changes. Both of these models did not include donor age. When adding donor age to models 3 and 4 to observe behavior, the result was once more an insignificant, slightly positive coefficient for donor age, with negligible alterations to other coefficients. Coefficients of the final models 3 and 4 are reported in Tables 5 and 6.

Table 5 Cox proportional hazards model – all variables; excluded retransplanted patients

Variable	Coefficient (95%CI)	Hazard ratio (95%CI)	P value
Donor pre-procurement cardiac arrest (yes)	0.393 (-0.0281, 0.813)	1.481 (0.972, 2.255)	0.067
Recipient age	0.001 (-0.039, 0.040)	1.001 (0.961, 1.041)	0.98
Donor CRP	0.002 (0.001, 0.004)	1.002 (1.001, 1.004)	0.006
Lab MELD	0.027 (-0.034, 0.088)	1.028 (0.967, 1.092)	0.380
BAR score	0.024 (-0.056, 0.104)	1.024 (0.946, 1.109)	0.557
Indication for LT-cancer (HCC, CCC)	-2.867 (-6.365, 0.631)	0.057 (0.002, 1.878)	0.108
Indication for LT-hepatitis C virus	-4.492 (-9.517, 0.532)	0.011 (0.000, 1.703)	0.080
Indication for LT-miscellaneous	-0.917 (-4.091, 2.257)	0.400 (0.017, 9.555)	0.571
indication for LT-cholestatic disease	0.325 (-3.841, 4.490)	1.384 (0.021, 9.146)	0.879
Lab MELD × cancer (HCC, CCC)	0.026 (-0.030, 0.083)	1.027 (0.970, 1.086)	0.363
Lab MELD × hepatitis C virus	-0.023 (-0.089, 0.044)	0.978 (0.915, 1.044)	0.500
Lab MELD × indication miscellaneous	-0.034 (-0.091, 0.024)	0.967 (0.913, 1.024)	0.253
Lab MELD × cholestatic disease	-0.177 (-0.331, -0.024)	0.838 (0.718, 0.977)	0.023
Recipient age × cancer (HCC, CCC)	0.047 (-0.009, 0.102)	1.048 (0.991, 1.107)	0.098
Recipient age × hepatitis C virus	0.103 (0.021, 0.186)	1.109 (1.022, 1.204)	0.013
Recipient age × indication miscellaneous	0.032 (-0.020, 0.083)	1.033 (0.980, 1.088)	0.228
Recipient age × cholestatic disease	0.038 (-0.036, 0.112)	1.039 (0.965, 1.118)	0.309

The final model did not include any transformations as they were insignificant, and the final model is the (linear) main effects model. Significant interactions between variables are presented. MELD Model for End-Stage liver disease; BAR: Balance of Risk; CRP: C-reactive protein; LT: Liver transplantation; HCC: Hepatocellular carcinoma; CCC: Cholangiocarcinoma.

Table 6 Cox proportional hazards model-excluded metrics (Model for End-Stage Liver Disease, Balance of Risk, and Eurotransplant Donor Risk Index score) and retransplanted patients

Variable	Coefficient (95%CI)	Hazard ratio (95%CI)	P value
Donor pre-procurement cardiac arrest (yes)	0.406 (-0.006, 0.817)	1.500 (0.994, 2.264)	0.053
Recipient age	0.035 (0.016, 0.055)	1.035 (1.016, 1.004)	< 0.001
Donor CRP	0.002 (0.000, 0.004)	1.002 (1.000, 1.004)	0.015
Indication for LT-cancer (HCC, CCC)	0.064 (-0.341, 0.469)	1.066 (0.711, 1.599)	0.757
Indication for LT-hepatitis C virus	1.058 (0.538, 1.578)	2.881 (1.712, 4.846)	< 0.001
Indication for LT-miscellaneous	0.365 (-0.128, 0.859)	1.442 (0.880, 2.361)	0.146
Indication for LT-cholestatic disease	-0.328 (-1.126, 0.470)	0.720 (0.324, 1.600)	0.420

The final model did not include any transformations and interactions, as they were insignificant, and the final model is the (linear) main effects model. CRP: C-reactive protein; LT: Liver transplantation; HCC: Hepatocellular carcinoma; CCC: Cholangiocarcinoma.

No transformations of variables were found significant in our data for any of the developed models, most likely due to the relatively low amount of data available, but also the appropriateness of Cox’s exponential modeling of the hazard function.

After conducting multivariate analyses, an additional comparison of two age groups was performed, to exemplify the similarity of outcomes between groups with clinically significant differences in donor age. No difference was found either in graft survival ($P = 0.92$) or in recipient survival ($P = 0.86$) between the two groups. Recipient survival at 1, 3, and 5 years post-transplant was 87%, 81%, and 80% for the older donor group and 88%, 81% and 77% for the younger group (Figure 1A). Graft survival at 1, 3, and 5 years post-transplant was 82%, 76%, and 76% for the older donor group and 83%, 76% and 74% for the younger group (Figure 1B). The older donor group had 18.3% of censored data with a survival median time of 734 days and the younger donor group had 19.3% of censored data with a survival median time of 792 d.

Table 7 Donor characteristics and comparison of the older and younger group

	Older (n = 87)	Younger (n = 124)	P value	Test
Gender			< 0.01	χ^2 test
Male	44 (50.57)	88 (70.97)		
Female	43 (49.43)	36 (29.03)		
Steatosis			0.4	χ^2 test
Negligible	70 (81.40)	96 (78.69)		
Mild	12 (13.95)	13 (10.66)		
Moderate	4 (4.65)	12 (9.84)		
Severe	0 (0)	1 (0.82)		
Cardiac arrest			0.01	χ^2 test
No	81 (93.1)	99 (79.8)		
Yes	6 (6.9)	25 (20.2)		
Age	77 (76-80)	32 (23-40)	< 0.01	Mann-Whitney
BMI (kg/m ²)	27.55 (25.23-29.4)	24.69 (22.75-26.31)	< 0.01	Mann-Whitney
ET-DRI	2.02 (1.85-2.05)	1.28 (1.15-1.46)	< 0.01	Mann-Whitney
Sodium(mEq/L)	147 ± 7.6 (133-165)	146 ± 8.9 (120-169)	0.51	t-test
ALT (U/L)	33.8 ± 51.3 (5-385)	93.9 ± 130.3 (8-898)	< 0.01	t-test
GGT (U/L)	48.5 ± 76.1 (4-581)	90.1 ± 163.1 (6-1129)	0.03	t-test
Bilirubin(mg/dL)	15.4 ± 10.9 (3-71)	13.6 ± 16.4 (1-146)	0.38	t-test
CRP (mg/L)	175.8 ± 104.7 (1-440)	157.6 ± 94.1 (1-360)	0.2	t-test
CIT (h)	6.44 ± 2.1 (2.17-11.45)	7.73 ± 2.7 (1.93-13.87)	< 0.01	t-test

Data are presented as mean ± SD with ranges (min-max) or median with IQR (interquartile ranges) when the distribution is skewed for continuous variables. Categorical variables are presented as counts (percentages). BMI: Body mass index; Na: Sodium; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; CRP: C-reactive protein; ET-DRI: Eurotransplant donor risk index; CIT: Cold ischemia time.

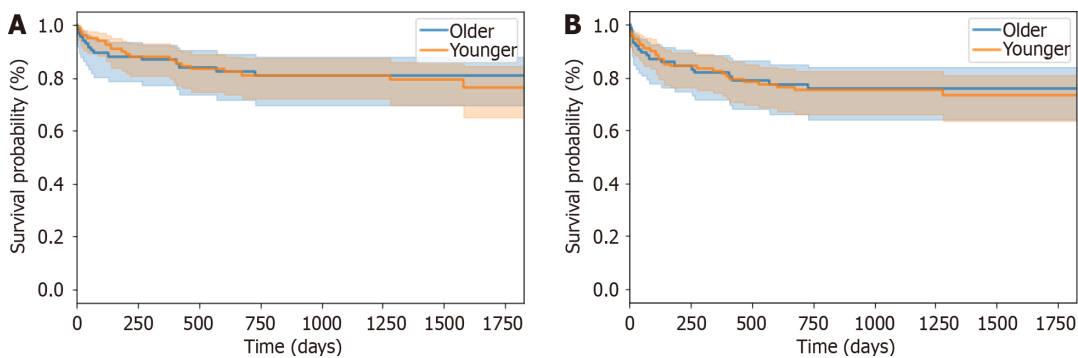


Figure 1 Kaplan Meier curves. A: Recipient survival; B: Graft survival.

A comparison of donor characteristics between groups is shown in Table 7. More of the donors from the younger group were male and the elderly donor group had a higher median BMI. Both donor groups were similar regarding the degree of steatosis, sodium, and bilirubin values. The younger donor group had higher mean values of ALT and GGT. Due to the difference in donor age between the two groups, ET-DRI was notably lower in the younger group. The younger group of donors also had a higher number of cardiac arrest events recorded. Mean CIT was lower in the younger donor group (6.44 h vs 7.73 h); however, it was kept below eight hours in both groups.

The comparison of recipient characteristics between groups, as well as the BAR score, is shown in Table 8. Apart from age, the two groups differed in BMI and gender distribution. Despite a difference in the median BMI, when BMI categories according to the World Health Organization are taken into account, there was no major clinical significance between the groups[21]. The groups were similar regarding their MELD scores and preoperative ICU status. All of the

Table 8 Recipient characteristics and comparison of the older and younger group

	Older (n = 87)	Younger (n = 124)	P value	Test
Gender			0.03	χ^2 test
Male	70 (80.46)	82 (66.13)		
Female	17 (19.54)	42 (33.87)		
Indication for LT			0.4	χ^2 test
Alcoholic cirrhosis	38 (43.68)	32 (25.81)		
Cancer (HCC, CCC)	33 (37.94)	29 (23.39)		
Viral hepatitis	6 (6.9)	18 (14.52)		
Miscellaneous	10 (11.5)	45 (36.32)		
Urgency				
Elective	87 (100)	118 (95.16)	0.04	Fischer's exact test
High	0 (0)	6 (4.84)		
Stay in ICU			0.57	χ^2 test
No	65 (74.71)	98 (79.03)		
Yes	22 (25.29)	26 (20.97)		
Age	60 (55-66)	58 (50-63)	< 0.01	Mann-Whitney
BMI (kg/m ²)	27.92 (24.61-29.91)	25.25 (23.45-27.3)	< 0.01	Mann-Whitney
MELD	15 (11-18)	16 (11-21)	0.13	Mann-Whitney
BAR	5 (4-9)	6 (2-9)	0.45	Mann-Whitney

Data are presented as mean \pm SD with ranges (min-max) or median with IQR (interquartile ranges) when the distribution is skewed for continuous variables. Categorical variables are presented as counts (percentages). BMI: Body mass index; LT: Liver transplantation; HCC: Hepatocellular carcinoma; CCC: Cholangiocarcinoma; ICU: Intensive care unit; MELD: Model for End-Stage Liver Disease; BAR: Balance of risk.

transplants with elderly grafts were elective, while 4.84% of the transplants using younger grafts had an urgent status. The most frequent indication for LT in both groups was alcoholic cirrhosis (43.68% in the older group and 25.81% in the younger group) followed by malignancy (HCC and cholangiocellular carcinoma) and viral hepatitis. As for the BAR scoring system, no difference was found between the groups, despite using the donor age for its calculation.

Postoperative complications were classified using the Clavien–Dindo scheme. Stage III and stage IV postoperative complications were observed in 21/87 patients in the older group and 24/124 patients in the younger group (Chi-square test; $P = 0.25$). With regard to the particular type of post-transplant complication, there was also no important difference between the two groups in the incidence of biliary and vascular complications.

As regards the serum markers of hepatocellular injury, AST and ALT values were higher in the group with younger liver grafts in the first days post-transplant, however, that difference disappeared by the end of the first week (Figure 2A and B). Postoperative values of bilirubin (Figure 2C), prothrombin time, and INR (Figure 2D) were comparable between the groups.

DISCUSSION

Increased donor age is reported to be one of the major donor determinants of poor post-transplantation outcomes[3,4,22]. Furthermore, increased donor age reportedly confers an additional risk for the development of arterial and biliary complications[5-7]. This has led to the judicious use of elderly grafts, especially in patient-oriented allocation systems where optimal matching between the donor and the recipient is not always possible. Moreover, when short CITs cannot be ensured either because of logistics or allocation policies, transplant centers may be reluctant to accept such grafts[3,4].

Within this study, diverse methodologies were employed to comprehensively assess the influence of the donor age on the outcomes of LT in our group. The outcomes of our study suggest that LT using elderly liver grafts is a safe procedure and that advanced donor age does not have a significant negative impact on the transplantation outcome. The univariate analysis identified the BAR score, which includes donor age as one of its predictors, as a variable of potential significance. The rest of the analysis, however, indicates that the influence is not due to the inclusion of donor age. Furthermore, in models without the BAR score, donor age remains unimportant and does not have a significant impact.

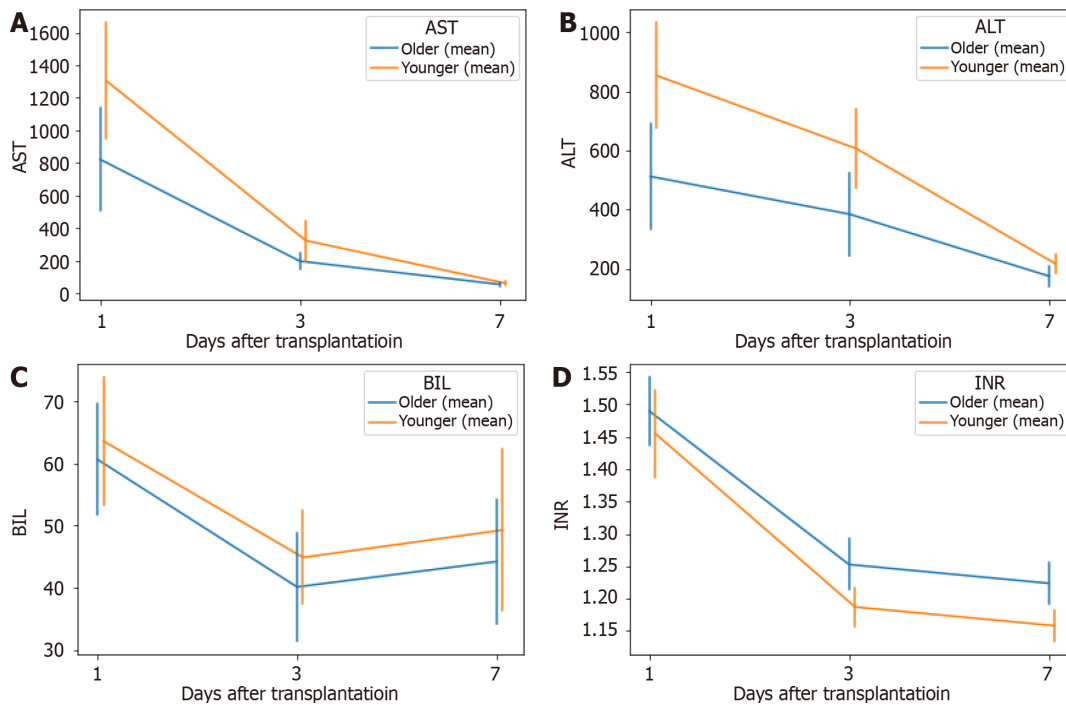


Figure 2 Recipients' postoperative laboratory values - comparison between groups. A: Comparison of mean postoperative aspartate aminotransferase values in older and younger donor groups with 95%CI; B: Comparison of mean postoperative alanine transferase values in older and younger donor groups with 95%CI; C: Comparison of mean postoperative bilirubin values in older and younger donor groups with a 95%CI; D: Comparison of mean postoperative international normalized ratio values in older and younger donor groups with 95%CI. AST: Aspartate aminotransferase; ALT: Alanine transferase; BIL: Bilirubin; INR: International normalized ratio.

In contrast, recipient age has been found as a significant variable in several models. As the proportion of elderly individuals continues to rise, a corresponding increase in the age of transplant recipients is observed, and this demographic is often accompanied by a higher prevalence of comorbidities, which can influence postoperative complications and overall survival. Despite older recipient age being identified as a risk factor in our models, the results indicate that advanced age alone should not serve as an exclusion criterion for LT. Instead, recipient selection should be conducted judiciously, accounting for individual comorbidities[23,24].

Results of the multivariate analysis show that particular emphasis should also be directed towards hepatitis C virus-related cirrhosis, a leading indication within our cohort that is linked to unfavorable outcomes due to its elevated recurrence rates, rapid cirrhosis progression, and diminished rates of both patient and graft survival. However, the introduction of novel antiviral regimens has resulted in a notable decrease in the number of patients on the waiting list for transplantation, thus mitigating the impact of hepatitis C on the overall prognosis[25,26].

We found that with careful matching and short CITs, graft/patient survival achieved using liver grafts older than 75 years of age is similar to survival with much younger grafts. Also, the incidence of serious complications, including vascular and biliary events, was similar in both groups. Finally, laboratory markers of ischemia/reperfusion injury and postoperative function of elderly grafts in the first postoperative week showed that the early liver function was not impaired when compared with younger donors.

Short CITs seem to be crucial for good results of LT with grafts from elderly donors[11]. Long CIT is a well-known risk factor for graft failure and it weighs heavily in most algorithms that evaluate the donor-associated risk[10,12]. It can be expected that the potential of an elderly liver to recover from ischemia is inferior to younger grafts. The proposed pathogenic mechanisms may include smaller liver volume, increase in the hepatic lipofuscin, muted response to oxidative stress, diminished rates of DNA repair, and reduced expression of growth regulatory genes[27,28]. Whatever the exact mechanism, research shows that livers from older donors are more likely to fail after long periods of CIT than livers from younger donors[11]. Our center's policy to insist on CIT of up to 8 h (and even less for elderly livers) seems to be a good strategy to deal with the increasing age of our donors and the pressure to expand the donor pool among the elderly. In recent years, we have seen increasing use of new preservation techniques such as machine perfusion that may allow for better and longer preservation of donor livers, including elderly grafts.

When considering donor-to-recipient matching, it must be pointed out that both groups were similar regarding recipients' MELD scores. However, MELD scores were relatively low in both groups (median values of 15 and 16), reflecting high transplantation activity and low waiting times for LT in Croatia[29]. Despite similar MELD scores of the recipients in the two groups, the groups are not entirely balanced with respect to the recipients' diagnoses. This reflects our allocation and matching policy. One of our center's policies is preferential use of younger liver grafts for recipients with hepatitis C, patients with urgent indications for LT, and patients with primary sclerosing cholangitis (PSC)[30-32]. Decreased survival has been reported with elderly liver grafts in the emergency setting, therefore, our center's policy is to try and avoid the use of very old grafts in urgent transplants whenever possible[33]. Finally, donor age is one of the

strongest determinants of PSC recurrence and the development of biliary strictures in PSC patients, so PSC patients are preferentially transplanted using younger grafts in our center (data not shown)[34].

We believe that the minimization of other donor risk factors could be responsible for our good results with elderly grafts. Steatosis is one of the factors strongly affecting outcomes, especially in older grafts and in transplants with longer CIT[35,36]. Therefore, we believe that it is likely important that the degree of steatosis was similar between the two groups and that in both groups the number of livers with significant steatosis was small.

Our report has limitations that need to be pointed out. Firstly, this is a single-center, retrospective study with a limited number of patients and all of the inherent biases. Moreover, the age limits of the younger and older groups in univariate analysis were decided upon arbitrarily, however, we deliberately chose the difference between the two to be large enough to exemplify the similarity of using young and old donor liver grafts and give more relevance to our results in addition to multivariate analysis where donor age was considered as a continuous variable. As stated earlier, the two groups of recipients are not matched concerning diagnosis. This is the result of our allocation policy and our results can be in part attributed to such decisions in matching.

CONCLUSION

The findings from this analysis suggest that donor age does not exert a significant impact on survival outcomes, and that utilization of elderly liver grafts can be a safe clinical practice. Based on our experience and previous studies, favorable outcomes when using elderly liver grafts could be attributed to keeping CIT short, alongside appropriate donor-recipient matching.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation (LT) is a vital treatment for end-stage liver diseases, but the demand for donor organs far exceeds their availability. The utilization of older liver grafts has emerged as a potential solution, challenging the historical perception of inferior outcomes associated with elderly donors. Traditionally, concerns regarding increased graft loss and complications have limited the use of older liver grafts. Our study, conducted at the University Hospital Merkur, Zagreb, reevaluates the impact of donor age on LT outcomes. By employing multivariate analysis and a comparative approach, we aim to provide a nuanced understanding of the relationship between donor age, patient survival, and graft viability. Our investigation goes beyond binary comparisons, treating donor age as a continuous variable and considering additional risk factors. The outcomes of this research have the potential to inform organ allocation strategies, refine donor selection criteria, and contribute to the broader discourse on optimizing LT programs.

Research motivation

Our study is motivated by the pressing challenges in LT, where the demand for donor organs exceeds their availability. This research seeks to optimize organ allocation strategies and reshape the perception of elderly liver grafts. Solving these challenges holds significance beyond immediate organ scarcity concerns, influencing future studies to redefine donor selection criteria and foster a more inclusive and efficient LT paradigm. This motivation aligns with the broader goal of optimizing LT programs, encouraging further exploration of alternative strategies to meet the growing demand for life-saving transplants.

Research objectives

Our focus is on a detailed evaluation of how donor age influences LT outcomes. We aim to conduct a meticulous multivariate analysis on 656 liver transplants, treating donor age as a continuous variable. Our objectives include assessing statistical significance, exploring transformations and interactions, and conducting a comparative analysis between elderly and young donor liver grafts. The significance of realizing these objectives extends to future research in the field. By challenging conventional beliefs and providing evidence-based insights, our study contributes to refining organ allocation strategies and donor selection criteria. The outcomes of our study will encourage future research in other centers with the overall goal of optimizing the LT programs.

Research methods

We analyzed a dataset of 656 liver transplants from 2013 to 2018. Our approach involved advanced statistical modeling, treating donor age as a continuous variable. This allowed us to assess its significance from several perspectives through different multivariate models. Additionally, to exemplify the similarity of using young and old donor liver grafts we conducted a comparative analysis between elderly and young donor groups. This methodology combines various statistical techniques to uncover the nuanced dynamics of donor age impact.

Research results

Through meticulous analysis, we discovered that donor age does not exert a significant impact on patient survival. The multivariate Cox analysis consistently showed its insignificance, even when considering potential transformations and

interactions. These results contribute valuable insights to the field, indicating that elderly liver grafts perform comparably to younger grafts when accounting for other risk factors. The study highlights the importance of factors beyond donor age in shaping transplantation outcomes. While our findings provide clarity on this aspect, challenges remain in further refining organ allocation strategies. Our results, therefore, not only contribute to the current body of research but also set the stage for addressing future challenges in LT.

Research conclusions

This study challenges existing paradigms by asserting that donor age is not a significant factor in LT outcomes. Our findings suggest a shift from conventional beliefs, emphasizing that elderly liver grafts perform similarly to their younger counterparts when considering additional risk factors. The study's contribution lies in debunking age-centric theories and fostering a more nuanced understanding of the factors influencing transplant success. While not introducing entirely new methods, our approach combines various statistical techniques in a novel way, providing a comprehensive assessment of donor age impact. The conclusions emphasize the need to reconsider the significance of donor age and advocate for a more holistic approach in shaping LT practices.

Research perspectives

Future research in this field should delve into refining organ allocation strategies, considering factors beyond donor age. The study's insights open avenues for exploring the impact of additional risk factors on transplantation outcomes. Further investigations could focus on optimizing matching criteria and identifying novel predictors for success in LT. As the landscape of LT evolves, future research should continue to challenge traditional beliefs and seek innovative approaches for enhancing overall transplant success.

FOOTNOTES

Author contributions: Bezjak M, Stresec I, and Mikulić D designed the study and contributed to data collection, drafting, and revising the manuscript; Kocman B, Jadrijević S, and Filipec Kanizaj T participated in data collection and they critically reviewed the manuscript; Stresec I, Antonijević M, and Dalbelo Bašić B contributed to the data analysis; all authors read and approved the final version of the manuscript.

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Data sharing statement: The statistical code and dataset associated with this research are available from the corresponding author upon request at [mikulicdanko@gmail.com] for researchers who provide a methodologically sound proposal. To gain access, data requestors will need to sign a non-disclosure agreement (NDA). All data have been anonymized, and the risk of identification is minimized. We may balance the potential benefits and risks for each request and then provide the data that could be shared.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

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Country/Territory of origin: Croatia

ORCID number: Miran Bezjak [0000-0001-6235-1162](https://orcid.org/0000-0001-6235-1162); Ivan Stresec [0000-0001-9107-4192](https://orcid.org/0000-0001-9107-4192); Branislav Kocman [0000-0003-1497-6031](https://orcid.org/0000-0003-1497-6031); Stipislav Jadrijević [0000-0002-0565-0665](https://orcid.org/0000-0002-0565-0665); Tajana Filipec Kanizaj [0000-0002-9828-8916](https://orcid.org/0000-0002-9828-8916); Miro Antonijević [0000-0001-9689-1378](https://orcid.org/0000-0001-9689-1378); Bojana Dalbelo Bašić [0000-0002-6028-133X](https://orcid.org/0000-0002-6028-133X); Danko Mikulić [0000-0001-8103-6045](https://orcid.org/0000-0001-8103-6045).

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