ORIGINAL RESEARCH

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Effect of Donor Ages on Long-term Graft and Recipient Survival in Liver Transplantation

Karaciğer Naklinde Uzun Dönem Alıcı ve Graft Sağkalımında Donör Yaşının Etkisi ve Karaciğer Naklindeki Önemi

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Abstract

Objective: Long waiting time and higher mortality rate are major problems for patients waiting for liver transplantation (LT). Many efforts expanding the liver donor pool are being made to increase the feasibilty of living donor liver transplantation (LDLT).

Method: We planned to examine the effect of living donors used in LDLT recipients on survival in different age groups. The study included a retrospective analysis of patients who had undergone LDLT. LDs were divided into multiple forms. Accordingly, three different LD age groups were established: 18-39, 40-49 and 50-59 years. The primary outcomes of the study were long-term recipient and graft survival and early recipient complications.

Results: The number of LDLTs performed by donor age category were as follows: Age 18-39 (n=95), age 40-49 (n=46) and age 50-59 (n=26). The first degree relative rate was significantly lower in the 50-59-year age group. The ≥5% steatosis rate (macro or micro) was significantly higher in the 50-59 year age group (42.3%). One-year LDLT recipient survival was 100% in all groups. The five-year survival rates of 18-39, 40-49 and 50-59 year age groups were 100%, 94.3% and 86.7%, respectively. However, 10 year survival rate was significantly higher in 18-39 year age group than others groups.

Conclusion: Recipient and graft survival rates of up to five years did not vary among age groups. From the recipient's perspective, the decision to use elderly LD should outweigh the risks for different LD options or DDLT waiting period.

Keywords: Donor age, living liver donor, liver transplantation, survival

Öz

Amaç: Uzun bekleme süresi ve yüksek ölüm oranı karaciğer nakli bekleyen hastalar için önemli sorunlardır. Canlı donör karaciğer naklinin (LDLT) uygulanabilirliğini artırmak için karaciğer donörü havuzunu genişletmek için birçok çaba sarf edilmektedir.

Yöntem: LDLT alıcılarında kullanılan canlı donörlerin farklı yaş gruplarında sağkalım üzerindeki etkisini incelemeyi planladık. Çalışma, LDLT geçiren hastaların retrospektif analizini içeriyordu. LDLT'ler birden fazla forma ayrıldı. Buna göre, üç farklı LD yaş grubu belirlendi: 18-39, 40-49 ve 50-59 yaş. Çalışmanın birincil çıktıları uzun vadeli alıcı ve greft sağkalımı ve erken alıcı komplikasyonlarıydı.

Bulgular: Donör yaş kategorisine göre gerçekleştirilen LDLT sayıları şu şekildeydi: 18-39 yaş (n=95), 40-49 yaş (n=46) ve 50-59 yaş (n=26). Birinci derece akraba oranı 50-59 yaş grubunda önemli ölçüde daha düşüktü. ≥%5 steatoz oranı (makro veya mikro) 50-59 yaş grubunda önemli ölçüde daha yüksekti (%42,3). Bir yıllık LDLT alıcı sağkalımı tüm gruplarda %100'dü. On sekiz-otuz dokuz, 40-49 ve 50-59 yaş gruplarının beş yıllık sağkalım oranları sırasıyla %100, %94,3 ve %86,7 idi. Ancak, 10 yıllık sağkalım oranı 18-39 yaş grubunda diğer gruplara göre önemli ölçüde daha yüksekti.

Sonuç: Alıcı ve greft sağkalım oranları beş yıla kadar yaş grupları arasında değişmedi. Alıcının bakış açısından, yaşlı LD kullanma kararı farklı LD seçenekleri veya DDLT bekleme süresi için risklerden daha ağır basmalıdır.

Anahtar kelimeler: Canlı karaciğer donör, donör yaşı, karaciğer nakli, sağkalım

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Introduction

Long waiting times and higher mortality rates are major problems for patients waiting for liver transplantation (LT). Many efforts expanding the living donor (LD) pool are being made to increase the feasibility of living donor liver transplantation (LDLT) in patients who have no other option due to massive organ shortages. In modern transplantation surgery, elderly LDs can be used to meet the needs and fulfill the expectations of patients, given the rapid increase in average life expectancy in the general population. The functional effect of aging was less pronounced in the liver than in the heart and kidney. The liver tends to have a 20-40% volume decrease with aging. This is more pronounced in women than in men. The hepatic arteriolar wall becomes thinner with a decrease in endothelial cell fenestration, resulting in decreased liver inflow. Bile acid secretion is also reduced, but most of the liver functions are generally protected in older individuals. In these individuals, metabolic changes are also observed. A decrease in gluconeogenic capacity and a physiological elevation of liver lipid accumulation increase lipotoxicity and steatosis (1-3). The ageing process is governed by imbalanced immune response and by imbalanced immune stimulation. As a result, the regeneration capacity of the elderly liver decreases. Insights into the mechanisms involved in normal liver aging are important for a better understanding of donor age in LT. In the context of deceased donor liver transplantation (DDLT), the independent effect of using aged donor grafts on graft and recipient survival has been extensively published in many studies, but this issue remains controversial (4,5). Deceased donor shortages increase the number of LDLTs. The use of elderly living donors in high-volume LDLT centers, raises some concerns for donor safety. Conversely, the relevance of increased donor age to ischemia perfusion injury on allograft endurance in LDLT is less worrisome (6-9). In 2021, one-third of liver transplants in the United States (US) used liver grafts from donors older than 50. Exclusion criteria for living liver donor are improving to further expand the liver donor pool for LDLT. Although the number of LDLTs using elderly donors is expected to increase in parallel with the aging population, the use of elderly donor grafts is still controversial (10). Thus, the upper limit of donor age in LDLT is recently regulated.

We aimed in this study that analysis the trend in option of grafts from elderly living donors is refered to the change in a parameter over a period of time between 2012 and 2018. 2) To evaluate the long-term recipient and graft survival relationship of elderly and young LDs, one needs to consider various factors, including age-related variables. 3) Analyze the relationship between donor age and recipient complications. In this context, we also aimed to analyze whether grafts taken from older donors can be used without creating a significant difference in survival and morbidity compared to younger donors. LT is a effective treatment for end-stage liver disease including primer liver cancers, metabolic diseases and infections. We hypothesized that outcomes of LT with older grafts have amended over time and the discrepancy in survival between elderly and younger.

Currently, LD has narrowed. Allocating donated livers across patients is a challenging process for the transplantation team. Using elderly donors would solve this gap.

Materials and Methods

A total of 520 liver transplants were performed in our center between December 2012 and January 2018. The study consecutively included a retrospective analysis of patients who had undergone LDLT. For LDLT, LDs were divided into multiple forms. Accordingly, three different LD age groups were established: young (18-39), middle-aged (40-49) and elderly (50-59) years. As descriptive analyses, t the following categories were used: <40 y, 40-49 y, 50-59 y. We did not evaluate donor age continuously (e.g., per decile) for donors under the age of 40. LD parameters included age, sex, relationship to liver recipient, steatosis rate based on donor liver biopsy, type of hepatectomy, estimated liver graft volume was defined as preoperative assessment of graft size by computed tomography, duration of operation. Recipient parameters included model for end-stage liver disease (MELD) score, etiology of liver disease, sex, age, duration of operation, length of postoperative hospital stay (day), graft rejection, post-transplantation complications (according to Clavien-Dindo classification), graft-to-recipient weight rate (GRWR), and body mass index (BMI). Our institute follows specific preoperative criteria for graft sizing. We have used left or right-lobe grafts. Patients were required following inclusion criteria: LDLT for any indication. Patients were excluded deceased donor liver transplantation, receiving simultaneous solid organ transplants, child recipients (<18 y), recipients with perioperative mortality in the first 30 days and cases with missing survival data or donor age.

Pre-LT assessment protocol should be performed to identify underlying cardiovascular disease. Comprehensive blood tests, imaging, endoscopy and pulmonary examinations

were also performed all of liver recipients. Recipients received standard immunosuppression treatment after transplantation. The determination of older donors typically varies in other centers. In the present study, we defined donors who were older than 50 years as elderly. Donor selection criteria included healthy individuals and aged 60 years or younger. Donors with comorbidities or underlying medical diesases were also excluded from living liver donations. Living donors were also followed with laboratory tests and abdominal ultrasonography at months 1, 3, and 6 during the first year after surgery and annually hereafter. Postoperative management and follow-up have been described previously (11,12). Indications for LDLT have been described previously (13). The primary outcome of the study was long-term survival (1, 3, 5 and 10 years) of the recipient and the graft. Recipient survival was the time from LDLT to death occurring or to the last follow-up time. Graft survival was determined as the loss of graft function due to HCV recurrence, infection, sepsis, ischemia, or vascular complications after LDLT, and it was also determined by the time to HCC recurrence. This study protocol was reviewed and approved by the Ethics Committee of Acıbadem University (no: ATADEK 2023-18/617) on 16.11.2023. This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the individual(s) for the publication.

Statistical Analysis

The distribution of variables was controlled with Kolmogorov-Smirnov test. In comparing basic recipient characteristics according to donor age groups, the Kruskal-Wallis test was used for continuous variables. Categorical variables among the 3 age categories of donors were compared using chi-square test or Fisher's exact tests.

Time-to-event analyses were used the relationship between LD age and recipient and graft survival. For comparison of normally distributed data among the three groups of donor age categories (18-39, 40-49, 50-59), the Student t-test was used. The Mann-Whitney U test was used for non-normally distributed data, and comparison of quantitative data. Kaplan-Meier curves were used for graft and recipient survival. Graft and recipient survival were compared using the logrank test. All analyses were performed using SPSS 28.0.

Results

The study included a total of 168 LDLT recipients. LDLTs numbers according to donor age categories were as follows: Young (n=95), middle-aged (n=47), and elderly (n=26). Recipient disease etiology was cryptogenic (25%), HBV (20.2%), HCV (14.3%), HCC (8.3%), autoimmune (7.7%), alcoholic (6.5%) and others (18%) (Table 1). There were few significant differences in recipient characteristics among the LD age groups. Table 2 shows recipient demographic characteristics. The proportion of female patients in the younger age group was significantly higher than in the elderly group. There was no difference in gender distribution between the young and elderly age groups. Graft liver volume was significantly higher in the 50 to 59-year-old age group than in the young and middle-aged groups. There was no significant difference in graft liver volume between the young and middle-aged groups. The first-degree relative rate was significantly lower in the elderly group than in the middle-aged group. The other biological relative rate and non-biological relative rate were significantly higher in the elderly group than in the young and middle-aged groups. The degree of biological closeness did not differ significantly between the young and middle-aged (Table 2). The relationship between donor and recipient differed by donor age. In the >50 year age group, 34.6% of donors were non-biological relationship with the recipients whereas 72.6% of donors in the <40 year age group and 59.6% of donors in the middle-aged groups were first-degree relatives with recipients.There was no significant difference between the young, middle-aged and elderly groups for the Clavien-Dindo complication rate, recipient MELD score and duration of operation for recipients. But the ≥5% steatosis rate (macro or micro) was significantly higher in the 50-59 year age group (42.3%) than in the 18-39 year (22.2%) and middle-aged groups (31.9%). However, the rate of steatosis did not differ significantly between the young and middle-aged groups. Median recipient survival, graft survival, and duration of operation for the recipients did not differ significantly between the young and middle-aged groups, but were significantly lower in the elderly group than in the young and middle-aged groups. The GRWR value was significantly higher in 50-59 year age group than in young and middle-aged groups. There was no significant difference in GRWR value between the young and middle-aged groups. Length of hospital stay was significantly shorter in elderly group than in young and middle-aged groups for recipient. There was no significant difference in length of hospital stay between young and middle-aged groups (Table 3). One-year LDLT recipient survival was 100% in all groups, while three-year survival rate was 100% in young, middle-aged groups, and 95.8% in the elderly group. The five-year survival rates of

young, middle-aged and elderly groups were 100%, 94.3% and 86.7%, respectively. However, 10-year survival rates were significantly higher in the young group (48.5%) than in the middle-aged and elderly groups (22.9% and 0%, respectively). Five-year graft survival rate of young, and middle-aged groups was 72.6 and 76.6%, respectively. But an 84.3% graft survival rate was observed in elderly group. After five years, donor age remained associated with recipient overall survival. In terms of the survival rates of LDLT recipient age groups, the predicted survival rate in the elderly group (68.3%) was significantly lower than that in middle-aged and young groups. The predicted survival time was significantly lower in the middle-aged and the elderly groups than in the young age group (Figure 1). In the graft survival analysis, the predicted graft survival times of young, middle-aged and elderly groups did not differ significantly (Figure 2). We showed the study population in a flow diagram (Figure 3).

Discussion

While previously considered highly risky, LT using elderly LD grafts has been increasing over time due to the significant

Table 1. Recipient demographic characteristics

		Min-max			Median	Mean ± SD/n-%		
Age		6.0	-	57.0	37.0	37.0	±	10.1
Recipient age		0.60	-	71.0	54.0	50.5	±	14.9
Gender	Female					84		50.0%
	Male					84		50.0%
BMI		14.0	-	47.0	26.0	26.6	±	4.8
Liver volume		10.0	-	71.0	64.0	60.7	±	12.4
First degree relative	(No)					66		39.3%
	(Yes)					102		60.7%
Other biological relative	(No)					123		73.2%
	(Yes)					45		26.8%
Non-biological relative	(No)					144		85.7%
	(Yes)					24		14.3%
Diagnosis								
Cryptogenic						42		25.0%
Hepatitis B virus						34		20.2%
Hepatitis C virus						24		14.3%
Hepatocelluler carcinoma						14		8.3%
Autoimmune						13		7.7%
Alcoholic						11		6.5%
Biliary cirrhosis						6		3.6%
Budd chiari						5		3.0%
Primer biliary sclerosis						4		2.4%
Biliary atresia						4		2.4%
Hyperoxa luria						2		1.2%
Primer biliary cholangitis						2		1.2%
Wilson disease						2		1.2%
Non-alcoholic steatohepatitis						2		1.2%
Caroli disease						1		0.6%
Liver failure						1		0.6%
Progresissive familial intrahepatic cholestasis						1		0.6%

SD: Standard deviation, BMI: Body mass index

gap in demand and supply. With increasing experience, elderly deceased donor transplantations, including those from octogenarian donors, are being achieved with excellent results in many centers around the world (14-16). LDLT is performed in LT centers with very few LDs who are ≥50 years of age. In this regard, there are only minor relative differences between the centers. Overall acceptance of centers of elderly living liver donors has not markedly changed. Studies from Asia with a high prevalence of HCC showed an inconsistent effect of increased LD age on graft and recipient outcomes (17-21). Again, although some studies showed that LDLT with carefully selected elderly LD is safe even with LDs over 60 years of age, well experienced LDLT centers' point of view, there are still major concerns about this (10,22). In Japan, the percentage of donor graft use for donors over the age of 50 is 18%, and for those over 60, it is 4%, respectively. According to volumetric measurements made with computed tomography after LDLT, impaired liver regeneration was shown in elderly donors (≥50 years of age) compared to younger donors (<30 years) (23). Donor age is a strong and independent prognostic factor in LDLT. However, some researchers have showed that LD grafts can be used safely even in donors older than 50 years, although the regeneration capacity is impaired (19,24-27). Compared to Europe and Asia, use of LD among the elderly in the US has lagged behind. This is likely due to multifactorial reasons including the increased risk perception from previous studies. The most recent study showed excellent results in the use of elderly LDs over 70 years of age in selected recipients (28). However, that study conducted an analysis of elderly DCD (donation after cardiac death) donors in the United Network for Organ Sharing (UNOS) database. In contrast, the US study showed a significant unfavorable effect of an elderly LD on graft results, reporting that 1/10 recipients with LD >50 were retransplanted within the first year. Nevertheless, 5- and 10-year long-term graft survival outcomes of 71.4% and 58.6%, respectively, were still acceptable. Interestingly, it was found that increasing donor age in LDLT compared to DDLT had deeper negative consequences for graft results (29). The data regarding the association of older LD age and outcomes in LDLT, came from the adult to adult living LDLT (A2ALL) study (30). The A2ALL study showed that older donor age was associated with early graft dysfunction (EAD) and high recipient mortality (31). However, A2ALL studies were performed during a period when selection criteria in LDLT centers were conservative, and the use of LDs over 50 years of age was rare. In fact, although long-

Table 2. Donor demographic characteristics

			Age 18-39[1]			Age 40-49[2]			Age 50-59[3]			p	
			Mean ± SD/n-%			Mean ± SD/n-%			Mean ± SD/n-%				
Age (year)	Mean ± SD		30.0	±	5.5	42.5	±	6.1	52.6	±	2.3		
	Median		31.0			43.0			52.0				
Recipient age (year)	Mean ± SD		50.0	±	14.6	49.5	±	18.4	54.1	±	6.9	**0.745**	K
	Median		53.0			55.0			54.0				
Gender	Female	n-%	39[2]		41.1%	36.0		76.6%	9[2]		34.6%	**0.000**	X^2
	Male	n-%	56		58.9%	11.0		23.4%	17		65.4%		
Body mass index	Mean ± SD		27.1	±	4.9	26.0	±	5.0	25.6	±	3.5	0.407	K
	Median		26.0			26.0			25.5				
Liver volume	Mean ± SD		60.0	±	12.3	59.3	±	15.1	65.9	±	3.5	**0.005**	K
	Median		63.0[3]			65.0[3]			66.0				
First degree relative	(No)	n-%	26		27.4%	19		40.4%	21		80.8%	**0.000**	X^2
	(Yes)	n-%	69[3]		72.6%	28[3]		59.6%	5		19.2%		
Other biological relative	(No)	n-%	70		73.7%	39		83.0%	14		53.8%	**0.026**	X^2
	(Yes)	n-%	25		26.3%	8[3]		17.0%	12		46.2%		
Non-biological relative		n-%	91		95.8%	36		76.6%	17		65.4%	**0.000**	X^2
	(Yes)	n-%	4[23]		4.2%	11		23.4%	9		34.6%		

X^2: Chi-square test, K: Kruskal-Wallis (Mann-Whitney U test), [2]: Difference with age 40-49 group p<0.05, [3]: Difference with age 50-59[3] group p<0.05, SD: Standard deviation

Table 3. Recipient characteristics and posttransplantation outcomes in the comparison study using elderly donors and younger donors in the living donor liver transplantation

			Age 18-39[1]			Age 40-49[2]			Age 50-59[3]			p	
			Mean ± SD/n-%			Mean ± SD/n-%			Mean ± SD/n-%				
Liver steatosis	0%	n-%	61[23]		64.2%	21		44.7%	8		30.8%	0.004	X^2
	1%	n-%	13		13.7%	11		23.4%	7		26.9%		
	5%	n-%	19		20.0%	10		21.3%	8		30.8%		
	10%	n-%	0		0.0%	4		8.5%	2		7.7%		
	15%	n-%	1		1.1%	0		0.0%	1		3.8%		
	20%	n-%	0		0.0%	1		2.1%	0		0.0%		
	100%	n-%	0		0.0%	0		0.0%	0		0.0%		
Clavien-Dindo complication	I	n-%	71		74.7%	38		80.9%	22		84.6%	0.479	X^2
	II	n-%	10		10.5%	8		17.0%	4		15.4%		
	III	n-%	13		13.7%	1		2.1%	0		0.0%		
	IV	n-%	1		1.1%	0		0.0%	0		0.0%		
MELD	Mean ± SD		19.1	±	6.4	18.8	±	6.0	19.8	±	4.3	0.349	K
	Median		17.0			17.0			19.0				
Operation time of donor (minute)	Mean ± SD		382.2	±	69.7	413.4	±	82.4	390.0	±	57.9	0.058	K
	Median		370[2]			410			388				
Graft survival (month)	Mean ± SD		77.8	±	46.0	68.4	±	36.8	62.0	±	20.3	**0.003**	K
	Median		92.0[23]			73.0			65.5				
Recipient survival (month)	Mean ± SD		77.8	±	46.0	66.8	±	38.0	62.0	±	20.3	**0.002**	K
	Median		92.0[23]			72.0			65.5				
Recipient operation time (minute)	Mean ± SD		643	±	106	596	±	104	556.0	±	76.7	**0.000**	K
	Median		630[23]			570			535				
Right hepatectomy	(No)	n-%	8		8.4%	5		10.6%	0		0.0%	0.247	X^2
	(Yes)	n-%	87		91.6%	42		89.4%	26		100%		
Left lateral hepatectomy	(No)	n-%	87		91.6%	42		89.4%	26		100%	0.247	X^2
	(Yes)	n-%	8		8.4%	5		10.6%	0		0.0%		
Live	(No)	n-%	26		27.4%	11		23.4%	4		15.4%	0.444	X^2
	(Yes)	n-%	69		72.6%	36		76.6%	22		84.6%		
Graft rejection	(No)	n-%	71		74.7%	39		83.0%	18		69.2%	0.368	X^2
	(Yes)	n-%	24		25.3%	8		17.0%	8		30.8%		
GRWR	Mean ± SD		0.99	±	0.22	1.1	±	0.33	1.1	±	0.17	**0.008**	K
	Median		0.97[23]			1.00			1.00				
Hospital stay	Mean ± SD		22.2	±	11.5	19.2	±	12.6	16.2	±	4.0	**0.004**	K
	Median		20.0[23]			14.0			15.5				
Died	(No)	n-%	68		71.6%	35		74.5%	22		84.6%	0.402	X^2
	(Yes)	n-%	27		28.4%	12		25.5%	4		15.4%		

X^2: Chi-square, K: Kruskal-Wallis (Mann-Whitney U test), [2]: Difference with age 40-49 group p<0.05, [3]: Difference with age 50-59[3] group p<0.05, SD: Standard deviation, GRWR: Graft-to-recipient weight rate, MELD: Model for end-stage liver disease

term survival outcomes in LDLT are believed to be better than DDLT, our study showed that this advantage is lost at advanced donor age. Several factors may contribute to this phenomenon. The meticulous selection of older donors is crucial. Age-related comorbidities may be more prevalent in older donors, potentially impacting post-transplant complitaions and long-term survival. Surgical difficulties and morbidites can be more frequent in the transplantation

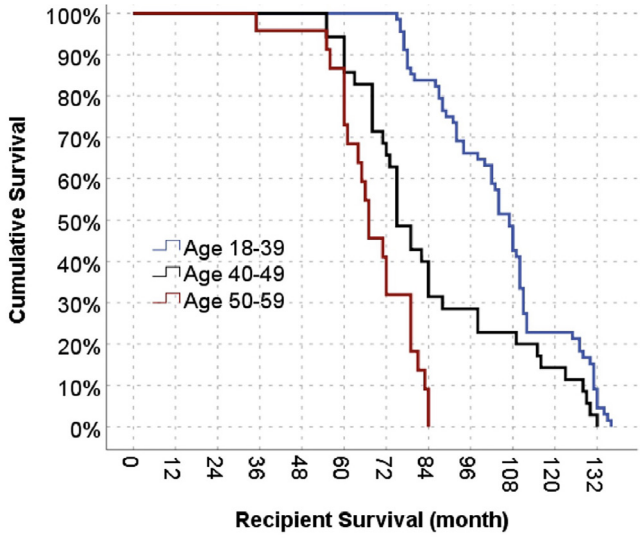

Figure 1. Recipient's overall survival graphic in different living age groups

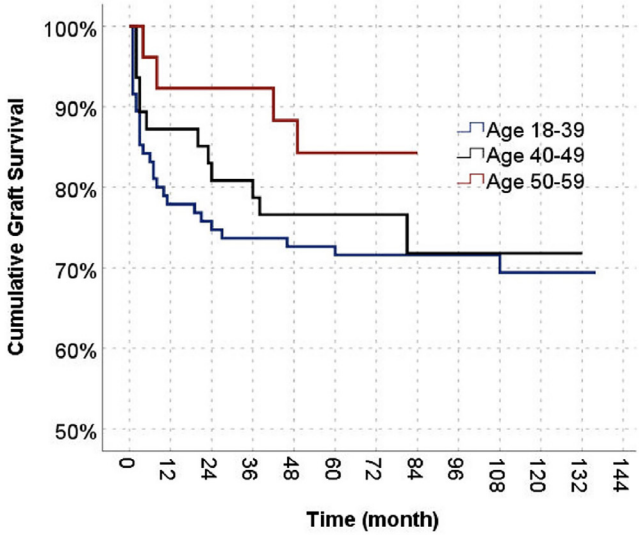

Figure 2. Graft survival curve in the recipient after liver donor graft using in different age groups

of livers from older donors. Immunological differences in older donors might affect the recipient's ability to accept the transplanted liver. Recipient characteristics and comorbidities play a vital role. The response of older donors' liver to immunosuppressive drugs may differ, influencing post-transplant survival. The combination of these factors may contribute to the observed trend where the advantage of superior long-term survival outcomes in LDLT diminishes with advanced donor age. We reported that the graft survival rate did not differ significantly among the groups for the long term. We evaluated this as graft failure if the graft failure due to HCV, NASH, HCC

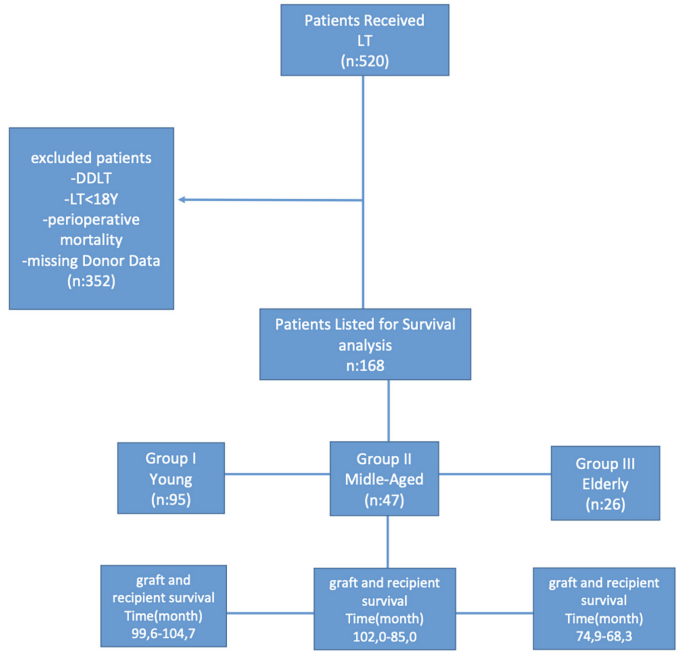

Figure 3. Flow chart illustrating our study population

DDLT: Donor liver transplantation, LT: Liver transplantation

recurrence, non-compliance with immunosuppressive treatment, graft rejection, infectious causes as sepsis or arterial-venous and biliary complications can not reversed with treatment. Therefore no patients in each cohort were diagnosed with small-for-size syndrome (SFSS). We did not assess portal venous pressure (PVP) during transplantation. Previous studies have shown that elevated PVP necessitates portal inflow modulation to prevent SFSS. No cases of EAD were observed in this study. These complications are frequently encountered during the early post-LT period. It was less common in recipient (50> LD). Recipient losses due to any other reason were not considered as graft loss in this statistics. Further graft liver volume and GRWR were significantly higher in the elderly group than in other groups. The GRWR could improve the prediction of 90-day graft survival (32). The decision to continue LDLT with elderly LD must take into account the clinical status of the recipient, the risk of death on the waiting list, and especially alternative donor availability. In this context, there is also a need to determine the appropriate recipient and donor selection practices in the elderly LD arrangement. The centers did not perform LDLT for more severe disease, nor with an elderly LD suitable for an elderly recipient. There was also no difference in the prevalence of normal weight compared to obese or overweight elderly LD. This finding was in line with the present study. Although the increased age of

LDs did not influence the decision to perform pre-LT liver biopsy, we found that the rate of steatosis was significantly higher in elderly donors than in younger donors in our study. This suggested preoperative liver biopsy in elderly donors. However, in our analysis, the inclusion of liver biopsy in LD for all LDLT could have resulted in selection bias because of the restrictive nature of the biopsy. The use of non-invasive measurement methods such as MR spectroscopy as an alternative to invasive liver biopsy could have made the steatosis evaluations more effective and safer in assessing the results of increased LD age (33-35). In our study, there were differences in recipient-donor relationships. Non-biological status was more common in the LD group of individuals over 50 years of age. This reflected the inability of potentially younger biologically-related donors to serve as suitable donors. Based on UNOS data, a study reported that early postoperative donor complications were not affected by donor age, but biliary complications were more common in LDs older than 55 years of age, although the age difference was not statistically significant (29).

One of the inherent challenges with UNOS data is that there may be less propensity for centers to report complications directly. A recent study, showed that elderly LD was associated with a higher risk of major morbidities (36). Some other studies showed that LDLT using elderly donor grafts induced more serious postoperative complications and resulted in higher mortality rates in recipients than those who received younger donor grafts (37,38).

In our study, we evaluated early (≤6 weeks) postoperative complications, including biliary and vascular complications, using the Clavien-Dindo classification for the first time. In this context, we did not observe a negative effect of donor age. Additional studies are needed to determine more comprehensively whether older liver donors are related to potential long-term effects on recipient survival. With the recent increase in the demand for LT in parallel with LD limitation, there is a need for updated donor results on a wide scale in the world LDLT community. Although many side effect discussions for donors are directly transferred from the seminal A2ALL studies, they do not fully reflect the concerns in the current era, when there is more LDLT experience. Experienced centers are now expanding their donor selection criteria and performing more LDLT. Due to some reservations about using LD in the elderly, it seems intuitively more prudent to prioritize patients with severe clinical conditions due to increased likelihood of graft dysfunction and decreased organ physiological reserve capacity. In the present study, the median recipient ages were 53, 55 and 54 years and MELD scores were 17, 17 and 19 in young, middle-aged and elderly groups, respectively. Although the MELD score, was higher in the elderly LD group, there was no statistically significant difference compared to the other groups. We observed a relatively stable MELD score over time in this study. Contrary to programs that tend to use elderly LD at lower MELD scores, the present study observed no difference in early complications, and graft and recipient survival, was observed between LDLT performed with elderly LD at high MELD values and younger age groups, at the same MELD value. There was no significant difference in recipient ages among the study groups. LT is technically more difficult in obese recipients. This may increase the operative time and the need for transfusion, as well as the risk of perioperative complications such as uncontrolled major bleeding in the inferior vena cava, bleeding adjacent to the liver, or damage to the hepatic artery (39). Noteworthy is the classification of our study participants as overweight (BMI: 25-29.9) without any individuals falling into the obese category (BMI: 30 and above), which is noteworthy. we observed that there were no significant differences in BMI among the groups.

In our study, we reported a significant difference in long-term recipient survival after five years. It is important to optimize donor-recipient matching here. Our findings also support the idea of discouraging the use of older LD grafts in younger recipients to benefit from the graft for a long time. In recent years, several studies have examined the long-term outcomes of using elderly LDs from the recipient's perspective. These reports stated that donor age is a factor affecting recipient survival (18,37-42). A number of studies indicated a difference in post-transplant survival between the use of old and young donors in the first year after the transplantation, which stabilizes thereafter (43). Our study is the first to evaluate the use of the LD graft in the LDLT simultaneously in three different age groups for long-term recipient and graft survival outcomes, and to include GRWR and Clavien-Dindo classification parameters in the analysis. An important aspect of LDLT safety is GRWR and donor graft volume. These parameters are predominant factors in the LD selection process. Dayangac in Turkey reported increased concerns about the relationship among high LD age, donor graft volume and recipient outcomes (44). In recent study, the predicted survival time in the elderly group (68.3 months) was significantly ($p<0.05$) lower than in the middle aged and young groups. Furthermore the predicted survival time in the middle- aged group was significantly ($p<0.05$) lower than in the young group. Our study also eliminated concerns about this relationship by more

accurately determining the impact of increased donor age. Considering the center heterogeneity in LDLT applications, large multicenter studies are essential to overcome this problem. Our study is likely to encourage these efforts. For patients awaiting LDLT and without suitable young donors, it is imperative to examine the potential survival benefit of proceeding with LDLT using elderly LD to better guide decision-making for both physicians and patients. This study shows that Length of postoperative hospital stay was significantly shorter in elderly group. The impact of donor age on postoperative hospital stay lengths in LT is significant, as older donors are often subject to more stringent selection criteria. Older donors may be preferentially used for less risky recipients. The meticulous surgical techniques might be used in transplants involving older donors (26,45,46). In fact, although long-term survival outcomes in LDLT are believed to be better than DDLT, our study showed that this advantage is lost at high donor age. Comparative and further studies would be beneficial in understanding these findings.

Study Limitations

Our study is limited by the lack of granularity regarding causes of graft loss or patient mortality. In addition to its single-centered and retrospective nature, the study was not suitable for involving the elderly group in the multivariable model due to the low power of the group. Still, we believe it helped to provide some perspective in terms of the older donor age. Portal inflow modulation was not performed during LT. Apart from GRWR and graft volume, factors including donor comorbidity and graft characteristics that affect early post-transplant mortality and morbidity, such as warm ischemia time, hypertension, diabetes, and use of blood products, were not evaluated. The biliary anatomy of the donor, which posed a potential risk for biliary complications, was also not taken into consideration. However, donor and liver graft factors were evaluated to predict recipient outcomes in LDLT. However, it is not clear to what extent these evaluations consider donor age and how they affect the results. Multiple regression analysis was not used in this study, therefore we could not conclude whether LD age of >50 years was an important predictor in long-term graft and recipient survival. Further studies need to be carried out on this.

Conclusion

The results of our study can be based on the following principles: Elderly donors can be selected for LDLT by paying close attention to donor safety, and with appropriate donor-recipient selection, there was no statistically significant difference between the groups in five-year recipient survival. Similarly, no difference was observed between the groups in long-term graft survival. Despite the increasing use of LDLT around the world, centers remain conservative in accepting the use of elderly donors in LDLT. This could be attributable to the low rate of GRWR and high steatosis in the elderly group compared with the younger groups. Many potential factors, such as improved surgical technique, perioperative care, and patient selection, can contribute to this success. From the recipient's perspective, the decision to use elderly living donors should be made by weighing the risks associated with other LD options or the deceased donor LT waiting period. While the use of elderly living donors could be considered in emergency, life-saving scenarios, it is important to note that long-term graft survival in the elderly group remains suboptimal. Consequently, these donors are typically selected with caution.

Ethics

Ethics Committee Approval: This study protocol was reviewed and approved by the Ethics Committee of Acıbadem University (no: ATADEK 2023-18/ 617) on 16.11.2023.

Informed Consent: Approval of the participants included in the study was obtained using a voluntary consent form.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.T., İ.B.B., Concept: U.T., Design: U.T., Data Collection or Processing: İ.B.B., Analysis or Interpretation: İ.B.B., Literature Search: U.T., Writing: U.T.

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