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Outcome after liver transplantation in elderly recipients (>65 years) — A single-center retrospective analysis

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ABSTRACT

Background: Liver transplantation (LT) in elderly recipients is controversially discussed in the literature with only little data on long-term outcome available. We aimed to evaluate the safety and efficiency of LT in elderly recipients (>65 years).
Methods: Between 1989–2016, 139 patients >65 years-old were listed for liver transplantation, and 76 (55%) were transplanted. Patient outcome and characteristics were evaluated separately for the time period before (1989–2004) and after (2005–2016) MELD-implementation. Post-transplant outcome was compared between the elderly cohort and LT-recipients aged 18–65 years (n = 1395).
Results: Overall survival of patients >65 years was better in the MELD-era compared to the earlier period (1- and 5-year-survival: 73%, 60% vs. 69%, 37%, respectively; p = 0.055). The main differences between the two groups included higher recipient age (p = 0.001) and BMI (p = 0.001), higher donor age (p < 0.001), less need of intraoperative red blood cells (p = 0.008) and a lower number of postoperative rejections (p = 0.03) after 2004. Comparing the overall survival of patients transplanted in the MELD-era aged 18–65 years vs. >65 years displayed comparable 1- and 5 year-survival rates (81%, 68% vs. 73% and 60%, respectively, p = 0.558).
Conclusion: In the modern era, outcome of patients receiving LT with >65 years is comparable to <65 year-old patients. After careful evaluation, patients >65 years old should be considered for LT.

1. Introduction

According to reports from the European Liver Transplant Registry (ELTR), the number of patients aged 60 or older waiting for liver transplantation (LT) is continuously increasing, accounting for around 25% in Europe [1]. In the United States, 1464 patients (18.7%) were aged at least 65 years or older among 7841 liver transplant recipients in 2016 [2]. Donor shortage and the high number of patients on the waiting list request a careful recipient selection. The goal remains to prevent patient death on the waiting list and to achieve optimal postoperative results. Several transplant centers have rejected the idea of an absolute age limit after comparable results between liver recipients of younger cohorts and those including elderly patients have been reported [3–5]. Poor outcome in elderly patients often affected isolated subgroups with no single common reasons. As of today no exclusive factor has been singled out to be predictive of postoperative outcome for elderly recipients, but age itself is generally not accepted as contraindication for LT. Besides the experience regarding LT in elderly patients is increasing, data on outcome of patients older than 65 years are still not satisfactory [6].

Several changes in patient management and donor allocation have improved the outcome after LT over the last decades. After the millenniums, the model of end stage liver disease (MELD) score has been implemented for prioritizing allocation for patients waiting for LT with liver cirrhosis by Eurotransplant, United Network for Organ Sharing (UNOS) and other centers [7,8]. This model allows the interpretation of the 3-months mortality by taking objective markers such as serum creatinine, serum bilirubin and INR into account [9,10]. The change to a MELD-based allocation system

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showed changes in the mortality rates on the waiting list and after transplantation [11]. Besides criticism towards an underestimation of abrupt changes in values and an often unsuitable donor–recipient matching has been expressed [12], good survival outcome has been shown in the MELD-era, even with donors ≥70 years [8].

The aim of the study was to evaluate the post transplant outcome of patients who were considered as "elderly recipients", with a cut-off of >65 years at the time of LT. We further evaluated whether there was a change in the outcome of this cohort after the MELD-based allocation has been implemented.

2. Patients and methods

Approval for the retrospective study has been obtained from the institutional ethical committee (EK-Nr. 1047/2016). The prospectively maintained database of our institution was reviewed for patients transplanted between 01/1989 and 12/2016. In total, 1395 patients received a LT at the age of 18 years or older in this period. Patients receiving LT with >65 years were defined as elderly recipients, with 76 patients being eligible for detailed analysis.

At our institution patients with a body-mass index (BMI) between 16 and 35 suffering from end-stage liver disease are considered for LT. A specialized team including surgeons, hepatologists, anaesthesiologists and psychologists evaluates patients and decides in consensus over the eligibility for transplantation. The physiological age and functional reserve is a more relevant measure than the actual age when a patient is evaluated for LT [6,13]. Thus, at our institution, elderly patients are assessed for physical fitness classified by the metabolic equivalent threshold (MET), and patients with a MET >3 are considered for LT. Specific cardiologic assessment prior to LT includes electrocardiography and cardioechography for all patients, as well as cardioangiography in patients >65 years. Additionally, cardioangiography is performed in diabetic patients >55 years. Furthermore, carotis angiography and lung function tests are performed in all patients to exclude carotic stenosis or severe pulmonary disease. All patients and medical reports are carefully assessed by specialized anaesthesiologists and intensivists and suggest either consideration for LT, or in presence of any relevant disease specialized therapy and re-evaluation after successful treatment. Patients with HCC have been included within Milano criteria after 2004, whereas they were also transplanted outside of Milano criteria before this period. Furthermore, there was no 6-months abstinence rule for patients with alcoholic liver disease, as previously reported [14]. Alcohol relapse was defined as any post-transplant alcohol consumption.

Patients' data have been prospectively collected in the institutional LT database, as previously reported [14]. This database includes recipients' data on age, gender, date of listing, date of transplantation, reasons for transplantation, date of graft loss, reason for graft loss/reason for re-transplantation, date of death, reasons for death, pre-transplant diagnosed comorbidities (hypertension, diabetes mellitus, cardiovascular disease and renal dysfunction), MELD score at the time of listing and at the time of transplantation. Furthermore, collected donor data included sex, age and BMI, cold ischemia time (CIT) and the donor risk index (DRI). There were no organs donated after circulatory death in this cohort. Organs with more than 30% of macrosteatosis were rejected.

Medical records during the patients' hospital stay as well as records from visits at the outpatient clinic were prospectively collected. Complications were documented and classified according to the Clavien–Dindo classification and patients that suffered from major post-operative complications where classified as Clavien–Dindo ≥3b [15]. For those patients who received a LT before the introduction of the Clavien–Dindo classification, complications were retrospectively graded. Follow-up was performed once a week during the first month after LT, twice a month during the second and third month after transplantation, twice a year during the first 2 years after LT and once a year thereafter, or when required. Our protocol for immunosuppression includes ATG for induction therapy and a combination of calcineurin inhibitors or mTOR inhibitors and glucocorticoids is used for immunosuppression maintenance. Patients who experienced a rejection episode after LT were identified.

Organ allocation has been changed in 2004 from a Child–Pugh-Score based to a MELD-score based system at our institution. Liver allocation at our center is based on the rules of Eurotransplant (Leiden, Netherlands). If there is no high urgency request within the Eurotransplant area, the livers are primarily allocated to the transplant center donating. Livers are assigned to patients who are ranked first on the waiting list based on blood group, weight classification (compatibility of organ/patient size), MELD-score and waiting time. To evaluate the change of post-transplant survival before and after the implementation of MELD-based allocation, subanalyses were performed with patients transplanted between 1989 and 2004 and patients transplanted between 2005 and 2016.

3. Statistical analysis

Statistical analysis was performed using SPSS 23 (SPSS, Inc., Chicago IL, USA). Means and standard deviation or median and range were used to report data. Overall survival was defined as time from transplantation till patients' death. Kaplan–Meier curves were used for the analysis of overall patient survival and log-rank test for the comparison of overall survival in different groups. For univariate and multivariate analysis, the cox-regression model was applied and results for hazard ratio (HR) and 95% confidence intervals (CI) are reported. Variables with p-values <0.2 in univariate analysis were included for multivariate analyses. Reasons for death after LT were classified and presented in a descriptive manner. To compare means in different groups, t-test was applied in case of normal distribution, and Man–Whitney-U test in case of non-normal distributed variables. To compare quantitative values, chi-squared test was used. All tests are two-sided and p-values <0.05 were considered statistically significant.

4. Results

4.1. Recipient and donor characteristics

Between 1989 and 2016, 139 patients >65 years old were listed for LT. 76 (54.7%) patients were transplanted, 26 (18.7%) died while on the waiting list and 37 (26.6%) were removed from the list (tumor progression n = 9, poor condition n = 8, clinical improvement n = 15, non-compliance = 5). From the 76 transplanted patients, the median follow-up was 53 months (range 0–199 months) and the mean MELD at transplantation was 17 (±6.2). The indications for transplantation as well as the basic characteristics of the 76 elderly recipients are summarized in Table 1. The mean recipient age was 67 years with a range of 66–72 years. 66% of the recipients were between 66 and 67 years (50/76), 26% between 68 and 70 years (20/76) and 8% >70 years old (6/76).

The mean donor age was 47 years (±16), with 53% of donors being younger than 50 years (Table 1). In total, 67% of recipients received an organ with a donor–recipient-age difference of ≥10 years. The mean CIT for donor organs was 8 h (±2.5) and the median DRI 1.6 (range 1.04–2.42) (Table 1).

4.2. Postoperative outcome

Overall one-, three- and 5-year-survival rates for patients transplanted with >65 years between 1989 and 2016 were 71%, 56%

Table 1
Summary of recipient and donor characteristics of 76 patients receiving LT with >65 years.

Recipient and donor characteristics (LT >65 years, n = 76)		
Recipient age, years (mean, range)		67 (range 66–72)
Recipient BMI (mean, SD)		26 (±4)
Female (n, %)		27 (36%)
Disease etiology (n, %)	Tumor	26 (34.2%)
	Viral	15 (19.7%)
	Alcohol	15 (19.7%)
	Bilary	7 (9.2%)
	Metabolic disease	6 (7.9%)
	Autoimmune	3 (3.9%)
	Acute liver failure	2 (2.6%)
	Other	2 (2.6%)
MELD at listing (mean, SD)		16 (±5.2)
MELD at transplantation (mean, SD)		17 (±6.2)
Creatinine ≥1.2 mg/dl preoperative		24 (31.6%)
DM preoperative		18 (24%)
CAD preoperative		7 (9%)
Hypertension preoperative		20 (26%)
Waitlist time, months (mean, SD)		4.7(±5.9)
ATG induction		66 (87%)
CSA initial IS therapy		46 (61%)
FK506 initial IS therapy		16 (21%)
Rejection postoperative		13 (17%)
Complication 1st year Clavien–Dindo ≥3b		16 (21%)
Donor age (mean, SD)		47 (±16)
Donor age <50 (n, %)		40 (53%)
Donor–recipient age difference ≥10 years		51 (67%)
Donor sex female (n, %)		41 (54%)
Donor BMI (mean, SD)		24.5 (±3.6)
DRI (median, range)		1.6 (1.04–2.42)
CIT (hours, mean, SD)		8 (±2.5)
Donor–recipient sex mismatch		26 (34%)
Time of LT 1989–2004		35 (46%)
1-, 3-, and 5-year patient survival		71%, 56% and 48%

BMI: body mass index, CAD: coronary artery disease, CIT: cold ischemia time, CSA: cyclosporine A, DM: diabetes mellitus, DRI: donor risk index, IS: immunosuppression, LT: liver transplantation, MELD: model of end-stage liver disease, SD: standard deviation.

and 48%, respectively (Table 1). Two patients received a re-transplantation, one because of chronic rejection and one because of thrombosis of the hepatic artery, 7 months and 14 days after the first LT, respectively. In total, 16 patients (21%) suffered from major postoperative complications classified Clavien-Dindo ≥3b (biliary complication n = 6, acute surgical abdomen n = 4, bleeding and hematoma n = 3, pancreatitis n = 1, revision portal vein n = 2). During the whole observation period, 48 (63%) patients died, 9 within the first 30 days after LT. 13 (17%) patients died because of an infection, 14 (18%) because of a tumor (7 with tumor recurrence and 7 with de novo tumor), 7 (9%) because of graft related reasons (biliary complication, intraoperative death, chronic rejection, recurrence of alcoholic liver disease), 3 (4%) because of viral recurrence, 5 (7%) because of cardio-cerebrovascular disease and 6 (8%) due to other reasons (Table 2).

4.3. Comparison of patient outcome before vs. after MELD-implementation

The proportion of patients transplanted with >65 years increased from 4% to 7.8% after 2005. Patients aged >65 years at time of transplantation and who were transplanted between 1989 and 2004 (n = 35) showed a one-, three- and 5-year survival rate of 69%, 46% and 37%, respectively. On the other side, patients with >65 years transplanted between 2005 and 2016 (n = 41) displayed a better one-, three- and 5-year survival rate with 73%, 67% and 60%, respectively, without reaching statistical significance (p = 0.055, Fig. 1). Comparing the two groups in terms of recipient and donor characteristics identified a lower rejection rate (n = 3 (7%) vs. n = 10 (29%), p = 0.03), a higher number of patients receiving ATG as induction therapy (n = 40 (98%) vs. n = 26 (74%); p = 0.004) as well as a higher recipient age (p = 0.001), higher donor age (p < 0.001) and less patients with a donor–recipient age difference ≥10 years (n = 21 (51%) vs. n = 30 (86%), p = 0.002) in the group transplanted in the MELD-era (Table 3). Furthermore, patients transplanted in the MELD-era received significantly less packed red blood cells intraoperatively compared to patients transplanted in the earlier period (p = 0.008, Table 3). There was no significant difference comparing MELD at time of transplantation (16.3 ± 6.8 vs. 17.4 ± 5.9, p = 0.54) between the two groups (Table 3).

Reasons for death were statistically similarly distributed when the two different time periods for transplantation (1989–2004 vs. 2005–2016) were compared (Table 2). However, more patients died because of infections (35% vs. 16%) and tumors (35% vs. 21%) in the earlier period, without reaching statistical significance. From the patients who were transplanted between 1989 and 2004 and who died because of tumor recurrence, 3 were out of Milan criteria in the post-transplant pathological work-up, and 2 were within Milan. From the 10 patients who died because of an infection and were transplanted in the earlier period, 6 patients died within the first year after transplantation (median follow up 4.5 months, range 0.89–9.97).

4.4. Influence of different factors on postoperative patient outcome

The number of packed red blood cells used intraoperatively showed a significant influence on overall survival of elderly recipients in univariate analysis (p = 0.007). Furthermore, patients who received an organ with a donor–recipient age difference of ≥10 years showed poorer outcome in univariate analysis (p = 0.029, Table 4). There was no significant difference in reasons for death comparing patients receiving a graft from a donor with ≥10 years donor–recipient age difference to those with <10 years donor–recipient age difference (p = 0.86). Additionally, preoperative creatinine of ≥1.2 mg/dl (p = 0.073), post-operative episode of rejection (p = 0.062), donor–recipient sex mismatch (p = 0.188) and time of LT (1989–2004 vs. 2005–2016) (p = 0.060) were

Table 2
Reasons for death from 48/76 patients receiving LT with >65 years who died in the observation period. The reasons for death are listed separately for the two time periods before and after MELD-implementation (1989–2004 vs. 2005–2016).

Reason for death	Died (n = 48)	LT 1989–2004 (n = 29)	LT 2005–2016 (n = 19)	p-Value
Infection	13 (17%)	10 (35%)	3 (16%)	p = 0.2
Tumor	14 (18%)	10 (35%)	4 (21%)	p = 0.35
	7 de novo	*5 de novo*	2 de novo	
	7 recurrence	*5 recurrence*	2 recurrence	
Graft related	7 (9%)	2 (7%)	5 (26%)	p = 0.1
Viral	3 (4%)	3 (10%)	0	p = 0.27
Cardio-cerebrovascular	5 (7%)	1 (3%)	4 (21%)	p = 0.07
Other	6 (8%)	3 (10%)	3 (16%)	p = 0.67

LT: liver transplantation, MELD: model of end-stage liver disease.

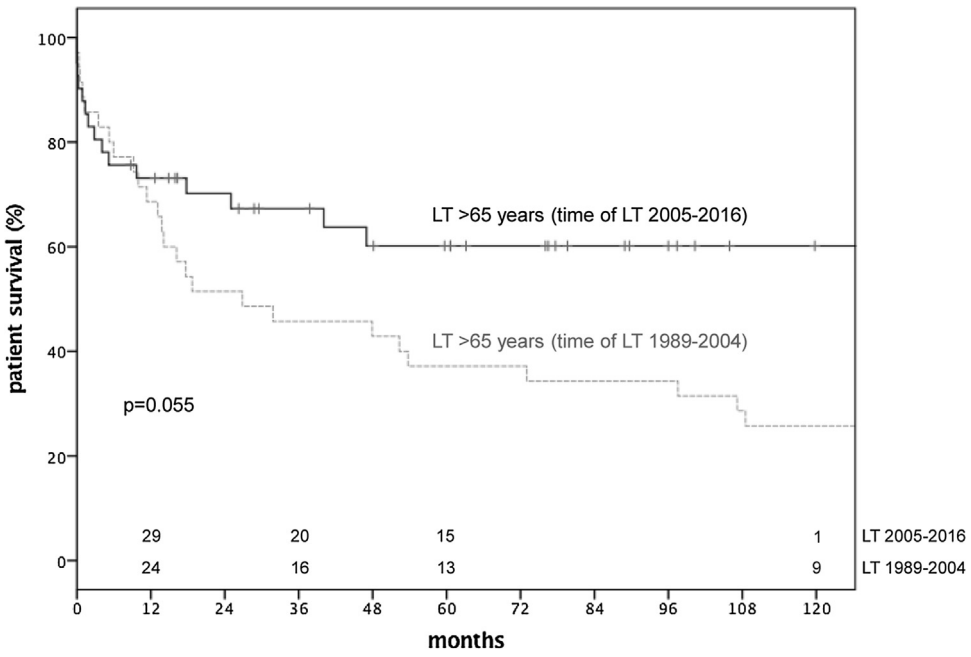

Fig. 1. Comparison of overall survival from >65 year old patients with LT transplanted in the earlier period (1989–2004, grey dotted curve) vs. in the later period (2005–2016, black curve).

Table 3
Patient and donor characteristics of patients receiving LT at the age of >65 years divided into the group transplanted between 1989 and 2004 (n = 35) and the group transplanted between 2005 and 2016 (n = 41).

Recipient and donor characteristics (n = 65)		Tx 1989–2004 (n = 35)	Tx 2005–2016 (n = 41)	p-Value
Recipient age (mean, SD)		66.7 (±0.87)	68 (±1.7)	p = 0.001
Recipient sex (female, n, %)		13 (37%)	14 (34%)	p = 0.82
Recipient BMI (mean, SD)		24.2 (±3.5)	27.3 (±3.8)	p = 0.001
MELD at listing (mean, SD)		15.5 (±7.1)	15.9 (±4.3)	p = 0.78
MELD at transplantation (mean, SD)		16.3 (±6.8)	17.4 (±5.9)	p = 0.54
MELD at transplantation >25 (n, %)		2 (5.7%)	5 (12.2%)	p = 1
Disease eti-ol-ogy (n, %)	Tumor	15 (43%)	11 (27%)	p = 0.16
	Viral	9 (26%)	6 (15%)	p = 0.26
	Alcohol	4 (11%)	11 (27%)	p = 0.15
	Biliary	4 (11%)	3 (7%)	p = 0.7
	Metabolic disease	0	6 (15%)	p = 0.03
	Autoimmune	1 (3%)	2 (5%)	p = 1
	Acute liver failure	2 (6%)	0	p = 0.21
	Other	0	2 (5%)	p = 0.5
DM preoperative (n, %)		7 (20%)	11 (27%)	p = 0.6
Hypertension preoperative (n, %)		10 (29%)	10 (24%)	p = 0.8
CAD preoperative (n, %)		3 (9%)	4 (10%)	p = 1
Creatinine pre-OP mg/dl (mean, SD)		1.29 (±0.74)	1.19 (±0.44)	p = 0.48
Packed red blood cells intraoperative (mean, SD)		7.3 (±6.9)	3.7 (±4.5)	p = 0.008
Fresh frozen plasma intraoperative (mean, SD)		7.8 (±9.6)	6.5 (±7.9)	p = 0.524
Platelets intraoperative (mean, SD)		0.86 (±1.6)	0.56 (±1.2)	p = 0.36
ATG induction		26 (74%)	40 (98%)	p = 0.004
CSA initial IS therapy		28 (80%)	18 (44%)	p = 0.002
FK506 initial IS therapy		6 (17%)	10 (24%)	p = 0.58
Complication 1st year Clavien–Dindo ≥3b		9 (25.7%)	7 (17.1%)	p = 0.41
Rejection postoperative		10 (28.6%)	3 (7.3%)	p = 0.03
Donor age (mean, SD)		38.6 (±14.7)	53.4 (±14.5)	p < 0.001
Donor–recipient age difference ≥10 years		30 (86%)	21 (51%)	p = 0.002
Donor sex (female, n, %)		17 (49%)	24 (59%)	p = 0.49
Donor BMI (mean, SD)		23.7 (±2.6)	25.2 (±4.2)	p = 0.13
CIT (hours)		8.5 (±3)	7.8 (±2)	p = 0.23
DRI (median, range)		1.5 (1.04–2.42)	1.61 (1.13–2.16)	p = 0.47

BMI: body mass index, CAD: coronary artery disease, CIT: cold ischemia time, CSA: cyclosporine A, DM: diabetes mellitus, DRI: donor risk index, LT: liver transplantation, MELD: model of end-stage liver disease, SD: standard deviation.

associated with higher risk of poor outcome. In multivariate analysis the number of packed red blood cells used during the operation (p = 0.037, HR: 1.086, 95% CI [1.005–1.173]) and a preoperative creatinine of ≥1.2 mg/dl (p = 0.027, HR = 2.039, 95% CI [1.086–3.830]) were independent predictors of patient outcome. Postoperative development of rejection (p = 0.158, HR = 2.125, 95% CI [0.746–6.056]), donor–recipient age difference ≥10 years (p = 0.143, HR = 1.948, 95% CI [0.798–4.755]), time period of transplantation 1989–2004 vs. 2005–2016 (p = 0.295, HR = 1.623, 95% CI [0.655–4.021]) and donor recipient sex mismatch (p = 0.068,

Table 4
Influence of different factors on overall survival in patients receiving LT with >65 years analysed by univariate cox-regression.

Factor	HR	95% CI	p-Value
Sex recipient	1.054	0.574–1.936	0.866
Sex donor	1.162	0.636–2.125	0.625
Disease etiology	0.962	0.807–1.147	0.664
MELD at transplantation	0.969	0.910–1.032	0.324
Creatinine ≥1.2 mg/dl preoperative	1.677	0.953–2.952	0.073
DM preoperative	1.004	0.495–2.036	0.992
CAD preoperative	0.971	0.346–2.722	0.955
Hypertension preoperative	0.712	0.357–1.420	0.334
Packed red blood cells intraoperative	1.069	1.018–1.122	0.007
ATG induction	1.434	0.597–3.447	0.420
Rejection postoperative	1.947	0.967–3.921	0.062
Complication 1st year Clavien–Dindo ≥3b	1.131	0.558–2.292	0.732
CIT	1.064	0.936–1.210	0.342
DRI	0.848	0.309–2.325	0.749
Donor–recipient age difference ≥10 years	2.206	1.086–4.483	0.029
Donor–recipient sex mismatch	1.512	0.817–2.801	0.188
Time of LT (1989–2004 vs. 2005–2014)	1.853	0.976–3.518	0.060

CAD: coronary artery disease, CIT: cold ischemia time, DM: diabetes mellitus, DRI: donor risk index, LT: liver transplantation, MELD: model of end-stage liver disease, SD: standard deviation.

HR = 2.017, 95% CI [0.950–4.285]) were not significantly associated with patient outcome in multivariate analysis.

4.5. Survival of liver transplant recipients >65 years old compared to younger recipients

Overall survival of all patients receiving LT from 1989 to 2016 between 18 and 65 years (n = 1395) at our institution was analysed and compared to patients receiving LT >65 years old (n = 76). Patients receiving LT at the age of 18–65 years showed a one-, three-, and 5-year survival rate of 76%, 67% and 62%, respectively. Comparing the younger group to the group receiving LT with >65 years, transplanted during the whole observation period (1989 to 2016) revealed a significant difference of postoperative survival, with patients >65 years old having poorer outcome (p = 0.004, Fig. 2a). This difference was even more prominent when only the time period from 1989 to 2004 was taken into account (p = 0.005). However, when only the MELD-era (2005 to 2016) was considered, there was no significant difference in these two age groups (p = 0.558) and the one-, three- and 5-year survival rates of patients >65 years with 73%, 67% and 60%, respectively, was comparable to the survival rate of patients between 18 and 65 years (81%, 74%, 67%, respectively, Fig. 2b).

5. Discussion

The mean age of LT registrants is increasing continuously and the proportion of patients waiting for LT with ≥60 years reached 41% in the United States in 2014 [16]. Although data about the safeness of transplanting liver grafts from older donors of more than 70 years of age are available [17,18], data on outcome of elderly liver recipients are rare [19]. At our institution, 4% of patients transplanted between 1989 and 2004 were >65 years old, and this number increased to 7.8% between 2005 and 2016. 5-year survival rates in recipients >60 years have been reported to range from 52% [20] to 73% [4] and many centers concluded that LT can be performed safely in recipients older than 60 years [21–25]. A recent study demonstrated that the transplant-related survival benefit is not affected by older age, besides an increasing mortality with increasing age [16]. This has been associated with the fact that both, post-transplantation survival and waitlist survival are equally diminished by age [16]. Chen et al recently analysed the Taiwanese National Health Insurance Research Database for recipient age and mortality risk after LT, including 474 recipients ≥60 years old among 2938 transplanted patients [26]. They found a higher mortality rate for LT recipients ≥60 years that was associated with dialysis, congestive heart failure, chronic kidney disease and peptic ulcer [26]. Data on recipients above 65 years are rare in the literature, however, our data confirm that increased pre-operative creatinine is an important factor with significant influence on postoperative outcome. Cross et al. analysed outcome of patients above 65 years (77 patients) and reported good survival rates, with a one- and 5-year survival rate of 82% and 73%, respectively [4]. Similar results were published by Malinis et al. analysing the UNOS database, where liver recipients aged between 65 and 69 years reached a 5-year survival rate of 65% [27]. Slattery et al. analysed 40 patients aged >65 years transplanted between 1993 and 2009 (Irish National Liver Transplant Unit) and reported 3-year survival rates of 64.5%, which was significantly lower in their analyses when compared to patients ≤65 years [28]. On the other side, Wilson et al analysed the Scientific Registry of Transplant Recipients (USA) for outcome of liver transplant recipients aged ≥70 years (n = 323) transplanted between 2007 and 2011 and reported similar results, with 5-year survival rates of 64.1% [29]. Additionally, the authors reported comparable graft and patient survival (p = 0.35 and p = 0.13, respectively) after matching the elderly cohort 1:1 to a younger cohort [29]. Another series from the UNOS database analysing 677 patients ≥65 years receiving simultaneous liver and kidney transplantation displayed similar patient and graft survival when compared to a younger cohort [30].

In our study cohort, survival analysis revealed that >65-year-old patients transplanted in the MELD-era display good survival rates, comparable to those of patients transplanted at an age between 18 and 65 years in the same time period (one-, three- and 5-year survival: 73%, 67%, 60% vs. 81%, 74% and 68%). This could not be shown for the whole observation period, from 1989 to 2016, where patients >65 years displayed lower survival rates compared to the younger cohort (p = 0.004). Comparing the patients' characteristics of the earlier (1989–2004) vs. the later period (2005–2016), revealed a significant difference in recipient age (66.7 vs. 68, p = 0.001), donor age (38.6 vs. 53.4, p < 0.001) and the number of patients with a donor–recipient age difference ≥10 years (86% vs. 51%, p = 0.002). Shin et al recommended donors not to be older than the recipient due to adverse outcomes, but without addressing a specific age group of recipients [31]. On the other side, Pagano et al. described a high donor–recipient age gradient as a potential independent risk factor for patient death [32]. They found a significantly better survival in age-matched patients compared to age-mismatched patients, and even more, older age-matched patients (recipients >60 years and donors >60 years) displayed better long-term survival [32]. This might partially support our finding of a better survival in elderly patients who received organs form donors with less than 10 years age difference. An important aspect to be considered when transplanting elderly patients is the principle of equity. In order to provide both, young and old recipients with an equal opportunity to receive a liver graft, Cucchetti et al. suggested age mapping during the allocation process, aiming to decrease the years of live lost between younger and older recipients [33]. The currently used MELD-based allocation system mainly represents a system that aims for justice, but it does not consider age as a factor [34]. However, although advanced donor age has been shown in several studies not to affect postoperative survival [35–37], there are also studies describing donor age as risk factor for graft survival [38]. Using donor organs from elderly donors has been reported to increase post-transplant biliary complications [39,40] and recurrence of hepatitis C [41,42] and high donor age might be a risk factor for the outcome after LT [43].

The significantly better outcome in the later time period in our cohort might also be explained by the growing experience of

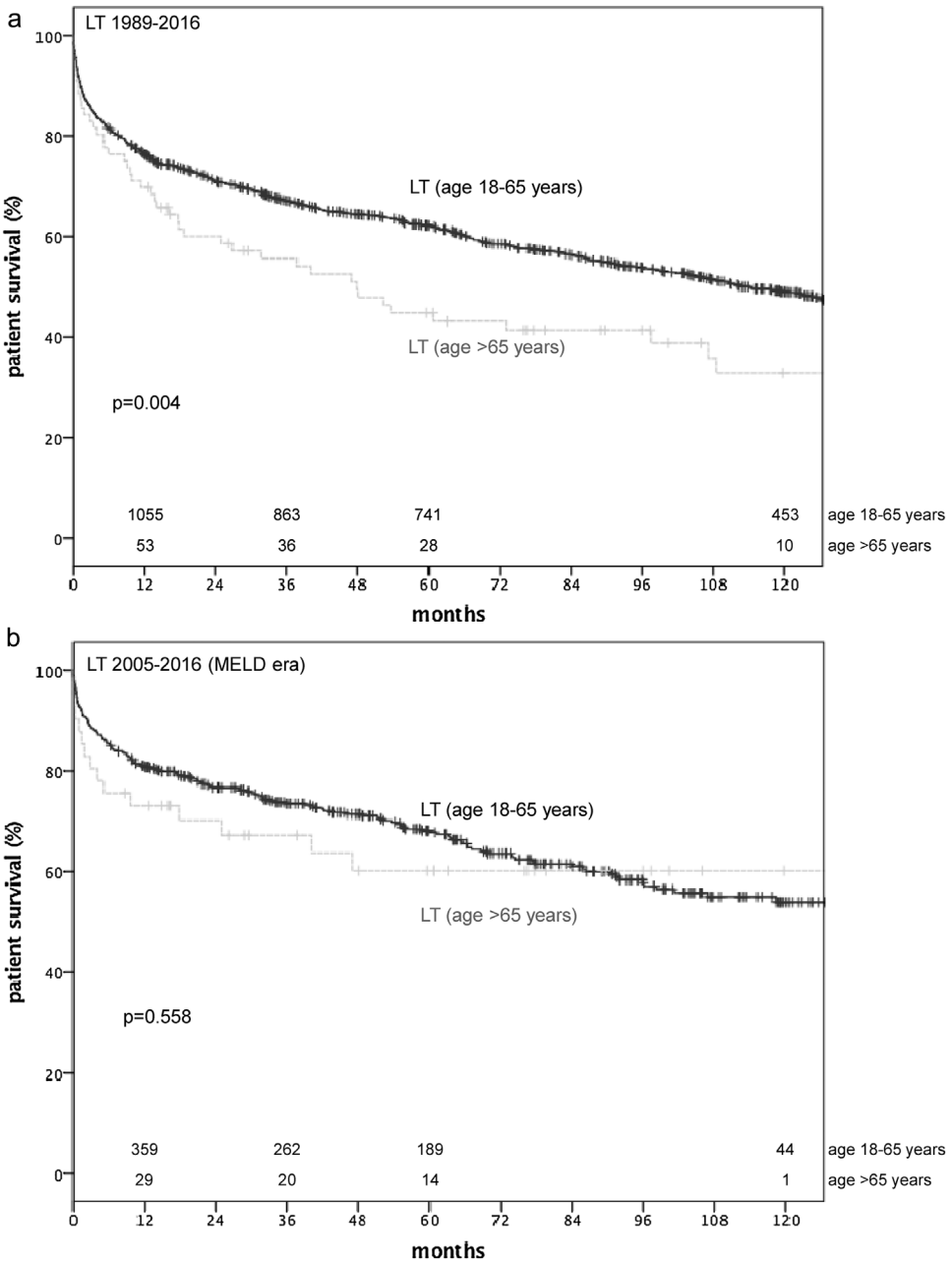

Fig. 2. Comparison of overall survival of two different age groups (group 1: age 18–65 years (black curve), group 2: age >65 years (grey dotted curve)) receiving liver transplantation in the time period between (a) 1989 and 2016 (whole observation period) and (b) 2005 and 2016 (MELD era).

the transplant center gained over the years, leading to improved perioperative patient care. Indeed, it has been reported that the experience of a transplant center strongly influences the postoperative patient- and graft survival [44,45]. In particular, surgical technique improved with increasing surgeons' experience, translating into reduced blood loss and decreased requirement of blood transfusion. Both, intraoperative blood loss and requirement of blood transfusion are independent risk factors for increased mortality after LT [46]. Furthermore, anaesthetic management changed in the last two decades aiming for low central venous pressures and substitution of coagulation factors during LT in order to reduce coagulopathy and blood loss [47–49]. In addition, monitoring serum levels of immunosuppressive drugs was routinely implemented in clinical follow ups, which allowed for adequate dosing and might have translated into better outcome after LT. Adequate immunosuppressive dosing is essential for reducing side effects such as rejection, infection or nephrotoxicity, all of which are associated with adverse long-term outcome [50]. However, careful patient selection remains to be of utmost importance, as for example the presence of pre-transplant coronary artery disease and arrhythmia are independent predictors of poor long-term outcomes in liver recipients ≥60 years of age [51]. Over the last years, awareness of factors influencing long-term outcomes increased and our pre-operative assessment and eligibility criteria for LT were regularly up-dated, possibly translating into improved survival.

The major limitations of our study are attributed to the small sample size of the elderly cohort that did not allow sufficient subgroup analysis, and the retrospective study design. Besides the limitations, reports on liver recipients older than 65 years old are important, as published articles about this age group are rare besides an increase of this population. Improved knowledge of this

patient cohort will allow us to better select and inform possible candidates for LT.

In conclusion, we could show that LT in patients >65 years old is safe and that this patient cohort has nowadays good long-term outcome, which is comparable to other age groups. Therefore, patients older than 65 years with end-stage liver disease should be considered for LT after careful evaluation.

Conflict of interest

None declared.

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