

OPEN

Impact of Recipient Age in Combined Liver-Kidney Transplantation: Caution Is Needed for Patients ≥ 70 Years

Burcin Ekser, MD, PhD,¹ William C. Goggins, MD,¹ Jonathan A. Fridell, MD,¹ Plamen Mihaylov, MD,¹ Richard S. Mangus, MD,¹ Andrew J. Lutz, MD,¹ Daiki Soma, MD, PhD,¹ Marwan S. Ghabril, MD,² Marco A. Lacerda, MD,² John A. Powelson, MD,¹ and Chandrashekhar A. Kubal, MD, PhD¹

Background. Elderly recipients (≥ 70 y) account for 2.6% of all liver transplants (LTs) in the United States and have similar outcomes as younger recipients. Although the rate of elderly recipients in combined liver-kidney transplant (CLKT) is similar, limited data are available on how elderly recipients perform after CLKT. **Methods.** We have previously shown excellent outcomes in CLKT using delayed kidney transplant (Indiana) Approach (mean kidney cold ischemia time = 53 ± 14 h). Between 2007 and 2018, 98 CLKTs were performed using the Indiana Approach at Indiana University (IU) and the data were retrospectively analyzed. Recipients were subgrouped based on their age: 18–45 (n=16), 46–59 (n=34), 60–69 (n=40), and ≥ 70 years (n=8). **Results.** Overall, more elderly patients received LT at IU (5.2%) when compared nationally (2.6%). The rate of elderly recipients in CLKT at IU was 8.2% (versus 2% Scientific Registry of Transplant Recipient). Recipient and donor characteristics were comparable between all age groups except recipient age and duration of dialysis. Patient survival at 1 and 3 years was similar among younger age groups, whereas patient survival was significantly lower in elderly recipients at 1 (60%) and 3 years (40%) ($P=0.0077$). Control analyses (replicating Scientific Registry of Transplant Recipient's survival stratification: 18–45, 46–64, ≥ 65 y) showed similar patient survival in all age groups. **Conclusions.** Although LT can be safely performed in elderly recipients, extreme caution is needed in CLKT due to the magnitude of operation.

(*Transplantation Direct* 2020;6: e563; doi: 10.1097/TXD.0000000000001011. Published online 28 May, 2020.)

In liver transplantation (LT), both recipients and donors are getting older. According to the recent data by the Scientific Registry of Transplant Recipients (SRTRs), the number of LT recipients who were ≥ 65 years almost tripled

from 2007 to 2017 (n=648 in 2007, n=1674 in 2017, 2.6-fold increase).¹ This increase was also reflected in the percentage of overall adult LT population. In 2007, while only 11% of all LT recipients were ≥ 65 years old, in 2017 it was 22.4% (100% increase).¹ In fact, the waiting list for LT mirrors the above picture. With improved diagnostics, better patient management, and newer and more efficient pharmacological agents, there are an increasing number of older patients with end-stage liver disease who have been benefitting and will continue to benefit from LT. According to the census.gov, the estimated percentage increase in population in the United States projects that older population ≥ 65 years will increase 48% by 2030 and 74% by 2050.² On the other hand, there is a projection that the size of mid-age population (45–64 y) will have a drop of 3.5% by 2030, and there will only be 13% increase by 2050 (Figure 1).

There are several single-center or SRTR reports analyzing the impact of recipient age in LT, especially in regard to elderly recipients who were ≥ 65 years old³ or ≥ 70 years old.^{4,7} A decade ago, a single-center report from the Mayo Clinic showed in a cohort of 42 patients that 5-year mortality and graft loss in elderly recipients (≥ 70 y) in LT were comparable with those in younger recipients (< 60 y).⁷ More recent reports with larger cohorts (SRTR analyses)^{4,5} showed that patient survival in elderly recipients (≥ 70 y) was significantly lower in an unadjusted analysis. However, Wilson et al⁵ reported

Received 15 April 2020.

Accepted 1 May 2020.

¹ Transplant Division, Department of Surgery, Indiana University School of Medicine, Indianapolis, IN.

² Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN.

The authors declare no funding or conflicts of interest.

Part of this paper was presented as an oral presentation at the American Transplant Congress 2019, Boston, MA.

B.E., W.C.G., and C.A.K. involved in study concept and design. B.E. involved in drafting the manuscript. All authors involved in acquisition, analysis, or interpretation of data and in critical revision of the manuscript for important intellectual content.

Correspondence: Burcin Ekser, MD, PhD, Transplant Division, Department of Surgery Indiana University School of Medicine, 550 University Blvd, Room 4601, Indianapolis, IN 46202. (bekser@iupui.edu).

Copyright © 2020 The Author(s). *Transplantation Direct*. Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001011

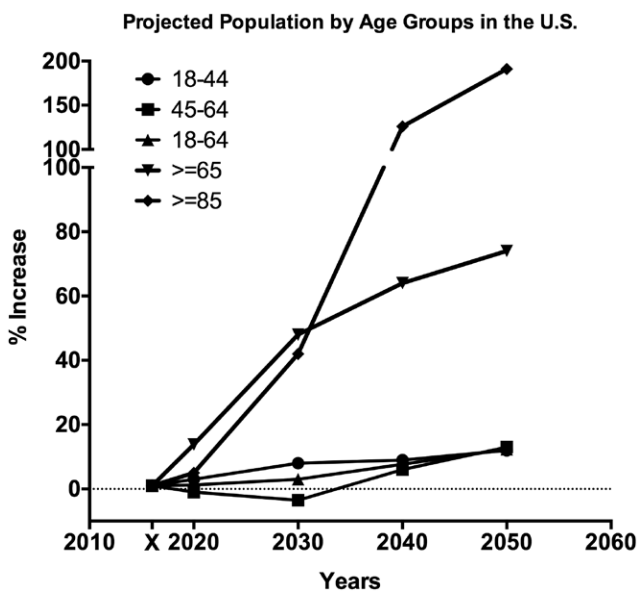


FIGURE 1. Projected percentage increase in population in the United States by 2050. X represents 2016, and all other y show percentage increase or decrease in national population compared with 2016. Eighteen to 44 age group will increase 2.8%, 7.7%, 9%, and 12%. Forty-five to 64 age group will increase -1%, -3.5%, 5.8%, and 13%. Age group 18-64 will increase 1.2%, 3%, 7.7%, and 12.3%. Age group ≥ 65 will increase 13.8%, 48%, 64%, and 74%. Age group ≥ 85 will increase 5%, 42%, 126%, and 191%. Census.gov: <https://www.census.gov/data/tables/2017/demo/popproj/2017-summary-tables.html>.

similar patient survival in elderly recipients with those who were 18-69 y old in an “adjusted” (1:1) case-match analysis.

Elderly recipients may carry a higher risk when it comes to the combined liver-kidney transplantation (CLKT, simultaneous liver-kidney transplantation) due to the magnitude of operation and higher chances of delayed graft function (DGF) of the transplanted kidney, which significantly correlates with patient’s mortality in CLKT.^{8,9} A recent report from Croome et al¹⁰ analyzed the SRTR data between 2002 and 2015 on patients undergoing CLKT who were ≥ 65 years ($n=677$) and <65 years ($n=4517$). The authors found that both older (≥ 65 y) and younger (<65 y) recipients have similar patient and graft survival. Recent discussions at national and international LT congresses in 2019 tried to identify the appropriate age cutoff for the CLKT. However, there are limited published data on elderly recipients (≥ 70 y) undergoing CLKT.¹¹ In the present study, we sought to identify the outcomes of elderly recipients undergoing CLKT using a homogenous cohort in a high-volume transplant center.

MATERIALS AND METHODS

Medical records of all patients who underwent CLKT between June 2007 to October 2018 at Indiana University Hospital were reviewed. Inclusion criteria for the data analysis included all adult (≥ 18 y old) transplant recipients undergoing CLKT, including kidney or liver retransplants. No exclusions were granted for intraoperative or perioperative mortality or graft loss, for nontransplant-related deaths, or for noncompliance. Retrospective review and analysis of data from the transplant center database was

approved by the Institutional Review Board of Indiana University School of Medicine.

Indications and Definitions

All CLKTs were performed using the Indiana Approach technique (see below) [9]. CLKTs performed using “simultaneous” liver-kidney transplantation before June 2007 were excluded to avoid the era effect and focus on a homogenous cohort of patients who received the CLKT under the same surgical technique and clinical experience in patient management. Recipient listing for CLKT was according to standard criteria and protocols as established by our center and United Network for Organ Sharing, which was recently updated in 2016.¹² Before 2016, patients who required CLKT were listed according to their eGFR <30 mL/min/1.73 m² calculated by the modification of diet in renal disease formula before transplant for chronic renal failure or their need for dialysis for >8 weeks, as proposed by United Network for Organ Sharing.^{13,14} DGF was defined as the need for dialysis within the first 7 days following kidney transplantation. Kidney graft failure was defined as removal of the graft or complete loss of graft function requiring retransplantation or permanent dialysis. Graft function was monitored clinically and by laboratory values (serum creatinine and eGFR).

Four different recipient age groups (18-45, 46-59, 60-69, and ≥ 70 y) were defined to study the real impact of recipient age. The SRTR data were used to compare the national outcomes with our center.^{10,15} In order to replicate the SRTR recipient age stratification (18-45, 46-64, and ≥ 65 y), a control analysis was ran using the 3 different age subgroups instead of 4 age subgroups.

Surgical Technique—Indiana Approach

Organ procurements (brain dead or donation after circulatory death [DCD] donors) were performed using standard surgical techniques and cold preservation.^{9,16-18} Details of the Indiana Approach have been reported previously.^{9,19-22} Briefly, to accommodate physiological needs for both liver and kidney allografts, LT is performed first while the kidney graft is placed on a hypothermic pulsatile perfusion machine. At our center, all deceased kidney allografts, regardless of their allocation as CLKT, kidney transplantation alone, or simultaneous pancreas and kidney transplant, are routinely maintained on continuous hypothermic pulsatile machine perfusion (Waters IGL perfusion machine) (Waters Medical Systems, Rochester, MN).¹⁸ Implantation of the kidney graft is usually delayed for 2 to 3 days post-LT which allows stabilization of LT patients’ hemodynamics and coagulopathy in the post-LT period, before implantation of the renal allograft. All recipients of CLKT are also supported by continuous venovenous hemodialysis initiated at the time of LT and continued during the intensive care unit until the kidney transplant is complete.

Immunosuppressive Therapy and Infection Prophylaxis

Details of the immunosuppressive regimen and prophylaxis protocol in CLKT recipients have been reported previously.^{9,19,21} Briefly, induction therapy included rabbit antithymocyte globulin (rATG) (2 mg/kg for 3 doses), and anti-CD20 monoclonal antibody (Rituximab, single dose 1.5 mg/m², maximum 300 mg), only in case of increased immunologic risk. rATG was administered before the implantation

of the kidney allograft on postoperative day 1 or 2, depending on recipient's hemodynamic stability. Almost all elderly recipients ≥ 70 years were excluded from the rATG induction, and they only received methylprednisolone 500 mg induction for 3 days and discontinued completely. For recipients 18–69 years old, a methylprednisolone bolus was administered as premedication for each of the 3 rATG infusions and then was discontinued completely. Maintenance immunosuppressive therapy included tacrolimus (target trough levels of 7–10 ng/dL for the first 3 mo posttransplant, and 6–8 ng/mL, thereafter) and mycophenolate mofetil (1000 mg BID).

Statistical Analysis and End Points

The primary end point was patient survival after CLKT in all age groups. The data were summarized using means with SDs, or medians with interquartile ranges for continuous variables, and percentages for discrete variables. Continuous variables were analyzed using Wilcoxon-Mann-Whitney test. For discrete variables, the ANOVA analysis was performed unless the event number for the given group was ≤ 5 , in which case Fisher exact test was performed. Patient survival probability was estimated using the Kaplan-Meier method, and differences in the curves were analyzed using a log-rank test. All statistical calculations were performed by IBM SPSS MacOs version (v1.0.0.701, NY). Images were created using GraphPad Prism 8 for MAC OS X (La Jolla, CA). A P value of <0.05 was considered statistically significant.

RESULTS

Donor and recipient demographics were comparable within all groups including kidney donor profile index score, the ratio of extended criteria donor and DCD kidneys, previous liver and kidney transplants, model for end-stage liver disease (MELD) score, and donor-model for end-stage liver disease score, except recipient age, as expected. However, elderly patients stayed longer on dialysis (median: 405 d) compared with younger age groups ($P < 0.05$) (Table 1). All CLKTs were performed using the Indiana Approach; therefore, mean kidney cold ischemia time was comparable in all groups (≈ 53 h, $P =$ not significant). Mean liver cold ischemia time was also similar and was kept below 6 hours in all age groups (Table 2).

Although DGF of transplanted kidneys was much lower compared with literature (overall 4% in our series),^{23,24} it was 25% in elderly (≥ 70 y) patients and significantly higher compared with younger recipients ($P = 0.017$). Intensive care unit stay and overall hospital stay were significantly longer in elderly recipients compared with younger recipients (Table 2). In group 4 (Table 2), there were 2 early deaths (2/8, 25%) within 7 days post-CLKT and it was significantly higher compared with younger recipients ($P < 0.001$). Both recipients died on postoperative day 5. In the first early death (72-y-old male), the transplanted kidney never worked and had primary nonfunction. He died due to stress cardiomyopathy despite attempted ECMO support. In the second early death (72-y-old female), the patient developed an acute respiratory distress syndrome and she died with functioning liver and kidney grafts. Causes of death in all age groups are reported in Table 3. The main cause of death was cardiovascular (6 cases in age groups 46 and higher). Though, we believe cardiovascular reasons would be even higher because 8 deaths

were reported as “unknown” as they happened at home with no known cause. In the youngest age group (18–45 y), we observed a noncompliance issue in a 38-year-old recipient and he eventually died with rejection and damage to the liver due to alcohol consumption. Although the percentage of deaths was comparable between groups within 1 year posttransplant (Table 2), at 3 years, Kaplan-Meier survival was significantly lower in elderly patients ≥ 70 years (log-rank test $P = 0.0077$) (Figure 2A).

Control Analyses Using the SRTR Age Stratification

We ran a separate control analyses (1) to replicate SRTR's recipient age stratification and (2) also to compare our cohort with the published literature. For this reason, Kaplan-Meier patient survival curves were calculated based on 3 different age groups (18–45, 46–64, and ≥ 65 y).^{1,10} We observed that patient survival at 3 years post-CLKT was comparable in all age groups ($P = 0.2420$) (Figure 2B), as it was observed by Croome et al¹⁰ in their SRTR analysis with CLKT.

DISCUSSION

The face of LT has changed in the last decades. The number of LTs performed each year in the United States and in Europe increased together with improved patient survival post-LT.²⁵ The potential pool of transplantable livers has enlarged due to a growing number of DCD LT which is expanded by using extended criteria DCD donors that have comparable outcomes to standard brain dead donors.²⁶ As a result of improved outcomes, LT is currently being offered to older and sicker patients. With the aging population, it is inevitable that patients with end-stage liver disease and those undergoing LT will get older. In fact, SRTR data showed a 100% increase of the percentage of LT recipients who were ≥ 65 years from 2007 to 2017.¹ As indicated by the census.gov data, we have to face even a worse situation within 30 years by 2050 (Figure 1).² It is also well-known that there is a substantial loss of nephrons in healthy human kidneys with aging.²⁷ Thus, the elderly population is more susceptible to kidney failure and elderly patients with end-stage liver disease will face higher chances of chronic kidney disease and therefore will require more CLKT.

What Is the Age Cutoff for CLKT?

Debates on the identification of age cutoff for LT and especially CLKT have been ongoing. Several studies reported mix outcomes in elderly recipients undergoing LT.⁴ Although recent SRTR data showed that LT can be safely performed in elderly recipients ≥ 70 years with comparable outcomes as in younger recipients (18–69 y),⁵ patients needing CLKT tend to be sicker than those needing LT alone and carry higher risk. Another recent SRTR analysis studied the impact of recipient age in CLKTs.¹⁰ This SRTR study spanned between 2002 and 2015 with 573 patients in the age group 65 and 69 years and 104 patients in the age group ≥ 70 years,¹⁰ but there was no detailed analysis for the age group ≥ 70 years. The authors came up with a scoring system based on multivariate analysis outcomes which indicated (1) MELD score (per 5 points increments), (2) recipient age ≥ 70 years, and (3) being on the ventilator at the time of CLKT significantly impacted the patient survival negatively. In fact, the authors stated that “using the scoring system,” CLKT should be avoided in patients ≥ 65 years of age on

TABLE 1.
Donor and recipient demographics in combined liver-kidney transplantation using the Indiana Approach

	Total (n = 98)	Group 1 (age 18–45) (n = 16)	Group 2 (age 46–59) (n = 34)	Group 3 (age 60–69) (n = 40)	Group 4 (age ≥70) (n = 8)	P
Recipient demographics						
Age (mean ± SD), y	57 ± 12	35 ± 9	55 ± 4	65 ± 3	73 ± 3	<0.001
Gender (n, %)						n.s.
Male	58, 59%	9, 56%	21, 62%	24, 60%	4, 50%	
Female	40, 41%	7, 44%	13, 38%	16, 40%	4, 50%	
Race (n, %)						n.s.
White	85, 87%	14, 88%	31, 91%	33, 83%	7, 88%	
African American	7, 7%	1, 6%	2, 6%	4, 10%	0, 0%	
Other	6, 6%	1, 6%	1, 3%	3, 7%	1, 12%	
Blood type (n, %)						n.s.
A	57, 45%	5, 32%	14, 41%	15, 38%	2, 25%	
B	14, 10%	2, 12%	6, 18%	6, 14%	2, 25%	
AB	5, 4%	1, 6%	1, 3%	0, 0%	0, 0%	
O	54, 41%	8, 50%	13, 38%	19, 48%	4, 50%	
Body mass index (mean ± SD), kg/m ²	27 ± 5	29 ± 5	27 ± 5	27 ± 5	26 ± 3	
Primary indication for transplant (n, %)						n.s.
ETOH	19, 19%	4, 25%	10, 29%	5, 13%	0, 0%	
Hepatitis C	24, 24%	0, 0%	9, 26%	15, 38%	0, 0%	
Autoimmune liver disease	12, 12%	3, 19%	4, 12%	2, 3%	3, 38%	
NASH	22, 22%	0, 0%	5, 15%	13, 33%	4, 50%	
Other	21, 21%	9, 56%	6, 18%	5, 13%	1, 12%	
Hepatitis C positivity (n, %)	32, 32%	1, 6%	13, 38%	18, 45%	0, 0%	
All diabetes (n, %)	34, 35%	5, 32%	11, 32%	15, 38%	3, 38%	n.s.
Cytomegalovirus status (n, %)						n.s.
D–/R–	12, 12%	3, 19%	7, 20%	1, 3%	1, 12%	
D–/R+	24, 24%	3, 19%	8, 24%	10, 25%	3, 38%	
D+/R–	19, 19%	2, 12%	7, 20%	8, 20%	2, 25%	
D+/R+	43, 43%	8, 50%	12, 36%	21, 52%	2, 25%	
MELD (mean ± SD)	28 ± 7	30 ± 8	28 ± 8	27 ± 7	26 ± 6	n.s.
D-MELD (mean ± SD)	960 ± 481	846 ± 465	1033 ± 515	956 ± 487	905 ± 339	n.s.
Previous kidney transplant (n, %)	5, 5%	4, 25%	0, 0%	1, 3%	0, 0%	n.s.
Previous liver transplant (n, %)	7, 7%	2, 13%	1, 3%	4, 10%	0, 0%	n.s.
Dialysis before transplant (%)	63%	75%	62%	55%	50%	n.s.
Duration of dialysis before transplant (median), d	180	180	360	360	405	<0.05
Duration of eGFR <30 mL/min/1.73 m ² for patients who were not on dialysis (median), d	90	90	105	105	90	n.s.
Donor demographics						
Age (mean ± SD), y	34 ± 13	28 ± 11	35 ± 12	35 ± 14	35 ± 12	n.s.
Gender (n, %)						n.s.
Male	60, 60%	10, 62%	20, 59%	24, 60%	6, 75%	
Female	38, 40%	6, 38%	14, 41%	16, 40%	2, 25%	
Body mass index (mean ± SD), kg/m ²	27 ± 6	24 ± 5	27 ± 7	27 ± 5	29 ± 6	n.s.
Cause of death (n, %)						n.s.
Stroke	19, 19%	3, 19%	6, 18%	8, 20%	2, 25%	
Trauma	46, 47%	10, 62%	13, 38%	19, 48%	4, 50%	
Anoxia/Other	33, 34%	3, 19%	15, 44%	13, 32%	2, 25%	
Donor hepatitis C positivity (n, %)	5, 5%	0, 0%	1, 3%	4, 10%	0, 0%	n.s.
Extended criteria donor kidneys (n, %)	10, 10%	2, 12%	1, 3%	7, 18%	1, 12%	n.s.
Donation after circulatory death kidneys (n, %)	7, 7%	0, 0%	3, 10%	3, 7%	1, 12%	n.s.
Donor KDPI (mean ± SD) (range)	33 ± 23 (1–92)	24 ± 20 (3–80)	35 ± 23 (1–79)	34 ± 24 (1–92)	30 ± 20 (6–71)	n.s.

D, donor; D-MELD, donor-model for end-stage liver disease; eGFR, estimated glomerular filtration rate; ETOH, alcoholic liver disease; KDPI, kidney donor profile index; MELD, model for end-stage liver disease; n.s., not significant; NASH, nonalcoholic steatohepatitis; R, recipient.

a mechanical ventilation before CLKT and in patients ≥70 years of age with a MELD score ≥30.¹⁰ However, the overall message was that outcomes of CLKT in patients ≥65 years compared with <65 years and also compared with ≥65 years receiving LT alone were similar.

We believe that this was due to the number of CLKT recipients between 65 and 69 y which made 85% of the studied SRTR population (573/677, 85%, ≥65 y).¹⁰ Our control analyses with the SRTR age stratification showed the similar patient survival in CLKT among age groups

TABLE 2.
Outcomes in combined liver-kidney transplantation

Transplant outcomes	Total (n=98)	Group 1 (age 18–45) (n=16)	Group 2 (age 46–59) (n=34)	Group 3 (age 60–69) (n=40)	Group 4 (age ≥70) (n=8)	P
Cold ischemia time (h) (mean ± SD)						
Kidney	53 ± 14	54 ± 14	50 ± 16	54 ± 12	59 ± 7	n.s.
Liver	5.6 ± 1.3	6.0 ± 1.7	5.6 ± 1.4	5.5 ± 0.9	5.4 ± 1.5	n.s.
Warm ischemia time (min) (mean ± SD)						
Kidney	38 ± 9	37 ± 7	39 ± 11	38 ± 8	38 ± 7	n.s.
Liver	20 ± 4	21 ± 4	20 ± 4	19 ± 5	22 ± 4	n.s.
Delayed graft function of renal grafts (n, %)	4, 4%	0, 0%	1, 3%	1, 3%	2, 25%	0.017
Intensive care unit stay (mean ± SD) (range) (median), d ^a	14 ± 21 (2–92) (6.5)	21 ± 35 (2–134) (7.5)	13 ± 17 (2–92) (5.5)	10 ± 14 (2–70) (5)	20 ± 23 (6–73) (12.5)	<0.001
Hospital stay (mean ± SD) (median), d ^a	35 ± 48 (6–399) (21.5)	37 ± 40 (6–151) (22.5)	32 ± 33 (8–146) (21)	36 ± 63 (7–399) (20)	36 ± 29 (6–92) (30.5)	<0.001
Death within 7 d posttransplantation (n, %)	2, 2%	0, 0%	0, 0%	0, 0%	2, 25%	<0.001
Death within 90 d posttransplantation (n, %)	7, 7%	2, 13%	3, 10%	0, 0%	2, 25%	0.052
Death within 1 y posttransplantation (n, %)	13, 14%	3, 19%	3, 10%	4, 10%	3, 38%	n.s.

^aMedian values were considered for statistical calculation.
n.s., not significant.

TABLE 3.
Causes of death

	Total (n=98)	Group 1 (age 18–45) (n=16)	Group 2 (age 46–59) (n=34)	Group 3 (age 60–69) (n=40)	Group 4 (age ≥70) (n=8)
Cardiovascular	6		2	3	1
Acute respiratory distress syndrome	1				1
Cancer	1			1	
Noncompliance	1	1			
Liver failure (including primary nonfailure)	2	1			1
Other/unknown	8	1	1	5	1
Total deaths throughout follow-up	19	3	3	9	4

18–45, 46–64, and ≥65 years (Figure 2B). The similar trend in the number of patients between 65 and 69 years (20/28, 71%, ≥65 y) was also seen in our cohort. Therefore, we believe if the recipient age stratification is kept as <65 and ≥65 years, good outcomes in the increased number of CLKT between 65 and 69 years will absorb the unfavorable outcomes in elderly recipients ≥70 years.

To understand the true impact of recipient age in CLKT in patients ≥70 years, we grouped recipients in 4 different age groups. Elderly recipients (≥70 y) showed the worse patient survival at 3 years following CLKT (Figure 2). Although circulatory source of mortality was expected, we observed only 1 death from cardiovascular complications in patients ≥70 years. Moreover, of 6 cardiovascular deaths seen in all recipients, 3 of them were in the age group 60–69 years (Table 3). Although 2 early deaths (within a wk post-CLKT) significantly impacted the survival rate of patients ≥70 years (2/8, 25%), it was still better than the SRTR data, which shown 50% higher mortality among recipients ≥70 years of age with a hazard ratio of 1.6.¹⁰

Limitations

Our study has some limitations. First of all, it is a retrospective cohort study. Although the percentage of recipients ≥70 years in CLKT was 4-fold more compared with the SRTR (8.2% at our center versus 2% SRTR), the total

number was only 8 patients. Considering that the SRTR had only 96 CLKT recipients who were ≥70 years in 12 years (2007–2018, same study period as the current study), our case series makes up 8.3% of the SRTR cohort. The technique for CLKT was the Indiana Approach which has been adopted by some US and European centers most recently.^{28,29} Overall surgical technique (Indiana Approach), immunosuppressive regimen, and patient management were similar for the studied cohort, however with time; we probably became more adept in managing sicker recipients. Although percentage of patients on dialysis before CLKT was similar among all age groups, recovery of native renal function following CLKT³⁰ could be a factor for better outcomes especially in younger recipients with better preserved nephron mass.²⁷ Moreover, the liver allocation system was changed from MELD 15 to Share 35 and most recently with mandatory CLKT (simultaneous liver-kidney transplantation) policy,¹² impacting the allocation of CLKT throughout the study period as well. Lastly, we did not include the frailty scale of recipients in the outcomes due to the 12-year study cohort.

In conclusion, we believe that our study plays a significant role in the ongoing discussions on the decision of age cutoff for CLKT and how the true impact of recipient age should be studied based on age groups. Although LT alone can be safely performed in elderly recipients ≥70 years, caution is needed in CLKT due to the magnitude of operation

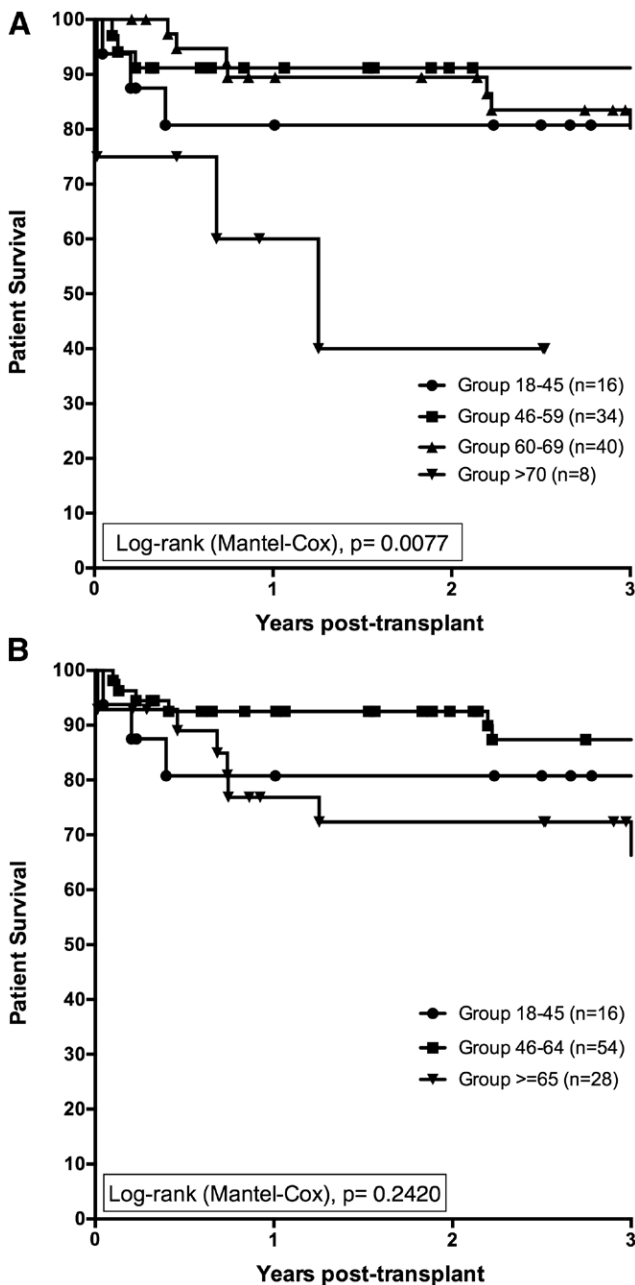


FIGURE 2. Patient survival curves. A, Kaplan-Meier patient survival in combined liver-kidney transplantation based on recipient age. B, Kaplan-Meier patient survival in combined liver-kidney transplantation based on the Scientific Registry of Transplant Recipient's recipient age stratification.

and expected inferior outcomes, despite delayed kidney transplantation in CLKT (Indiana Approach) which was shown to offer excellent patient survival.^{9,19-22,28,29} Further studies with larger cohorts are needed to determine the true age cutoff for CLKT and what the future will be since we cannot ignore the aging population in LT.

ACKNOWLEDGMENTS

Burcin Ekser, MD, PhD was an invited speaker on the topic of combined liver-kidney transplantation at the American Transplant Congress 2017.

REFERENCES

- Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2017 Annual Data Report: liver. *Am J Transplant.* 2019;19(Suppl 2):184-283.
- United States Census Bureau. 2017 *National Population Projections Tables: Main Series.* 2017. Available at <https://www.census.gov/data/tables/2017/demo/popproj/2017-summary-tables.html>. Accessed June 12, 2019.
- Kollmann D, Maschke S, Rasoul-Rockenschaub S, et al. Outcome after liver transplantation in elderly recipients (>65 years) - a single-center retrospective analysis. *Dig Liver Dis.* 2018;50:1049-1055.
- Su F, Yu L, Berry K, et al. Aging of liver transplant registrants and recipients: trends and impact on waitlist outcomes, post-transplantation outcomes, and transplant-related survival benefit. *Gastroenterology.* 2016;150(2):441-453.e6; quiz e16.
- Wilson GC, Quillin RC 3rd, Wima K, et al. Is liver transplantation safe and effective in elderly (≥ 70 years) recipients? A case-controlled analysis. *HPB (Oxford).* 2014;16:1088-1094.
- Asrani SK, Saracino G, O'Leary JG, et al. Recipient characteristics and morbidity and mortality after liver transplantation. *J Hepatol.* 2018;69:43-50.
- Aduen JF, Sujay B, Dickson RC, et al. Outcomes after liver transplant in patients aged 70 years or older compared with those younger than 60 years. *Mayo Clin Proc.* 2009;84:973-978.
- Hibi T, Sageshima J, Molina E, et al. Predisposing factors of diminished survival in simultaneous liver/kidney transplantation. *Am J Transplant.* 2012;12:2966-2973.
- Ekser B, Mangus RS, Fridell W, et al. A novel approach in combined liver and kidney transplantation with long-term outcomes. *Ann Surg.* 2017;265:1000-1008.
- Croome KP, Lee DD, Burns JM, et al. Simultaneous liver and kidney transplantation in elderly patients: outcomes and validation of a clinical risk score for patient selection. *Ann Hepatol.* 2016;15:870-880.
- Shekhtman G, Huang E, Danovitch GM, et al. Combined dual-kidney liver transplantation in the United States: a review of United Network for Organ Sharing/Organ Procurement and Transplantation Network Data between 2002 and 2012. *Liver Transpl.* 2018;24:1570-1577.
- Formica RN, Aeder M, Boyle G, et al. Simultaneous liver-kidney allocation policy: a proposal to optimize appropriate utilization of scarce resources. *Am J Transplant.* 2016;16:758-766.
- Nadim MK, Sung RS, Davis CL, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant.* 2012;12:2901-2908.
- Feng S, Trotter JF. Can we stop waiting for godot? Establishing selection criteria for simultaneous liver-kidney transplantation. *Am J Transplant.* 2012;12:2869-2870.
- UNOS (United Network for Organ Sharing). Available at <http://www.unos.org>. Accessed June 26, 2019.
- Mangus RS, Lutz AJ, Fridell JA, et al. Minimal improvement in glomerular filtration rate in the first year after liver transplantation. *Transplantation.* 2015;99:1855-1861.
- Kubal C, Mangus R, Fridell J, et al. Optimization of perioperative conditions to prevent ischemic cholangiopathy in donation after circulatory death donor liver transplantation. *Transplantation.* 2016;100:1699-1704.
- Shah AP, Milgrom DP, Mangus RS, et al. Comparison of pulsatile perfusion and cold storage for paired kidney allografts. *Transplantation.* 2008;86:1006-1009.
- Ekser B, Mangus RS, Kubal CA, et al. Excellent outcomes in combined liver-kidney transplantation: impact of kidney donor profile index and delayed kidney transplantation. *Liver Transpl.* 2018;24:222-232.
- Ekser B, Mangus RS, Kubal CA, et al. Graft quality matters: impact of KDPI and delayed kidney transplantation in combined liver-kidney transplantation. *Clin Transplant.* 2017. [Epub ahead of print].
- Ekser B, Kubal CA, Fridell JA, et al. Lack of benefit and potential harm of induction therapy in simultaneous liver-kidney transplants. *Liver Transpl.* 2019;25:667-668.
- Ekser B, Chen AM, Kubal CA, et al. Delayed kidney transplantation after 83 hours of cold ischemia time in combined liver-kidney transplant. *Transplantation.* 2019;103:e382-e383.
- Weeks SR, Luo X, Haugen CE, et al. Delayed graft function in simultaneous liver kidney transplantation. *Transplantation.* 2020;104:542-550.
- Ekser B, Contreras AG, Andraus W, et al. Current status of combined liver-kidney transplantation. *Int J Surg.* 2020. [Epub ahead of print].

25. Durand F, Levitsky J, Cauchy F, et al. Age and liver transplantation. *J Hepatol*. 2019;70:745–758.
26. Mihaylov P, Mangus R, Ekser B, et al. Expanding the donor pool with the use of extended criteria donation after circulatory death livers. *Liver Transpl*. 2019;25:1198–1208.
27. Denic A, Lieske JC, Chakkera HA, et al. The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol*. 2017;28:313–320.
28. Lauterio A, De Carlis R, Di Sandro S, et al. Delayed kidney transplantation in combined liver-kidney transplantation for polycystic liver and kidney disease. *Transpl Int*. 2019;32:1336–1338.
29. Lunsford KE, Agopian VG, Yi SG, et al. Delayed implantation of pumped kidneys decreases renal allograft futility in combined liver-kidney transplantation. *Transplantation*. 2019. [Epub ahead of print].
30. Levitsky J, Baker T, Ahya SN, et al. Outcomes and native renal recovery following simultaneous liver-kidney transplantation. *Am J Transplant*. 2012;12:2949–2957.