

Outcome of kidney transplantation from senior deceased donors: a single centre study

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Summary

BACKGROUND: Addressing the current demographic development, the efficacy and safety of kidney transplantations from very senior donors needs to be carefully evaluated. The aim of this study was to analyse patient and graft outcomes of kidney allograft recipients stratified by donor age.

METHODS: We retrospectively investigated $n = 491$ patients from a prospective, observational renal transplant cohort. Patients with kidneys from very old donors ($n = 75$, aged >70 years), elderly donors ($n = 158$, between 60–70 years), and regular donors ($n = 258$, aged <60 years) were investigated. The primary outcome was death-censored graft survival within the predefined donor age groups.

RESULTS: Overall, $n = 57$ death-censored graft losses occurred. Graft loss was proportionally highest in the very old donor group ($n = 11/75$), but this did not reach statistical significance when compared to the elderly ($14/158$) and regular donor groups ($32/258$); ($p = 0.37$). Kaplan-Meier analysis demonstrated that 3-year/5-year death-censored graft survival in the very old donor group was 96%/86% and did not differ from the other age groups ($p = 0.44$). Median estimated glomerular filtration rate (eGFR), calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (in ml/min/1.73 m² of body surface) 12 months post-transplant did not differ between the elderly donor and very old donor groups ($p = 0.53$). However, patients who received regular donor kidneys had higher median eGFR compared to recipients in both the elderly and very old donor groups ($p < 0.0001$). During follow-up, 31% of patients developed at least one acute rejection episode. Time-to-event analysis demonstrated no difference in occurrence of any acute rejection event across all three groups ($p = 0.11$).

CONCLUSIONS: This study demonstrates that kidney transplantation from carefully selected very old donors seems a valid option with reasonable short- and mid-term outcomes.

Introduction

Kidney transplantation is the therapy of choice for many patients with end stage renal disease and has evolved

rapidly during the past few decades. However, due to the progressively increasing gap between the number of available organs and the number of patients on kidney transplantation wait lists (in Switzerland as well as in other countries) strategies to expand the donor pool – such as using living donors, ABO-incompatible transplantation, donation after cardiac death, and extending the age limit for deceased kidney donors – have been developed [1, 2]. In Switzerland, in 2022, there were 1041 patients with end stage renal disease registered on the waiting list for a kidney transplantation: 231 kidney transplantations were performed from deceased donors, of which 91 organs were from donation after cardiac death; and 111 kidney transplantations were performed from living kidney donors (data received from <https://www.swisstransplant.org>). In 2002, the United Network for Organ Sharing (UNOS) proposed increasing the kidney donor pool by considering kidneys from expanded criteria donors [3], even though previous studies addressing the use of expanded criteria donors (in general defined as aged ≥ 60 years or 50–59 years old with comorbidities) indicated that the discard rate of these kidneys is high [4]. During the past decade in the United States, $>40\%$ of expanded criteria donor kidneys were not transplanted [4]. A single centre study performed in a transplant centre in Europe investigated the outcomes of performed transplantations and kidney discard rate (KDR) of potential expanded criteria donors, stratified by age groups (50–59 years old, 60–69 years old, 70–79 years old, and ≥ 80 years old) between 2003 and 2013 [5]. The KDRs of the three younger age groupings were similar and ranged between 15.4% and 20.1%, whereas the KDR of potential octogenarian donors was 48.2% [5]. In a Swiss national cohort study, Kuhn et al. recently reported that the KDR at all Swiss transplant centres was about 20% [6]. They further pointed out that donor candidates who were refused were older, had a higher prevalence of cardiac death, heart disease, hypertension, diabetes mellitus, acute kidney injury, and preexisting kidney disease compared to donor candidates whose kidneys were transplanted [6]. Furthermore, the long-term survival of expanded criteria donor kidneys is about 10–40% lower than those of younger donors [7, 8]. Nevertheless, large studies have shown that transplanting allografts from marginal donors is preferable to remaining on renal replace-

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ment therapy [7, 9]. To date, reports of kidney transplantations from donors aged 70 years and older, with long-term follow-up, are limited [6, 10–15].

Taking the changing donor epidemiology and current demographic development into account, the efficacy and safety of kidney transplantations from very senior donors needs to be carefully evaluated. To address these questions, this study aimed to retrospectively analyse patient and graft outcomes of kidney allograft recipients from very old donors (aged >70 years old) compared to elderly (between 60–70 years old) and younger donors (<60 years old).

Materials and methods

Patient population

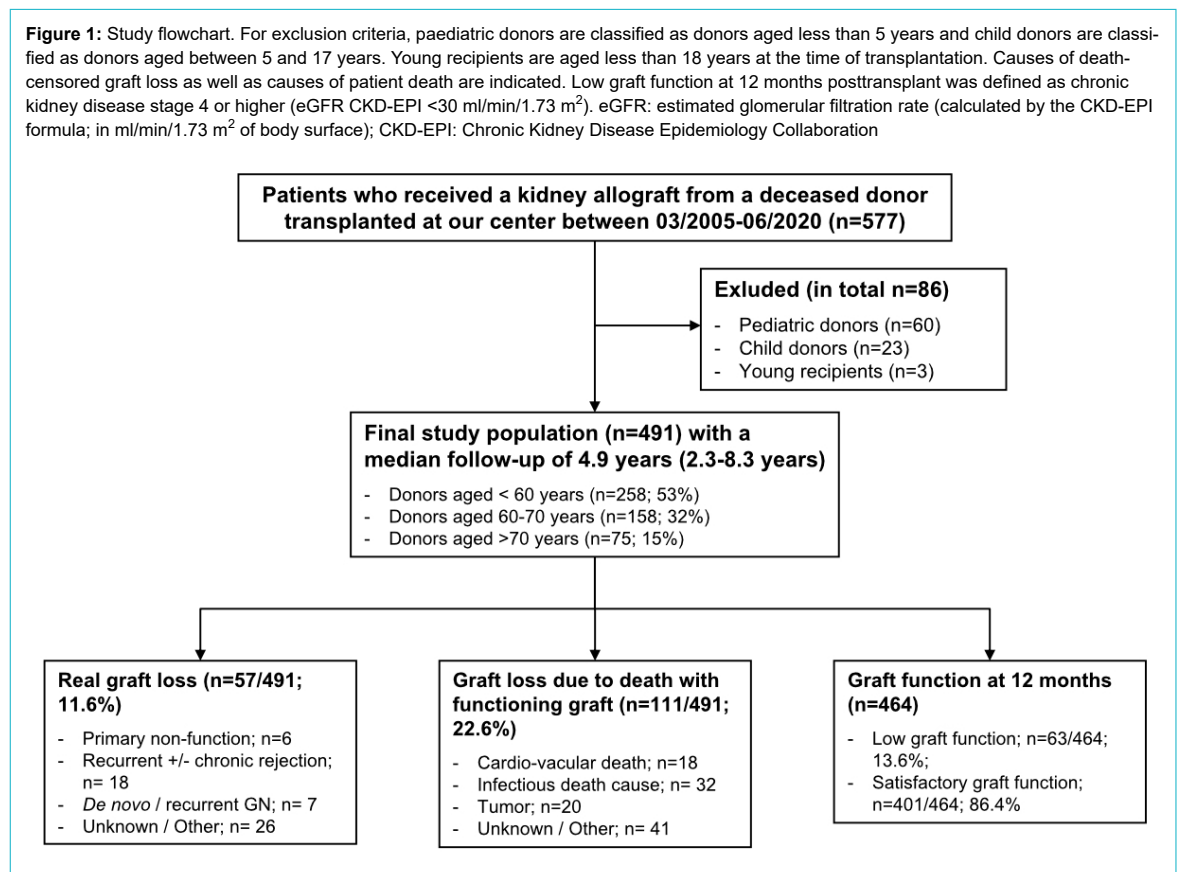
This retrospective study was performed with the approval of the ethics committee of Northwestern and Central Switzerland (www.eknz.ch; project-ID 2021-01475). Patients from a prospective, observational renal transplant cohort, who were transplanted at our centre between March 2005 and June 2020 were selected for the study. We took advantage of a cohort that had prospective risk stratification, with an adaptation of the induction regimen, and received contemporary maintenance immunosuppression consisting of tacrolimus (Tac) and mycophenolate acid (MPA). Inclusion criteria were a kidney transplantation from a deceased adult donor and a minimum follow-up period of 1-year posttransplant. Exclusion criteria were living donor transplantations, combined transplantations, and donor/recipients aged <18 years at the time of transplantation. Briefly, between March 2005 and June 2020, 577 patients received a kidney allograft from a deceased donor at

our centre. Of those, n = 60 were from paediatric donors (aged less than 5 years), n = 23 were from child donors (aged between 5 and 17 years), and n = 3 recipients were under 18 years of age at the time of transplantation, and were therefore excluded. The final study population consisted of n = 491 adult recipients of deceased donor kidney transplantations. Outcomes were evaluated until September 13, 2021 (figure 1).

Posttransplant management

Initial immunosuppression was selected based on the pretransplant risk stratification policy used at our centre; i.e., the presence or absence of pretransplant donor-specific human leukocyte antigen (HLA)-antibodies determined by single-antigen flow bead (SAFB) technology on a Luminex platform (LABScreen single antigen, OneLambda, West Hills CA, USA) as described previously [16–19]. Briefly, recipients of an allograft without pretransplant donor-specific HLA-antibodies received induction therapy with basiliximab (Simulect, Novartis) and triple therapy with Tac-MPA-prednisone. In the case of a rejection-free clinical course, immunosuppression was modified and reduced within the first six months to establish a dual Tac-MPA therapy in the long-term. Target trough levels of tacrolimus were 10–12 ng/ml for the first month, 8–10 ng/ml for months two to three, and around 6 ng/ml thereafter. Recipients with pretransplant donor-specific HLA-antibodies received an induction therapy with polyclonal anti T-cell globulin (Grafalon) prior to reperfusion of the allograft and on day 1–4, or anti-thymocyte globulin (Thymoglobuline, Sanofi-Aventis) for 4 days, as well as intravenous immunoglobulins [16, 17]. Maintenance immuno-

Figure 1: Study flowchart. For exclusion criteria, paediatric donors are classified as donors aged less than 5 years and child donors are classified as donors aged between 5 and 17 years. Young recipients are aged less than 18 years at the time of transplantation. Causes of death-censored graft loss as well as causes of patient death are indicated. Low graft function at 12 months posttransplant was defined as chronic kidney disease stage 4 or higher (eGFR CKD-EPI <30 ml/min/1.73 m²). eGFR: estimated glomerular filtration rate (calculated by the CKD-EPI formula; in ml/min/1.73 m² of body surface); CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration



suppression and target trough levels were the same as for renal allograft recipients without pretransplant donor-specific HLA-antibodies. Steroids were started at 0.5 mg/kg of bodyweight and tapered biweekly to 0.1 mg/kg body weight by month three posttransplant, and maintained at this level. All biopsy-proven acute rejection episodes were treated according to the histological phenotype and severity, including borderline rejection, as described in earlier studies [17, 18].

Investigated parameters and outcomes

Recipient characteristics and outcomes were collected from patient charts and stored in a research database. Donor derived factors were retrieved from the SOAS database (Swiss Organ Allocating System). Baseline values such as: recipient age, sex, history of kidney transplantation, dialysis status, time of renal replacement therapy before transplantation, cold ischemia time, serum creatinine and eGFR (CKD-EPI), as well as number of rejection episodes and rejection phenotypes, were extracted from the research database. Kidney Donor Risk Index (KDRI) combines a variety of donor factors to summarise the risk of graft failure after kidney transplantation into a single number, including donor age (<https://optn.transplant.hrsa.gov>). Thus, from the SOAS database, donor age, sex, and further values to calculate the Kidney Donor Risk Index and cause of donor death, were extracted. Donor age was categorically grouped into regular donors (age <60 years), elderly donors (age between 60 and 70 years), and very old donors (age >70 years).

The primary outcome was to investigate death-censored graft survival within the predefined age groups. Secondary outcomes were patient survival and graft outcome (i.e., evaluation of graft function at one and five years post-transplant). Furthermore, we analysed the incidence of (sub)clinical allograft rejection for the predefined donor age groups during follow-up. In addition, we investigated independent predictors of graft loss.

Renal allograft biopsies

From 2005 until September 2017, surveillance biopsies were routinely performed at 3 and 6 months posttransplant. Due to a change of policy at our centre, from September 2017 onwards no surveillance biopsies were performed anymore at 3/6 months posttransplant. Clinically indicated allograft biopsies were performed when serum creatinine increased by more than 20% from baseline, or in cases of increasing proteinuria or glomerular haematuria. Histology work-up followed standard procedures (of 2 biopsy cores obtained with a 16-gauge needle) including evaluation by light microscopy, immunofluorescence (staining for immunoglobulins, complement including C4d, and HLA-DR), and immunohistochemistry (staining for SV40 large T-antigen). All biopsies were scored and classified according to the Banff 2013/2015 classification conventions [20, 21].

Statistical analysis

We used JMP software version 16.0 (SAS Institute Inc., Cary, NC) for statistical analysis. Categorical data are presented as counts and percentages and were analysed by

Fisher's exact test or Pearson's chi-square test as appropriate. Continuous data are summarised as median and interquartile ranges (IQR) unless stated otherwise and analysed by the Wilcoxon or Kruskal-Wallis rank sum tests. No sample size calculation was performed since this represents a retrospective analysis. Recipient and donor baseline characteristics are shown within table 1 for the entire study population and stratified by donor age. Furthermore, donor age was compared across different transplant periods during the observation time and represented with violin plots. Patient, graft, and death-censored graft survival was analysed by the Kaplan-Meier method and groups were compared using the log-rank test. Allograft function at one and five years posttransplant was compared across the donor age groups and represented with violin plots. Kidney Donor Risk Index was calculated according to the guidelines for calculating and interpreting KDRI (available from <https://optn.transplant.hrsa.gov>) using R version 4.0.2 and the package *transplant*. Mainly due to missing creatinine values of the donors, sufficient donor factors to calculate KDRI were only available for 431 patients. Multivariable Cox proportional hazards regression analysis was performed to adjust for potential confounders. Potential confounders were selected based on pre-existing knowledge about worse graft outcome and graft loss. No p-value threshold or automated variable selection was used. For all models, transplantations with primary non-function organs (n = 6) were excluded. The final model was chosen based on the number of events and the consensus of requiring 10 events per independent variable. The variables chosen for the final model were delayed graft function, cold ischemia time, donor-specific HLA-antibodies, HLA-mismatches, donation after cardiac death, and the variable of interest: donor age group. The proportional hazard assumption was tested using Schoenfeld residuals. A two-tailed p-value <0.05 was considered to indicate statistical significance. No imputation was used to address missing values.

Results

Recipient and donor baseline characteristics stratified by donor age

In this study we investigated 491 patients with a median follow-up of 4.9 years (IQR 2.3–8.3 years) as shown in figure 1. The final study population consisted of 258 (53%) regular donors (aged <60 years), 158 (32%) elderly donors (age between 60 and 70 years), and 75 (15%) very old donors (aged >70 years). We compared recipient and donor baseline characteristics between the three groups (table 1). At the time of transplantation, recipients of very old donor grafts were generally older (median age 64 years; IQR 57–69 years) compared to recipients of elderly (median 61 years; IQR 54–66 years) and regular (median 55 years; IQR 44–62 years) donor grafts (p = 0.04 and p <0.0001, as well as overall p-value <0.0001; figure S1). Immunological parameters such as number of transplantations, presence of pretransplant donor-specific HLA-antibodies, and donor-specific HLA-antibody classes, differed slightly between the groups (p ≤ 0.04), whereas HLA-mismatches were not significantly different. Patients with pre-

transplant donor-specific HLA-antibodies were younger and (accordingly to risk stratification rules) received more induction therapy with polyclonal anti T-cell globulin +/- intravenous immunoglobulins (p-value overall = 0.0001). Baseline immunosuppression did not differ between the groups (table 1). Pre-emptive transplantations were rare, and the median time on dialysis before transplantation was 39.4 months (IQR 23.3–65.7 months) and comparable between the groups (table 1).

The median age of donors did not increase throughout different transplantation periods during our observation time (figure 2). The incidence of cerebrovascular death was significantly higher in very old donors (75%) compared to elderly donors (64%) and regular donors (51%) (overall p-value <0.0001; table 1). Donations accepted for transplantation after cardiac death were highest in the elderly donor group (p = 0.0008). Delayed graft function was also highest in patients who received a kidney from an elderly donor (50%) compared to the other two groups (both 29%; p = 0.0002). Median cold ischemia time was below 12 hours for all groups, however cold ischemia time significantly differed between the groups (p = 0.002; table 1).

Donor age is an essential determinant of the KDRI value. Thus, Kidney Donor Risk Index was lowest in the regular donor group, with a stepwise increase in Kidney Donor Risk Index from the regular to the elderly donor group (p <0.0001), and to the very old donor group (p <0.0001; table 1).

Graft and patient survival of kidney allograft recipients stratified by donor age

During the observation period, 168 grafts were lost – most of them due to death with a functioning graft (n = 111). The number of deaths with a functioning graft did not differ between the groups (p = 0.73). In addition, we observed n = 57 death-censored graft losses during follow-up. The causes of death, as well as death-censored graft loss, are depicted in figure 1. Graft loss was proportionally highest in the very old donor group (n = 11/75), but this did not reach statistical significance compared to the elderly donor group (14/158), and the regular donor group (32/258) (p = 0.44; figure 3A).

Table 1: Recipient and donor baseline characteristics stratified by donor age, n = 491.

		Entire study population (n = 491)	Donors aged <60 years (n = 258)	Donors aged between 60 and 70 years (n = 158)	Donors aged >70 years (n = 75)	p-value*
Recipient						
Age (years)		58 (49–65)	55 (44–62)	61 (54–66)	64 (57–69)	<0.0001
Female, n (%)		165 (34)	88 (34)	51 (32)	26 (35)	0.91
Primary disease, n (%)	Adult polycystic kidney disease	79 (16)	32 (13)	30 (19)	17 (23)	0.01
	Diabetic	59 (12)	24 (9)	24 (15)	11 (15)	
	Vascular	54 (11)	24 (9)	24 (15)	6 (8)	
	Glomerulopathy	163 (33)	93 (36)	45 (29)	25 (33)	
	Other	87 (18)	57 (22)	23 (14)	7 (9)	
	Unknown	49 (10)	28 (11)	12 (8)	9 (12)	
Immunological parameters	Number of transplant, % 1/2/≥3	79/18/3	74/23/3	83/13/4	85/14/1	0.04
	Pretransplant DSA, % 0/1/2/≥3	81/10/5/4	75/12/6/7	83/9/6/2	93/3/4/0	0.01
	DSA Class, % I/II/I+II	40/35/25	35/35/30	50/35/15	60/40/0	0.03
	Cumulative MFI	3183 (1393–7717)	3766 (1362–10947)	2357 (1311–5433)	4152 (1372–4303)	0.50
	HLA-A/B/DR/DQ MM	5 (4–7)	5 (4–6)	5 (4–6)	5 (4–7)	0.59
Induction therapy	Basiliximab, n (%)	374 (76)	180 (70)	128 (81)	66 (88)	0.0001
	ATG +/- IvIg, n (%)	109 (22)	76 (29)	24 (15)	9 (12)	
	None, n (%)	8 (2)	2 (1)	6 (4)	0	
Baseline IS	Tac-MMF/Myf-P, n (%)	447 (91)	232 (90)	146 (92)	69 (92)	0.66
	Tac-MMF/Myf-mTOR, n (%)	44 (9)	26 (10)	12 (8)	6 (8)	
Dialysis, n (%)		479 (98)	254 (98)	155 (98)	70 (93)	0.04
Dialysis time, months		39.3 (23.4–56.7)	40.4 (25.4–59.3)	39.7 (22.6–58.3)	31.9 (20.4–63.5)	0.07
Deceased donor						
Age, y		59 (47–67)	48 (39–54)	65 (62–68)	75 (72–79)	<0.0001
Female, n (%)		208 (42)	112 (43)	67 (42)	29 (39)	0.006
CIT, h		9.3 (7.6–12.0)	9.0 (7.1–11.5)	9.3 (7.8–11.6)	11.6 (8.1–13.4)	0.002
DGF, n (%)		175 (36)	74 (29)	79 (50)	22 (29)	0.0002
DCD, n (%)		51 (10)	20 (8)	28 (18)	3 (4)	0.0008
Cerebrovascular death, n (%)		288 (59)	131 (51)	101 (64)	56 (75)	<0.0001
KDRI, median (IQR)		2.0 (1.5–2.5)	1.6 (1.3–1.8)	2.4 (2.1–1.6)	3.2 (2.8–3.4)	<0.0001

ATG: polyclonal anti-thymocyte globulin; CIT: cold ischemia time; DSA: donor-specific HLA-antibodies; DCD: donation after cardiac death; IvIg: intravenous immunoglobulins; DGF: delayed graft function; HLA: human leukocyte antigen; IS: immunosuppressive therapy; IQR: interquartile ranges; KDRI: kidney donor risk index. Values are median and IQR if not otherwise stated; MFI: mean fluorescence intensity; MM: mismatches; MMF: mycophenolate-mofetil; Myf: mycophenolate-sodium; P = prednisone; mTOR: mechanistic target of rapamycin inhibitors (sirolimus or everolimus); Tac: tacrolimus.

*p-values refer to statistical analyses between the different groups stratified by donor age.

Kaplan-Meier analysis on kidney allograft recipients stratified by donor age demonstrated that death-censored graft survival, as well as graft and patient survival, did not differ across the age groups (figure 3A–C). Specifically, 3-year and 5-year death-censored graft survival in the very old donor group was 96% and 86%, respectively, and did not significantly differ from the other two age groups ($p = 0.44$; figure 3A). As expected, 3-year and 5-year graft survival, which was mainly triggered by events of death with a functioning graft, was lower compared to death-censored graft loss, but did not differ statistically across all age groups ($p = 0.71$; figure 3B). Specifically, 3-year and 5-year graft survival in the very old donor group was 84% and 66%, respectively (figure 3B). In addition, 3-year and 5-year patient survival in the very old donor group was 87% and 77%, respectively, and did not differ significantly from the other two age groups ($p = 0.87$; figure 3C).

Lower graft function in allograft recipients of elderly and very old donor organs

Graft function was analysed at 12 months and five years posttransplant by calculating estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (ml/min/1.73 m² of body surface). Of the entire study population, 27 patients did not reach the 12-month follow-up visit, either due to early death with a functioning graft ($n = 14$) or very early graft loss ($n = 13$). Therefore, a total of 464 (95%) patients had eGFR values at 12-month follow-up. Median allograft function was 57 ml/min/1.73 m² (IQR 44–70 ml/min/1.73 m²) in the regular donor group, 41 ml/min/1.73 m² (IQR 31–52 ml/min/1.73 m²) with the elderly donor group, and 37 ml/min/1.73 m² (IQR 29–50 ml/min/1.73 m²) in the very old donor group (figure 4). Statistically, median eGFR values did not differ between the elderly and very old donor groups ($p = 0.53$). However, patients with regular donors had significantly higher median eGFR at their 12-month follow-up visit compared to the elderly and very old donor groups (both with p -value <0.0001 ; figure 4). Ultimately, 12 months after transplantation, low graft function – defined as chronic kidney disease stage 4 or higher (eGFR <30 ml/min/1.73 m²) – was found in 5% (regular donor group), 21% (elderly donor

group), and 28% (very old donor group) of patients (overall $p <0.0001$).

Early death-censored graft loss (in total $n = 13$) consisted of $n = 6$ grafts with primary non-function, $n = 2$ with ongoing rejection, $n = 1$ with *de novo* glomerulonephritis, and $n = 4$ with early graft loss due to another problem. Concerning donor age grouping: there were $n = 3$ donor organs with primary non-function in the regular donor group; $n = 1$ in the elderly donor group, and $n = 2$ in the very old donor group. Furthermore, patients with early graft loss were more likely to have received a kidney allograft from a very old donor than those without early graft loss (26% vs. 15%), however this did not reach statistical significance ($p = 0.15$) – data not shown.

Allograft function did not change over a period of five years posttransplant. In total, 234 (48%) patients had

Figure 3: (A) Death-censored graft survival, (B) graft survival, and (C) patient survival of patients ($n = 491$) stratified according to age groups.

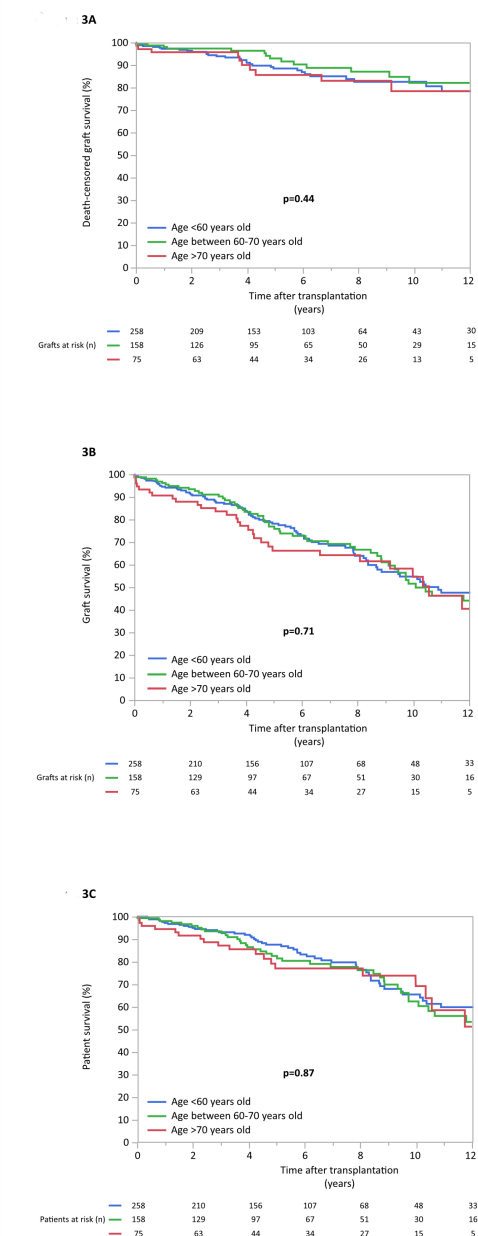
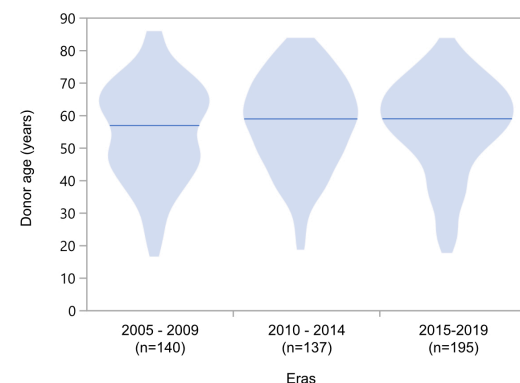


Figure 2: Evolution of donor age across different periods (years 2005–2019). Due to low numbers, transplantations performed in 2020 ($n = 19$ as of June 2020) were excluded from illustrations of donor age by violin plots, however median donor age during different periods was the same.



5-year follow-up visits and contributed to the 5-year analysis of graft function. Median allograft function was 60 ml/min/1.73 m² (IQR 43–72 ml/min/1.73 m²) in the regular donor group, 41 ml/min/1.73 m² (IQR 29–51 ml/min/1.73 m²) in the elderly donor group, and 39 ml/min/1.73 m² (IQR 31–49 ml/min/1.73 m²) in the very old donor group. Median eGFR values did not differ between the elderly and very old donor groups (p = 1.0), but did between the regular and elderly donor groups (p <0.0001), as well as between the regular and very old donor groups (p <0.0001) – data not shown.

Rejection rates of allograft recipients stratified by donor age

Of the entire study population, 327 (67%) patients had at least one surveillance biopsy within the first 6 months posttransplant. Furthermore, 280 (57%) patients had one or more clinically indicated allograft biopsy during the entire observational period, even though most of the patients (81%) were evaluated for deteriorating kidney function within the first year posttransplant. During the entire follow-up period, 153 (31%) patients developed at least one acute rejection episode, however most of the acute re-

jection episodes occurred within the first three years post-transplant (91%) as shown in figure 5A. Time-to-event analysis demonstrated no difference of occurrence of any acute clinical rejection event when all three groups, stratified by donor age, were compared with each other (p = 0.11; figure 5A). Patients who belonged to the regular donor group (n = 89/258) as well as the elderly donor group (n = 49/158) had numerically more acute clinical rejection episodes compared to the very old donor group (n = 15/75), however this difference was statistically significant only between the regular and very old donor groups (p = 0.03; figure 5A). During the entire follow-up period, 274 (56%) patients developed at least one acute subclinical rejection episode. As surveillance biopsies were routinely done at 3 and 6 months posttransplant, figure 5B shows the occurrence of subclinical rejection episodes only within the first 12 months posttransplant. Again, we found no statistically significant difference in occurrence of any sub-clinical rejection event when all three groups were compared (p = 0.99; figure 5B).

(Sub)clinical T-cell-mediated rejection occurred in n = 205 patients (42%), and (sub)clinical antibody-mediated rejection occurred in n = 98 patients (20%). Time-to-event analysis demonstrated no difference, either in the occurrence of T-cell-mediated rejection between the groups stratified by donor age (p = 0.62; supplementary figure S2A), or in the occurrence of any antibody-mediated rejection between the groups (p = 0.15; supplementary figure S2B).

Independent predictors of graft loss

In a multivariable Cox proportional hazards analysis – adjusting for potential confounders which were available at the time of transplantation or the early posttransplant period – donor age was not a significant predictor of graft loss (very old donors vs regular donors: Hazard Ratio HR 0.81 [95 confidence interval CI 0.38–1.89], p-value 0.61; elderly donors vs regular donors: Hazard Ratio HR 1.49 [95 confidence interval CI 0.77–3.02], p-value 0.24). Presence of pretransplant donor-specific HLA-antibodies (yes vs no) remained the only independent predictor within the multivariable model (HR 2.53, 95% CI 1.38–4.54; p = 0.003) (table 2).

Figure 4: Kidneys from elderly donors (ED; age between 60 and 70 years), and very old donors (VOD; age >70 years) achieved lower eGFR (CKD-EPI) at 12 months posttransplant, compared to regular donor kidneys (RD; age <60 years). eGFR: estimated glomerular filtration rate (calculated by the CKD-EPI formula; in ml/min/1.73 m² of body surface); CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

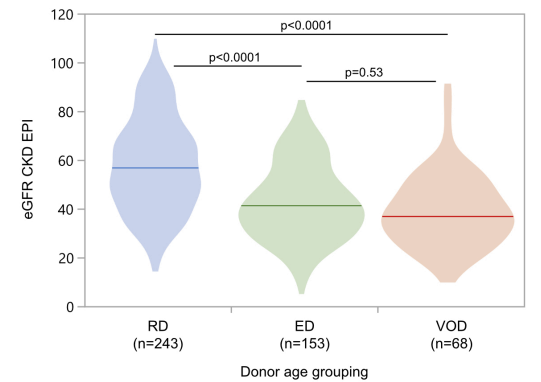
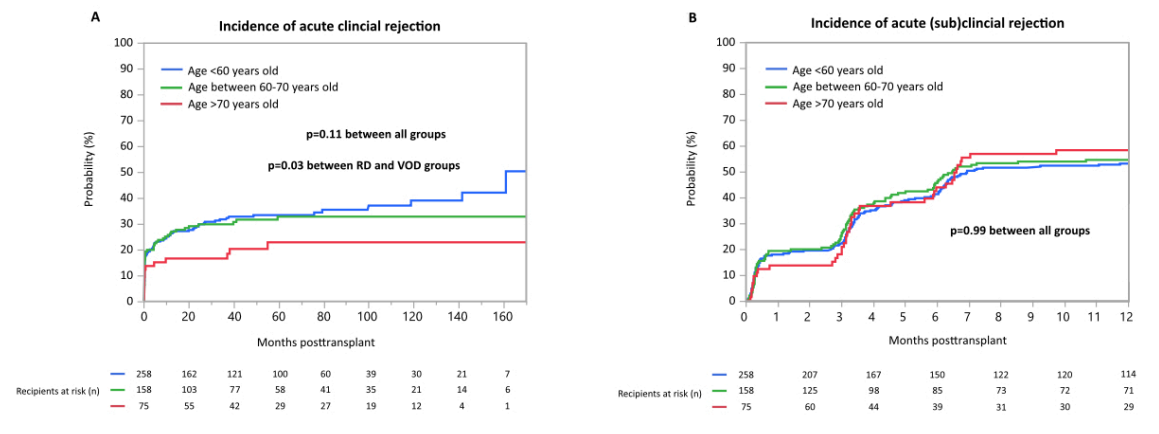


Figure 5: Incidence of acute rejection. (A) Incidence of acute clinical rejection over time, (B) incidence of clinical and subclinical rejection within the first year post-transplant. Surveillance biopsies were obtained at 3 and 6 months post-transplant.



Discussion

The most striking observation of this study was that transplantations from very old donors did not show inferior death-censored graft survival compared to transplantations from elderly donors or regular donors. We found no difference in early and overall graft loss between the groups. In addition, organs showing a primary non-function were not exclusively those harvested from the very old donors. It is important to highlight that Kaplan-Meier analysis demonstrated remarkable 3- and 5-year death-censored graft survival of transplanted patients who received grafts from very old donors. As expected, graft survival – which was mainly triggered by death rate with a functional graft – was lower than death-censored graft loss, but again did not differ statistically across age groups. Furthermore, when we adjusted our survival model for possible confounders, donor age was not an independent predictor of death-censored graft loss.

Moreover, we showed a significant relationship between donor age and eGFR at 12 months posttransplant. Importantly, achievement of eGFR at 12 months did not differ among donors aged 60 years and older. As expected, patients with transplantations from donors younger than 60 years had significantly higher median eGFR at their 12-month follow-up visit, but this had no influence on mid-term graft and patient outcomes. It is important to put these results into context and compare them to alternative treatment options; most notably to long-term dialysis, which has a high annual death rate, especially for older patients [22]. Nevertheless, inferior graft function might have an impact on quality of life and might therefore reduce the patient benefit gained from a transplantation. Among other factors affecting graft outcome, we demonstrated that acute allograft rejection episodes were highest in patients who belonged to the regular donor group than to the very old donor group, which was mainly triggered by late acute rejection episodes. Therefore, we may speculate that the better organ function of kidneys from younger donors, represented by better eGFR 12 months after transplantation, may be negatively affected by the occurrence of more late acute rejections in long-term. Interestingly, patient survival was similar across all age groups although recipients of very old grafts were older at time of transplantation. This may be explained by the fact that older transplant recip-

ients must be relatively healthy to be accepted onto the transplant waiting list.

The current study demonstrated that, at the time of transplantation, there was a strong relationship between recipient and donor age. Previously, large transplant centres have established specific old-for-old transplantation programs, where older donors are allocated to senior candidates on the waiting list [23–25]. While such an approach seems a valuable tool for large transplant centres and extensive catchment areas, it is not feasible for smaller transplant programs like the one in Switzerland. Nevertheless, in the daily clinical practice of our centre, represented by the current study, the donor/recipient pairs were well matched by age. Because older kidney transplant recipients have a shorter life expectancy at the time of transplantation compared to younger ones, they arguably need less kidney function over time (i.e., until their end of life). From this perspective, the promising outcomes seen in kidney allograft recipients with organs harvested from very old donors within this study, support a centre-specific process of allocating suitable “very old” donor kidneys to elderly kidney allograft candidates, within the legally compliant allocation of organs to recipients (allocation is coordinated on a national level in Switzerland).

Another interesting observation is that transplantations from very old donors were performed more frequently without the presence of donor-specific HLA-antibodies. Although our model selection to explore independent predictors of death-censored graft loss was based on donor age as a confounder, the multivariable model identified the presence of donor-specific HLA-antibodies as the only significant risk factor for death-censored graft loss, which is consistent with the literature. It is possible that, within the first years after transplantation, similar rates of rejection-free outcomes in very old donor transplantations are the result of an overall lower immunological risk associated with these types of transplants.

Study limitations

Firstly, this is a single centre study; and although we used an unselected, consecutive patient population over a long period, the number of patients who received kidneys from very old donors was rather limited. This might increase the possibility of a type II error. However, given that we did not find an association, it can be assumed that the overall effect would be rather low. Secondly, this is a retrospec-

Table 2:
Independent predictors of death-censored graft loss (n = 485)*.

Predictors of graft loss		Recipients with death-censored graft loss (n = 51)	Recipients without graft loss (n = 434)	Univariate Cox proportional analysis Hazard ratio (95% CI); p-value	Multivariable Cox proportional analysis** Hazard ratio (95% CI); p-value
DGF (yes vs no), n (%)		22 (43)	153 (35)	1.57 (0.90–2.73); 0.12	1.71 (0.96–3.00); 0.07
CIT, hours		9.8 (6.7–13.1)	9.3 (7.6–11.8)	1.04 (0.98–1.09); 0.18	1.03 (0.97–1.09); 0.29
Donor age group	<60 y vs >70 y, n	29/9	226/64	0.96 (0.45–2.03); 0.91	0.81 (0.38–1.89); 0.61
	<60 y vs 60–70 y, n	29/13	226/144	1.36 (0.70–2.62); 0.36	1.49 (0.77–3.02); 0.24
DSA (yes vs no), n (%)		20 (39)	73 (17)	2.52 (1.44–4.43) 0.002	2.53 (1.38–4.54); 0.003
HLA-A/B/DR/DQ MM		5 (3–6)	5 (4–7)	0.97 (0.84–1.11); 0.66	
DCD (yes vs no), n (%)		1 (2)	50 (12)	0.60 (0.08–4.44); 0.58	

CI: Confidence interval; CIT: cold ischemia time; DCD: donation after cardiac death; DGF: delayed graft function; DSA: donor specific antibodies; HLA: human leukocyte antigen; MM: mismatch.

* Transplantations with primary non-functioning organs (n = 6) were excluded for analysis of independent predictors of death-censored graft loss.

** The last column represents the whole multivariable model.

tive analysis of a prospective cohort and therefore it was not possible to obtain missing data. We did not collect serial sera to screen for *de novo* donor-specific HLA-antibodies post-transplant for the entire study population. Thus, we were not able to include data for the occurrence of *de novo* donor-specific HLA-antibodies within the multivariate model. However, our screening method for donor-specific HLA-antibodies is applicable to all kidney recipients, independent of donor age, and therefore random absence is most likely. Thirdly, given the retrospective analysis and the possibility to decline a transplant offer, a bias by indication may be present. Although we tried to adjust our statistical model to known confounders, we were limited by the small sample size and therefore may have residual confounding. Even if this limits the possibility of finding independent effects of very old donor organs, the results that carefully selected very old donors show reasonable outcomes are encouraging.

Conclusion

This study demonstrates that kidney transplantation from very old donors seems to be a valid option, taking patient and allograft outcome into account, with reasonable short- and mid-term outcomes.

Acknowledgements

The authors thank the staff of the University Hospital Basel Renal Transplant Unit for the outstanding patient care, and the histocompatibility laboratory for collection and processing of blood samples for immunological work-up before transplantation. Furthermore, the authors thank Agim Thaqi from the Federal Office of Public Health for assisting with extraction of donor derived factors from the Swiss Organ Allocating System database.

Author contribution: The individual contribution of each co-author is briefly summarised as follows: Designed research/study: PHM; Performed research/study: PHM, KM, DM; Collected data: PHM, SS, CW, PA, MD, JS; Analysed data: PHM, KM, DM; Wrote paper: all.

Financial disclosure

The need for extra funding was not necessary to conduct the study as it was performed as a part of a master thesis.

Potential competing interests

DM received a research grant from the Swiss National Science Foundation (P500PM_214237). CW has a salary grant from the University of Basel for the promotion of young clinical researchers (3MS1065). JS holds a grant from the Swiss National Science Foundation to conduct the Swiss transplant cohort study (STCS) as principal investigator (SNSF project 33CS30/201385 / 1). PMH has salary support from the Astellas foundation for biomedical research (grant CH-02-RG-248). All the reported grants are used outside the scope of this work.

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Appendix: supplementary figures

Figure S1: At the time of transplantation, recipients of very old donor grafts were older (VOD; median age 64 years; IQR 57–69 years) compared to recipients of elderly donor grafts (ED; median 61 years; IQR 54–66 years) and regular donor grafts (RD; median 55 years; IQR 44–62 years). IQR: interquartile range

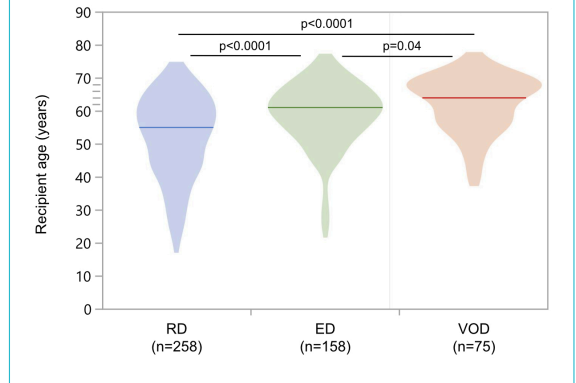


Figure S2: (A) Incidence of acute subclinical T-cell-mediated rejection (TCMR), (B) incidence of acute (subclinical) antibody-mediated rejection (ABMR) during follow-up.

