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Early outcomes and long-term survival after kidney transplantation in elderly versus younger recipients from the same donor in a matched-pairs analysis

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Abstract

The elderly are the fastest-growing population on waiting lists for kidney transplantation (KTx). Recognized barriers to KTx in the elderly is early post-transplant mortality and morbidity. To analyze the outcomes of KTx in recipients older than 60 years and, simultaneously, in their younger paired recipients, receiving a graft from the same donor.

We included 328 kidney transplant recipients in the study. The elderly kidney transplant recipients (EKT) group included 164 patients aged 65 standard deviation (SD4) years. They were paired with younger kidney transplant recipients (YKT) aged 45 (SD12) years.

The studied groups (EKT vs YKT) did not differ from the graft function estimated 1 year after the transplantation (50.7 mL/min vs 54.0 mL/min), while the estimated glomerular filtration rate decline was significantly faster in the YKT group. One-year patient survival (93.9% vs 97.0%), 1-year graft survival (90.4% vs 82.3%), and incidences of delayed graft function and acute rejection did not differ between the EKT and YKT groups. Significantly more cardiovascular complications and post-transplant diabetes mellitus were noticed in the EKT group. The long-term patient and graft survivals were poorer in the EKT group versus the YKT group, but death-censored graft survivals were the same. After having excluded donor-derived graft factors, there were no differences in the first-year outcome of KTx between recipients younger and older than 60 years. As life expectancy is lower in the EKT group, the probability of patient and graft survival was also significantly lower in this group. However, death-censored graft survival was not different in the EKT and YKT groups.

Abbreviations: AR = acute rejection, CMV = cytomegalovirus, DGF = delayed graft function, eGFR = estimated glomerular filtration rate, EKT = kidney transplant recipients, ESRD = end-stage kidney disease, KTx = kidney transplantation, MACE = major adverse cardiac events, PTDM = post-transplant diabetes mellitus, RRT = renal replacement therapy, SD = standard deviation, YKT = younger kidney transplant.

Keywords: elderly, kidney transplantation, mortality

1. Introduction

Old age is the third major phase of life and may last between 20 and 40 years. This extended phase receives surprisingly little attention in research and clinical medicine, even if the increase of the geriatric population is a well-established fact. Accordingly, we observed the increase in the age of patients with end-stage kidney disease (ESRD) receiving renal replacement therapy (RRT) and enlisted on transplant waiting lists. In the United

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States, the number of transplantations in recipients aged above 65 years has increased 3-fold in the last decade,[1] with a similar trend being observed in other countries.

Presently, it is widely accepted that chronological age does not constitute a contraindication for KTx. The many benefits of KTx versus dialysis therapy that have been demonstrated so far also apply to elderly recipients, even though the mortality and risk of graft loss increase with the recipient's age.[2] As it was reported, kidney graft recipients had a more positive view of successful aging and saw their transplant as a facilitator of aging successfully that dialysis would not have allowed.[3] Older kidney transplant recipients experienced improvements in energy and quality of life,[4] some claimed to feel "the best for 20 years."[4] Nevertheless, the uniqueness of the needs of elderly transplant recipients, and the outcomes of kidney transplantation in the elderly, are poorly recognized. The gaps in knowledge originate, among others, from the limitations of reports based on the data from registries. Various, often complicated, allocation programs dedicated to elderly recipients in different transplant centers make the analysis of outcomes challenging. Notably, the elderly most often receive organs from older donors,[5] or even organs discarded from regular transplantation procedures.[6] Such variations may have a substantial impact on patient and graft survival and preclude reliable conclusions from observational studies. These abovementioned biases may be avoided by designing a study in a matched-pair manner, in which each of the 2 kidney recipients, the older and the younger recipients, receives an organ from the same deceased donor. In our previous study,[7] in an analysis of 44 pairs of recipients from the same donor, we showed that kidney transplantation is a good option for RRT in patients older than 60 years. However, some studies indicate a higher mortality risk during the early time after transplantation in older recipients.

In patients older than 70 years the 3-fold higher risk of death was reported in KTRs compared with the waitlisted group in the first 3 months, and still not offset by month 36.[8] In another study, in patients of the same age the risk of death at 45 days posttransplant was 2.26 times greater than the risk of death on dialysis with improved survival at 548 days post-transplant.[9] This indicates the importance of proper qualification and selection of older patients for a kidney transplantation to improve early patient survival in the elderly KTRs. Assessing early complications in the first year after transplantation may have the highest impact on adjudicating upon the controversies regarding the risks and benefits of pursuing this option of treatment in older patients.

Our multicenter study introduces a new approach to the analysis of outcomes after kidney transplantation. Due to pairing patients from the same donor, we excluded factors rooted in the quality of the transplanted organ from the analysis. The latter is the main limitation of the studies published to date, as there is a worldwide trend towards allocating older organs to older recipients. Benefitting from the multicenter design of the study, we managed to show results from 328 patients and proved that the outcomes of kidney transplantation in the elderly are not inferior compared with those of their younger counterparts.

The primary objective of the present study was to compare the first-year post-transplant outcome of kidney transplantation in pairs of older and younger recipients who received kidneys from the same deceased donor.

A secondary objective was to assess the impact of kidney transplantation on long-term patient and graft survival in older versus younger recipients.

2. Patients and methods

We performed a multicenter, retrospective, observational study in 3 transplant centers in Poland (Gdańsk, Bydgoszcz, and Bialystok). Patients that underwent kidney transplantation procedures performed between January 1994 and December 2016 were checked for eligibility for the study. The approval of the Ethical Committee number NKBBN 429/2019, KBE 109/2009, and R-I-002/330/2016 applied to the collection and analysis of blinded data.

The study was based on the use of routinely collected data, did not require additional funding. Inclusion criteria comprised patients not previously transplanted, aged 60 or above, who received paired kidneys from the same donor. We excluded cases in which both recipients from the same donor were older than 60 years, when only one kidney was transplanted, or when one of the kidneys from the pair was lost to follow-up before completing the first-year observation. Data concerning comorbidity at the time of transplantation, the immunosuppressive regimen, and other variables related to the study outcome were retrieved from hospital records. Outcome variables included delayed graft function (DGF); biopsy-proven or clinically diagnosed acute rejection (AR) in the first year of post-transplant observation; creatinine in mg/dL (1 mg/dL = 88.4 μmol/L) and estimated glomerular filtration rate (eGFR) estimated by the chronic kidney disease epidemiology formula in the third, sixth, and twelfth months after KTx; major adverse cardiac events (MACE); hospitalizations and surgical complications in the first year of post-transplant observation; the diagnosis of post-transplant diabetes mellitus (PTDM); infection with the cytomegalovirus (CMV); the loss of graft function; and death. We defined DGF as the need for dialysis during the first week after KTx. We defined surgical complications as the need for reoperation in the first year post-transplantation. We defined CMV infection as a positive pp65 protein or the number of CMV copies regarded as significant by the local molecular laboratory. We defined PTDM as fasting glucose >126 mg/dL (7 mmol/L) on more than one occasion or random glucose >200 mg/dL (11.1 mmol/L) with symptoms or 2-hour glucose after a 75-g OGTT of >200 mg/dL (11.1 mmol/L). We defined MACE as a nonfatal myocardial infarction, a cardiovascular intervention, or a nonfatal stroke. The graft function decline, expressed as differences between eGFR after the third and sixth months, as well as after the sixth and twelfth months, was used as a surrogate of the graft function in the first year after KTx. The long-term survival of patients and grafts were analyzed using data from 1 transplant center (160 patients). The characteristics of patients from that center as compared with patients not included into long-term analysis are provided in the Table, Supplemental Digital Content, http://links.lww.com/MD2/A754. The longest observation period lasted for 23 years and the shortest lasted for 3 years. The deaths and losses of graft function in the first year post-transplantation were reported in all transplant centers.

2.1. Statistical analysis

Data are shown as mean and standard deviation or percentages and event rates, depending on the nature of the variable. Continuous variables were compared using *t* student statistics or the Mann–Whitney *U* test if the variables were not normally distributed. Categorical variables were compared with chi-square statistics. Patient and graft survival were estimated through Kaplan–Meier curves (log-rank test). Significance was considered when $P < .05$.

Complete case analysis was used.

3. Results

3.1. Characteristics of the study participants

A total of 328 kidney transplant recipients were eligible to be included in the study. They constituted 164 pairs comprising a recipient younger than 60 years old and a recipient equal to or older than 60 years old. The youngest recipient was 14 years old and the oldest was 81 years old. Men constituted 62% of the study population. The mean time of RRT before transplantation was 35 months. Of the recipients, 81% were treated with hemodialysis, 14% were treated with peritoneal dialysis, and 5% were transplanted pre-emptively. The clinical characteristics of the EKT versus YKT groups and the immunosuppressive regimen chosen at the day of transplantation (intention to treat) are shown in Table 1.

3.2. Primary objectives

3.2.1. Kidney function. Kidney function in the first year after transplantation, expressed as mean creatinine value, eGFR calculated using the chronic kidney disease epidemiology formula, and a decline of eGFR after 6 and 12 months, is displayed in Table 2.

3.2.2. Major post-transplant complications. Major post-transplant complications in the first year after transplantation are displayed in Table 3. CMV infection, PTDM, and MACE were more common in older kidney recipients. There was no difference in the incidence of AR, DGF, and surgical complications.

3.3. Secondary objectives

3.3.1. Patient and graft survival in the first year. Patient deaths and graft losses in the first year are shown in Table 4. The most common causes of death during the first year after transplantation were fatal infections and cardiovascular events.

3.3.2. Long-term patient and graft survival. In the follow-up period (3–23 years), 59 out of 160 patients died. Forty deaths

Table 1

Demographic and clinical characteristics among kidney transplant recipients aged 60 years (EKT) and <60 years (YKT) from the same donor.

	Elderly recipient N = 164	Younger recipient N = 164	*P* value
Age, yrs, (SD)	64.8 (4)	44.6 (11.5)	<.001
Males, number, %	102 (62.2)	104 (63.4)	.91
Primary kidney disease number of cases, %			
DM	29 (17.7)	12 (7.3)	.012
GN	40 (24.4)	68 (41.5)	.019
HTN	19 (11.7)	15 (9.2)	.51
Interstitial	21 (12.8)	16 (9.8)	.44
ADPKD	21 (12.8)	14 (8.5)	.26
Reflux/obstructive	0	4 (2.4)	.14
CAKUT	0	4 (2.4)	.14
UNK	34 (20.6)	32 (18.9)	.82
Modality of RRT prior to KTx number of cases, %			
HD	137 (83.5)	129 (78.7)	.72
PD	21 (12.8)	26 (15.8)	.49
Pre-emptive	6 (3.7)	9 (5.5)	.99
Duration of RRT, months (SD)	43.3 (51.1)	29.2 (32.5)	.004
Cardiovascular disease history prior to KTx number of cases, %			
CHD	67 (40.9)	25 (15.2)	.003
PTCA	19 (11.6)	11 (6.7)	.16
CABG	13 (7.9)	3 (1.8)	.013
Stroke	7 (4.3)	10 (6.1)	.65
Immunosuppressive regimen at the moment of transplantation number of cases, %			
Induction ATG/Thymoglobulin	5 (3.0)	3 (1.8)	.49
Induction a—IL2	11 (6.7)	6 (3.6)	.24
Steroids	163 (99.4)	164 (100)	.97
AZA	43 (26.2)	33 (20.1)	.30
MPA	116 (70.7)	120 (73.2)	.84
CsA	93 (56.7)	90 (54.9)	.86
TAC	69 (42.0)	72 (43.9)	.83
mTOR	9 (5.5)	12 (7.3)	.53

ABG = coronary artery bypass, AC = tacrolimus, ACUT = congenital anomalies of the kidney and the urinary tract, AZA = zathioprine, D = hemodialysis, D = peritoneal dialysis, HD = coronary heart disease, M = diabetes mellitus, N = glomerulonephritis, NK = unknown aetiology, PA = mycophenolic acid, RT = renal replacement therapy, sA = cyclosporine, TCA = percutaneous transluminal coronary angioplasty, TN = ischemic and vascular nephropathy, TOR = mammalian target of rapamycin kinase inhibitor, Tx = kidney transplantation.

Table 2

A comparison of graft function between older and younger recipients in the first year after kidney transplantation.

	Elderly recipient N = 164	Younger recipient N = 164	*P* value
Creatinine, mg/dL*, (SD)			
Month 3	1.69 (0.70)	1.97 (1.79)	.07
Month 6	1.52 (0.64)	1.58 (0.50)	.33
Month 12	1.50 (0.65)	2.39 (8.78)	.28
eGFR			
Month 3	44.44 (18.46)	51.58 (25.16)	.007
Month 6	49.57 (18.90)	52.80 (18.72)	.09
Month 12	50.73 (19.06)	54.01 (21.59)	.24
eGFR decline			
Δ 6–3	4.74 (12.96)	−1.98 (19.93)	.003
Δ 12–3	5.42 (12. 26)	−1.17 (19.62)	.014

eGFR = stimated glomerular filtration rate.
* Conversion factor to SI units is 88.4.

Table 3

Major post-transplant complications in the first year after transplantation.

	Elderly recipient N = 164	Younger recipient N = 164	*P* value
AR	60 (36.6%)	46 (28.0%)	.24
DGF	62 (37.8%)	64 (39%)	.88
Surgical complications	63 (38.4%)	58 (35.4%)	.70
MACE	37 (22.6%)	17 (18.9%)	.012
Hospitalization	111 (67.7%)	101 (61.6%)	.59
PTDM	52 (31.7%)	26 (15.8%)	.008
CMV infection	71 (43.2%)	54 (32.9%)	.07

ACE = major adverse cardiovascular events, AR = acute rejection, GF = delayed graft function, MV = cytomegalovirus, TDM = post-transplant diabetes mellitus.

Table 4

Patients' deaths and graft losses in the first year after transplantation.

	Elderly recipients N = 164	Younger recipients N = 164	*P* value
Deaths	10 (6.1%)	5 (3.0%)	.21
Deaths with a functioning graft	6 (3.7%)	5 (3.0%)	.99
Graft losses	16 (9.6%)	29 (17.7%)	.07

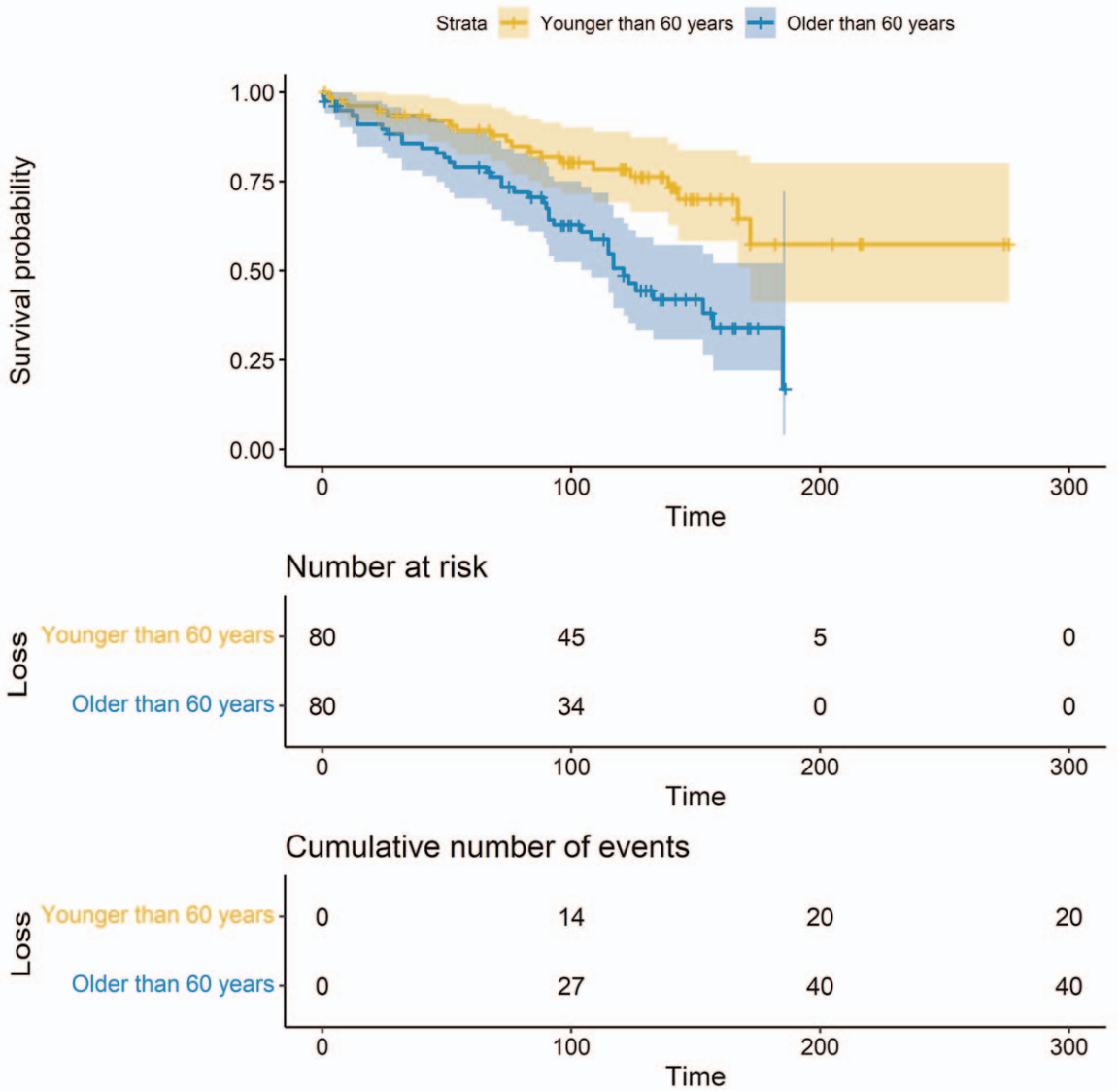

Figure 1. Estimates of long-term patient survival probability in the EKT and YKT groups (by Kaplan–Meier curves). EKT = kidney transplant recipients, YKT = younger kidney transplant.

occurred in the EKT group and 19 in the YKT group ($P = .004$). Long-term patient and graft survival are displayed in Kaplan–Meier curves (Figs. 1 and 2, respectively). The most common cause of death after the first year was neoplasia, followed by cardiovascular events and infections. Long-term patient and graft survival were significantly worse in the elderly group. Death-censored graft survival is displayed in Fig. 3 and does not differ between the groups.

4. Discussion

By applying a paired kidney analysis method, we were able to compare the outcomes of KTx in recipients from different age groups in the most accurate and reliable way possible. That is, we obviated the selection biases, in which the older recipients were offered organs from older or expanded-criteria donors. In general, we have shown that the early outcome of KTx in the recipients aged 60 years or older does not differ significantly from that observed in the younger group.

Due to immunosenescence, both the comorbidity and mortality rates increase with the age of the recipients.[10] Indeed, similarly to others,[11] we observed that cardiovascular disease and diabetes mellitus were more common prior to transplantation in the EKT group compared with the YKT group. Accordingly, more adverse events and complications (MACE, PTDM) occurred in the first year of observation in the elderly group. Notably, DGF, AR, and the number of hospitalizations or surgical complications were similar between the groups. These findings were not unexpected. Previous studies have already indicated that the ageing of the immunological system may reduce the rate of organ rejection but may also place elderly patients at a higher risk of serious infection.[12] There was a trend toward a more frequent occurrence of CMV infection in the elderly group. The hospitalization rate did not differ between groups in our material. However, it has been previously reported

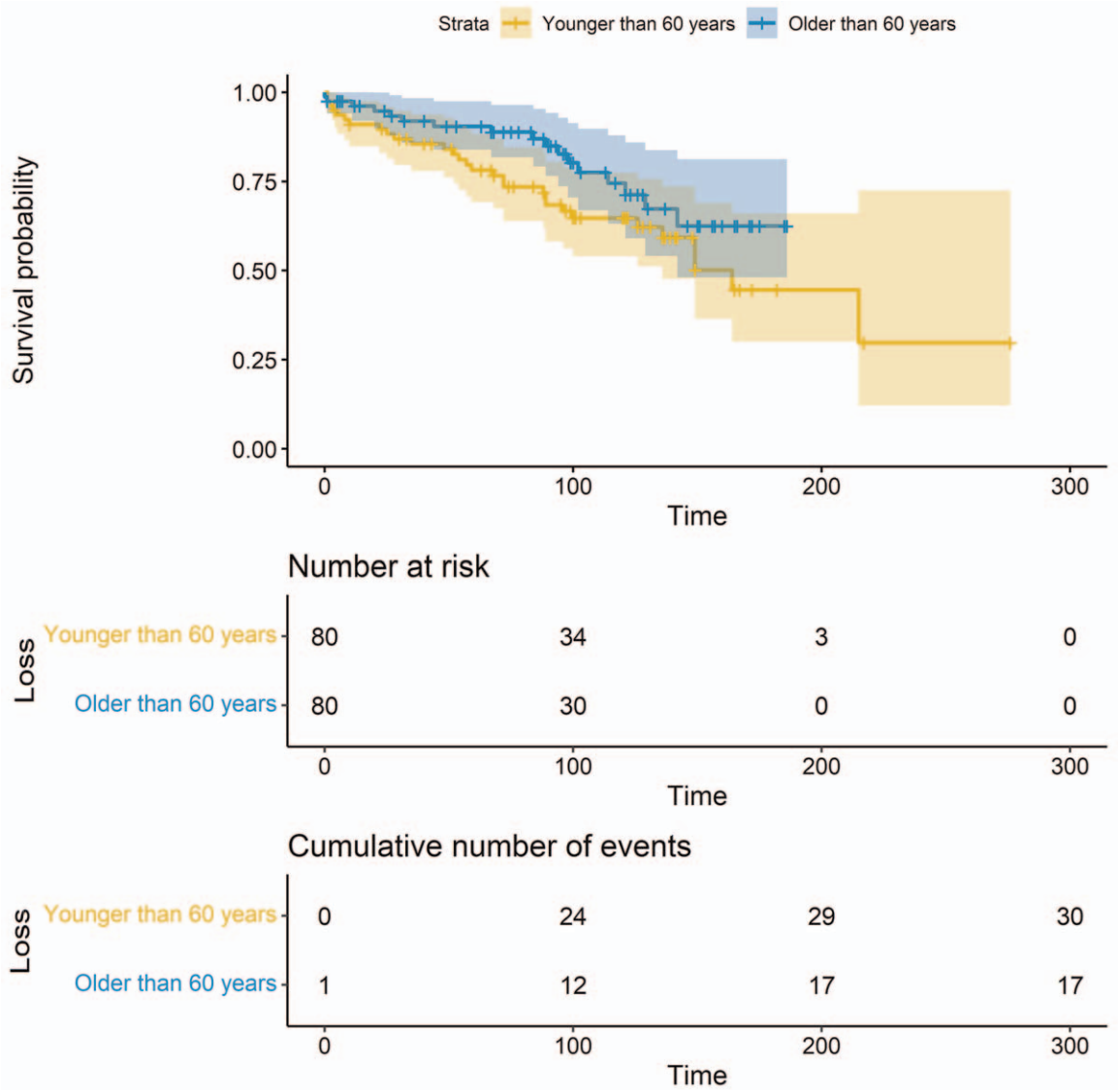

Figure 2. Estimates of long-term graft survival probability in the EKT and YKT groups (by Kaplan–Meier curves). EKT = kidney transplant recipients, YKT = younger kidney transplant.

that early rehospitalizations (within 1 month after KTx) were more frequent in older patients and were associated with a higher incidence of renal graft loss.[13]

Kidney graft function measured with the use of the eGFR formula was poorer after 3 months post-transplantation in the elderly group but subsequently improved, whereas eGFR in the YKT group deteriorated with time. As a consequence, the decline of eGFR was higher in the YKT group in the first year. There is no sound evidence present in our data that may explain this interesting finding. However, we may hypothesize that the underlying factors that contributed to this were better adherence to prescribed treatment and/or smaller doses of calcineurin inhibitors in the EKT group. This may have occurred even if the EKT group in our study was treated with similar immunosuppression regimens as the younger group.

The study by Gill et al[14] showed that perioperative mortality among recipients older than 65 years was strongly dependent not only on recipient comorbid conditions but also on the type of donor. Our study provides the rationale that perioperative and early post-transplant morbidity and mortality are inherently dependent on the quality of the organ and may not differ between age groups. Thus, perioperative mortality and morbidity should not be regarded as barriers to transplantation in the elderly. Such an approach is important, as mortality related to dialysis is still unacceptably high. Further, many age-related conditions, including frailty, falls, cognitive impairments, dementia, a high rate of hospitalizations, and early hospital readmission, which typically deteriorate in patients undergoing dialysis, may improve after transplantation.[15,16]

Cardiovascular disease remains one of the leading causes of death during the early post-transplant period in all age groups. Presently, no strategy or intervention has been shown to improve this unfavorable outcome. During the long-term observation, survival probability favored the YKT group due to their longer life expectancy. In the long-term follow-up, deaths occurred more frequently in the EKT group, but, in most cases, the graft function

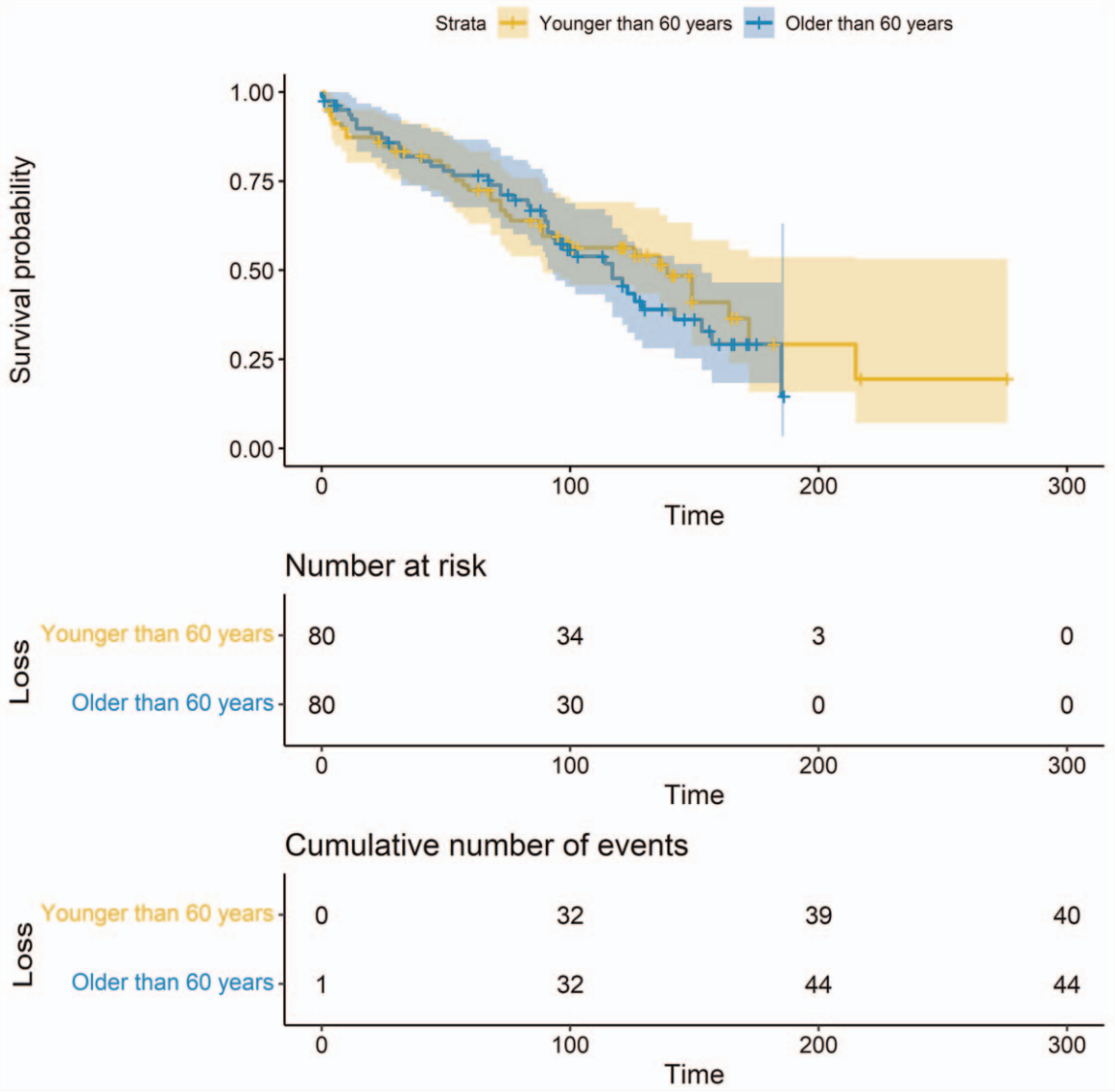

Figure 3. Estimates of long-term death-censored graft survival probability in the EKT and YKT groups (by Kaplan–Meier curves). EKT = kidney transplant recipients, YKT = younger kidney transplant.

was preserved. Our findings indicate overall good prognosis and favorable long-term outcomes of the KT procedure in the elderly recipients.

There were several limitations to our study. First, we selected the age of 60 as the cut-off point to discriminate between the groups, while in many studies the age of 65 is used. The age of 65 was chosen by the Social Security Administration of the United States for retirement purposes and has been replicated by researchers thereafter. There is no medical justification to use this particular age, especially considering that according to the World Health Organization's arbitrary definitions, old age begins at 60. Further, the life expectancy of a person with ESRD in their sixties equals that of a healthy octogenarian. Thus, biologically, we suggest that the age of 60 should be treated as the advised cut-off point in studies on elderly ESRD patients.

Secondly, the short follow-up period could potentially lead to erroneous inferences; however, regarding the view that most life-threatening complications of KTx in the elderly occur in the first months after the procedure,[8] we chose the 1-year follow-up as the most appropriate and manageable to maintain the accuracy of reported data.

Finally, therapeutic drug levels were not collected, so the intensity of immunosuppression may have varied between groups, even if the regimens were not different. We cannot rule out that in the EKT group, the target therapeutic drug levels were lower. A dose reduction of immunosuppressive drugs may have occurred in the EKT group, as many physicians regard it to be safe in the elderly. Even if this had indeed occurred, such a fact would not change the conclusions. On the other hand, it might have explained the flatter slope of the eGFR decline in the EKT group versus that of the YKT group.

Despite these limitations, our multicenter study was able to show that the outcomes of kidney transplantation in elderly patients could be satisfactory and, in general, similar to those of their younger paired recipients. Increased cardiovascular morbidity and PTDM incidence is inherent to age and is, possibly, a non-modifiable factor.

In our study long-term patient and graft survival were significantly worse in the elderly group, but death-censored graft survival did not differ in the elderly, which indicates that most of the EKT deaths occurred while the recipient still had the functioning graft. The same observation was done in other studies, there was no difference in death censored allograft survival in patients following deceased donor kidney transplantation aged >60 and <60 years.[17]

The elderly population is underrepresented in published studies, and we believe that our unique methodological approach may at least modestly contribute to filling the existing gaps in knowledge.

Author contributions

Magdalena Jankowska and Alicja Debska-Slizien conceived the concept of the study. Jolanta Malyszko and Maciej Slupski contributed to the design of the research. Magdalena Jankowska, Beata Bzoma, Jolanta Malyszko, Jacek Malyszko, and Grażyna Kobus were involved in the data collection. Magdalena Jankowska and Alicja Debska-Slizien analysed the data. Magdalena Jankowska and Beata Bzoma wrote the manuscript. Boleslaw Rutkowski, Zbigniew Wlodarczyk, and Alicja Debska-Slizien critically reviewed the study. All authors edited and approved the final version of the manuscript.

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