Received: 10 March 2017 | Revised: 11 July 2017 | Accepted: 1 August 2017

DOI: 10.1111/ajt.14459

ORIGINAL ARTICLE

AJT

Long-term outcome of renal transplantation from octogenarian donors: A multicenter controlled study

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To assess whether biopsy-guided selection of kidneys from very old brain-dead donors enables more successful transplantations, the authors of this multicenter, observational study compared graft survival between 37 recipients of 1 or 2 histologically evaluated kidneys from donors older than 80 years and 198 reference-recipients of non–histologically evaluated single grafts from donors aged 60 years and younger (transplantation period: 2006-2013 at 3 Italian centers). During a median (interquartile range) of 25 (13-42) months, 2 recipients (5.4%) and 10 reference-recipients (5.1%) required dialysis (crude and donor age- and sex-adjusted hazard ratio [95% confidence interval] 1.55 [0.34-7.12], $P = .576$ and 1.41 [0.10-19.54], $P = .798$, respectively). Shared frailty analyses confirmed similar outcomes in a 1:2 propensity score study comparing recipients with 74 reference-recipients matched by center, year, donor, and recipient sex and age. Serum creatinine was similar across groups during 84-month follow-up. Recipients had remarkably shorter waiting times than did reference-recipients and matched reference-recipients (7.5 [4.0-19.5] vs 36 [19-56] and 40 [24-56] months, respectively, $P < .0001$ for both comparisons). Mean (± SD) kidney donor risk index was 2.57 ± 0.32 in recipients vs 1.09 ± 0.24 and 1.14 ± 0.24 in reference-recipients and matched reference-recipients ($P < .0001$ for both comparisons). Adverse events were similar across groups. Biopsy-guided allocation of kidneys from octogenarian donors permits further expansion of the donor organ pool and faster access to a kidney transplant, without increasing the risk of premature graft failure.

KEYWORDS

clinical research/practice, clinical trial, donors and donation: donor evaluation, graft survival, kidney transplantation/nephrology, organ allocation, organ procurement, organ procurement and allocation, pathology/histopathology

Abbreviations: aMDRD, abbreviated Modification of Diet in Renal Disease; BMI, body mass index; CI, confidence interval; CKD-Epi, CKD Epidemiology Collaboration; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HR, hazard ratio; IQR, interquartile range; IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico; KDPI, kidney donor profile index; KDRI, kidney donor risk index; mTOR, mechanistic target of rapamycin; NIT, Nord Italia Transplant; OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing.

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1 | INTRODUCTION

To reduce the progressively increasing gap between the number of available organs for kidney transplantation and the number of patients who need transplants, in 2002 the American United Network for Organ Sharing (UNOS) proposed increasing the kidney donor pool by considering kidneys from expanded criteria donors (ECDs).[1] However, the average 3-year survival of ECD kidneys is 70% lower than the survival of "ideal" kidneys from young donors.[2,3] Moreover, despite this policy, >40% of ECD kidneys recovered in the United States during the past decade have never been transplanted.[4] This discard rate could be reduced by allocating to dual transplantation kidneys that are considered unsuitable for a single transplantation because of at least 2 of the following criteria: (1) donor age >60 years, (2) estimated creatinine clearance <65 mL/min, (3) rising serum creatinine to >2.5 mg/dL at the time of organ recovery, (4) comorbidities such as hypertension or diabetes, or (5) glomerulosclerosis >15% and <50%.[5] This strategy reduced the proportion of discarded kidneys to 20% but was associated with excess patient death and graft failure.[5] Pretransplantation biopsy evaluation was not mandatory, however, and patients could receive kidneys that, due to severe structural changes, could fail prematurely posttransplantation.[6]

In June 2013, the Organ Procurement and Transplantation Network (OPTN) approved a new allocation policy that stratifies deceased donors according to a kidney donor profile index (KDPI) that takes into account donor age, height, weight, ethnicity, history of hypertension and diabetes, cause of death, serum creatinine level, hepatitis C virus status, and donation after circulatory death status.[7] This scale is aimed to predict the kidney donor risk index (KDRI)—that is, the failure risk of a graft from a given deceased donor compared with the failure risk of a graft from an average donor of the previous year.[8] Despite this novel approach, however, the discard rates of kidneys recovered for transplantation by using the kidney donor profile index (KDPI) scale (18.3%) did not differ appreciably from the discard rate previously observed during the ECD era (18.1%).[9] Moreover, most of the kidneys obtained from donors with the highest KDPI values continued to be discarded.[4]

Notably, similarly to ECD, the KDPI scale has been implemented to predict the risk of graft failure on the basis of clinical parameters only, independent of histologic data from a pretransplantation kidney biopsy. According to KDPI, the risk of premature failure of a kidney from a 60- to 70-year-old white donor with hypertension and/or diabetes who is brain death from cerebrovascular events is predicted to exceed by 2- to 2.5-fold the failure probability of a graft obtained from an average donor identified during the previous year.[7] In sharp contrast with these figures, we previously found that the short-term[10] and long-term[11] outcomes of kidneys from donors older than 60 years of age—in most cases, with a history of hypertension and/or diabetes, renal disease and/or cerebrovascular death—which had been systematically allocated for single or dual transplantation or discarded based on predefined standardized histologic criteria, were similar to those of kidneys from young donors selected according to standard clinical criteria. Similar results were obtained when the same biopsy-guided strategy was extended to donors who were 70 or older.[12] Another study, however, found that 2-year graft loss exceeded 30% when kidneys from donors older than 75 years were used for single or dual transplantation according to the biopsy findings.[13] These data suggest that there is an upper donor age limit that should not be exceeded to avoid an excess risk of transplant failure. Alternatively, data could be explained by poorly restrictive histologic criteria used for kidney allocation to the single or dual transplantation.[13] To formally address this issue, we compared the outcomes of 37 recipients of 1 or 2 histologically evaluated kidneys from donors aged 80 or older with the outcomes of 198 recipients of single kidneys from donors aged 60 or younger, which had been allocated according to the same Nord Italia Transplant (NIT) network standard criteria but without preimplantation histologic evaluation and were expected to have a survival rate similar to that of kidneys from an average donor.

2 | MATERIALS AND METHODS

This matched cohort study[14] involved 235 consecutive patients referred to transplantation centers in Padua, Verona, and Bergamo (Italy) between 2006 and 2013. To assess the impact of donor age on transplantation outcomes, we compared the outcomes of 37 patients who had received 1 or 2 kidneys from brain-dead donors aged 80 years or older who had been histologically evaluated before implantation[10-12] ("recipients") with the outcomes of 198 patients who had received 1 kidney from "ideal" brain-dead donors aged 60 years or younger who had been selected and allocated for transplantation according to the same standard criteria of the Nord Italia Transplant (NIT) network ("reference-recipients") but without biopsy evaluation.[15,16] To minimize the potential role of confounding factors that could affect outcome data in addition to donor (and recipient) age, the outcomes of the 37 recipients were also compared with the outcomes of 74 of the 198 reference-recipients who had been matched with corresponding recipients by using a propensity score model[17] ("matched reference-recipients").

All patients provided written informed consent to undergo renal transplantation according to the NIT guidelines.[15,16,18] Patients who were to receive histologically evaluated kidneys provided additional written consent to receiving either 1 or 2 kidneys, depending on the results of a preimplantation biopsy. The biopsy-guided organ selection and allocation program was approved by the NIT organization.[18] This program aimed to offer patients aged 50 or older the option of organ transplantation that was an addition to the option of the transplantation of a single kidney from a young donor without a pretransplantation biopsy. At each renal transplant center, recipients and reference-recipients were treated, as per the centers' standard procedure, with a similar immunosuppressive protocol combining induction therapy with basiliximab and/or thymoglobulins and maintenance therapy with calcineurin inhibitors and/or mechanistic target of rapamycin (mTOR) inhibitors, mycophenolate mofetil or azathioprine, with or without steroids, and were managed by the same surgical and

medical team according to the same standardized monitoring protocol. According to NIT guidelines, the transplantation was performed only when the antidonor PRA test was negative. In all patients, serum creatinine levels were measured according to the isotopic dilution mass spectrometry standardized method.

The primary efficacy variable was graft function loss requiring chronic dialysis therapy. Secondary efficacy variables were a combined endpoint of need for dialysis or death and changes in serum creatinine levels from month 3 posttransplantation to study end. All data, including adverse events, were monitored and recorded by the Monitoring Unit of the Aldo e Cele Daccò Clinical Research Center of the IRCCS – Mario Negri Institute for Pharmacological Research, Bergamo. Data were used according to NIT standard regulations for data registration and use and for the preservation of patients' anonymity and privacy.[15,16,18]

2.1 | Donor and kidney evaluations

All potential brain-dead donors—including octogenarian donors and the donors of reference-recipients and matched reference-recipients—were identified, screened, and selected according to predefined protocols of the NIT network based on the same demographic, anthropometric, clinical, and laboratory parameters and an instrumental workup that included ultrasound assessment of renal parenchyma and urinary tract and an echo color-Doppler evaluation of the aorta, renal vascular tree, and kidney perfusion.[15,16,18] Computed tomography scanning or angiographic evaluations were considered only in selected cases with specific indication. Information about donor ethnicity, comorbidities, kidney function, and cause of death was recorded and data were subsequently used to calculate the KDPI and KDRI of each study donor by using the OPTN calculator (available at https://optn.transplant.hrsa.gov/resources/allocation-calculators/kdpi-calculator/).

According to standard NIT guidelines, kidneys were discarded that, during donor ultrasound evaluation or direct evaluation after explantation, showed severe macroscopic parenchymal abnormalities (including diffuse scarring or hypoplasia, or neoplastic masses) or major vascular abnormalities (eg, severe, diffuse atherosclerotic changes or calcifications of the aorta or renal vascular tree that in the surgeon's judgment prevented the possibility of successful anastomoses with recipient artery vessels or were at high risk of posttransplantation thrombosis). Detection of urologic abnormalities conditioning obstruction that could be addressed and of benign renal cysts was not a contraindication to transplantation. Eligible kidneys from donors aged 60 years or younger were not evaluated histologically. Tissue samples were obtained with a 16-gauge needle by surgeons from the inferior pole of both kidneys from octogenarian donors at the time of bench evaluation, were fixed in formalin and paraffin embedded, and were evaluated by general pathologists who were on call at participating centers. Changes in vessels, glomeruli, tubules, and connective tissue in biopsy specimens were quantified on a scale from 0 (no changes) to 3 (severe changes) by using a standardized score predefined by an international panel of pathologists[10-12] that reliably predicted the scoring of the structural changes observed at autoptic evaluation of the whole kidneys[19] and was validated in prospective controlled studies.[10-12] When kidneys had a score between 0 and 3, they were used for 2 single transplantations. When one kidney had a score between 0 and 3 and the other kidney had a score of 4 or greater, or when both kidneys had a score between 4 and 6, the 2 kidneys were transplanted together into the same recipient. If one kidney had a score between 4 and 6 and the other kidney had a score of 7 or greater, or both kidneys had a score of 7 or greater, the 2 kidneys were discarded.[10-12] In dual transplant recipients, the 2 kidneys were implanted through 2 bilateral incisions or a single incision as per center practice. Duration of surgery averaged approximately 5 hours for dual transplantations with bilateral incisions, 4 hours for dual transplantations with unilateral incisions, and 2 hours 30 minutes for single transplantations.

2.2 | Statistical analyses

Descriptive statistics at renal transplantation (baseline) of recipients and reference-recipients were based on frequency and percentage analysis for categorical variables and on mean (SD) or median (interquartile range [IQR]) values for continuous variables. Donor and patient baseline characteristics were compared by using the Pearson χ^2 test, the Fisher exact test for categorical variables, or the Welch 2-sample *t* test or Wilcoxon rank-sum test for continuous variables. Normality assumption was assessed by using the Shapiro-Wilk test. Kaplan-Meier curves were shown for descriptive purposes only. Cumulative incidences were compared with the use of hazard ratios (HRs), and their 95% confidence intervals (CIs) were obtained by using Cox regression analysis. Participants who did not experience the event of interest were right-censored on the last day of the observation period. Unadjusted and adjusted HRs were obtained to compare survival until the first event between the recipients and reference-recipients. The proportional hazards assumption was checked by using Schoenfeld residuals. For analyses of posttransplantation renal function recovery, serum creatinine levels of patients with graft loss were carried forward to the end of the observation period. The same approach was used for posttransplantation glomerular filtration rate (GFR) that was estimated by using both the abbreviated Modification of Diet in Renal Disease (aMDRD) and the **CKD** Epidemiology Collaboration (CKD-Epi) prediction equations.

Matched cohort analyses were carried out by using a propensity score–based algorithm,[17] identifying 74 of the 198 reference-recipients, who were matched with the 37 corresponding recipients in the context of a 1:2 matched cohort design (matched reference-recipients). Variables at the time of transplantation considered for matching included the transplant center, the year of transplantation (±1 year vs corresponding recipients), donor sex, recipient sex, recipient age, mismatches, and donor:recipient body mass index ratios. Associations between baseline covariates and the group of interest (ie, recipients or reference-recipients) were obtained by using logistic regression in the pooled baseline data. Next, a stepwise selection algorithm using the SAS macro "OneToManyMTCH"

was considered to reach the final propensity score model. Survival analysis comparing 37 recipients and the corresponding 74 matched reference-recipients was carried out with a shared frailty model by using STATA.[20] Two-sided *P*-values <.05 were considered statistically significant. Recorded data were analyzed with the use of SAS, version 9.2 (SAS Institute, Cary, NC) and STATA software, version 13 (StataCorp, College Station, TX), at the Laboratory of Biostatistics of the Clinical Research Center.

2.3 | Role of the funding source

This was a fully academic, internally funded study. No sponsor was involved in study design, in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the manuscript for publication.

3 | RESULTS

Eight of 58 potential kidney donors aged 80 or older were not considered for kidney donation because severe renal vascular, parenchymal, or urinary tract abnormalities (see Materials and Methods) were detected during the standard ultrasound evaluation that is routinely performed in any potential kidney donor according to NIT guidelines and independent of donor age (Figure 1). Thus, 100 kidneys were recovered from 50 octogenarian donors. Fourteen kidneys from 7 of these donors were discarded before pretransplantation biopsy because of severe and diffuse atherosclerotic changes of the aorta and renal artery and the ramifications found during the macroscopic evaluation, and 12 kidneys from 6 other donors were discarded because the biopsy evaluation revealed severe tissue damage. Thus, 74 kidneys from 37 (74%) of 50 available donors were suitable for transplantation. Kidneys from 33 of these donors were allocated to dual transplantation in 33 recipients. Kidneys from the remaining 4 donors were allocated to single transplantation: 4 kidneys were transplanted at study centers and the outcomes of the 4 recipients were considered here, whereas the other 4 kidneys were transplanted elsewhere. The recipients of these 4 kidneys were not included in present analyses to avoid the confounding effect of different monitoring and treatment strategies at centers out of the study network. Thus, 37 recipients were available for comparative analyses with 198 reference-recipients and 74 matched reference-recipients who received a single kidney transplant from donors aged 60 or younger at the same centers and during the same observation period.

3.1 | Donor and patient characteristics

3.1.1 | Donors

Octogenarian donors were 34.4 ± 9.4 and 32.8 ± 7.0 years older than donors of reference-recipients (*P* < .0001) and matched reference-recipients (*P* < .0001), respectively (Table 1). Octogenarian donors were more frequently female and weighted less than donors of reference-recipients, and their kidneys had longer cold ischemia times before implantation than the kidneys from younger donors. Other parameters considered, including ethnicity, kidney function, and the distribution of comorbidities and causes of death, were similar across groups; in particular, they were very well balanced between octogenarian donors and donors of matched reference-recipients, with the exception of the per-protocol difference in donor ages. Of interest, estimated GFR (by aMDRD or CKD-Epi equations) was in the normal range in most of octogenarian donors and was only slightly, but nonsignificantly, lower than in donors of reference-recipients or matched reference-recipients (Table 1). Noteworthy, KDPI was 100% in 34 of the 37 octogenarian donors and ranged from 97% to 98% and 99% in the other 3 octogenarians. Conversely, KDPI was <95% in all donors of reference-recipients and matched reference recipients, respectively (Figure 2). The difference in KDPI distribution in octogenarian donors compared with the other donor groups was highly significant (*P* < .0001 for both comparisons, Figure 2). Consistently, mean KDPI was significantly higher and KDRI was more than double in octogenarian donors than in the other 2 donor groups (Table 1, Figure 3A), whereas the proportion of patients progressing to end-stage kidney disease (ESKD) was much the same in the 3 groups (Figure 3B).

3.1.2 | Patients

Recipients were 17.9 ± 9.3 and 16.4 ± 8.7 years older than reference-recipients (*p* < .0001) and matched reference-recipients (*p* < .0001) and had significantly more HLA mismatches compared with their corresponding donors. Time on dialysis was significantly shorter for recipients than for reference-recipients and matched reference-recipients, and this difference was fully explained by the significantly shorter time on a waitlist for recipients compared with recipients in the 2 reference groups. Consistently, time on dialysis before inclusion in a waitlist was similar in the 3 groups (Table 2, Figure 4). Second transplantations tended to be less frequent in recipients than in reference-recipients; this nonsignificant difference, however, was fully blunted when matched reference-recipients were considered for comparative analyses vs recipients. A significantly higher proportion of kidneys from female donors were transplanted into male patients among recipients compared with reference-recipients. Consistently, the donor:recipient body weight and mass index ratios were significantly lower for recipients than for reference-recipients. These differences where blunted in the context of the matched cohort comparisons. Recipients spent a 5- to 6-fold shorter time on a waitlist compared with patients in both control groups. Other characteristics, including follow-up duration, were similar in the 3 groups. Distribution of causes of ESKD was very well comparable in particular between recipients and matched reference-recipients (Table 2). Distribution of medications administered for induction and maintenance immunosuppression was similar in the 3 groups with a nonsignificant trend to a less frequent use of calcineurin inhibitors and a more frequent use of mTOR inhibitors in recipients than in reference- and matched reference-recipients (Table 3).

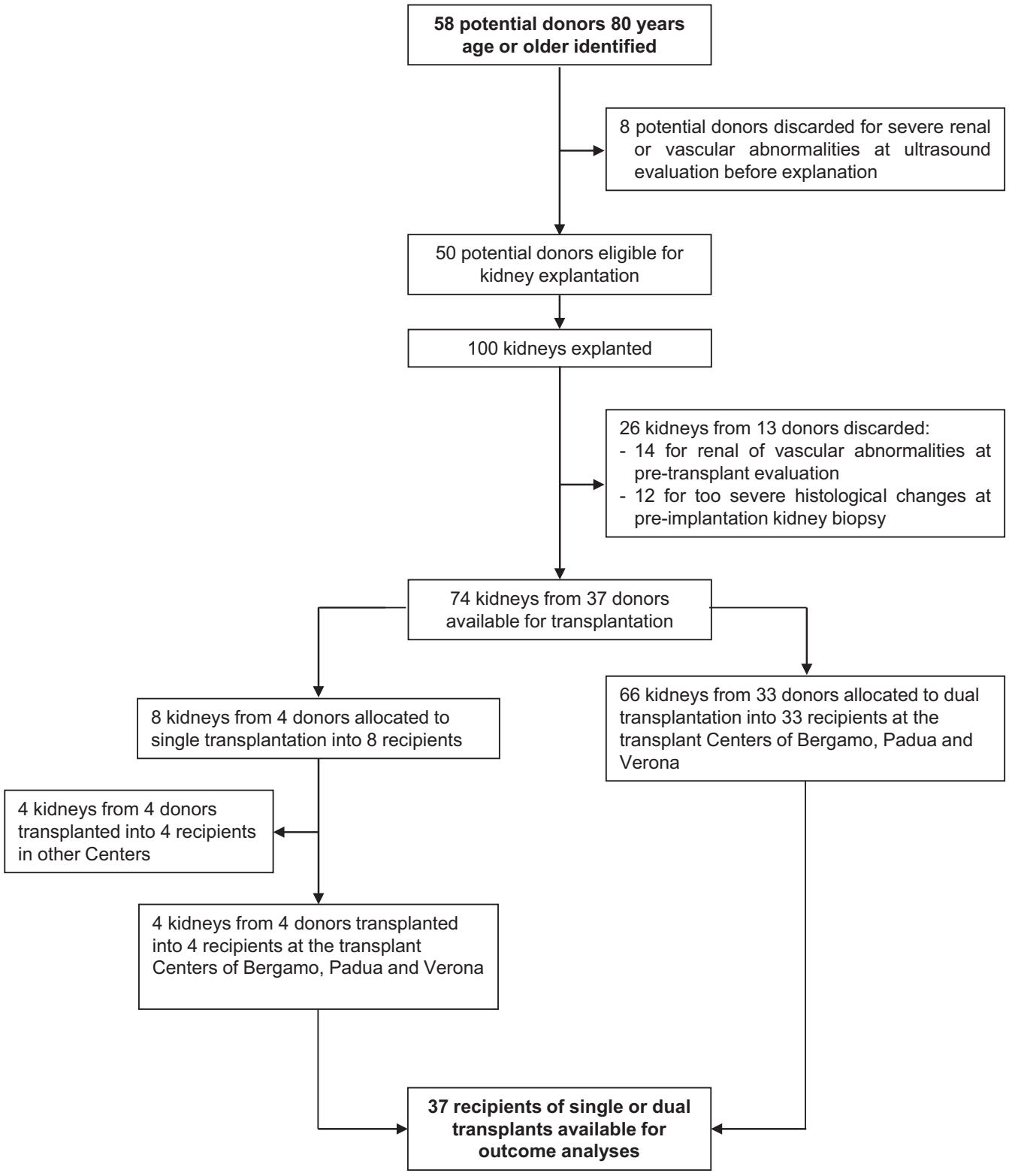


FIGURE 1 Flowchart of selection and allocation of kidneys from octogenarian donors

3.2 | Graft and patient survival

During a median (IQR) of 25 (13-42) months, 2 (5.4%) of the 37 recipients and 10 (5.1%) of the 198 reference-recipients required chronic renal replacement therapy by dialysis (HR [95% CI] 1.55 [0.34-7.12], $P = .576$). Outcomes were similar (HR [95% CI] 1.41 [0.10-19.54], $P = .798$) even after prespecified adjustment for donor age and sex (Figure 5 and Table 3). Thus, graft survival was similar between groups despite KDPI and KDRI being significantly higher for octogenarian donors than for young donors of reference-recipients (Table 1, Figure 3). Two recipients

TABLE 1 Donor characteristics at the time of transplantation

	Donors of recipients (n = 37)	Donors of reference-recipients (n = 198)	Donors of matched reference-recipients[a] (n = 74)
Age, y	82.0 ± 2.1	47.6 ± 10.0‡	49.1 ± 8.5‡
Age range, y	80-86	16-60	19-60
Male sex, n (%)	10 (27.0)	118 (59.6)†	23 (31.1)
Ethnicity, n (%)			
White	37 (100)	191 (96.5)	72 (97.3)
African American	0	1 (0.5)	1 (1.4)
Other/unknown	0	6 (3.0)	1 (1.4)
Comorbidities, n (%)			
Hypertension	27 (73.0)	45 (22.7)‡	18 (24.3)‡
Diabetes	6 (16.2)	7 (3.5)*	4 (5.4)
Hepatitis C virus	0	1 (0.5)	0
Body weight, kg	66.9 ± 10.0	76.4 ± 19.8‡	70.6 ± 15.1
BMI, kg/m^2	25.0 ± 3.0	29.0 ± 35.5	24.8 ± 4.2
Serum creatinine, mg/dL	0.83 (0.24)	0.92 (0.44)	0.86 (0.52)
eGFR, mL/min/1.73 m^{2b}	85.3 ± 35.3	99.8 ± 39.7	102.5 ± 43.6
Cold ischemia time, h	16 (13-18)	14 (11-17)*	14 (12-18)
Cause of death, n (%)			
Cerebrovascular/stroke	28 (75.7)	125 (63.1)	53 (71.6)
Head trauma	8 (21.6)	43 (21.7)	15 (20.3)
Anoxia	0	22 (11.1)	5 (6.8)
Central nervous system tumor	0	2 (1.0)	1 (1.4)
Other/unknown	1 (2.7)	6 (3.0)	0
KDPI score (%)	99.8 (0.6)	55.6 (21.0)‡	60.1 (20.8)‡
KDRI score (%)	2.57 (0.32)	1.09 (0.24)‡	1.14 (0.24)‡

Donor characteristics are according to groups of patients who received 1 or 2 histologically evaluated kidneys from donors ≥80 y ("recipients") or 1 non–histologically evaluated kidney from ≤60-y donors considered as a whole ("reference-recipients") or in the context of the 1:2 matched-cohort design ("matched reference-recipients").

[a]Matching by the propensity score model.

[b]According to abbreviated Modification of Diet in Renal Disease (aMDRD) equation.

*P < .01, †P < .001, ‡P < .0001 vs recipients with donors ≥ 80 y. Data are given as mean ± SD or median (IQR) or n (%).

(5.4%) died by the age of 63 and 73 of stroke and sepsis, respectively. Four reference-recipients (2.0%) died by the age of 39, 44, 59, and 62 from metastatic colon cancer, sepsis, bacterial pneumonia, and lung cancer, respectively (Table 3). Thus, 4 recipients (10.8%) and 14 reference-recipients (7.1%) required dialysis or died (HR [95% CI] 2.31 [0.75-7.07], P = .144). Similar results were obtained (HR [95% CI] 3.66 [0.48-27.87], P = .210) when the analyses were adjusted for donor age and sex.

In addition to the 2 recipients, 4 (5.4%) of the 74 matched reference-recipients also required dialysis (HR [95% CI] 1.25 [0.24-6.56], P = .795) (Figure 6, Table 3). Again, graft survival was similar between groups despite KDPI and KDRI being significantly higher for octogenarian donors than for donors of matched reference-recipients (Table 1, Figure 3) Only 1 matched reference-recipient (1.3%) died, aged 62 of lung cancer. Thus, in addition to the 4 recipients, 5 (6.7%) matched reference-recipients also required dialysis or died (HR [95% CI] 2.07 [0.57-7.49], P = .270).

3.3 | Posttransplantation kidney function recovery

At 3 months posttransplantation serum creatinine was higher in recipients than in reference-recipients and matched reference-recipients (1.69 ± 0.68 vs 1.51 ± 0.56 vs 1.38 ± 0.41 mg/dL, respectively), and the difference between recipients and matched reference-recipients was significant (P < .05). Consistently, estimated GFR (eGFR) (by aMDRD equation) was significantly lower in recipients than in reference and matched reference-recipients (46.89 ± 19.13 vs 55.42 ± 22.81 vs 57.99 ± 20.15, P < .05 and P < .01, respectively). However, on follow-up, serum creatinine levels were relatively stable in recipients, whereas they tended to progressively increase in both reference groups (Figure 7, A and B). However, differences between groups were never significant. Consistently, eGFR (aMDRD and CKD-Epi) was stable in recipients and progressively declined in both reference groups (data not shown).

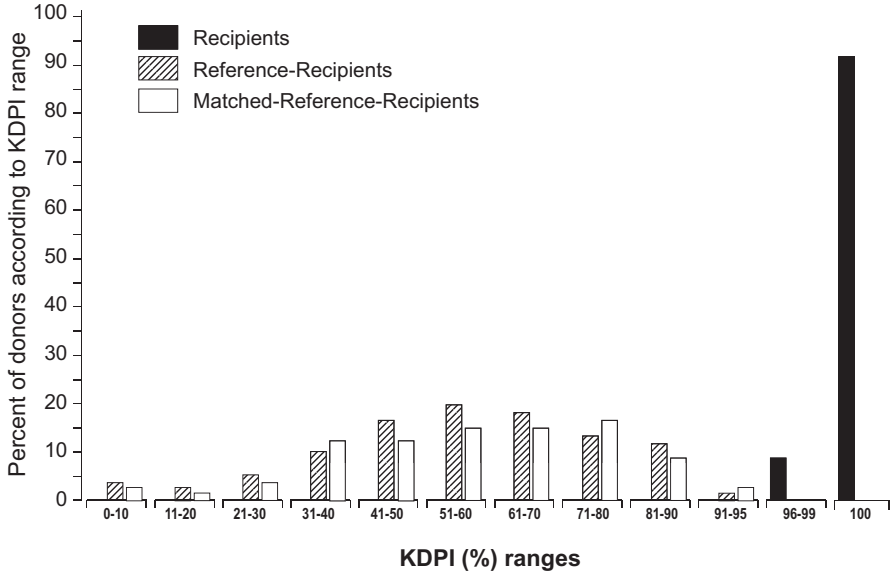


FIGURE 2 Distribution of donors of recipients, reference-recipients, and matched reference-recipients according to their kidney donor profile index (KDPI). The distribution was significantly different between donors of recipients and donors of the other 2 control groups ($P < .0001$ for both comparisons), whereas KDPI distribution did not differ between donors of reference-recipients and matched reference-recipients

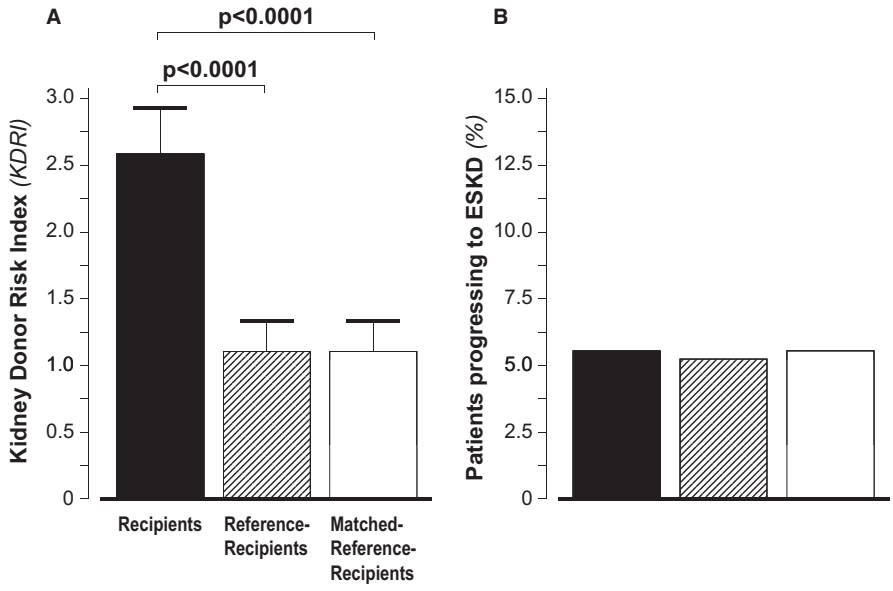


FIGURE 3 Mean (SD) kidney donor risk index (KDRI) (A) predicted on the basis of kidney donor profile index (KDPI) and percentage of patients progressing to end-stage kidney disease (ESKD) during the study (B) in recipients, reference-recipients, and matched reference-recipients. KDRI was significantly higher for recipients than for the 2 other groups ($P < .0001$ for both comparisons), whereas the incidence of ESKD was identical among the 3 groups

3.4 | Safety

There were relatively few fatal and nonfatal serious adverse events, and they were distributed similarly across groups (Table 3). The 5 cases of graft loss owing to chronic allograft nephropathy were observed in reference-recipients.

4 | DISCUSSION

This study indicates that the survival of kidney grafts recovered from donors aged 80 or older and selected and allocated for single or dual transplantation according to both standard clinical criteria and biopsy findings before transplantation was similar to that of single grafts from donors aged 60 or younger selected and allocated based on standard clinical criteria only. The 1:2 matched-cohort study comparing the outcomes of recipients of older grafts with those of recipients of younger grafts, who had been identified and matched based on predefined characteristics (including transplant center, year of transplantation, donor and recipient sex, and recipient age), produced similar findings. Notably, posttransplantation graft and patient survival, as well as renal function recovery, were similar across all considered groups, despite grafts from octogenarian donors being almost 35 years older than those from younger donors and recipients of octogenarian kidneys being approximately 17 years older than recipients of younger kidneys. Notably, in 34 of our 37 octogenarian donors, the KDPI was 100%. In the remaining 3 donors, it ranged between 97% and 99%. Consistently, their KDRI exceeded by more than 2-fold the KDRI of donors aged 60 years or younger. Thus, it is conceivable that a very small minority, probably none, of these donors would have been considered for organ explantation on the basis of the KDPI-based kidney allocation system. Thus, our present findings provide the evidence that extending

TABLE 2 Characteristics of patients

	Recipients (n = 37)	Reference-recipients (n = 198)	Matched reference-recipients[a] (n = 74)
Age, y	65.7 ± 6.2	47.8 ± 9.8‡	49.3 ± 9.6‡
Age range, y	54-81	23-76	27-76
Male sex, n (%)	26 (70.3)	131 (66.2)	47 (63.5)
Ethnicity, n (%)			
White	37 (100)	190 (96.)	69 (93.2)
African American	0	7 (3.5)	4 (5.4)
Hispanic	0	1 (0.5)	1 (1.4)
Cause of ESKD, n (%)			
Glomerular disease	17 (45.9)	75 (37.9)	31 (41.9)
Hypertension/ nephroangiosclerosis	3 (8.1)	17 (8.6)	10 (13.5)
Diabetes	2 (5.4)	4 (2.0)	2 (2.7)
ADPKD	8 (21.6)	31 (15.7)	10 (13.5)
Congenital/interstitial disease	2 (5.4)	37 (18.7)	9 (12.2)
Systemic disease	0	6 (3.0)	1 (1.4)
Other/unknown	5 (13.5)	28 (14.1)	11 (14.9)
HLA-DR mismatches vs donor, n	5 (4-5)	4 (3-4)‡	4 (4-5)*
Body weight, kg	72.6 ± 13.3	69.7 ± 13.6	69.2 ± 12.5
BMI, kg/m^2	25.0 ± 3.2	24.3 ± 4.0	24.2 ± 3.8
Body weight ratio (donor:recipient)	0.95 ± 0.23	1.13 ± 0.38†	1.04 ± 0.29
BMI ratio (donor:recipient)	1.02 ± 0.19	1.23 ± 1.58†	1.05 ± 0.24
Donor-to-recipient sex mismatches, n/n[b]	18/2	48/35*	31/7
Time on dialysis, mo	18.0 (11.0-33.0)	48.5 (31.0-72.0)‡	48.0 (30.0-71.0)‡
Time on waitlist, mo	7.5 (4.0-19.5)	36.0 (19.0-56.0)‡	40.0 (24.0-56.0)‡
Time on dialysis before waitlist inclusion, mo	11.5 (2.0-18.5)	12.0 (6.0-21.0)	14.0 (6.0-22.0)
Dual transplantations, n (%)	33 (89.2)	0	0
Second transplantations, n (%)	0	30 (15.1)#	3 (4.0)
Follow-up, mo	24 (12-36)	26 (14-48)	25 (18-48)

Characteristics of patients who received 1 or 2 histologically evaluated kidneys from donors ≥80 y (recipients) or 1 non–histologically evaluated kidney from ideal ≤60-y donors considered as a whole (reference-recipients) or in the context of the 1:2 matched-cohort design (matched reference-recipients).

ESKD, end-stage kidney disease; BMI, body mass index; ADPKD, autosomal dominant polycystic kidney disease.

[a]Matching by the propensity score model.

[b]Female donor–to–male recipient/male donor–to–female recipient.

*P < .01, †P < .001, ‡P < .0001 vs recipients with donors ≥80 y. Data are given as mean ± SD or median (IQR) or n (%).

a biopsy-guided policy of graft selection and allocation to old or very old donors is expected to further and substantially expand the donor pool and the number of transplantations, without affecting the pool of organs potentially suitable for "standard" single transplantations and, at the same time, without increasing the risk of premature graft failure.

Actually, an increased number of available organs translated into 5- to 6-fold shorter mean waitlist time for recipients of kidneys from octogenarian donors compared with recipients of younger kidney donors. This finding has major implications, because recipients of kidney grafts, including those from older donors, have substantially reduced mortality

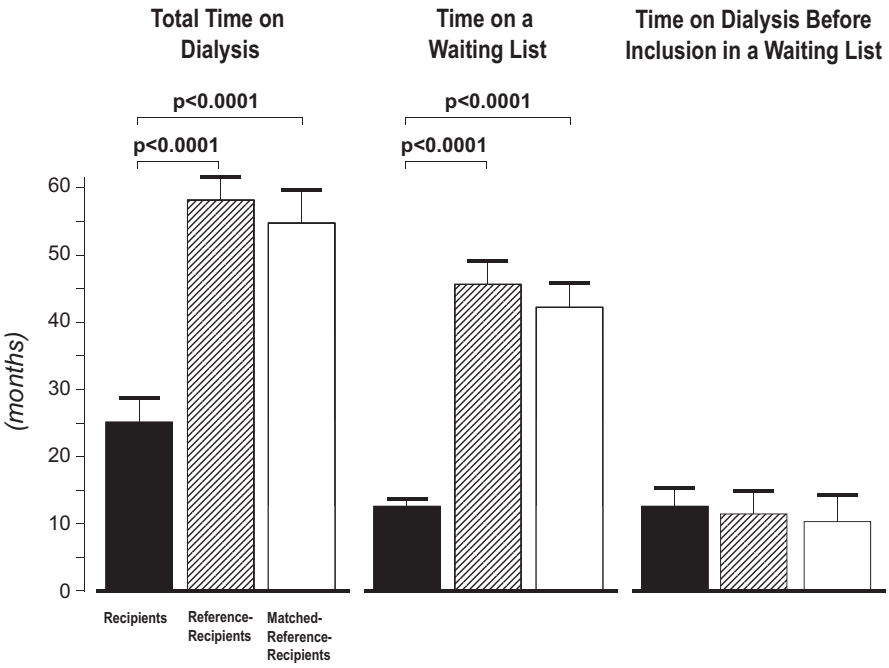


FIGURE 4 Total time on dialysis (left), time on a waitlist (middle), and time on dialysis before inclusion in a waitlist (right) in recipients, reference-recipients, and matched reference-recipients. All data are mean ± SEM. Total waiting time and time on a waitlist were significantly longer for reference-recipients and matched reference-recipients ($P < .0001$ for both comparisons), whereas time on dialysis before inclusion on a waitlist was similar in the 3 groups

TABLE 3 Induction and maintenance immunosuppressive therapy of patients

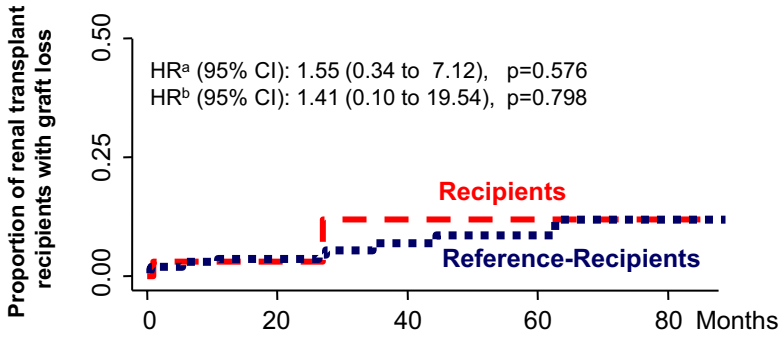
Immunosuppressive therapy	Recipients (n = 37)	Reference-recipients (n = 198)	Matched reference-recipients[a] (n = 74)
Induction, n (%)			
Basiliximab alone	13 (35.1)	119 (60.1)	41 (55.4)
Thymoglobulin alone	18 (48.6)	49 (24.7)	17 (23.0)
Basiliximab plus low-dose thymoglobulin	6 (16.2)	27 (13.6)	14 (18.9)
None	0	2 (1.0)	1 (1.4)
Unknown	0	1 (0.5)	1 (1.4)
Maintenance			
Steroids	34 (91.9)	169 (85.4)	61 (82.4)
Cyclosporine or tacrolimus	24 (64.9)	185 (93.4)	67 (90.5)
Mycophenolate mofetil or azathioprine	25 (67.6)	166 (83.8)	63 (85.1)
Sirolimus or everolimus	24 (64.9)	32 (16.2)	11 (14.9)
Belatacept	0	7 (3.5)	5 (6.8)

Data are given as n (%).
Induction and maintenance immunosuppressive therapy of patients who received 1 or 2 histologically evaluated kidneys from donors ≥80 y (recipients) or 1 non–histologically evaluated kidney from ideal ≤60-y donors considered as a whole (reference-recipients) or in the context of the 1:2 matched-cohort design (matched reference-recipients).
[a]Matching by the propensity score model.

rates and improved life expectancy compared with transplant candidates on maintenance dialysis treatment.[2] Shortening the waiting time for a transplant may also have major clinical implication becausee prolonged time on a waitlist is one of the strongest modifiable risk factors for poor outcome posttransplantation.[21]

All patients had a negative donor-specific PRA test at the time of transplantation; the proportion of second transplantations was similar among groups (in particular between recipients and matched reference-recipients); and the number of HLA-DR mismatches and the distribution of immunosuppressive medications were also similar in the 3 groups. Thus, study findings were unlikely confounded by different immunologic risk in different groups. With the exception of the expected age difference, main anthropometric, clinical, and laboratory characteristics were also similar in the 3 patient groups.

Our present findings are in harmony with data from a recent retrospective analysis of 442 single or dual transplantations of kidneys from marginal donors that had been selected and allocated on the basis of a pretransplantation donor biopsy by using the same histologic score

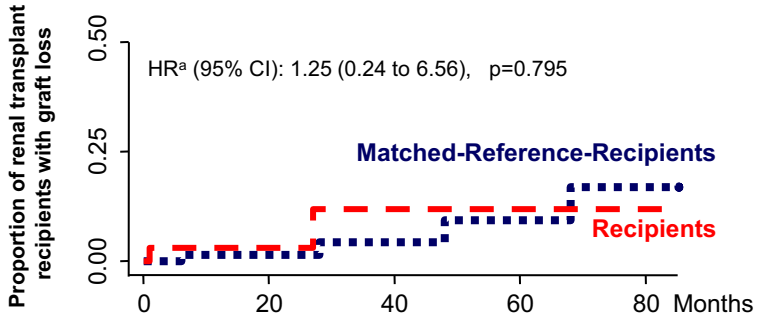


Patients at risk

Recipients	37	20	6	2	2
Reference-Recipients	198	140	61	32	23

[a]Cox unadjusted, [b]Cox adjusted for donor age and gender.

FIGURE 5 Kaplan-Meier survival curves for progression to end-stage kidney disease during a 80-month period in 37 recipients of 1 or 2 kidneys from donors aged 80 or older allocated based on preimplantation histologic evaluation and in 198 reference-recipients who received 1 kidney from donors aged 60 or younger that was not evaluated histologically before implantation. [Color figure can be viewed at wileyonlinelibrary.com]



Patients at risk

Recipients	37	20	6	2	2
Matched-Ref.-Recipients	74	54	23	13	10

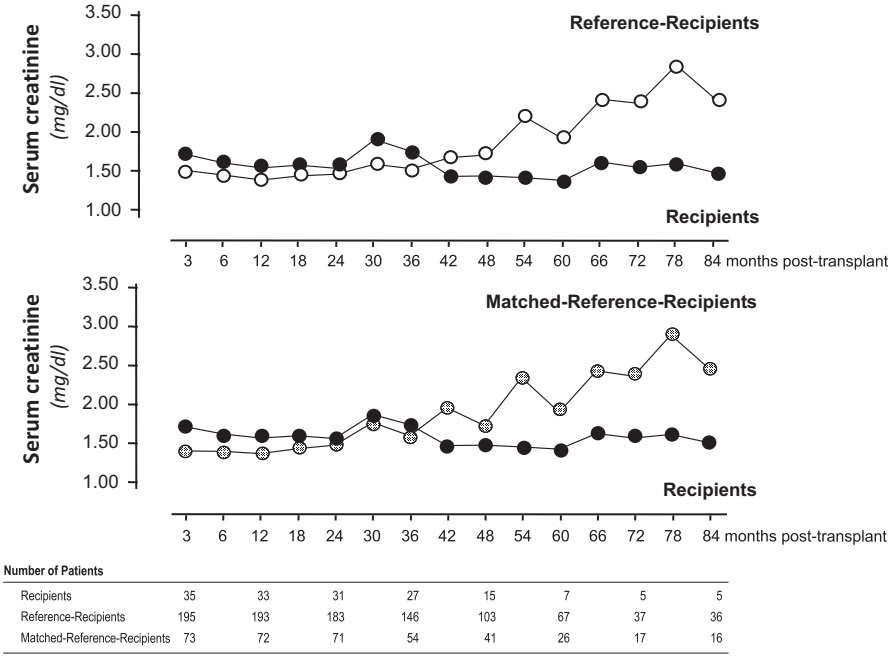
[a]Frailty Cox

FIGURE 6 Kaplan-Meier survival curves for progression to end-stage kidney disease during a 80-month period in 37 recipients of 1 or 2 kidneys from donors aged 80 or older allocated based on preimplantation histologic evaluation and in 74 matched reference-recipients identified by the propensity score model in the context of a 1:2 matched-cohort study who received 1 kidney from donors aged 60 or younger that was not evaluated histologically before implantation. [Color figure can be viewed at wileyonlinelibrary.com]

we originally implemented[10] and tested in clinical studies[10-12] including the present one. Data showed that biopsy-guided allocation of marginal kidneys halved the relative discard rate and allowed a >25% absolute increase in the rate of recovery of kidneys with a KDPI score >80.[22] These findings were estimated to correspond to an overall increase in transplantation of approximately 4% considering the entire donor pool.[22] In that study, however, donor age averaged 60 years and only 5 (1.1%) of the donors were aged 80 or older. According to data of the OPTN/UNOS Registry, 88% of kidneys from donors with KDPI ranging from 90% to 100% and potentially available for single or dual transplantation were discarded between 2002 and 2012.[4] This is explained by the fact that selection and allocation of kidneys from these donors without preimplantation histologic evaluation are expected to translate into an unacceptable excess risk of premature graft failure. Notably, KDPI exceeded 96% in all our octogenarian donors.

On the other hand, finding that 75% of kidneys recovered from octogenarian donors were suitable for transplantation confirms that biopsy-guided organ allocation is an efficient strategy to further reduce the number of discarded kidneys, even when very old donors are considered. These benefits largely offset the extra time and costs required to select and allocate kidneys based on biopsy findings. Notably, almost half of the donors with unsuitable kidneys were identified before explantation through a standard screening protocol that is applied by any center of the NIT network and is based on the use of simple and inexpensive procedures, including an abdominal ultrasound evaluation, which is easily accessible in any intensive care unit and is a key component of screening protocols of any potential donor, independent of age, in everyday clinical practice. Kidneys from only 13—less than one-fourth—of the 59 considered octogenarian donors were eventually discarded after explantation because of macroscopic vascular abnormalities or histologic changes that were too severe.

Indeed, an additional advantage of preimplantation biopsy evaluation of older kidneys[10-12] is that it may protect patients from receiving grafts with structural changes that are too severe and may be associated with the donor's hypertension, diabetes, or other concomitant diseases or just reflect renal ageing[23] and that may predict poor kidney survival.[24] This may explain why posttransplantation functional recovery of octogenarian kidneys was similar to that of young kidneys from ideal donors and old grafts appeared to be protected from chronic allograft nephropathy. Indeed, chronic injury in renal allografts



Number of Patients								
Recipients	35	33	31	27	15	7	5	5
Reference-Recipients	195	193	183	146	103	67	37	36
Matched-Reference-Recipients	73	72	71	54	41	26	17	16

FIGURE 7 Posttransplantation serum creatinine changes during 84 months of follow-up in 37 recipients of 1 or 2 kidneys from donors aged 80 or older allocated based on preimplantation histologic evaluation and in 198 reference-recipients (top) or matched reference-recipients identified by the propensity score model (bottom) who received 1 kidney from donors aged 60 or younger that was not evaluated histologically before implantation

is sustained, at least in part, by an imbalance between graft filtration power and recipient metabolic demand, which results in compensatory hyperfiltration of glomeruli surviving reperfusion injury, rejection, and drug toxicity.[25] As observed in experimental[26] and human[27] chronic nephropathies characterized by reduced nephron mass, these (mal) adaptive changes may accelerate renal function deterioration and progressive glomerulosclerosis up to terminal renal failure.[25] These events could conceivably be prevented, even when kidneys from extremely old donors are used, thanks to biopsy-guided appropriate dosing of supplied nephrons with single or dual transplantation.[28] Consistently, patient and graft outcomes in recipient groups were similar despite the large majority of female donors, the much more frequent allocation of kidneys from female donors to male recipients, and the lower donor:recipient body weight ratio observed in recipients of octogenarian kidneys compared with the 2 control groups. These findings appear to be in contrast with well-established evidence that short- and long-term graft survival is relatively poor when kidneys from female donors are transplanted into male recipients[29] and/or allograft size is small relative to recipient body weight.[30] Conceivably, these adverse outcomes can be prevented if appropriate nephron numbers for transplant recipients are ensured by pretransplantation biopsy evaluation. These findings may have important clinical implications, because female donors account for the majority of older donors, whereas most patients waiting for a kidney transplant are male.[31] The clinical relevance of adequate nephron dosing is highlighted by results of a recent important report[32] that compared the outcomes of recipients of single or dual kidney grafts (histologically evaluated in most, but not all, cases) from ECD donors categorized according to donor age. In contrast with our present data, graft survival was approximately 10% lower in recipients of kidneys from octogenarian donors (65.9%) than in recipients of kidneys from younger (50 to 79 years) donors considered as a whole (approximately 75%). A large part of this difference was driven by a graft failure rate that approximated 50% in recipients of single transplants from octogenarian donors. Independent of the potential role of allocation of some organs without previous histologic evaluation, these data were most likely explained by the fact that kidneys with a score of 4 were allocated to single rather than to dual transplantations.[10-12] Conceivably, the nephron mass supplied with a single, octogenarian kidney with a score of 4 is not sufficient for the metabolic demand of the recipient, which may translate into maximized hyperfiltration of residual nephrons and accelerated graft function exhaustion, up to terminal failure. On the other hand, allocation of these kidneys to a single transplantation may further increase the organ pool and transplant options for older recipients. Thus, the most performant biopsy-guided allocation strategy to enhance the number of successful transplantations from old and very old donors should be tested in the context of a controlled, prospective study.

4.1 | Safety

Only 2 recipients of kidneys from octogenarian donors died with a functioning kidney aged 63 and 72, respectively. Thus, the mortality rate was relatively low compared with mortality reported in previous series of recipients of single or dual ECD grafts.[2,3] The incidence of nonfatal complications was also low and similar in different patient groups, and no graft was lost because of complications with the preimplantation biopsy, which confirmed that biopsy-guided transplantation of 1 or 2 kidneys from extremely old donors to relatively old recipients was a safe and well-tolerated procedure. Moreover, the cold ischemia time (time between procurement of the organ and transplantation) of octogenarian kidneys exceeded the ischemia time of young kidneys by only 2 hours, a difference that was fully blunted in the context of matched-cohort comparisons. Combined, these findings underline that no kidney from an octogenarian donor was discarded because

ischemia time was too long, indicating that evaluating a preimplantation biopsy specimen is compatible with routine organ procurement and allocation. This may have clinical implications because the duration of cold ischemia time is a major determinant in graft outcomes, in particular when marginal kidneys are used for transplantation.[2,3]

4.2 | Limitations and strengths

This was a prospective outcome analysis of data that, however, had been already retrospectively recorded for other (clinical) purposes. Thus, some data concerning the number of octogenarians that were not considered for donation and of sensitized patients or patients with donor-specific antibodies as well as information about dimensions of transplanted kidneys were not available. Proteinuria was also reported in a minority of cases. Moreover, because of the relatively small number of patients and short follow-up, the results must be considered with caution. However, they can pave the way to larger and more powerful studies aimed to optimize the use of older donors to increase transplant activity without affecting transplantation outcomes. On the other hand, patients were identified, treated, and monitored based on predefined and standardized protocols that were similar for all considered cohorts. These protocols are shared by NIT centers and are the same protocols that are applied to any average kidney transplant recipient in everyday clinical practice. This enhances the generalizability of our findings to the real world. Moreover, no additional, time-consuming, and expensive tests such as computed tomography scanning or angiographic evaluations were routinely required and were performed only on the basis of specific indications, as for any average donor. Thus, the evaluation of octogenarian donors did not imply extra human work and costs that could be directly related to the donor age. On the other hand, the use of octogenarian donors is progressively increasing with encouraging results also in liver transplantation.[33-36] Thus, octogenarian donors could be evaluated for both kidney and liver transplantation. This will further increase the cost-effectiveness of organ procurement from very old donors. Of note, octogenarian donors and their old recipients had a relatively low prevalence of classic cardiovascular (and renal) risk factors such as obesity, diabetes, or hypertension. This most likely explained their longevity. Conceivably, this also explained why kidney function of octogenarian donors was almost similar to that of ideal donors and why recipients of octogenarian kidneys had a posttransplantation rate of cardiovascular events that was similar to that of younger recipients. This further enhances the cost-effectiveness of donor pool expansion with the use of octogenarian donors.

Biopsy samples can be evaluated by a general pathologist without specific training in renal pathology, which enhances the feasibility of the procedure. The use of a propensity score model in the context of a matched-cohort design limited the role of potential confounding factors. The sample size was not calculated a priori based on an expected difference across groups in the primary outcome variable; however, the study size was similar to that of studies reported previously in a similar context.[10-12] Long-term follow-up and careful patient monitoring and data recording were major strengths.

5 | CONCLUSIONS

Kidneys from donors aged 80 or older can provide excellent graft survival and renal function recovery for up to 7 years after transplantation, provided they are allocated as single or dual transplants according to biopsy findings before transplantation and that kidneys with more severe, chronic changes are discarded. These data confirm that there should not be any predefined upper age limit to screening and evaluation of a potential brain-deceased kidney donor. The study findings highlight a simple and safe procedure that can enable further expansion of the donor organ pool to enhance the opportunities for successful transplantation, even for recipients of kidneys from extremely old donors, and at the same time ensure that the dual transplantation procedure is restricted to organs that are not suitable for single transplantations and would otherwise be discarded. Whether transplant activity can be further optimized with an integrated use of the biopsy score and the KDPI/KDRI scales is worth investigating.

ACKNOWLEDGMENTS

The authors thank Nadia Rubis and Alessandro Villa for data monitoring, Giovanni Antonio Giuliano for his help with data handling, Antonietta Chianca for her contribution to implementing the frailty models for the matched-cohort study, and Angela Russo for her contribution to the iconography of the manuscript. The authors are also grateful to Annarita Plati and all the physicians and nurses who were involved in patient care and monitoring at the study centers, as well as the pathologists and technicians who were involved in processing and evaluating the kidney biopsy samples. The staff of the Nord Italia Transplant network organized donor identification and kidney allocation.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

AUTHOR CONTRIBUTIONS

Paolo Rigotti, Giuseppe Remuzzi, and Luigino Boschiero had the original idea. Piero Ruggenenti wrote the initial draft and the final version of the manuscript and contributed to data interpretation. Annalisa Perna performed the statistical analyses. Paolo Rigotti, Cristina Silvestre, Lucrezia Furian, Luigino Boschiero, and Giovanni Rota performed the transplantations and contributed to patient care and data recording. Giuseppe Rossini contributed to organ allocation and data recording. All the authors had full access to data, critically revised the manuscript, and approved the final version. Giuseppe Remuzzi is the corresponding author and had final responsibility for the decision to submit the publication. No medical writer was involved. The study was funded internally, and no sponsor or company was involved in conducting the study.

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How to cite this article: Ruggenenti P, Silvestre C, Boschiero L, et al. Long-term outcome of renal transplantation from octogenarian donors: A multicenter controlled study. *Am J Transplant*. 2017;17:3159–3171. https://doi.org/10.1111/ajt.14459