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Living Donor Kidney Transplantation Should Be Promoted Among "Elderly" Patients

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Background. Age criteria for kidney transplantation have been liberalized over the years resulting in more waitlisted elderly patients. What are the prospects of elderly patients on the waiting list? **Methods.** Between 2000 and 2013, 2622 patients had been waitlisted. Waiting time was defined as the period between dialysis onset and being delisted. Patients were categorized according to age upon listing: <25; 25–44; 45–54; 55–64; and >64 years. Furthermore, the influence of ABO blood type and panel reactive antibodies on outflow patterns was studied. **Results.** At the end of observation (November 2017), 1957 (75%) patients had been transplanted, 333 (13%) had been delisted without a transplantation, 271 (10%) had died, and 61 (2%) were still waiting. When comparing the age categories, outflow patterns were completely different. The percentage of patients transplanted decreased with increasing age, while the percentage of patients that had been delisted or had died increased with increasing age, especially in the population without living donor. Within 6 years, 93% of the population <25 years had received a (primarily living) donor kidney. In the populations >55 years, 39% received a living donor kidney, while >50% of patients without a living donor had been delisted/died. Multivariable analysis showed that the influence of age, ABO blood type, and panel reactive antibodies on outflow patterns was significant, but the magnitude of the influence of the latter 2 was only modest compared with that of age. **Conclusions.** "Elderly" (not only >64 y but even 55–64 y) received a living donor kidney transplantation less often. Moreover, they cannot bear the waiting time for a deceased donor kidney, resulting in delisting without a transplant in more than half the population of patients without a living donor. Promoting living donor kidney transplantation is the only modification that improves transplantation and decreases delisting/death on the waiting list in this population.

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Over the years, elderly patients were increasingly referred for renal transplantation and this eventually led to liberalization of age criteria for transplantation,[1-3] resulting in an increase in the representation of elderly patients on the waiting list (Figure 1). In most studies, elderly was defined as ≥65 years. Although patient survival is better in the elderly population that received a kidney transplantation, compared with dialysis,[2-4] age is still an important factor for nonreferral for kidney transplantation.[5,6] In Rotterdam, no age limit is used. All patients are screened based on total health and social support status. However, because elderly more often suffer from comorbidities[7] the chance to be declined is higher compared with younger candidates.

In some countries, living donor kidney transplantation (LDKT) is performed on a large scale. In the Netherlands, LDKT even outnumbers deceased donor kidney transplantation (DDKT).[8] Patients are preferentially transplanted with a living donor kidney, because the outcomes of LDKT are superior compared with those of DDKT.[9] Additionally, LDKT can be performed without the delay of waiting time. Patients without a living donor are placed on the waiting list for a deceased donor transplant. In our center, a liberal policy regarding acceptance of donation after circulatory death and donation after brain death is applied. Our center also participates in the Eurotransplant Senior Program[10] and the Acceptable

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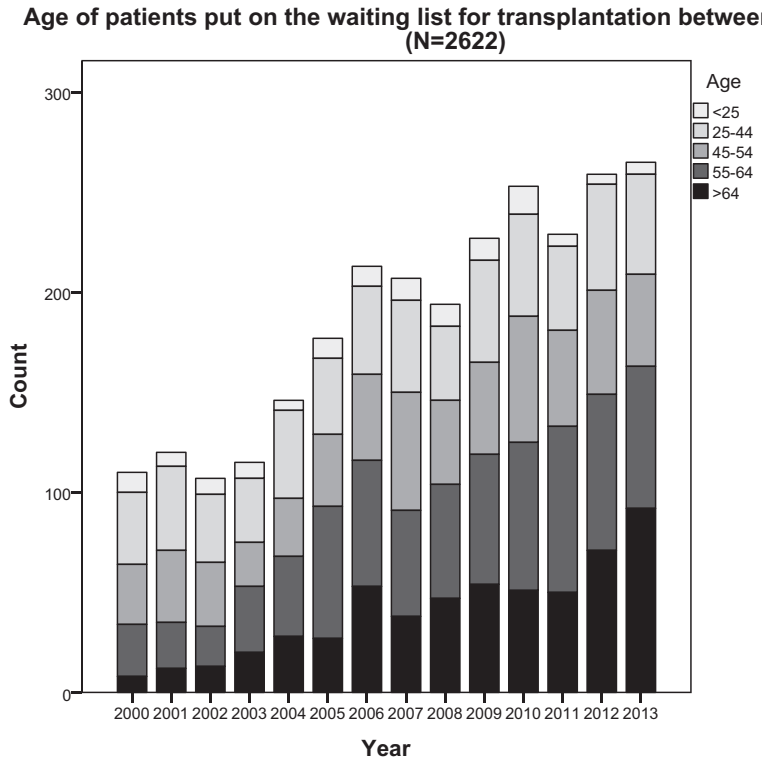

FIGURE 1. Age distribution of patients on the waiting list for kidney transplantation in the study period per y.

Mismatch Program.[11] In the Netherlands, the availability of deceased donor organs has been stable throughout the years. In the Eurotransplant area, waiting time starts when dialysis is started. Unfortunately, waiting time may be up to several years, while both age and waiting time are important risk factors for death on the waiting list.[12,13]

What is the chance of receiving a kidney transplant while on the waiting list and what is the influence of age on this chance? Blood type and panel reactive antibodies (PRA) are known to influence outflow from the waiting list.[14-18] In order to put the influence of age in perspective, we also included these variables and their interactions into the analysis.

MATERIALS AND METHODS

Study Sample

Between January 1, 2000 and December 31, 2013, 2663 patients had been placed on the regional waiting list for kidney transplantation. Forty-one patients were removed from the waiting list; 6 due to wrong listing and 35 since their renal function had recovered. Consequently, 2622 patients were included in this retrospective cohort study (Figure 2). Waiting time was defined as time between first dialysis date and being removed from the waiting list. For enlisted transplant patients whose transplant failed within 90 days, waiting time for the previous transplant was added to current waiting time.

The waiting list was retrieved from Eurotransplant. For patients for whom no dialysis onset date was present in the Eurotransplant database, patient records of our hospital system were checked. This resulted in 147 corrections. In 56 cases (2.1%), information on dialysis could not be retrieved from the patient records. In these cases, Eurotransplant data were used which means that for these patients waiting time was zero as we presumed that dialysis had not been initiated.

Variables

Available variables were age, ABO blood type, maximum PRA, and patient gender. Nine hundred eighty-seven patients were females and 1635 males. Patients were categorized into 5 categories according to age at inflow on the waiting list (Table 1). In the oldest age category, 58 patients were >74 years and 7 patients were between 80 and 84 years. The mean age in the oldest category was 69.6, the median age 69, and the SD 3.6 years. Patients were categorized into 4 categories according to maximum PRA at inflow on the waiting list (Table 1). ABO blood type of all patients was included (Table 1).

Reasons for outflow from the waiting list were: (1) died or delisted, (2) still waiting, (3) DDKT, and (4) LDKT. Patients transplanted abroad all received a living donor kidney and thus were included in LDKT. Observation was until November 1, 2017.

Patient Data and Ethics

The data for this study were retrospectively retrieved from patient files and Eurotransplant registry data. All patient data were anonymized. According to the Dutch law on medical research on human subjects, it was not deemed necessary to obtain written informed consent from the patients for this study.

Patients whose data were retrieved for this study were treated in accordance with the Declaration of Helsinki and the Declaration of Istanbul.

Statistical Analyses

Outflow patterns were created by scoring outflow reasons before dialysis (time point 0) and at 1, 2, 3, 4, 5, and 6 years after dialysis onset for each patient. For instance, when a patient had been on dialysis for 2.5 years before receiving a

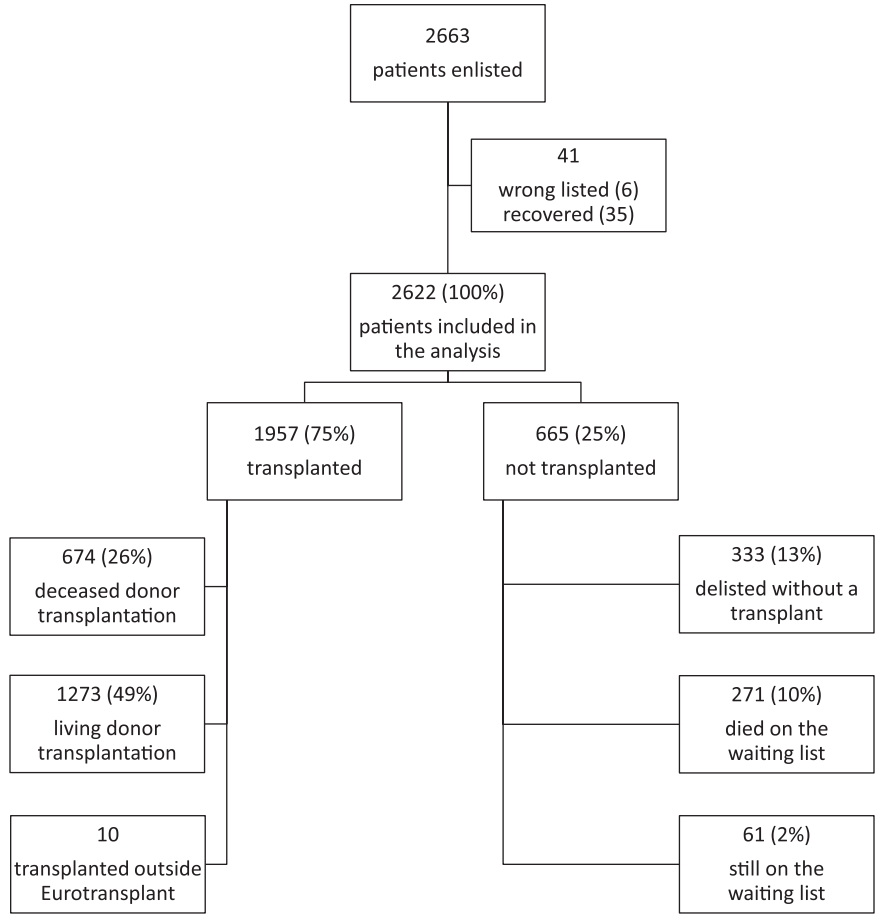

FIGURE 2. Flowchart of outflow of patients enlisted between January 2000 and December 2013. End of observation was November 1, 2017.

LDKT, time points 0, 1, and 2 were scored as still on the waiting list and time points 3, 4, 5, and 6 as LDKT. Patients with an observed waiting time shorter than 6 years were censored. Chi-square tests were performed to test the difference in outflow reasons between the age categories, ABO blood types, and PRA categories. Age, ABO blood type, maximum PRA, and gender were included in multivariable Cox proportional hazard analysis to assess the likelihood of either a living or deceased donor transplantation. Age was included as continuous variable. Cases with missing values were excluded. SPSS version 25 (IBM Corporation, Armonk, NY) was used to perform all statistical analyses. *P* values <0.05 were considered significant.

RESULTS

Out of the 2622 waitlisted patients, 1957 (75%) had been transplanted before November 2017: 674 patients had received a DDKT, 1273 an LDKT, and 10 had been transplanted abroad (Figure 2). Out of the 665 (25%) patients who

TABLE 1.

Percentages of ABO blood type, PRA, and gender per age category

			Age category					
			<25 (N = 122)	25–44 (N = 600)	45–54 (N = 584)	55–64 (N = 752)	>64 (N = 564)	Overall *P*
ABO	A	N = 1046	38.5	40.3	38.4	43.8	36.2	0.002
	AB	N = 125	3.3	4.3	5.5	4.0	5.9	
	B	N = 361	18.9	14.5	18.0_{b}	10.9_{a}	11.3_{a}	
	0	N = 1090	39.3	40.8	38.2_{b}	41.4	46.6_{a}	
PRA	0	N = 1391	56.2	46.0_{b}	51.9	55.3_{a}	59.6_{a}	<0.001
	1–4	N = 638	17.4	25.3	22.7	26.4	24.5	
	5–85	N = 508	19.8	23.7_{c}	$23.0_{b,c}$	$17.2_{a,b}$	14.4_{a}	
	86–100	N = 69	6.6_{a}	5.1_{a}	2.4	1.1_{b}	1.6_{b}	
Gender	F	N = 987	45.1	42.2_{b}	38.0	36.6	32.3_{a}	0.004
	M	N = 1635	54.9	57.8_{b}	62.0	63.4	67.7_{a}	

Different subscript letters in the same row mean a significant difference at the 0.05 level.
PRA, panel reactive antibodies.

had not been transplanted, 333 had been delisted without a kidney transplantation and 271 had died while on the waiting list. The remaining 61 (2%) patients were still waiting in November 2017.

Most important reasons for delisting were a deteriorated condition (76%) and patient withdrawal (12%). For the different age categories "unfitness for transplantation" was responsible for delisting in 0% in the youngest; 58% in 25–44 years; 65% in 45–54 years; 82% in 55–64 years; and 81% in the oldest age group.

Outflow per Year

In Figure 3, the reasons for outflow per year for the total population and per age category are shown. The x-axis shows waiting time in years after dialysis onset, the y-axis shows the percentage of patients. Light gray represents the percentage of patients who had received an LDKT and medium gray the patients who had received a DDKT. The shaded area represents censored patients. Their period on dialysis and/or their observation time was <6 years. White represents the patients who were still on the waiting list. Finally, dark gray represents the patients who had died or had been delisted without a transplant.

Time Point 0

Figure 3 shows that in none of the age categories the percentage of patients waiting at time point 0 was 100%. This means that some patients were removed from the list because of preemptive transplantation or because of death or delisting before dialysis onset. The percentage of preemptive transplantation decreased with increasing age category (P = 0.005), while the percentage of patients who had died or had been delisted before dialysis onset increased with increasing age (P < 0.001). Patients who were not on dialysis at the end of

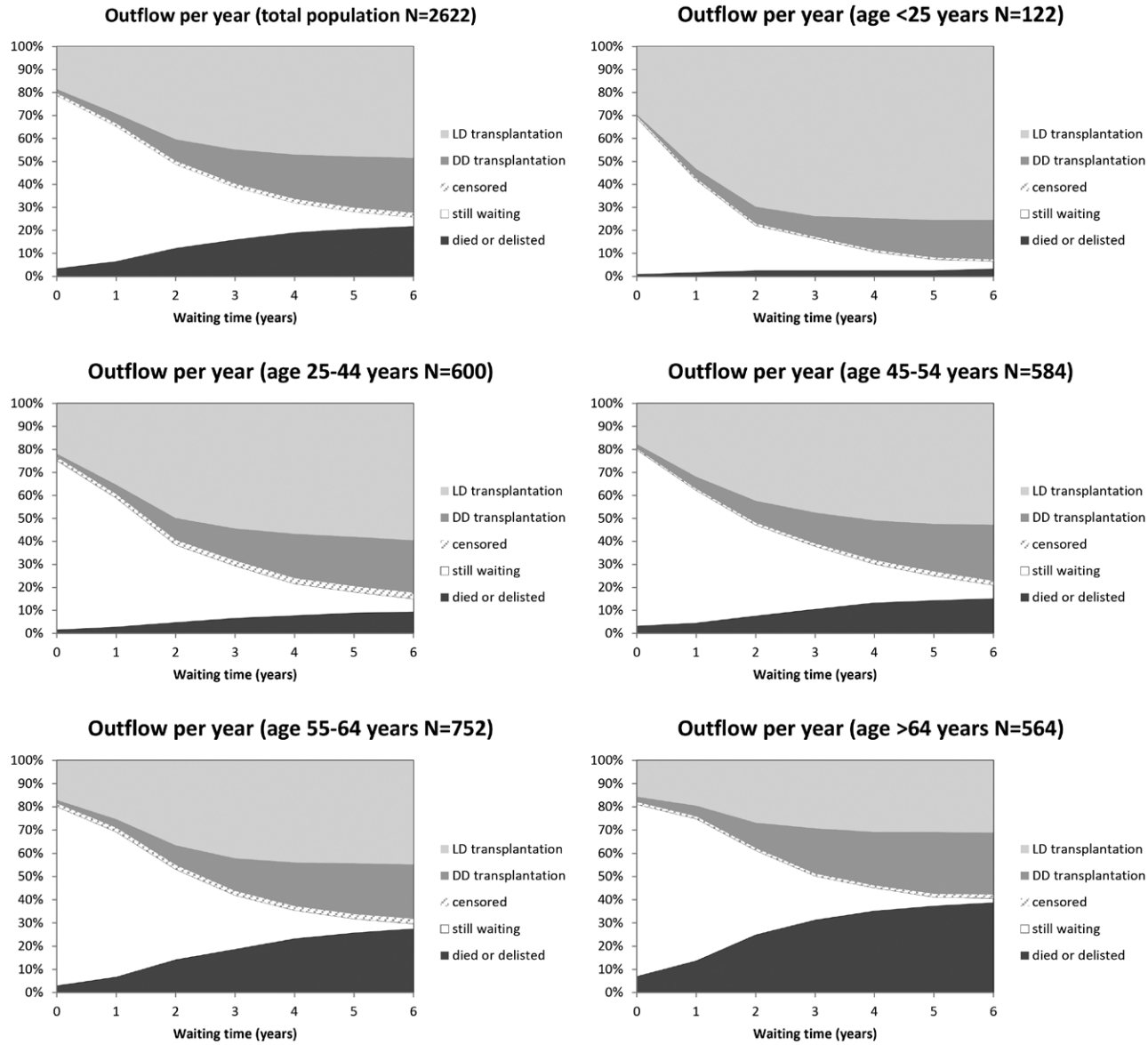

FIGURE 3. Percentage of patients who had died or been delisted (dark gray), still waiting (white), censored (shaded), or underwent deceased donor (DD; medium gray) or living donor (LD; light gray) kidney transplantation per y for the total population and each age category. Patients who were not waiting on time point 0 had been preemptively transplanted, been censored, died, or been delisted before dialysis onset.

observation (November 1, 2017) were censored (shaded area in Figure 3).

Time Point 6

After 6 years observation, 93% of patients in the youngest category had been transplanted, the vast majority with an LDKT (Figure 3; light gray). Both the percentage of patients transplanted within 6 years and the proportion of LDKT decreased with increasing age ($P < 0.001$, $P < 0.05$). In age category 25–44 years, 82% had been transplanted; in category 45–54, 77%; in category 55–64, 68%; and in category >64 only 58% had been transplanted. Slightly more than half of transplanted patients >64 years received an LDKT. In contrast, the percentage of patients who had died or had been delisted without a transplant increased with increasing age ($P < 0.001$). Within 6 years, respectively, 3%; 9%; 15%; 27%; and 39% of patients in the consecutive age categories had died or had been delisted.

Patients Without Living Donor

When patients with an LDKT and censored patients are excluded from the observation (excluding the light gray and shaded areas in Figure 3), the contribution of DDKT decreased with increasing age. The contribution of delisting/death increased from 14%, in the youngest, to 52% in age category 55–64 years and even 57% in the population >64 years.

The Influence of Time on Outflow Patterns

As illustrated in Figure 3, the differences between the age categories occurred within the first few years. In all age categories, most LDKTs had been performed preemptively or within 2 years after dialysis onset. However, this accounted for the majority (70%) of youngest patients but only for a minority (27%) of oldest patients. From 2 years onwards, LDKT leveled off. The proportion of DDKT gradually increased over time from T0 onwards. In the first few years, the proportion of patients who had died or had been delisted without a transplant increased with age. After 2 years, 25% of patients in the oldest age category had died or had been delisted. The percentage leveled off after 4 years. Over the course of the 6 years, in the oldest age category, the cumulative number of patients who had died or had been delisted was significantly higher compared with the number of patients who had received a DDKT as is shown in Figure 3 ($P < 0.05$). Reasons for outflow differed significantly between the age categories ($P < 0.001$) at all time points (0–6 y).

ABO Blood Type

In Figure 4, the reasons for outflow per year per ABO blood type are shown. The mean age was 52.3 years in patients with blood type A (N = 1046); 53.5 in blood type AB (N = 125); 50.6 in blood type B (N = 361); and 53.1 in blood type O (N = 1090) ($P = 0.002$). Reasons for outflow significantly differed between the ABO blood types ($P < 0.001$) at all time points (0–6 y). From 4 years onwards, significantly more patients with blood type O had died/been delisted compared with blood type A ($P < 0.05$). After 6 years, 19% (A); 18% (AB); 20% (B); and 25% (O) of patients had died or had been delisted. Patients with blood type O (from 2 y onwards) and blood type B (from 1 y onwards) had received an LDKT significantly less often than patients with blood type A ($P < 0.05$). At all time points, patients with blood type AB had received a DDKT more often than the other categories ($P < 0.05$). At all time points, significantly fewer patients

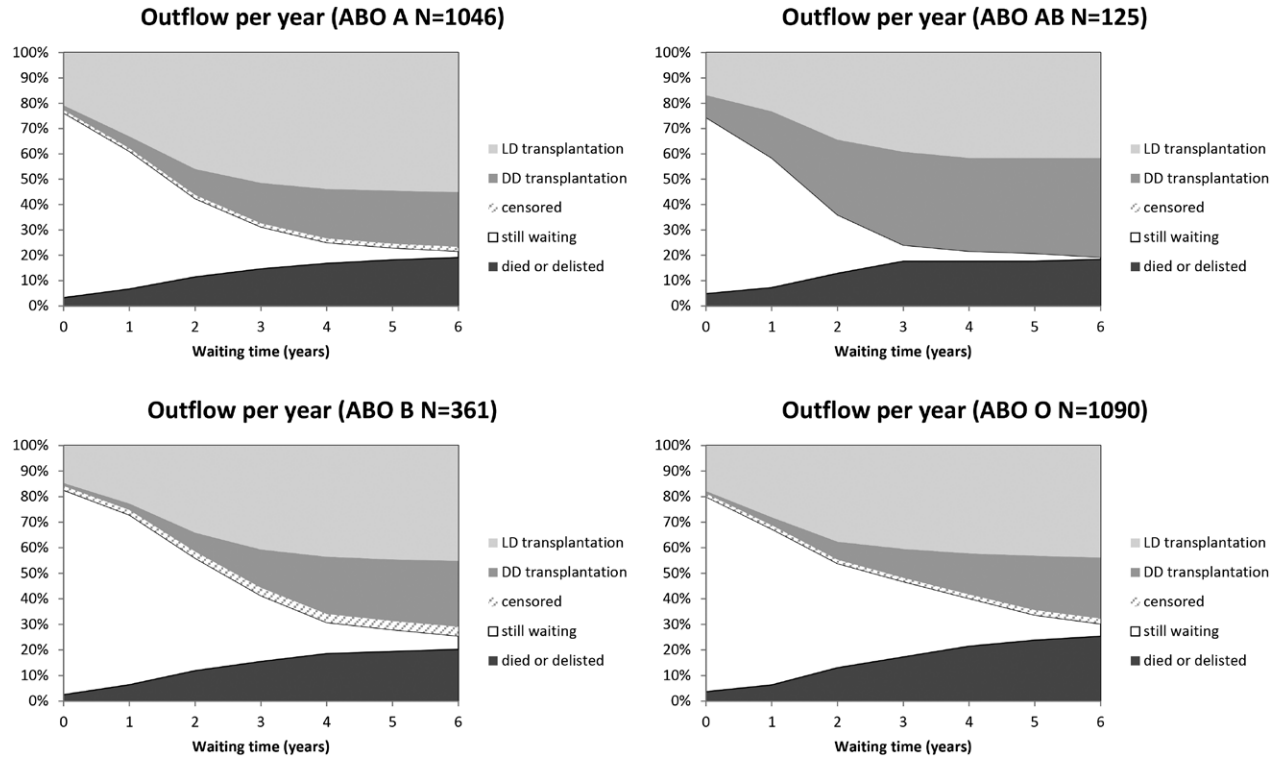

FIGURE 4. Percentage of patients who had died or been delisted (dark gray), still waiting (white), censored (shaded), or underwent deceased donor (DD; medium gray) or living donor (LD; light gray) kidney transplantation per y per ABO blood type. Patients who were not waiting on time point 0 had been preemptively transplanted, been censored, died, or been delisted before dialysis onset.

with blood type O and, until year 4, blood type B had been transplanted with either an LDKT or DDKT compared with patients with blood types A and AB ($P < 0.05$). After 6 years, 77% of patients with blood type A; 81% with blood type AB; 71% with blood type B; and 68% with blood type O had been transplanted.

Panel Reactive Antibodies

In Figure 5, the reasons for outflow per year per PRA category are shown. PRA was missing in 16 cases (0.6%). The mean age was 53.5 years in patients with PRA 0 (N = 1391); 52.9 in PRA 1–4 (N = 638); 50.4 in PRA 5–85 (N = 508); and 43.8 in PRA 86–100 (N = 69) ($P < 0.001$). The percentage of patients who had received an LDKT was lower in the highest PRA category (86–100) compared with unsensitized patients (PRA 0 and PRA 1–4) ($P < 0.05$). From 2 years onwards, the difference in LDKT between PRA 86–100 and PRA 5–85 was significant as well ($P < 0.05$). In contrast, more patients in the highest PRA category (86–100) had received a DDKT compared with all other categories from 1 year onwards ($P < 0.05$). At all time points except year 1, significantly more patients with PRA 0 had been transplanted with either an LDKT or DDKT compared with patients with PRA 5–85 ($P < 0.05$). The differences between all other categories were not significant. After 6 years, in PRA category 0, 75%; in category 1–4, 72%; in category 5–85, 67%; and in category 86–100, 65% had been transplanted. The differences in patients who had died or had been delisted without a transplant were not significant. After 6 years, respectively, 21%; 22%; 25%; and 19% of patients in the consecutive PRA categories had died or had been delisted.

Adjusted Analysis

Table 1 shows percentages of ABO blood type, PRA, and gender per age category. The difference in age distribution was significant for all other covariates. The overall P values were 0.002; <0.001; and 0.004, respectively. Patients in the oldest age group more often had blood type O, but PRA was lower in the oldest patients.

In multivariable Cox proportional hazard analysis age, ABO blood type, PRA, and gender had a significant influence on the likelihood of transplantation ($P < 0.001$; <0.001; <0.001; 0.007, respectively). The likelihood of transplantation decreased per year with increasing age (relative risk [RR] = 0.987). Compared with ABO blood type A, the likelihood of blood type AB was higher (RR = 1.260; $P = 0.029$), and of blood types B and O lower (RR = 0.733; $P < 0.001$ and RR = 0.705; $P < 0.001$ respectively). Compared with PRA 0%, the likelihood of PRA 5%–85% and PRA 86%–100% was lower (RR = 0.731; $P < 0.001$ and RR = 0.535; $P < 0.001$, respectively). The difference between PRA 0% and PRA 1%–4% was not significant. The likelihood of transplantation was lower for female patients than for male patients (RR = 0.879; $P = 0.007$). There was no significant interaction between age and the other covariates and between ABO blood type and PRA ($P > 0.500$ for all interactions).

As an example, in Figure 6, the combined influence of patient age, ABO blood types A and O, and PRA 0% and 86%–100% on the likelihood of receiving either a living or deceased donor transplant is shown, based on the multivariable Cox proportional hazard model described above. The reference value is the likelihood of a 20-year-old patient with blood type A and PRA 0% (RR = 1). The likelihood of transplantation decreased considerably with increasing age.

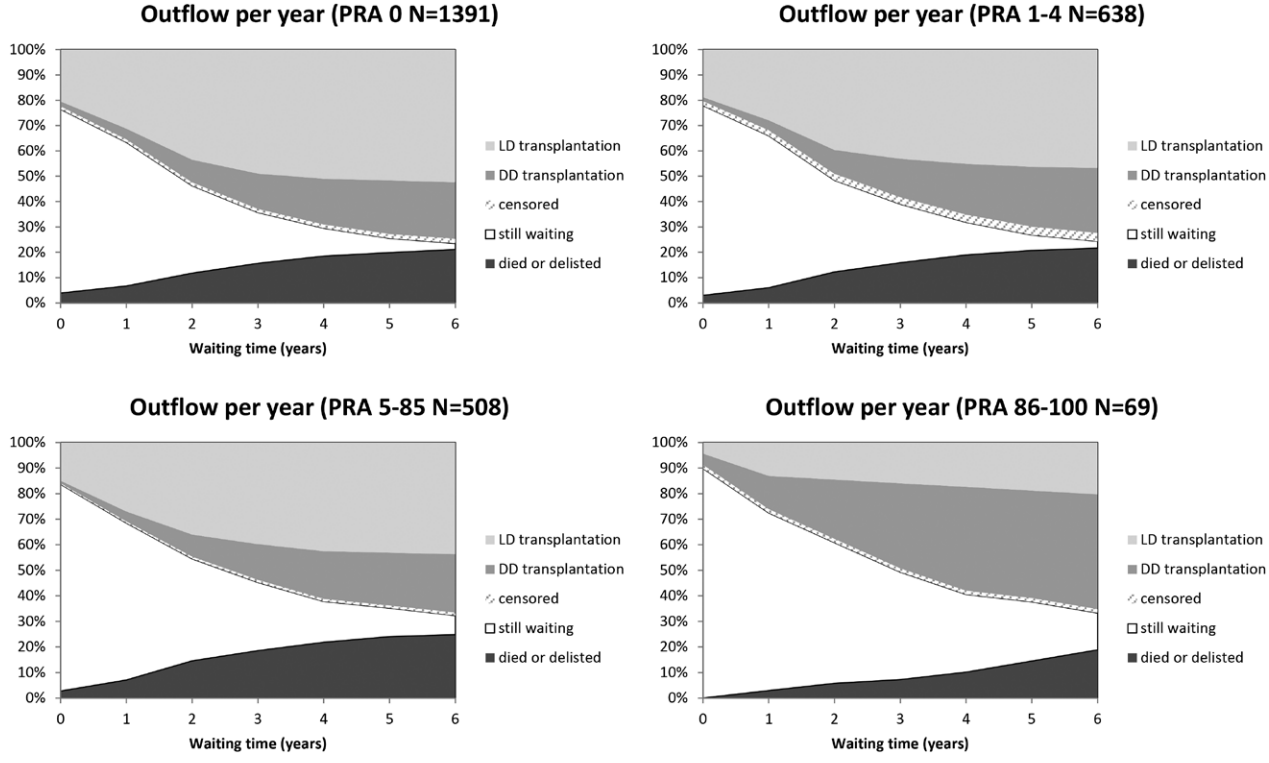

FIGURE 5. Percentage of patients who had died or been delisted (dark gray), still waiting (white), censored (shaded), or underwent deceased donor (DD; medium gray) or living donor (LD; light gray) kidney transplantation per y per PRA category. Patients who were not waiting on time point 0 had been preemptively transplanted, been censored, died, or been delisted before dialysis onset. PRA, panel reactive antibodies.

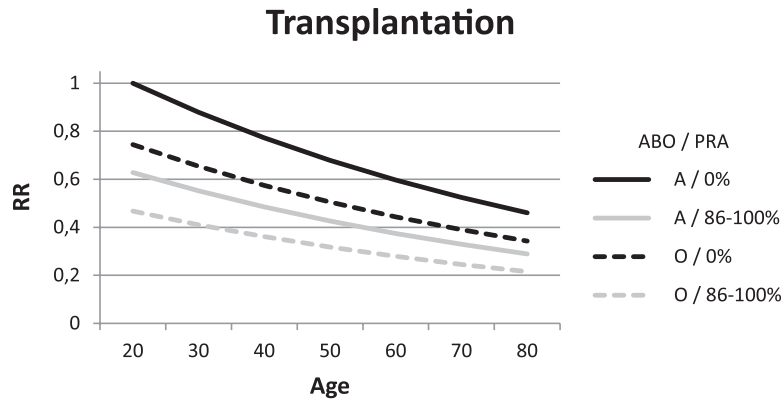

FIGURE 6. The combined influence of patient age, ABO blood types A (solid lines) and O (dashed lines), and PRA 0% (dark lines) and 86%–100% (light lines) on the likelihood (RR) of receiving either a living or deceased donor transplant. The reference value is the likelihood of a 20-y-old patient with blood type A and PRA 0% (RR = 1). Between ages 20 and 60 y, the RR decreased by 40%. The RR of patients with blood type O was 26% lower than blood type A. The RR of patients with PRA 86%–100% was 37% lower than PRA 0%. PRA, panel reactive antibodies; RR, relative risk.

Furthermore, Figure 6 shows that the likelihood of transplantation was highest for young, unsensitized patients with blood type A, but also that highly sensitized blood type A patients had a slightly lower likelihood than unsensitized blood type O patients. The results of blood type B patients were comparable to those of blood type O patients (data not shown). As expected, the likelihood for patients with blood type AB was highest (data not shown).

DISCUSSION

For patients who are being placed on the waiting list for DDKT, the most relevant question is how long they will have to wait for a kidney offer. To answer that question, the median waiting time can be given. However, that does not take into account other reasons for delisting; LDKT, death, or a deterioration in condition. Thus, an additional question that should be answered is whether or not they will survive the waiting time and stay in adequate condition until transplantation. To date, only a few papers have been published in which all reasons for outflow from the waiting list were taken into account.[15-18] Factors that were found to significantly influence the chance of becoming transplanted were the well-known variables age, ABO blood type, PRA, and HLA frequency.[15-17] In 2009, Schold et al[18] found that nearly half of elderly (>60 y) waitlisted patients were estimated to die before DDKT. However, results were not compared with those of younger patients as they were not included in the study. Moreover, in the Kaplan-Meier analysis that was used, transplantation and delisting (due to decreased physical condition) were not accounted for. In our current analysis, the results represent the actual situation in the population.

Figure 3 shows that outflow patterns are time dependent and that there are differences between outflow patterns for categories of patients. Outflow from the waiting list is a dynamic process whereby outflow patterns vary with both age and time after listing. The effect of time on outflow reasons is clearly visible: LDKT was primarily performed in the first 2 years after start dialysis, whereas DDKT gradually increased after dialysis onset. Most cases of death or delisting occurred in the first 2 years after start dialysis and the increase diminished after that time.

In the current study, large differences in outflow from the waiting list between the age categories were found. In the 2 highest age categories, 27% (55–64 y) and 39% (>64 y) of patients accepted for transplantation were not transplanted because they had died or their condition had deteriorated within 6 years on dialysis. For patients who did not have a living donor, percentages were even higher. More than half the patients aged >54 years without a living donor had not been transplanted (Figure 3). As was shown, the number of elderly patients who had died or had been delisted increased profoundly in the first years after start dialysis. As the mean waiting time for DDKT is 3–4 years, they did not survive the wait for a deceased donor kidney in adequate condition.

In a previous study, we found that patients with ABO blood type O and patients with a PRA >85 have a significantly longer waiting time.[14] In the present study, we confirmed that blood types O and, to a lesser extent, B waited longer. Percentages of patients with LDKT and DDKT were significantly different between blood types as shown in Figure 4. However, the difference in percentage of patients who had died or had been delisted between ABO blood types O and A was only significant from 4 years onwards. Although the influence of ABO blood type on the percentage of patients who had died or had been delisted was significant, the difference between ABO blood types was only modest (range 18%–25%). On the other hand, the influence of age on the percentage of patients who had died or had been delisted was also significant, but the magnitude of the difference between the age categories is noteworthy (range 3%–39%).

The longer waiting time of highly sensitized patients was confirmed as well. Because of the Acceptable Mismatch Program, these patients received a DDKT more often.[11] However, the percentage of LDKT was very low. The difference in percentage of patients who had died or been delisted between PRA categories was not significant.

As was shown in multivariable analysis age, ABO blood type, and PRA all had an independent influence on the likelihood of transplantation. Figures 3, 4, and 5 clearly show the paramount importance of age on outflow from the waiting list. ABO blood type and PRA were less influential when comparing both the percentages of patients who had died or had been delisted and the percentages of patients who had been transplanted after 6 years. In multivariable analysis, there was

no interaction between the variables studied, but of course the likelihood of transplantation decreases in the presence of multiple unfavorable variables.

In the elderly population, fewer patients are transplanted with a living donor kidney. Also, when observing the population that already received a kidney transplantation, there is a preponderance of DDKT in the elderly.[19-21] In the elderly population with renal disease, comorbidity is more prevalent.[7] A longer period on dialysis may further decrease the physical condition, precluding transplantation. As survival among transplanted patients with comorbidity generally is better compared with patients who remain on dialysis,[7,22] transplantation should not be delayed but should be performed when their condition is at best. Promoting LDKT is the only modifiable factor that may increase the number of transplantations performed in elderly patients with or without comorbidity.

A reduction of racial disparity in access to LDKT has been attained by including patients' social networks in education on renal replacement therapies using house call interventions.[23,24] Such interventions may be useful in the elderly population as well. They could try to find peers, relatives, or other persons from their social network to donate to them. This is challenging due to increasing age and the likelihood of contraindications in their peers.

In Eurotransplant, deceased donor allocation, apart from Eurotransplant Senior Program and pediatric status, age is not a selection criterion for matching. The allocation policy of Eurotransplant is comparable to policies in for instance the United States, United Kingdom, Scandinavia, and Australia and New Zealand.[25-29] Generally, the most important matching criteria in all allocation systems are ABO blood type, HLA-matching, waiting time, and distance from donor hospital. PRA is an allocation criterion in Eurotransplant, the United Kingdom, Scandinavia, and Australia but not in the United States and New Zealand.

A possible limitation of single-center studies in general may be the generalizability. In our center, there is a relatively large population of LDKT recipients. In the population that received an LDKT, younger patients and patients without comorbidity are overrepresented.[7] However, a relatively large percentage of the elderly received an LDKT. Although patient selection for medical reasons cannot be completely ruled out, DDKT allocation is independent of the presence of an LDKT program. After exclusion of the LDKT population, it is obvious that the elderly population that is dependent on DDKT lags behind and half of them are removed from the waiting list without a transplant. In centers without an LDKT program, percentages of elderly patients delisted without a transplant may even be higher.

Another limitation is that no information on active listing was available. The proportion of (temporarily) not transplantable elderly patients could be higher than the proportion of (temporarily) not transplantable younger patients. This may have led to longer waiting times, less transplants, and more delisting/deaths in the older age categories. In the future, active listing status should be registered so that in follow-up studies this information can be taken into account to verify the outflow patterns.

In conclusion, our study on the influence of age, ABO blood type, and PRA on the outcome of patients on the waiting list showed that age far overrides the influence of both other factors.

The percentage of patients who had been delisted or had died without a transplant increased strikingly with age. When no living donor was available, 54% of patients >54 years had died or been delisted after 6 years. As LDKT is the only modifiable factor to promote transplantation without delay in this population, our results stress the importance of finding a living donor for these "elderly" patients.

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