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VIEW POINT ARTICLE

Should kidney allografts from old donors be allocated only to old recipients?

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SUMMARY

In several deceased donor kidney allocation systems, organs from elderly donors are allocated primarily to elderly recipients. The Eurotransplant Senior Program (ESP) was implemented in 1999, and since then, especially in Europe, the use of organs from elderly donors has steadily increased. The proportion of ≥60-year-old donors reported to the Collaborative Transplant Study (CTS) by European centers has doubled, from 21% in 2000–2001 to 42% in 2016–2017. Therefore, in the era of organ shortage it is a matter of debate whether kidney organs from elderly donors should only be allocated to elderly recipients or whether <65-year-old recipients can also benefit from these generally as "marginal" categorized organs. To discuss this issue, a European Consensus Meeting was organized by the CTS on April 12, 2018, in Heidelberg, in which 36 experts participated. Based on available evidence, it was unanimously concluded that kidney organs from 65- to 74-year-old donors can also be allocated to 55- to 64-year-old recipients, especially if these organs are from donors with no history of hypertension, no increased creatinine, no cerebrovascular death, and no other reasons for defining a marginal donor, such as diabetes or cancer.

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Introduction

Although high donor age is one of the strongest factors that adversely influence death-censored graft survival in kidney transplantation [1-4] (Fig. 1), shortage of available organs has resulted in a continuously increasing use of kidney organs from elderly donors. The percentage of ≥60-year-old deceased kidney donors reported to the Collaborative Transplant Study (CTS) from Europe was 21% during 2000–2001 and as high as 42% during 2016–2017 (Fig. 2a). This trend was accompanied by a similar increase in recipient age; the percentage of ≥60-year-old recipients was 22% during 2000–2001 and 39% during 2016–2017 (Fig. 2b). The median age of deceased kidney donors in Eurotransplant (ET) countries rose from 46 in 2000 to 54 years in 2017 [5,6]. As many as 69% of kidneys from ≥65-year-old deceased donors were allocated in 2017 via the ET Senior Program (ESP) to ≥65-year-old recipients [7]. The percentage of kidney transplantations via ESP increased from 9% in 2000 to 17% in 2017 [5,7]. Therefore, the optimal use of organs from elderly donors represents an increasingly important issue in organ transplantation.

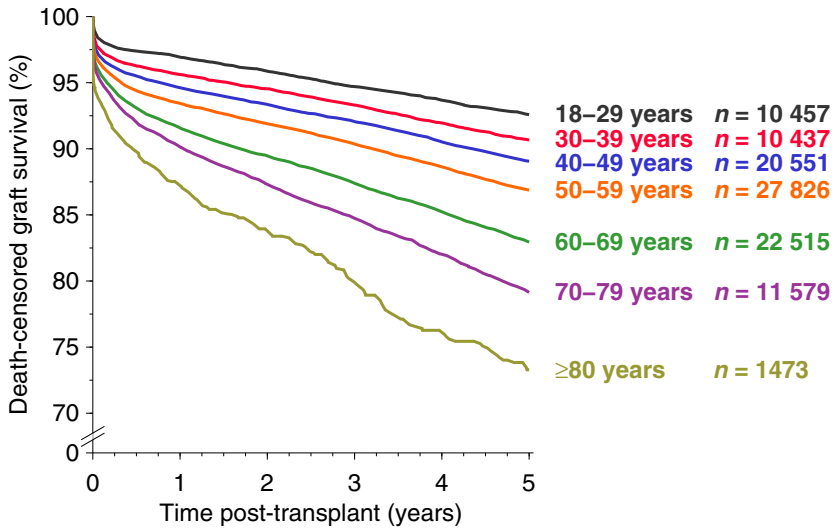

Figure 1 Impact of donor age on death-censored graft survival in first adult kidney-only transplantations performed in Europe during 2000–2017 and reported to CTS (log-rank $P < 0.001$).

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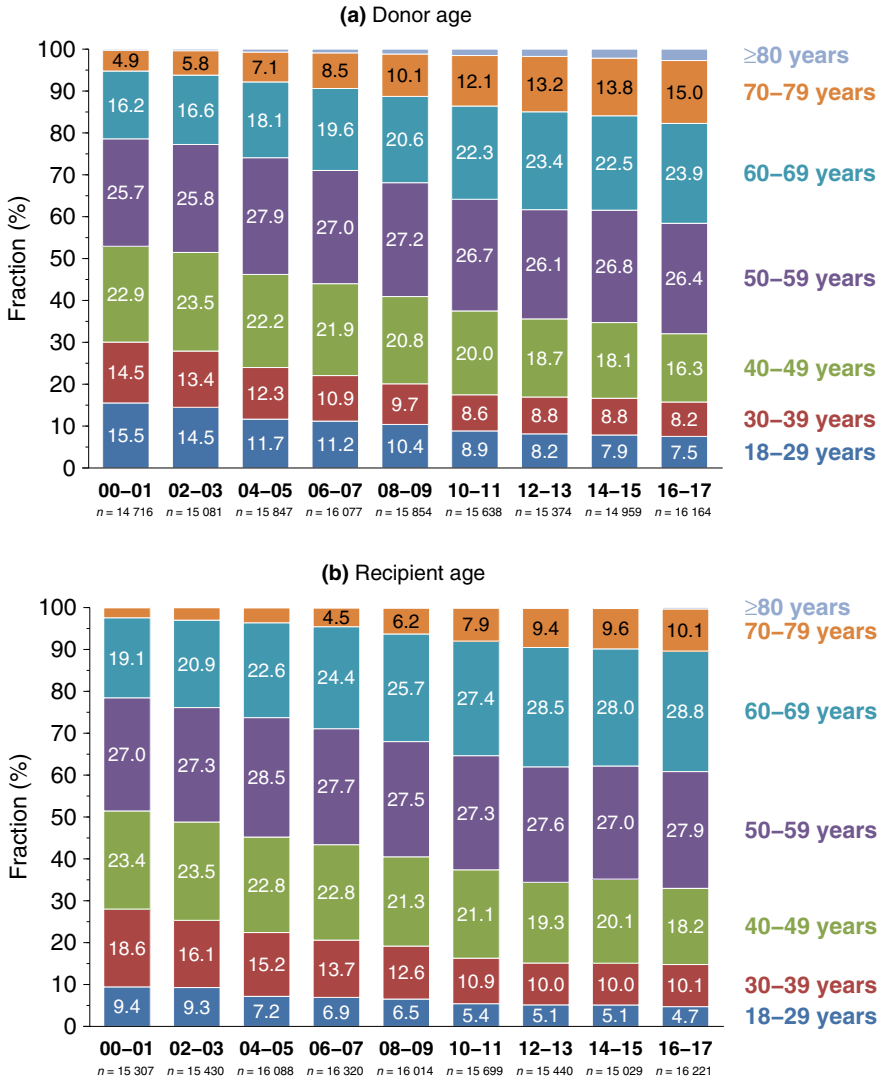

Figure 2 Transplant year-related age distribution of (a) adult deceased kidney donors and (b) adult recipients from 2000 to 2017 in transplantations performed at European centers and reported to CTS.

History of hypertension, increased creatinine, and cerebrovascular death are additional factors that decide the quality of a deceased donor kidney organ [8]. Besides the donor age above 60 years, the presence of two of these factors is also accepted to define an expanded criteria donor (ECD) in the donor age-group 50–59 years. Compared to standard criteria deceased donor (SCD) kidney transplantation, ECD kidney transplantation is associated with inferior graft and patient survival [8-10]. On the other hand, in the era of organ shortage and improving graft survival rates, allocation of kidneys from donors aged ≥65 years, who do not have additional ECD characteristics, to patients under the age of 65 years may increase the chance of transplantation with acceptable outcomes for this group of <65-year-old recipients. During a CTS-initiated European Expert Meeting in April 2018, the question of whether the use of kidney organs from elderly donors should only be limited to ≥65-year-old recipients was discussed in detail. A pro/con debate between Uwe Heemann from Munich and Jens Lutz from Mainz (currently in Koblenz) stimulated the discussion.

Different views

Arguments in favor of allocating kidneys from 65- to 74-year-old donors only to ≥65-year-old recipients (Jens Lutz)

According to an analysis of the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry data, <60-year-old recipients of ECD kidneys had an

excess risk of all-cause mortality and death with functioning graft due to cardiovascular death as compared to recipients of SCD kidneys [11]. This is a strong argument against the use of organs from elderly donors in young recipients. The presence of circulating donor-specific HLA antibodies (DSA) and longer cold ischemia time (CIT) were identified as independent risk factors for failure of ECD grafts [9]. A recent study in a Dutch cohort showed a lower hazard ratio for graft loss with ECD kidneys in ≥60-year-old than <60-year-old recipients [10]. These findings suggested that caution is required in the allocation of ECD kidneys to <60-year-old recipients.

Eurotransplant Senior Program is an allocation scheme based on matching kidneys from ≥65-year-old deceased donors to ≥65-year-old recipients with a negative cytotoxic cross-match but without consideration of HLA matching [12]. Apart from a more efficient use of kidneys from elderly donors, ESP aims to reduce CIT of ECD organs by local, regional, or national allocation. Early analyses revealed that ESP allocation did not affect graft and patient survival negatively [13-16]. Compared to 60- to 64-year-old patients who received a kidney from a donor of any age, in ≥65-year-old ESP recipients CIT was reduced and the median waiting time was shortened from 4.6 to 3.6 years. Availability of elderly donors had doubled since initiation of the ESP in 1999. However, 5-year results revealed lower death-censored graft survival rates in ESP patients than in 60- to 64-year-old patients who received a kidney from a donor of any age, but similar death-censored graft survival rates compared to recipients of any age who received an organ from a ≥65-year-old donor [17].

Cold ischemia time >16 h, dialysis vintage, overweight, and kidney retransplantation were associated with delayed graft function (DGF) and primary nonfunction within the ESP population [18]. Moreover, CIT >15 h, DGF, and kidney retransplantation were significant risk factors for poor graft survival, suggesting that ESP results could further be improved by keeping the CIT short and paying attention to DSA, as increasingly practiced. HLA typing prior to allocation and virtual cross-matching have become clinical routines and that are able to prevent prolongation of CIT also in ESP.

Higher Kidney Donor Risk Index (KDRI) scores in ESP kidneys were associated with reduced graft survival and increased serum creatinine levels at discharge [19], indicating that donor quality should be assessed while selecting organs for older recipients who usually have a high degree of comorbidity. Lai *et al.* reported that survival after kidney transplantation did not differ with kidneys from 50- to 59-year-old or over 60-year-old expanded criteria donors, when a biopsy-driven selection was performed in over 60-year-old donors. They speculated that biopsy-driven pretransplantation selection could achieve similar outcomes with ECD kidneys as compared to kidneys from nonbiopsied younger donors [20]. Histopathologic evaluation of donor kidney and evaluation of the KDRI score may lead decision-making to choose dual transplantation, improve transplant outcomes, and decrease discard rates in ESP [21-24]. On the other hand, a biopsy-driven selection of the donor organ can prolong CIT, and consequently, the benefit of ESP could be lost. There seem to exist also region-specific differences in outcomes as ≥65-year-old recipients of kidneys from ≥65-year-old deceased donors in the United States (U.S.) showed significantly lower allograft survival rates and a higher incidence of death with functioning graft than patients transplanted via ESP [25]. Determination of reasons for these international differences is also important in order to understand the risk factors for adverse outcomes in elderly recipients.

In conclusion, as compared to SCD kidneys, ECD kidneys were not associated with increased mortality or graft failure in ≥65-year-old recipients in Europe, and marginal kidney grafts according to KDRI or graft biopsy had only a minor influence on long-term outcome in older recipients. As the relative risk of graft loss and mortality with ECD versus SCD kidneys were reported to be higher in young than old recipients, Jens Lutz stimulated the discussion with the statement that kidneys from 65- to 74-year-old donors should only be allocated to ≥65-year-old recipients.

Arguments in favor of allocating kidneys from 65- to 74-year-old donors also to <65-year-old recipients (Uwe Heemann)

A Dutch cohort study of 3597 deceased donor kidney transplant recipients revealed that ≥65-year-old recipients of kidneys from ≥65-year-old donors did not experience a survival benefit compared to those remaining wait-listed on dialysis [26]. Renal function was inferior in elderly recipients (≥65 years) of kidneys from elderly (≥65 years) compared to young (<65 years) donors, and only 53% of them were alive with a functioning graft after 5 years, indicating that elderly recipients do not benefit from elderly donor organs. Mezrich *et al.* also reported that elderly patients who received ECD kidneys had significantly lower 5-year patient and graft survival rates than elderly recipients of SCD allografts. In

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contrast, 5-year patient and graft survival rates did not significantly differ between recipients of ECD and SCD kidneys in the group of 40- to 59-year-old transplant recipients [27]. Solá *et al.* compared <60-year-old recipients who received grafts from ≤60 versus >60-year-old donors and found better renal function in recipients of kidneys from ≤60-year-old donors. However, 1-, 5-, and 10-year patient and graft survival rates were also similar [28]. In a paired matched analysis between 823 recipients from ≥65-year-old deceased donors and wait-listed dialysis patients, the risk of death was 2.66 times higher for patients in the dialysis group [1]. Importantly, the highest death-censored graft survival benefit was found in 55- to 64-year-old recipients. Similarly, Pèrez-Saéz *et al.* [29] reported in <65-year-old recipients a higher benefit in patient survival of kidney transplantation from ≥75-year-old donors over remaining on dialysis.

Uwe Heemann concluded that patients younger than 65 years should not be precluded from kidneys of donors older than 65 years. Recipients with low life expectancy without transplantation, such as lack of vascular or peritoneal access, extremely long waiting time due to blood group, rare HLA alleles or preformed antibodies, and high burden of comorbidities, may especially benefit from kidneys of elderly donors.

Discussion of pro/con arguments

Using the U.S. Renal Data System and U.S. Scientific Renal Transplant Registry databases, Ojo *et al.* [30] analyzed in 2001 patients awaiting a deceased donor kidney transplant and found an increase of 5 years in life expectancy in recipients of kidneys from marginal donors than patients who remained on dialysis without transplantation. Merion *et al.* [31] reported in 2005 that due to excess mortality in the perioperative period, the cumulative survival of ECD recipients did not equal the survival of non-ECD transplanted or wait-listed patients until 3.5 years post-transplantation. However, significant survival benefit was observed in >40-year-old recipients of ECD kidneys, non-Hispanics, nonsensitized patients, and patients with diabetes or hypertension. The group advised that ECD kidney transplantation should be offered to candidates older than 40 years in organ procurement organizations with long waiting times (>1350 days).

Current data from the CTS study indicate that the previously reported higher mortality associated with ECD kidneys [11] is not restricted to <60-year-old recipients (Fig. 3). Furthermore, as discussed further below in detail, the CTS data support the assumption that nowadays good quality kidneys from ≥65-year-old donors can also be allocated to <65-year-old recipients with good outcomes. The main challenge hereby is accomplishment of the appropriate donor–recipient matching to obtain the best patient and graft survival. In the U.S. study mentioned above [25], ≥65-year-old recipients of kidneys from ≥65-year-old deceased donors had significantly lower allograft survival rates and a higher incidence of death with functioning graft than patients transplanted via ESP. However, in contrast to the findings for all-cause graft loss and death with functioning graft, death-censored graft loss was not statistically different between ESP and US patients in the multivariable analysis [25]. When ≥50-year-old first graft recipients transplanted during 2010–2017 at European CTS centers were analyzed, deceased donor kidney transplants from 65- to 79-year-old donors demonstrated lower, but still good 3-year death-censored graft survival rates than kidneys from 50- to 64-year-old donors (Fig. 4a). In all subgroups of 50- to 74-year-old recipients, kidneys from ≥65-year-old donors showed similarly good 3-year death-censored graft survival rates (log-rank with trend $P = 0.41$; Fig. 4b). Transplant centers belonging to the ET region were excluded from this analysis in order to avoid a possible influence of the ESP program. Inferior death-censored graft survival was observed only in ≥50-year-old recipients of kidneys from ≥80-year-old donors (Fig. 4a).

Further in-depth analysis of data from the CTS indicates that allocation of so-called Category I donor kidneys from 65- to 74-year-old donors with no history of hypertension, no increased creatinine, no cerebrovascular death, and no other reasons for defining a marginal donor to younger recipients aged 55–64 years results in similar death-censored graft survival rates as transplantation of kidneys from 55- to 64-year-old donors to 55- to 64-year-old recipients (Fig. 5a) [32], importantly, without a difference in mortality (Fig. 5b). As approximately one-quarter of the 65- to 74-year-old donors belongs to this "nonmarginal" category, it seems that this allocation strategy can be used to expand the donor pool with a more favorable use of organs as compared to the strict "old to old" matching. In this analysis, the donors after cardiac death were not excluded (35% in Category I and 13% in Category II of 65- to 74-year-old donors; 18% in 55- to 64-year-old donors).

Currently, approximately 50% of graft losses are due to death of the patient with a functioning graft, and because of the shortage of deceased donor organs, the lifetime of a transplant in young and elderly recipients needs to be also considered during organ allocation.

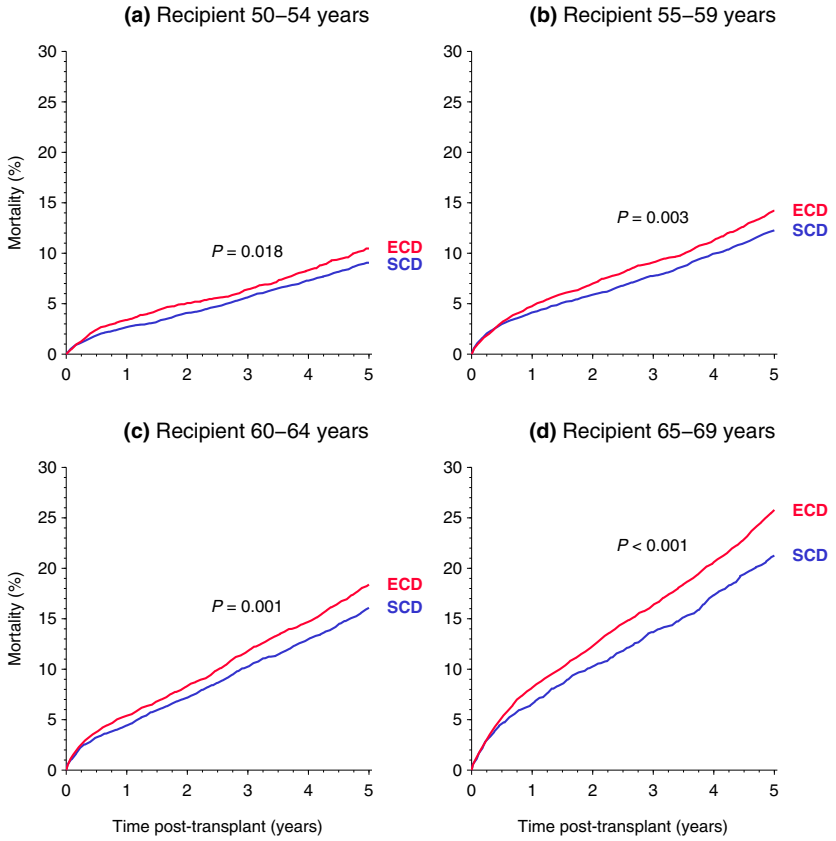

Figure 3 Cumulative incidence of all-cause mortality in European recipients of standard criteria donor (SCD) and expanded criteria donor (ECD) kidneys, stratified by recipient age. First deceased donor kidney-only transplantations performed between 2000 and 2017 were analyzed. Log-rank *P* values of Kaplan–Meier analyses are shown.

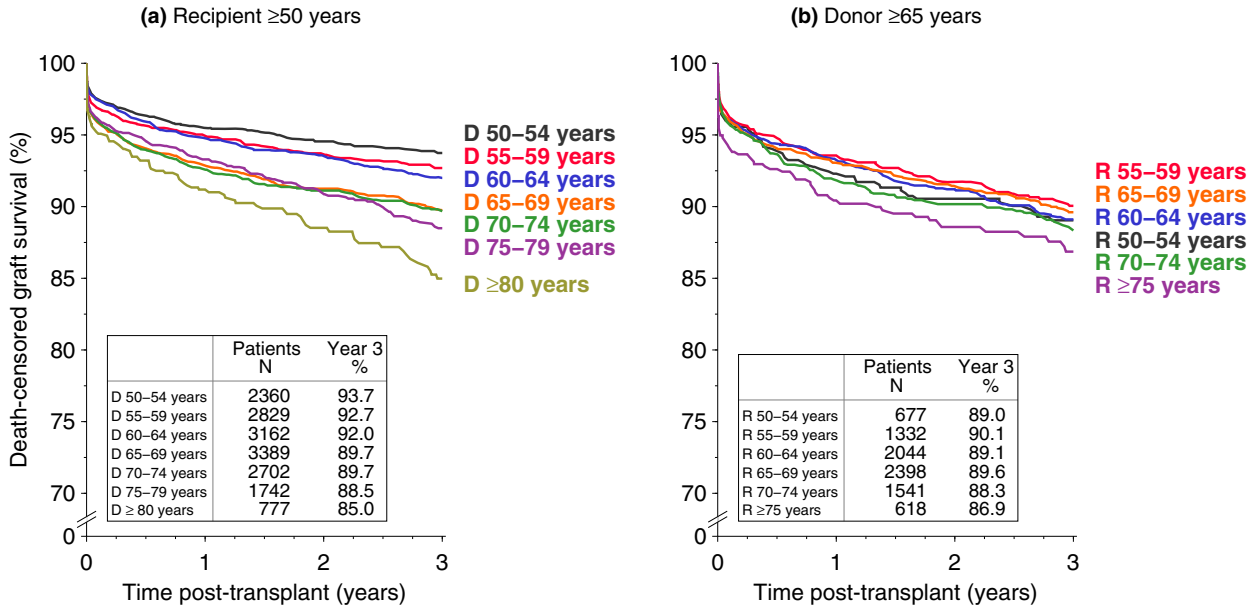

Figure 4 Influence of (a) donor age on death-censored graft survival in ≥50-year-old recipients and (b) influence of recipient age on death-censored graft survival in patients who received a kidney graft from a ≥65-year-old deceased donor. First graft recipients transplanted during 2010–2017 in Europe were analyzed. Current Eurotransplant countries were excluded. D, donors; R, recipients.

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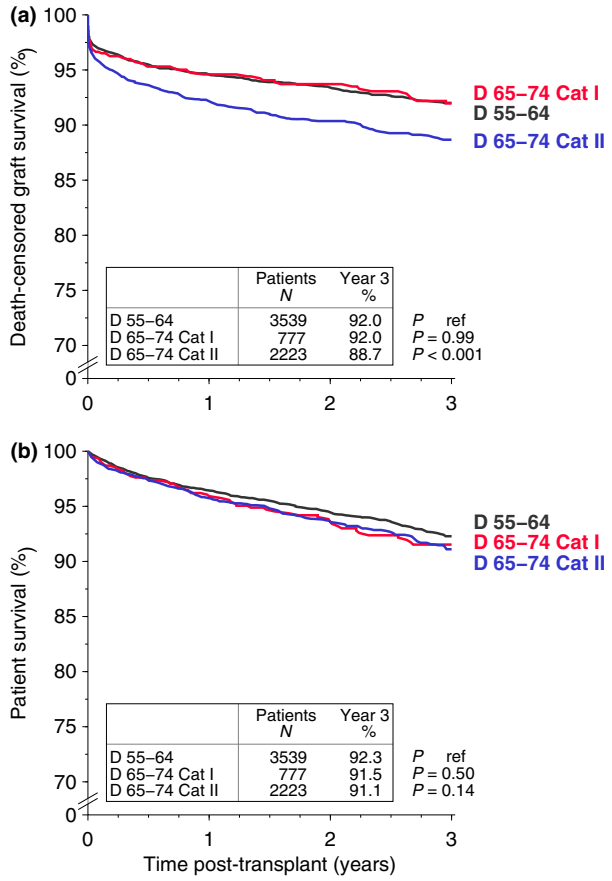

Figure 5 Death-censored graft (a) and patient (b) survival in 55- to 64-year-old recipients according to donor age, categorized by expanded criteria donor parameters. Category I: Donor age 65–74 years with no history of hypertension, no increased creatinine, no cerebrovascular death, and no other reasons for defining a marginal donor, such as diabetes or cancer. Category II: Donor age 65–74 years with history of hypertension or cerebrovascular death or increased creatinine or other reason(s) for defining a marginal donor. Patients transplanted during 2010–2017 in Europe were analyzed. Current Eurotransplant countries were excluded.

The current analysis of European CTS data from 2000 to 2017 shows that failed transplants from ≥65-year-old donors had functioned significantly longer in 55- to 64-year-old recipients than in ≥65-year-old recipients (3.3 vs. 2.3 years).

Consensus

Considering all these facts, it was unanimously concluded that selected kidney organs from 65- to 74-year-old deceased donors should also be considered for 55- to 64-year-old recipients, especially if these organs are from donors with no history of hypertension, no increased creatinine, no cerebrovascular death, and no other reasons for defining a marginal donor, such as diabetes or cancer. Otherwise, due to the continuous increase in donor age, a rigorous old-for-old allocation is expected to result in further prolongation of waiting time in 18- to 64-year-old recipients.

Additional aspects of transplantation of organs from elderly donors

Treckmann *et al.* and Moers *et al.* [33,34] reported that, compared to cold storage, recently applied machine perfusion procedures reduced the risk of primary nonfunction as well as DGF of kidney transplants and improved 1-year graft survival, while the survival advantage was highest in ECD kidneys and those with DGF, suggesting the possibility of a broader use of these as marginal categorized organs, for example, in younger patients. The same group reported a survival benefit of machine perfusion also for kidneys transplanted via ESP [35]. These promising observations, however, need further confirmation.

The quality of life (QoL) was reported to greatly improve after kidney transplantation [36,37], and this was also shown for patients who received grafts from in median 64-year-old donors [38]. Important is also the reduction of waiting time. According to data reported to CTS, there is a strong negative impact of dialysis time on graft survival if the patient received an organ from a ≥60-year-old donor [39]. Analyzing kidney transplant recipients aged ≥60 years in the United States, Rose *et al.* [25] showed that the probability of patient survival with a functioning allograft at 5 years was higher with ECD transplants (≥65-year-old donor) when the patient was transplanted within the first year after wait-listing as compared to delayed non-ECD transplantation performed ≥3 years after wait-listing. Therefore, QoL and waiting time are important aspects that must be considered in the discussion of pros and cons of transplantation of organs from elderly donors.

The immune system undergoes both morphologic and functional changes with aging, including modifications in T-cell phenotypes and functions. Age-related decline of immune functions, designated as immunosenescence, contributes to the increased susceptibility of elderly persons to infectious diseases, vaccination failures, and cancer [40]. Both acute and chronic rejections are less commonly seen in elderly recipients. Therefore, death is the leading cause of graft loss [41,42], in the majority of the cases due to infectious complications, while the prevalence of malignancy as cause of death is also increased [41,43]. As illustrated in Fig. 3, the mortality rate is potentiated by the use of ECD kidneys in all recipient age-groups.

Tullius *et al.* [44] reported a decrease in graft survival with increasing recipient age. However, when the analysis was censored for patient's death with a functioning kidney transplant, graft survival improved with each decade of increasing recipient age. This was even more surprising as elderly recipients had received less well-matched organs of poorer quality. At the same time, the frequency of acute rejections decreased dramatically with increasing age, emphasizing the effect of age on the vigor of the recipient's immune responses. In contrast to high recipient age, high donor age was associated more frequently with acute rejection episodes and grafts from elderly donors were shown to be more immunogenic, especially in the early period after transplantation [26,45,46]. Moreover, the presence of acute rejection episodes was reported to shorten graft survival in patients transplanted from >55-year-old deceased donors [47]. Analysis of immune responses in ESP kidney recipients versus <65-year-old patients receiving kidneys from <65-year-old donors with comparable HLA mismatches demonstrated that elderly patients receiving organs from elderly donors had elevated numbers of memory T cells, activated cytotoxic and alloreactive T cells, and higher levels of tumor necrosis factor-α [48]. Since death with a functioning graft due to infections is the dominant reason of early graft loss in elderly, more intense clinical immunosuppression to prevent or treat acute rejection in recipients of grafts from elderly donors is expected to be counterproductive and result in increased mortality. Therefore, it should rather be strived for improved HLA matching in transplantation of such organs without prolonging the cold ischemia time extensively.

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Conflicts of interest

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