INVITED COMMENTARY

Three is not enough

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In the current issue of *Transplant International,* Assfalg *et al.* [1] address the question whether, in times of organ shortage, it is justified to perform a repeat kidney re-transplant (e.g. third or fourth transplant). Compared to a first or second allograft, repeat kidney re-transplants were reported to show strongly impaired outcome [2].

The authors analysed 1464 patients from 42 centres in the Eurotransplant area who received a third or fourth kidney transplant during 1996–2010. A total of 38 173 first graft recipients transplanted during the same 15-year time period served as controls. Recipients of a repeat re-transplant were significantly younger than first transplant recipients (43 vs. 50 years in median, $P < 0.001$) and had more frequently a 'favourable' HLA match (89% vs. 84%, $P < 0.001$). Despite this demographic advantage, repeat re-transplant recipients showed reduced patient survival (third graft: HR 1.62, $P < 0.001$) as well as higher rates of graft loss (third graft: HR 2.13, $P < 0.001$), death with functioning graft (third graft: HR 1.35, $P = 0.001$) and primary nonfunction (13% vs. 7%, $P < 0.001$). Therefore, Assfalg *et al.* come forward with the idea of setting an upper limit for the number of sequential transplantations in order to consider also the prospects of success of transplantation.

A few points in the work of Assfalg *et al.* require more detailed analysis and comment.

The majority of patients in the study of Assfalg *et al.* were transplanted in a time period during which sensitive HLA antibody-detection techniques were not available. As an example, at the Heidelberg transplant centre it was not until the year 2009 that single-antigen bead assays were introduced to clinical routine that allowed a more precise definition of acceptable and nonacceptable HLA antigen mismatches and goal-oriented application of preventive measures, such as peri-transplant antibody removal and potent immunosuppression. As a consequence, antibody-mediated graft losses could greatly be avoided in presensitized patients, including the recipients of repeat re-transplants [3]. Figure 1 illustrates the impressive improvement in the survival of repeat re-transplants in Europe from the 1996 to 2010 period analysed by Assfalg *et al.* to the more recent 2011–2018 period during which the outcome of a fourth graft is not anymore different from that of a third graft.

In the study of Assfalg *et al.*, HLA matching had a strong influence on the number of graft losses in first

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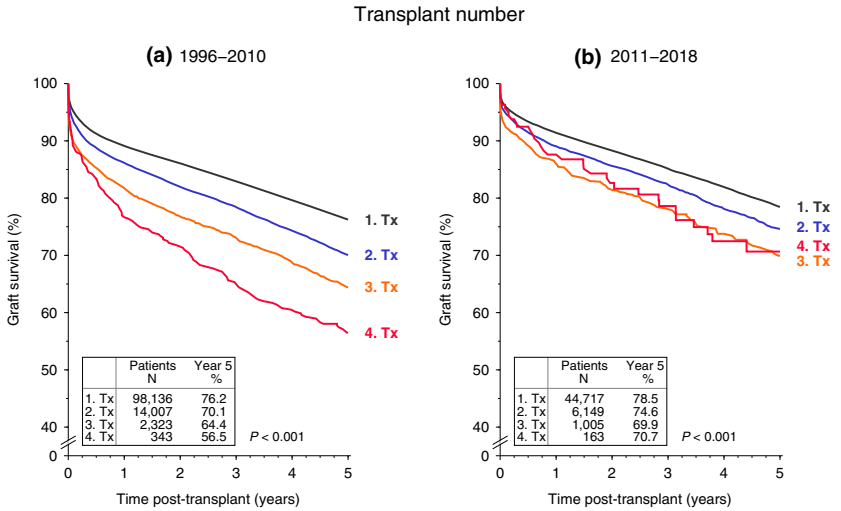

Figure 1 Deceased donor kidney transplantations performed at European CTS centres during (a) 1996–2010, the period considered in the manuscript of Assfalg *et al.* [1], and (b) the more recent era 2011–2018. From 1996–2010 to 2011–2018, there was a general improvement of graft survival, which was especially pronounced in recipients of a fourth graft (red curve) who in the meantime show a similar outcome as third graft recipients (orange curve).

transplant recipients (HR 1.47, $P < 0.001$), whereas such a strong impact of HLA matching was missing in recipients of repeat re-transplants (HR 1.09, $P = 0.651$). One possible explanation for the latter rather surprising observation is that many of the repeat re-transplantations in the Eurotransplant region are performed via the Acceptable Mismatch (AM) Program in which HLA antibody/HLA antigen constellations are evaluated precisely and a high number of HLA mismatches are avoided. Indeed, Heidt *et al.* [4] reported that, in contrast to the strong impact of HLA matching in highly sensitized patients transplanted via the regular kidney allocation, HLA mismatches did not influence the outcome significantly when the same patients were transplanted via the AM Program. The reason for the strong HLA matching effect observed in first transplant recipients, on the other hand, might partly be hidden in the demographics of this cohort. As many as 91–93% of first transplant recipients had a favourable HLA match when they were less than 65 years old, as compared to the much lower 56% rate when they were ≥65 years old. The majority of patients in the latter group was most likely transplanted via the Eurotransplant Senior Program, which abandons HLA matching for the sake of a short ischaemia time and which, at the same time, is expected to be associated with a less favourable outcome due to the combination of high donor and recipient age. Altogether, this might have resulted in an additionally and artificially strengthened outcome difference in first transplant recipients with favourable and unfavourable HLA mismatches.

Moreover, only 3% of repeat re-transplant recipients were ≥65 years old as compared to a strikingly higher 20% rate of these elderly patients among first transplant recipients. Ideally, given this strongly unequal distribution of elderly patients in the two groups and their

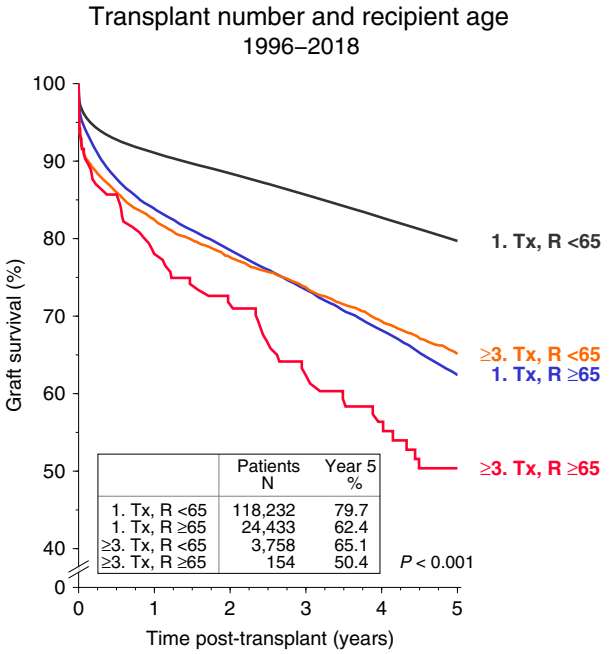

Figure 2 Univariate analysis of graft survival in <65- or ≥65-year-old recipients (R) of a first (1. TX) or repeat re-transplant (≥3. TX). Deceased donor kidney transplantations performed at European CTS centres during 1996–2018 were analysed. Graft survival in <65-year-old recipients of a repeat re-transplant was not very much different from that in ≥65-year-old recipients of a first transplant.

special characteristics, such as poor HLA matching and inferior outcome, these patients should have been omitted from the analysis to receive a clearer picture. Presumably, this would have even further supported the main finding of the paper, namely the poor outcome in recipients of repeat re-transplants during 1996–2010.

Assfalg *et al.* add valuable data to the current literature on repeat re-transplantations and ask for a better HLA match during the first and second kidney transplantation to avoid a sensitization-related inferior outcome in repeat re-transplantation. Based on their data, however, the authors also discuss whether a repeat re-transplant should rather be declined to better balance 'demand with success'. We regret to say that in this point we like to disagree with the authors. If we followed their argumentation, the current practice of deliberately allocating the kidneys primarily to a particular patient group with rather inferior results, for example to elderly patients, could also be questioned. In their study, as many as 6681 ≥65-year-old patients received a first kidney allograft, which is 5 times more than the number of 1312 patients who received a repeat re-transplant. No all-cause graft loss rates are given in the study of Assfalg *et al.*, but based on data from European CTS centres shown in Fig. 2, we expect that the overall graft survival was not significantly different between <65-year-old repeat re-transplant and ≥65-year-old first transplant recipients. The only difference between the two groups is that recipients of repeat re-transplants lose their grafts, whereas ≥65-year-old patients lose their lives at a higher rate, leading to increased graft loss either way.

Therefore, in contrast to Assfalg *et al.*, we believe that mostly young repeat re-transplant recipients as well as any other special group of patients cannot be generally denied access to transplantation and the question of a repeat re-transplantation should always be assessed on an individual basis, also because of the continuously improving outcome. Given the high number of transplants in elderly patients, graft lives could rather be saved by improving the old-for-old concept than by forbidding a fourth transplant.

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Conflicts of interest

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