# Review of: "Interactions Between Donor Age and 12-Month Estimated Glomerular Filtration Rate on Allograft and Patient Outcomes After Kidney Transplantation"

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## Predicting long-term kidney-allograft survival: an ageing conundrum.

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Many factors contribute to kidney-allograft failure. Clinical trials that have focused on hard clinical endpoints, such as allograft survival, are often not feasible in kidney transplantation, i.e., they would require thousands of patients observed over very long periods to record sufficient events. Since the first publication in 2002[1], estimated glomerular-filtration rate (eGFR) has been used as a surrogate marker of allograft survival and this will most likely continue. Very recently, the DIVAT consortium showed that 3-month post-transplant eGFR and proteinuria were independent predictors for a return to dialysis and that there was a strong correlation between eGFR at 3 and 12 months, i.e., the predictive accuracy of 3-month eGFR was within a similar range and did not differ significantly from the 12-month eGFR in either the derivation cohort or the validation cohort[2].

Specific donor factors, including donor age and comorbidities, may influence short- and long-term outcomes after kidney transplantation[3]. In this issue of *Transplant International*, Lim et al. assessed whether donor age and type (living or deceased) modify the associations between 12-month allograft function (eGFR) and the risk of long-term allograft and patients' outcomes in a contemporary cohort (2000-2017) of 11,095 kidney-transplant recipients from the Australian and New Zealand registry[4]. They found that "that the effects of reduced short-term allograft function at 12-month on longer term allograft outcome differs in recipients of younger and older donor kidneys, with the magnitude of the risk for overall allograft loss being higher for recipients of younger donor kidneys with lower 12-month eGFR values than those who

received older donor kidneys. The inflection point for the increased risk of allograft loss occurred at a lower eGFR for older donor kidneys than younger donor kidneys."These results infer that younger kidneys with low one-year eGFR fare worse than older kidneys with the same low eGFR.

This study has however major limitations, i.e., it is derived from registry data and the only post-transplant variables included, apart from eGFR, were body-mass index at 1-year and initial immunosuppression. Major parameters that occur within the first post-transplant year, such as occurrence of delayed graft function, acute T-cell mediated rejection (TCMR) or antibody-mediated rejection (ABMR), viral infections (cytomegalovirus [CMV], BK virus [BKV]), post-transplant diabetes mellitus (PTDM), exposure to calcineurin inhibitors in terms of trough levels or C(0)/D ratio, daily doses of acid mycophenolic, or weaning of steroids were not taken into account. The following is a list of studies demonstrating how these factors independently influence graft survival and thus need to be taken into account.

A recent study that included 858 *de novo* kidney-transplant recipients, of which 16.92% presented with **DGF**, had one-year graft survival rates of 93.6% and 99.7%, respectively, for the groups with and without DGF ($p<0.05$)[5].

In a prospective cohort of 1,001 kidney-transplant recipients that underwent a surveillance allograft biopsy at 1-year, Loupy et al. report that **subclinical ABMR** at 1 year was independently associated with a 3.5-fold increase in graft loss (95% CI: 2.1--5.7) along with eGFR and proteinuria ($p<0.001$). In addition, subclinical ABMR was associated with more rapidly progressing transplant glomerulopathy[6].

Regarding TCMR, Rampersad et al. very recently reported on a prospective series of 775 kidney-transplant recipients and their serial allograft histologies[7]. They found that both a first and second **TCMR** event correlated with death-censored and all-cause graft loss when adjusted for baseline covariates and other significant time-dependent covariates, such as DGF and ABMR. TCMR events were particularly noted in those with intermediate and high HLA-DR/DQ molecular mismatch scores, thus suggesting under immunosuppression.

BKV, CMV, and Epstein-Barr virus (EBV) reactivations are common after kidney transplantation and associated with increased morbidity and mortality. Blazquez-Navarro et al. conducted a prospective study in *de novo* kidney-transplant recipients, and assessed the replication of **BKV, CMV,** and EBV within the first year post-transplantation and at different time-points by PCR[8]. They found that BKV--CMV combined reactivation had a deep impact on renal function by 1-year post-transplantation and therefore, most likely, on long-term allograft function, even at low viral loads. These findings were confirmed in another cohort of 723 kidney-transplant recipients[9].

In a large series of 3,663 Taiwanese kidney recipients that received a transplant between 1997 and 2011, the incidence of **PTDM** peaked within the first year after kidney transplantation; in addition, PTDM negatively affected graft and patients' outcomes. Finally, the magnitude of cardiovascular and survival disadvantages from PTDM were more pronounced in recipients aged less than 55 years[10].

In the current era of maintenance immunosuppression after kidney transplantation, most cases receive an association of tacrolimus plus mycophenolic acid (MPA), with or without steroids. The **tacrolimus trough concentration/dose**(C0/D) ratio of tacrolimus has recently been proposed as a prognostic marker for a poor outcome after kidney transplantation. We performed a retrospective study on 1,029 kidney-transplant recipients (2004--2016) and found that the C0/D ratio within the first year post-transplant was an independent and early predictor of death-censored graft survival[11]. Regarding MPA exposure, there is no evidence that it affects kidney-allograft survival[12]. With regards to **steroid avoidance and**

**withdrawal** after kidney transplantation, a recent updated systematic Cochrane review reported that it significantly increased the risk of acute rejection; however, there was no evidence to suggest a difference in patients' mortality or graft loss within 5 years post-transplantation, but the long-term consequences of steroid avoidance and withdrawal still remain unclear[13].

While the conclusions of Lim et al. are quite intriguing, predicting long-term kidney-allograft survival from registry data is still a major challenge. Clearly, many 1-year post-transplantation factors affect long-term allograft survival and cannot be taken into account in most registry-data studies. It is therefore mandatory to have a large and well-phenotyped kidney-transplant cohort included from the time of transplantation to identify the most robust predictors of kidney-allograft loss.

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