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INVITED COMMENTARY

Early kidney allograft loss—Is there scope for improvement?

Paolo Ferrari[1,2]

1 Department of Nephrology, Ospedale Civico Lugano, Ente Ospedaliero Cantonale, Lugano, Switzerland
2 Clinical School, University of New South Wales, Sydney, NSW, Australia

Correspondence
Paolo Ferrari MD, Department of Nephrology, Ospedale Civico Lugano, Via Tesserete, 6900 Lugano, Switzerland.
Tel.: 0041 91 811 14 36;
e-mail: paolo.ferrari@eoc.ch

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The 1-year kidney graft survival has increased remarkably from approximately 50% in the early 1970s [1], to 80% in the mid-1980s, and over 90% in the modern era (Fig. 1) [2]. Much of the improvement in early graft survival over the years has been ascribed to improved immunosuppressive regimens with a consequent reduction in graft loss due to acute rejection, improved human leukocyte antigen (HLA) matching and routine HLA antibody screening of recipients, better surgical and medical care, and better management of infections and other complications [3].

Unfortunately, there has been little improvement in long-term death-censored graft survival since the late 1980s, particularly in first deceased donor transplant recipients [4,5]. This lack of a significant improvement in graft survival half-life after the first year after transplantation has been the subject of extensive investigations. In contrast, in recent years, only a few studies have drawn their attention to the early kidney graft survival and the factors leading to early graft loss in the current era [5,6]. Most of these studies have focused primarily on immediate or very early loss of graft function during the first 30 days after transplantation and on donor-related factors and identified donation after circulatory death (DCD) or expanded criteria donors (ECD) as the main causes for very early graft loss [6].

In this issue of *Transplant International*, Helenterä and coworkers analyzed the causes of early allograft loss among a cohort of 2 447 kidney transplant recipients performed between June 2004 and October 2016 in the only transplant center in Finland in an attempt to better characterized the reasons of graft loss in the first year post-transplant [7]. Of all the recipients included in the analysis, 95% were recipients of donors after brain death (DBD), with the remainder being live donor allograft recipients. The majority (74%) were on a cyclosporine-based immunosuppression, and only 11% were recipients of a second or subsequent transplant. The first striking observation from this study is that 1-year patient survival was 98% and graft survival was 96%. This low incidence of early graft loss in these patients could be due to the lack of DCD donors in the Finnish cohort.

Among the 109 patients with early graft loss, death with a functioning kidney accounted for 38.5% of cases

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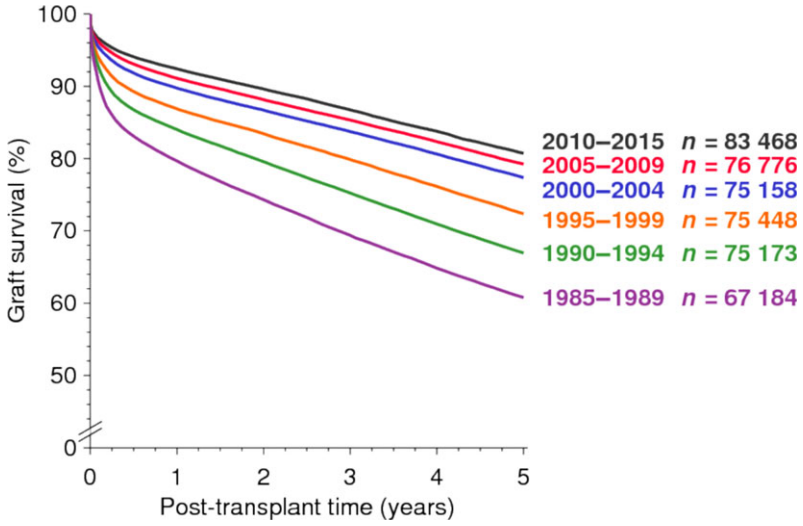

Figure 1 Graft survival in kidney transplant recipients by era: The graft survival at 1 year has improved from 80% during the 1985–1989 period to >90% in the 2010–2015 period (K-14001-0817, Courtesy of Caner Süsal, CTS Registry).

(1.7% of the whole cohort), which is lower than the 1-year mortality rate reported from the USA (4.7%) [8] or the UK (3%) [9]. The main cause of death was cardiovascular disease, while infectious death was rare, possibly owing to a restricted use of induction therapy and primarily cyclosporine-based and not tacrolimus-based immunosuppression. The two key predictors associated with early death were duration of dialysis >3 years and diabetes. In the current era of increased utilization of ECD kidneys, it is reassuring to acknowledge that using high Kidney Donor Profile Index (KDPI) grafts with the goal of avoiding or limiting time on dialysis is associated with lower mortality hazard at least in elderly patients [10]. The remainder of patients with early graft loss experienced graft failure and returned to dialysis within 1 year; interestingly, acute rejection accounted for graft loss only in 15% of cases (0.4% of the whole cohort). Increased cold ischemia time and increase in both percent PRA I and PRA II were the key predictors for early graft failure. There were 14 cases of primary nonfunction, who underwent multiple kidney graft biopsies and testing for donor-specific antibodies and found negative, ruling out acute antibody-mediated or cellular rejection. Thus, how an increased PRA is associated with early graft loss in this population is unclear.

The current study has some limitations that make generalizability of the findings to other populations challenging. Some of the limitations are the relatively uniform donor population that possibly does not reflect current trends in organ donation, the predominantly cyclosporine-based immunosuppression, the restricted use of anti-CD25 or antilymphocyte antibody induction, and the small sample size. In comparison, studies from the USA and UK included close to or in excess of 20 000 kidney transplant recipients each [5,6]. On the other hand, this single center cohort has the advantage of uniformity of protocols and processes and of having complete follow-up data.

Donor characteristics, including age, gender, and genetic and environmental factors, are known to influence kidney transplant outcomes. In the current study, donor factors were limited to donor age and living versus deceased donor, but it was not possible to assess the effect of DCD or ECD, which are important determinants of early outcome [6]. Because this was a single center study from a national program, it would have been interesting to compare outcomes within pairs of kidneys, as the incidence of DGF and short-term and medium-term renal function shows a significant relationship within pairs of kidneys transplanted from the same donor [11].

In 43% of cases of early graft failure (1.3% of the whole cohort), it could be argued that the reason may be a technical or surgical issue (venous or arterial thrombosis) and it would have been interesting to have some more details about the anatomy of these kidneys (left versus right, single versus multiple vessels).

A study from the ANZDATA Registry demonstrated that the 1-year graft survival was lower for right kidneys (89.1%) compared to left kidneys (91.1%, $P = 0.001$) and that this was primarily attributed to failures because of surgical complications (66 for right versus 35 for left kidneys) [12].

BK virus infection and nephropathy are a recognized causes of graft failure even early after transplantation [13]. Interestingly, among the 109 cases of early graft loss in the Finnish cohort, none was allegedly reported to be due to BK infection. This, again, may be due to

the immunosuppressive regimen used in these recipients or a nonsystematic screening for the infection.

Despite such limitations, the study by Helenterä *et al.* has some merits that may help in clinical decision-making, in particular the identification that the key risk factors for composite endpoint of early graft failure or death are increased PRA, diabetic recipient, and an increased donor age. This would suggest that the decision to allocate a kidney from an older donor to a recipient with diabetes and high PRA should be exerted with caution, because this could increase the risk of losing the graft within 1-year from transplantation by 10- to 20-fold. On the other hand, the current data do not allow making any inferences on long-term risks and outcomes, and a risk prediction estimate would require to consider both short-term and long-term outcomes.

Increased longevity matching to optimize long-term kidney allograft survival has been central to the effort of appropriate allocation of deceased donor kidneys, as the demand for kidney transplant continues to grow faster than organ availability. The current data should prompt an analysis in a larger, independent cohort to assess whether predictors of short-term graft survival can improve KDPI-based decisions when considering whether to accept or decline a deceased donor kidney offer.

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Conflict of interest

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