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REVIEW

Factors influencing long-term outcome after kidney transplantation

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Summary

Many factors influence the long-term outcome of kidney transplantation, which is defined very schematically by patient death or renal dysfunction leading to graft loss. The most important of these factors is most likely the quality of the transplant itself, with kidneys from living donors showing a positive impact, while kidneys from expanded criteria donors show deleterious impacts. Various clinicopathological scores exist to predict mid- to long-term outcomes and avoid the transplantation of kidneys displaying inferior results. The key factors related to the recipient include their age as well as disease recurrence, HLA matching, HLA immunization, ethnic background, time on dialysis, and cardiovascular comorbidities. Renal function, defined based on estimated GFR and/or proteinuria values, is a result of all these factors. Delayed graft function has a detrimental long-term impact, as does the level of renal function impairment either in stable condition or in case of progressing dysfunction. Finally, although current immunosuppression regimes are highly efficient in preventing acute rejection, the burden of specific (diabetes, nephrotoxicity) and nonspecific (infection and cancer) side effects has significant negative long-term consequences that may well be worse in the future because of the increasing ages of both donors and recipients. The development of safer immunosuppression strategies is therefore crucial to improve long-term outcomes.

Introduction

Although the short-term results of kidney transplantation have improved steadily over the past 20 years, the long-term results have improved either minimally or not at all [1]. The definition of long term is not perfectly clear in the literature, but schematically, it represents patient death and renal dysfunction leading to graft loss from the fifth year post-transplantation on. A recent comparison of results in Europe and in the United States of America gives the following figures: Overall 5- and 10-year graft survival rates were 77% and 56%, respectively, in Europe and 67% and 43% in the USA [2].

There are many potential explanations for this discrepancy, such as the increasing use of expanded criteria donor (ECD) kidneys, the aging of the recipient population, difficulties in understanding the causes of chronic allograft dysfunction, and the current inability to efficiently treat chronic rejection, among others. Schematically, half of transplant recipients will die with a functioning allograft, while the other half will lose the graft because of various causes [3]. Multiple intricate factors influence long-term outcomes following kidney transplantation.

This review is intended to dissect some of these complex relationships to outline the most significant, and more importantly, the most readily modified among them. At the time of kidney transplantation, at an individual level, there are a number of well-identified but nonmodifiable characteristics of both the donor and recipient that will impact long-term outcomes. More interesting are the potentially

modifiable factors such as the choice of immunosuppressive regimen, delayed graft function and its determinants, renal function under stable conditions, and the causes of chronic allograft dysfunction, most of which are clearly complex issues (Table 1).

Donor factors: the "quality" of the kidney

Among the many factors influencing the long-term outcome of kidney transplantation, donor factors are most likely the most significant. The "quality" of the kidney may be defined using broad categories such as living versus deceased donor kidneys, subgroups of deceased donors based on various simple or sophisticated scores, and finally, clinico-histopathological scores based on preimplantation biopsy data.

First, the data in the literature are concordant regarding the conclusion that living donor kidneys function far better than those from deceased individual [4] in almost all instances, except may be in young recipients receiving a kidney from a young standard criteria donor (SCD). The nonimmunological reasons for superiority of living donor kidneys are quite clear, including the precise pretransplantation evaluation of kidney donor function, lack of detrimental pre-agonal and agonal phases, short or very short cold ischemia time, and the involvement of more experienced surgeons. Moreover, long-term results are even better when there is complete HLA matching or no HLA mismatches (depending on the way kidneys are attributed) between the donor and recipient.

Second, by definition, kidneys coming from ECDs lead to worse results than kidneys from SCDs [5,6]. The most popular criteria that are broadly used to define an ECD are an age ≥60 years or an age between 50 and 59 years and the presence of 2 of the following 3 factors: cerebrovascular death, a past history of hypertension, or terminal serum creatinine levels >1.5 mg/dl [7]. However, the reality is considerably more complex, and this definition, although commonly used in most countries worldwide, represents an oversimplification. Several authors have clearly demonstrated that predictive value may be improved using more sophisticated scores including many more variables [8,9]. It is therefore possible to define subgroups of ECDs associated with varying long-term outcomes.

Third, the category of donor after cardiac death (DCD) kidneys is of interest because although short-term data show a higher incidence of primary nonfunction and delayed graft function for such kidneys because of severe ischemia reperfusion injury, long-term data from various countries show similar results compared with SCDs [10].

Finally, it is also possible to improve predictions of long-term prognosis using combined scores including demographic data as well as serum creatinine and histological data from preimplantation biopsies. For example, using the predefined Pirani's histological score, Remuzzi *et al.* [11] were able to show improved long-term results for either single or dual kidneys from donors >60 years of age, provided the grafts were evaluated histologically before implantation. Along the same lines, within our research group, Anglicheau *et al.* [12] showed that it was possible to predict a poor short-term outcome and, thus, a poor long-term one using a simple composite score based on a donor serum creatinine level >150 μM, donor hypertension, and% of sclerotic glomeruli >10.

It is therefore important to stress that, whatever scoring method is used, precisely defining the category of the donor, and subsequently, the "quality" of the transplanted kidney is undoubtedly the most powerful means of making long-term predictions.

Recipient factors at the time of transplantation

Age

The kidney transplant population is growing increasingly older in most countries and transplant programs. Age at the time of transplantation is clearly correlated with long-term outcome, as reported recently in both Europe and the United States of America [2]. This effect is further reinforced by the fact that most official or nonofficial allocation policies preferentially give kidneys from old donors to old recipients [13,14]. The most recent data coming from the OPTN and SRTR in the United States [15] show that 5-year patient survival is 67.2% when recipient age is ≥65 years, while it is 80.1% when recipient age is ≤65 years. Five-year graft survival is 60.9% in the former group and 71.3 in the latter group. Interestingly, within this age range, the age of the donor makes a difference: In the Eurotransplant Senior Program, in which kidneys from donors aged >65 years are preferentially allocated to recipients aged >65 years, the mid-term results are clearly better when SCD kidneys are allocated to "old" recipients [13]. This is also true when kidneys from living donors are given to "old" recipients [14]. Therefore, allocating an "old" kidney to an "old" recipient leads to statistically better results than remaining on dialysis, but allocating a younger kidney to the same "old" recipient leads to better results than using an "old" kidney donor!

Recurrence of native kidney disease

With regard to long-term outcomes, the deleterious influence of the recurrence of native kidney disease is no longer a subject of controversy [16–19]. It represents the third cause of allograft loss 10 years after transplantation. The risk of recurrence mainly observed in metabolic diseases and glomerulonephritis is highly variable among diseases,

ranging from rare to one hundred percent for dense deposit disease, being influenced by many factors and associated with a wide range of prognoses. In some cases, the risk of recurrence is highly correlated with the presence of circulating antibodies or with the activity of the underlying disease, such as in antiglomerular basement membrane disease. Transplantation is therefore usually discouraged until the disappearance of autoantibodies and/or control of the disease is observed. Interestingly, for most of diseases, the true rate of recurrence is not known. In fact, it is difficult to appreciate such rates because many nephropathies, such as IgA or membranous nephropathy, may occur without any clinical manifestation and are detectable only with protocol biopsies. Indeed, the rate of recurrence for IgA nephropathy varies from 20% to 60% and that for membranous nephropathy from 7% to 44% [16–18], according to the biopsy policy of the center. While these two diseases seem to have a limited impact on the allograft survival rate, many other diseases are associated with a poor prognosis, such as recurrent primary focal and segmental sclerosis (FSGS) or membrano-proliferative glomerulonephritis (MPGN). FSGS frequently recurs after kidney transplantation (20–40%), and such recurrences are associated with compromised allograft survival. Luckily, recent therapeutic advances have improved the rates of both clinical and histological remissions, which are two critical parameters influencing prognoses [17]. Either type II or I MPGN recurs frequently following transplantation and is associated with a reduced allograft survival rate. Interestingly, type II MPGN often results from uncontrolled alternative complement pathway activation. In this particular setting, eculizumab, an anti-C5 monoclonal antibody, may represent a potential therapeutic option that requires further investigation. In atypical HUS, characterized by constitutional or acquired dysregulation of the alternative C3 convertase, with a very high recurrence rate post-transplantation, eculizumab has proven to be a very promising treatment option [19].

In addition to the recurrence of glomerulonephritis, other diseases such as antiphospholipid nephropathy (APSN) may recur, affecting long-term allograft survival. Although thrombosis is considered the key feature of vascular disease in antiphospholipid syndrome, chronic arterial and arteriolar lesions are frequently observed in the kidney. These lesions mainly involve thickening of the intima and media and are often associated with increased cellularity of the two layers. These vascular changes result in fibrotic lesions that progressively lead to ESRD. Interestingly, we have observed that kidney transplant recipients who exhibit antiphospholipid antibodies, primarily with the lupus anticoagulant, are at greater risk of developing thrombotic complications. In addition, these patients develop typical features of APSN recurrence on the allograft that led to a rapid decline of renal function, potentially leading to transplant loss [17].

HLA compatibility

The use of HLA-matched has always had a significant favorable long-term impact on kidney transplantation, but the magnitude of this effect has decreased over the years. This positive effect is acknowledged in many allocation policies, mainly but not only, in Europe, for example, in the policies of the United Kingdom [20]. Examining the most recent data from the Collaborative Transplant Study [21], Süsal *et al.* confirmed the beneficial long-term influence of HLA matching not only on graft survival and patient death from infection but also on various factors such as the need for lower dosages of immunosuppressive agents; a lower incidence of side effects of immunosuppression, including the incidence of PTLDs; a lower incidence of hip fractures; and a lower grade of sensitization, which is especially important when a second transplant is planned. Very recently, using the US Renal Data System, Foster *et al.* [22] found that both donor age and HLA mismatches are important in determining the survival of deceased donor grafts. Interestingly, the advantages of younger donors offset the disadvantages of poorer HLA matching, while better HLA matching offsets the disadvantages of older donor age! Another consequence of poor HLA matching is the increased incidence of acute rejection, which has been documented in the Eurotransplant Senior Program in the "Old for old" group [13,14].

Anti-HLA immunization

Anti-HLA immunization also plays a deleterious role in the long-term outcome of kidney transplantation. This effect has been noted from the beginning of transplantation history [23]: HLA-immunized recipients show inferior results compared with nonimmunized recipients, at least partly explaining why second and third transplantations display inferior results compared with first transplantations. This phenomenon is observed regardless of the method used to detect HLA immunization and, especially, donor-specific anti-HLA antibodies, that is, the microlymphocytotoxicity, ELISA, or Luminex® (Austin, TX, USA) method. Indeed, Lefaucheur *et al.* [24] reported that the presence of DSAs in both historical and day 0 sera negatively influences graft survival, with historical serum being the most informative. More recently [25], using Luminex® technology, these authors were able to further dissect the influence of the presence of DSAs, setting a threshold of approximately 3000 MFI units, beyond which the risk of acute humoral rejection was 100-fold higher than in patients with an MFI <465 MFI units! Many groups, including ours, have

obtained similar results, and a recent review of the literature [26] clearly confirms the deleterious influence of the presence of DSA prior to transplantation, where the higher the level, the higher the risk of humoral rejection and the poorer the resultant graft survival. What is true for anti-HLA DSAs is most likely (although less well documented) also true for non-HLA DSAs [27], such as angiotensin II type 1 receptor antibodies [28]. Post-transplant HLA immunization also conveys a risk of antibody-mediated rejection and poor outcomes, which will be further discussed [29].

Ethnic background

Ethnic background has been considered for many years to have a major deleterious impact on graft outcome for both immunological and nonimmunological reasons. The literature concerning this role mainly comes from the United States [30]. In the most recent data from the OPTN/SRTR database [29], graft outcomes were shown to vary by racial/ethnic group, irrespective of donor type, and the differences tended to increase with time post-transplantation. An analysis of graft survival at various time points (3 months, 1, 5, and 10 years) showed that African Americans presented the lowest graft survival at each time interval. This finding was explained by a higher incidence of delayed graft function and acute rejection because of incompletely understood mechanisms, including higher levels of co-stimulatory molecules and expression of Duffy antigens on erythrocytes. The results from Europe indicate that these differences do not occur in all countries. For example, in France, the results in African Europeans were not different from those in white recipients, suggesting a role of access to care [31]. However, taking this factor into account, it was recently shown that the difference in the results persists even when access to care conditions is similar [30].

Miscellaneous

Two other linked factors influence long-term outcomes. The first is the time spent on dialysis. The role of this factor was described at the beginning of the 2000s by Meier-Kriesche *et al.* [32], indicating that the longer the time on dialysis, the poorer the long-term outcome. Cardiovascular complications at the time of transplantation are the second important factor to consider, and their frequency is clearly correlated with time spent on dialysis [33]. It is well recognized that patients with end-stage renal disease exhibit an increased risk of premature cardiovascular disease, with the risk for individuals on hemodialysis being between 10 and 20 times that of the general population. Although kidney transplantation presents a reduced risk compared with dialysis, the burden of cardiovascular disease negatively influences the long-term outcome of transplantation. However, it is not yet known whether pretransplantation intervention in coronary artery disease would have a positive impact on long-term post-transplantation results.

Graft function in the course of transplantation

Delayed graft function

In as many as 50% of cases, the immediate postkidney transplantation course is complicated by early kidney dysfunction related to ischemia reperfusion injury-induced acute kidney injury, modulated by multiple donor and recipient factors [34]. This early dysfunction, as a consequence of various intricate factors, may lead to slow or delayed graft function and to primary nonfunction in the most severe cases. Because of the complexity of its pathophysiology, defining delayed graft function is difficult and leads to over-simplification, explaining why more than 18 definitions coexist in the literature [35], the most frequent of which is a single dialysis session during the first 7 days post-transplantation.

The incidence of DGF varies greatly, ranging from <10% when using living donor kidneys to more than 50% for DCD kidneys. The short-term clinical consequences of DGF are obvious: There is a need for several post-transplantation dialysis sessions, leading to increased morbidity, an increased length of hospitalization, and, hence, increased costs.

More interesting are the long-term consequences of DGF, which are still a matter of debate. The classical view [36] is that DGF is associated with increasing cold ischemia time and an increased risk of long-term graft failure, as a consequence of acute kidney injury, together with various repair mechanisms involving both adaptive and nonadaptive immunities. The incidence of acute rejection is also increased.

What may be more puzzling is the most recent suggestion that cold ischemia time may have more subtle consequences. Indeed, Kayle *et al.* [37] recently studied the impact of cold ischemia time on graft survival among ECD transplant recipients through a paired kidney analysis (kidneys derived from the same donor, but transplanted into 2 different recipients). Not surprisingly, the incidence of DGF was higher in pairs with a greater difference in the cold ischemia time, but the incidence of graft loss was not found to be different, even in multivariate models adjusted for recipient factors. This first analysis was followed by a second [38] in which the impact of cold ischemia time-induced DGF on long-term graft loss was studied in paired kidneys where the kidney given to one recipient experienced DGF, whereas that in the second recipient did not. Interestingly, the author concluded that while the incidence of DGF increased with an increasing cold ischemia time, as

expected, graft loss was again similar in the two groups. This finding strongly suggests that cold ischemia time-induced DGF may not have deleterious long-term consequences and, hence, that kidneys should not be discarded because of anticipated prolonged ischemia time! This phenomenon is in line with the common observation that patients receiving a kidney transplanted from a DCD donor show a high incidence of DGF, while their long-term results are not significantly different from those of patients receiving an SCD kidney, who show a much lower incidence of DGF. This again highlights the complexity of DGF pathophysiology!

It is possible to nonselectively prevent DGF or at least decrease its incidence through the improvement of donor management, reduction in cold ischemia time, and application of machine perfusion. The beneficial impact of reducing the cold ischemia time is excellently demonstrated by the lower incidence of DGF observed between living and deceased donor kidney transplants! In a very large-scale European trial, Moers *et al.* [39] demonstrated that the application of hypothermic machine perfusion, rather than cold storage, was able to reduce the incidence and duration of DGF and improve 1-year graft survival. At 3 years, the benefit was still present, especially in kidneys recovered from ECDs. However, it is interesting that even though the incidence of DGF was reduced in kidneys recovered following cardiac death, no improvement of graft survival was observed. However, the main conclusion of a more recent meta-analysis was that hypothermic machine perfusion reduces DGF but does not alter primary nonfunction, acute rejection, or patient and graft survivals [40]. Closely related to these findings, the choice of a preservation solution may lead to a decreased incidence of DGF, with the most robust results being demonstrated with a UW solution [41].

Glomerular filtration rate

Graft function in a stable condition is the consequence of many factors related to the donor, the recipient, the post-transplantation period, and the immunosuppressive regimen. This stable period usually occurs between 3 months and 1 year post-transplantation. At the beginning of the 2000s, Hariharan *et al.* [42] described the influence of renal function at 1 year on long-term outcomes. Not surprisingly, the better the renal function was (whatever method used to define it), the longer the graft survival was observed to be! This finding that kidney allograft function is an important predictor of graft failure has been confirmed by many studies, including the most recent one on this topic [43]. In this last study, renal function at 1 year, estimated using the MDRD equation, was strongly associated with subsequent graft failure, death-censored graft failure, and death with function (Fig. 1). The decrease in eGFR between

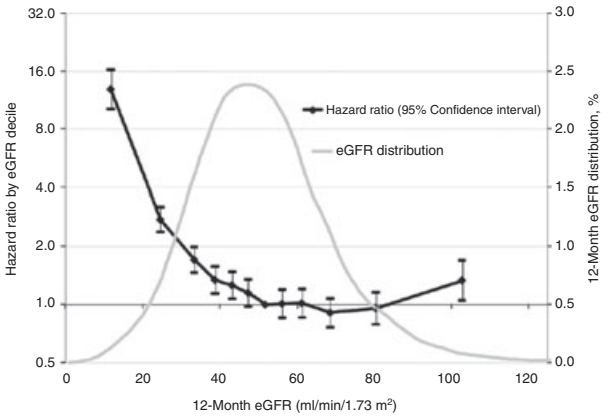

Figure 1 Relationship between the estimated glomerular filtration rate (eGFR) and graft failure over 10 years of follow-up (left axis) based on a Cox proportional hazards analysis adjusted for multiple covariates. The gray line shows the frequency distribution of eGFR at 12 months (right axis). From ref [42].

3 months and 1 year was also predictive of subsequent graft failure. One of the mechanisms explaining this negative influence is the fact that renal function is a strong and independent risk factor for cardiovascular disease and, thus, mortality, as observed in patients with chronic kidney disease. In the setting of renal transplantation, other risk factors such as hypertension, dyslipidemia, and smoking behavior are significantly associated with cardiovascular disease burden. This was observed for the first time by Meier-Kriesche *et al.* [44] and confirmed by Fellström *et al.* [45] using the data from the ALERT study and, more recently, by Weiner *et al.* [46] in a *post hoc* analysis of data from the FAVORIT trial (Folic Acid for Vascular Outcome Reduction In Transplantation). In stable kidney transplant recipients, a lower eGFR is independently associated with cardiovascular events. Improving and/or stabilizing renal function using non-nephrotoxic drugs, such as mTOR inhibitors or belatacept, would therefore constitute an ambitious and useful goal.

Proteinuria

Although it has been disregarded for several years, proteinuria is a strong, sensitive, and independent predictive factor for long-term outcomes [47,48]. Halimi recently reviewed the transplant literature on proteinuria following kidney transplantation, leading to the following main conclusions: (i) Early and/or late proteinuria has a negative long-term impact on graft as well as patient survival, (ii) this impact is observed whatever the level of proteinuria, (iii) this impact occurs regardless of the composition of proteinuria (albuminuria, micro-albuminuria, and nonalbumin proteinuria), and (iv) this negative impact decreases when proteinuria is decreased because of treatment intervention.

Table 1. Factors influencing long-term outcomes following kidney transplantation.

Donor factors: the «quality» of the kidney
Living donor versus deceased donor
SCD versus ECD versus DCD donor
Preimplantation biopsy data
Recipient factors at the time of transplantation
Age
Native kidney disease
HLA matching
Anti-HLA immunization
Time on dialysis
Cardiovascular comorbidities
Graft function in the course of transplantation
Delayed graft function
Graft function in a stable condition
Chronic allograft dysfunction
Immunosuppression effects
Prevention of rejection and compliance
Specific side effects
Nonspecific side effects: infections and cancer

SCD, standard criteria donor; ECD, expanded criteria donor.

Proteinuria is therefore most likely the best biomarker for allograft damage in renal transplantation. Unfortunately, the correlations between proteinuria and histological data presented in the literature are still scarce.

Chronic allograft dysfunction

We have described a long-term deleterious influence of delayed graft function and impaired graft function (evaluated through eGFR and proteinuria) at the time when the graft is considered to be functioning in a stable condition. It is therefore not surprising that chronic allograft dysfunction plays a role in the fate of transplanted kidneys [49,50]. There are many immunological and nonimmunological factors explaining chronic allograft dysfunction. In their seminal paper on the natural history of chronic allograft loss, Nankivell *et al.* [51] outlined the role of subclinical histological lesions in the pathogenesis of chronic allograft dysfunction and, especially, CNI nephrotoxicity. Subsequently, many transplant centers attempted to minimize this nephrotoxicity. However, more recent data have modified our understanding of this phenomenon: (i) CNI nephrotoxicity has been less common in the recent years, (ii) none of the lesions associated with CNI nephrotoxicity are specific [52], and (iii) most importantly, the role of antibody-mediated rejection has become more prevalent and better described [29]. Of course, the balance between CNI nephrotoxicity and chronic rejection is still a matter of debate [53–56]. As alluded to earlier, the appearance of *de novo* DSAs represents a negative long-term impact, similar to their pretransplant counterparts [57]. Worthington [58] and Lachmann [59] described the deleterious role of post-transplantation DSAs, which was thoroughly studied on a prospective basis by Wiebe *et al.* [60]. Of course, all DSAs are not the same, and apart from their levels, the C1q fixing of DSAs might serve as a sensitive marker of a poor prognosis [61] Finally, several new findings have explained (i) the worse outcome observed in the presence of vascular lesions in the case of antibody-mediated rejection [62] and (ii) the correlation between antibody-mediated rejection and nonadherence [29], which is a well-known factor related to a poor long-term outcome.

Therefore, renal function, be it delayed, stable, or impaired, is a major long-term prognostic factor. Clearly, immunosuppressive therapy has a role to play, even though this role is not an obvious one.

Immunosuppression: which role?

Modern immunosuppression methods have decreased the incidence of acute rejection by approximately 10% during the first months post-transplantation. Surprisingly, however, at least at first glance, this decreased incidence has not resulted in significant improvement over the long term [1]. The role of specific immunosuppressive drugs or combinations of drugs in the long term is most likely minimal, although reliable data related to this issue are not available. Indeed, immunosuppressive drugs play a beneficial role in the prevention of rejection but also a deleterious role because of their specific and nonspecific side effects.

In addition to CNI nephrotoxicity, whose responsibility is obvious in nonkidney organ transplant recipients but whose current impact is still a matter of debate in kidney transplantation, CNIs, especially tacrolimus, are a risk factor for new onset diabetes following transplantation (NODAT) [63,64]. It is now well recognized that NODAT, similar to pretransplant diabetes, is a strong predictive factor for cardiovascular morbidity and mid- to long-term mortality. In that setting, belatacept, a non-nephrotoxic and nondiabetogenic drug, will probably play a significant role in preserving renal function but also in decreasing the incidence of cardiovascular diseases and diabetes. The same deleterious consequences are observed with regard to both infection- and cancer-related mortality [65,66]. Although mTOR inhibitors appear to show the potential to prevent cancer (mainly skin cancers thus far), their possible beneficial effects in the long-term remain to be clearly demonstrated.

In contrast, the role of nonadherence [67], even though its diagnosis is not simple to ascertain, is considered to be a very significant factor of graft loss probably because of the occurrence of anti-HLA DSA leading to antibody-mediated rejection.

In summary, the main long-term predictor of a long-lasting kidney transplant is clearly the quality of the

transplanted kidney. Many factors related to the donor, the recipient, and immunosuppression have consequences for the function of the graft, which is the result of all of these injuries. It is therefore not surprising that renal function is such a potent prognostic factor, regardless of the method used to define it. The role of current combinations of immunosuppressive agents is more difficult to ascertain because the prevention of rejection is counterbalanced by nonspecific side effects, such as infection and cancer. There is therefore an urgent need to obtain equally potent, but much better-tolerated immunosuppressive agents as we are increasingly transplanting of older kidneys into older recipients!

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References

1. Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant* 2012; **11**: 450.
2. Gondos A, Döhler B, Brenner H, Opelz G. Kidney graft survival in Europe and the United States: strikingly different long-term outcomes. *Transplantation* 2013; **95**: 267.
3. El-Zoghby ZM, Stegall MD, Lager DJ, *et al.* Identifying specific causes of kidney allograft loss. *Am J Transplant* 2009; **9**: 527.
4. Matas AJ, Smith JM, Skeans MA, *et al.* OPTN/SRTR 2011 Annual Data Report kidney. *Am J Transplant* 2013; **23**(Suppl. 1): 11.
5. Rao PS, Ojo A. The alphabet soup of kidney transplantation: SCD, DCD, ECD. Fundamentals for the practicing nephrologist. *Clin J Am Soc Nephrol* 2009; **4**: 1827.
6. Pascual J, Zamora J, Pirsch JD. A systematic review of kidney transplantation from expanded criteria donors. *Am J Kidney Dis* 2008; **52**: 553.
7. Port FK, Bragg-Gresham JL, Metzger RA, *et al.* Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002; **74**: 1281.
8. Nyberg SL, Matas AJ, Kremers WK, *et al.* Improved scoring system to assess adult donors for cadaver renal transplantation. *Am J Transplant* 2003; **3**: 715.
9. Schold JD, Howard RJ, Scicchitano MJ, Meier-Kriesche HU. The expanded criteria donor policy: an evaluation of program objectives and indirect ramifications. *Am J Transplant* 2006; **6**: 1689.
10. Hoogland ER, Snoeijs MG, van Heurn LW. DCD kidney transplantation: results and measures to improve outcome. *Curr Opin Organ Transplant* 2010; **15**: 177.
11. Remuzzi G, Cravedi P, Perna A, *et al.* Long-term outcome of renal transplantation from older donors. *N Engl J Med* 2006; **354**: 343.
12. Anglicheau D, Loupy A, Lefaucheur C, *et al.* A simple clinico-histopathological composite scoring system is highly predictive of graft outcomes in marginal donors. *Am J Transplant* 2008; **8**: 2325.
13. Frei U, Noeldeke J, Machold-Fabrizii V, *et al.* Prospective age-matching in elderly kidney transplant recipients: a 5-year analysis of the Eurotransplant Senior Program. *Am J Transplant* 2008; **8**: 50.
14. Boesmuller C, Biebl M, Scheidl S, *et al.* Long-term outcome in kidney transplant recipients over 70 years in the Eurotransplant Senior Kidney Transplant Program: a single center experience. *Transplantation* 2011; **92**: 210.
15. Knoll GA. Kidney transplantation in the older adult. *Am J Kidney Dis* 2013; **61**: 790.
16. Challimpamontree W, Dmitrienko S, Li G, *et al.* Probability, predictors, and prognosis of post-transplantation glomerulonephritis. *J Am Soc Nephrol* 2009; **20**: 843.
17. Canaud G, Audard V, Kofman T, Lang P, Legendre C, Grimbert P. Recurrence from primary and secondary glomerulopathy after renal transplant. *Transpl Int* 2012; **25**: 812.
18. Floege J, Gröne HJ. Recurrent IgA nephropathy in the renal allograft: not a benign condition. *Nephrol Dial Transplant* 2013; **28**: 1070.
19. Legendre CM, Licht C, Muus P, *et al.* Terminal complement inhibitor eculizumab in atypical Hemolytic-Uremic Syndrome. *N Engl J Med* 2013; **368**: 2169.
20. Johnson RJ, Fuggle SV, Mumford L, *et al.* A new UK 2006 National Kidney Allocation Scheme for deceased heart-beating donor kidneys. *Transplantation* 2010; **89**: 387.
21. Süsal C, Opelz G. Current role of human leukocyte antigen in kidney transplantation. *Curr Opin Organ Transplant* 2013; **18**: 438.
22. Foster BJ, Dahhou M, Zhang X, Platt RW, Hanley JA. Relative importance of HLA mismatch and donor age to graft survival in young transplant recipients. *Transplantation* 2013; **96**: 469.
23. Terasaki PI. A personal perspective: 100-year history of the humoral theory of transplantation. *Transplantation* 2012; **93**: 751.
24. Lefaucheur C, Suberbielle-Boissel C, Hill GS, *et al.* Clinical relevance of preformed HLA donor-specific antibodies in kidney transplantation. *Am J Transplant* 2008; **8**: 324.
25. Lefaucheur C, Loupy A, Hill GS, *et al.* Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. *J Am Soc Nephrol* 2010; **21**: 1398.

26. Mohan S, Palanisamy A, Tsapepas D, *et al.* Donor-specific antibodies adversely affect kidney allograft outcomes. *J Am Soc Nephrol* 2012; **23**: 2061.
27. Opelz G, Collaborative Transplant Study. Non-HLA transplantation immunity revealed by lymphocytotoxic antibodies. *Lancet* 2005; **365**: 1570.
28. Giral M, Foucher Y, Dufay A, *et al.* Pretransplant sensitization against angiotensin II type 1 receptor is a risk factor for acute rejection and graft loss. *Am J Transplant* 2013; **13**: 2567.
29. Sellares J, de Freitas DG, Mengel M, *et al.* Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and non-adherence. *Am J Transplant* 2012; **12**: 388.
30. Malek SK, Keys BJ, Kumar S, Milford E, Tullius SG. Racial and ethnic disparities in kidney transplantation. *Transpl Int* 2011; **24**: 419.
31. Pallet N, Thervet E, Alberti C, *et al.* Kidney transplant in black recipients: are African Europeans different from African Americans. *Am J Transplant* 2005; **5**: 2682.
32. Meier-Kriesche HU, Schold JD. The impact of pretransplant dialysis on outcomes in renal transplantation. *Semin Dial* 2005; **18**: 499.
33. Jardine AG, Gaston RS, Fellström BC, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. *Lancet* 2011; **378**: 1419.
34. Cavaillé-Coll M, Bala S, Velidedeoglu E, *et al.* Summary of FDA workshop on ischemia reperfusion injury in kidney transplantation. *Am J Transplant* 2013; **13**: 1134.
35. Yarlagadda SG, Coca SG, Garg AX, *et al.* Marked variation in the definitions and diagnosis of delayed graft function: a systematic review. *Nephrol Dial Transplant* 2008; **23**: 2995.
36. Sharif A, Borrows R. Delayed graft function after kidney transplantation: the clinical perspective. *Am J Kidney Dis* 2013; **62**: 150.
37. Kayler LK, Magliocca J, Zendejas I, *et al.* Impact of cold ischemia time on graft survival among ECD transplant recipients: a paired kidney analysis. *Am J Transplant* 2011; **11**: 2647.
38. Kayler LK, Srinivas TR, Schold JD. Influence of CIT-induced DGF on kidney transplant outcomes. *Am J Transplant* 2001; **11**: 2657.
39. Moers C, Smits JM, Maathuis MH, *et al.* Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med* 2009; **360**: 7–19.
40. O'Callaghan JM, Morgan RD, Knight SR, *et al.* Systematic review and meta-analysis of hypothermic machine perfusion versus static storage of kidney allografts on transplant outcomes. *Br J Surg* 2013; **100**: 991.
41. O'Callaghan JM, Knight SR, Morgan RD, *et al.* Preservation solutions for static cold storage of kidney allografts: a systematic review and meta-analysis. *Am J Transplant* 2012; **12**: 896.
42. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int* 2002; **62**: 311.
43. Kasiske BL, Israni AK, Snyder JJ, *et al.* The relationship between kidney function and long-term graft survival after kidney transplant. *Am J Kidney Dis* 2011; **57**: 466.
44. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation* 2003; **75**: 1291.
45. Fellström B, Jardine AG, Soveri I, *et al.* Renal dysfunction is a strong and independent risk factor for mortality and cardiovascular complications in renal transplantation. *Am J Transplant* 2005; **5**: 1986.
46. Weiner DE, Carpenter MA, Levey AS, *et al.* Kidney function and risk of cardiovascular disease and mortality in kidney transplant recipients: the FAVORIT trial. *Am J Transplant* 2012; **12**: 2437.
47. Halimi JM. Low-grade proteinuria and microalbuminuria in renal transplantation. *Transplantation* 2013; **96**: 121.
48. Legendre Ch, Anglicheau D. Transplantation: Proteinuria in kidney transplantation: an ongoing story. *Nat Rev Nephrol* 2013; **9**: 251.
49. Ekberg H, Johansson ME. Challenges and considerations in diagnosing the kidney disease in deteriorating graft function. *Transpl Int* 2012; **25**: 1119.
50. Nankivell BJ, Kuypers DJ. Diagnosis and prevention of chronic kidney allograft loss. *Lancet* 2011; **378**: 1428.
51. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. *N Engl J Med* 2003; **349**: 2326.
52. Snanoudj R, Royal V, Elie C, *et al.* Specificity of histological markers of long-term CNI nephrotoxicity in kidney-transplant recipients under low-dose cyclosporine therapy. *Am J Transplant* 2011; **11**: 2635.
53. Gaston RS. Chronic calcineurin inhibitor nephrotoxicity: reflections on an evolving paradigm. *Clin J Am Soc Nephrol* 2009; **4**: 2029.
54. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc nephrol* 2009; **4**: 481.
55. Chapman JR. Chronic calcineurin inhibitor nephrotoxicity – Lest we forget. *Am J Transplant* 2011; **11**: 693.
56. Matas AJ. Chronic progressive calcineurin nephrotoxicity: an overstated concept. *Am J Transplant* 2011; **11**: 687.
57. Loupy A, Jordan SC. Transplantation: donor-specific HLA antibodies and renal allograft failure. *Nat Rev Nephrol* 2013; **9**: 130.
58. Worthington JE, McEwen A, McWilliam MJ, Picton ML, Martin S. Association between C4d staining in renal transplant biopsies, production of donor-specific HLA antibodies and graft outcome. *Transplantation* 2007; **83**: 398.
59. Lachmann N, Terasaki PI, Budde K, *et al.* Anti-human leukocyte antigen and donor-specific antibodies detected by Luminex post-transplant serve as biomarkers for chronic rejection of renal allografts. *Transplantation* 2009; **87**: 1505.
60. Wiebe C, Gibson IW, Blydt-Hansen TD, *et al.* Evolution and clinical pathologic correlations of de novo donor-

specific HLA antibody post kidney transplant. *Am J Transplant* 2012; **12**: 1157.
61. Loupy A, Lefaucheur C, Vernerey D, *et al.* Complement-binding anti-HLA antibodies and kidney allograft survival. *N Engl J Med* 2013; **369**: 1215.
62. Lefaucheur C, Loupy A, Vernerey D, *et al.* Antibody-mediated vascular rejection of kidney allografts: a population-based study. *Lancet* 2013; **381**: 313.
63. Sharif A, Baboolal K. Complications associated with new-onset diabetes after kidney transplantation. *Nat Rev Nephrol* 2011; **8**: 34.
64. Hecking M, Werzowa J, Haldinger M, *et al.* Novel views on new-onset diabetes after transplantation: development, prevention and treatment. *Nephrol Dial Transplant* 2013; **28**: 550.
65. Webster AC, Wong G, Craig JC, Chapman JR. Managing cancer risk and decision making after kidney transplantation. *Am J Transplant* 2008; **8**: 2185.
66. Colett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK registry audit. *Am J Transplant* 2010; **10**: 1889.
67. Schäfer-Keller P, Steiger J, Bock A, *et al.* Diagnostic accuracy of measurements methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *Am J Transplant* 2008; **8**: 616.

