FRAILTY AND GERONTOLOGY (M MCADAMS-DEMARCO, SECTION EDITOR)

Immunosuppression Considerations for Older Kidney Transplant Recipients

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Abstract

Purpose of Review While kidney transplantation improves the long-term survival of the majority of patients with end-stage kidney disease (ESKD), age-related immune dysfunction and associated comorbidities make older transplant recipients more susceptible to complications related to immunosuppression. In this review, we discuss appropriate management of immunosuppressive agents in older adults to minimize adverse events, avoid acute rejection, and maximize patient and graft survival.
Recent Findings Physiological changes associated with senescence can impact drug metabolism and increase the risk of post-transplant infection and malignancy. Clinical trials assessing the safety and efficacy of immunosuppressive agents in older adults are lacking. Recent findings from U.S. transplant registry–based studies suggest that risk-adjusted death-censored graft failure is higher among older patients who received antimetabolite avoidance, mammalian target of rapamycin inhibitor (mTORi)–based, and cyclosporine-based regimens. Observational data suggest that risk-adjusted mortality may be increased in older patients who receive mTORi-based and cyclosporine-based regimens but lower in those managed with T cell induction and maintenance steroid avoidance/withdrawal.
Summary Tailored immunosuppression management to improve patient and graft survival in older transplant recipients is an important goal of personalized medicine. Lower intensity immunosuppression, such as steroid-sparing regimens, appears beneficial whereas mTORi- and cyclosporine-based maintenance are associated with greater potential for adverse effects. Prospective clinical trials to assess the safety and efficacy of immunosuppression agents in older recipients are urgently needed.

Keywords Aging · End-stage kidney disease · Immunosuppression · Kidney transplant · Medication safety

This article is part of the Topical Collection on *Frailty and Gerontology*

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Overview of Kidney Transplant Outcomes in Older Adults

Older adults (often defined as age ≥ 65 years) make up an increasing proportion of patients listed for and receiving kidney transplants worldwide [1–7]. In the USA, kidney transplantation for patients ≥ 65 years old increased over the past decade, from 2518 in 2008 to 4427 in 2018 [8]. This trend likely reflects the changing demographics of patients developing end-stage kidney disease (ESKD) [1,8–11], successful outcomes of kidney transplantation in older recipients, and the development of new strategies for increasing access, such as directed use of expanded criteria donor (ECD) organs.

For appropriate candidates, kidney transplantation is the best treatment for ESKD, as it results in improved survival, lower health care costs, and better quality of life than treatment

with dialysis [4,12]. Although the absolute survival benefit of kidney transplant is greater in younger ESKD patients, patients of all age groups gain additional years-of-life with a kidney transplant compared with those who remain on dialysis [4,5]. The survival benefit of kidney transplantation among older adults, including those older than 75 years, has been identified in single-center and registry-based studies (Table 1) [5–7,13–16]. For example, in a retrospective registry study of patients age 70 years and older (1990–2004), Rao et al. found a 41% reduction in mortality after transplant compared to remaining on the waitlist [17]. A survival advantage was also observed in older patients who received ECD

kidneys and in those with significant comorbidities including diabetes [17]. Recent data confirms the benefit of transplant with higher risk kidneys, as defined by higher kidney donor profile index (KDPI) for recipients older than 60 years [18]. Given these benefits, international guidelines recommend against the use of advanced age as an absolute exclusion criterion for kidney transplant [19,20]. However, some transplant programs currently offer kidney transplantation only to older candidates with living donors, due to concern for mortality while awaiting a deceased donor transplant offer [21,22].

Despite survival benefits compared to dialysis, older patients experience lower patient and graft survival than younger

Table 1 Summary of recent studies reporting outcomes of kidney transplantation in older adults

Reference, year	Design and participants	Follow-up (years)	Recipient age	Donor characteristics	Outcomes
Wolfe et al., 1999 [4]	U.S./USRDS (1991–1997) 23,275 KTx recipients vs. 22,889 waitlisted ESKD patients	7 (maximum)	≤74 years old	Deceased donors	Adjusted mortality risk KTx vs. Waitlist: Age 40–59 years: 0.3 (95% CI: 0.3–0.4) Age 60–74 years: 0.4 (95% CI: 0.3–0.5)
Johnson et al., 2000 [5]	Australia/Queensland registry (1993–1997) 67 KTx recipients vs. 107 waitlisted ESKD patients	2.8 (mean)	>60 years old	Deceased donors	Adjusted mortality risk at 5 years: KTx vs. Waitlist: 0.2 (95% CI: 0.1–0.4)
Oniscu et al., 2004 [6]	Scotland/National data (1993–1997) 128 KTx recipients vs. 197 waitlisted ESKD patients	9 (maximum)	≥60 years old	Deceased donors	Adjusted mortality risk at 5 years: KTx vs. Waitlist: 0.4 (95% CI: 0.2–0.5)
Rao et al., 2007 [17]	U.S./SRTR (1990–2004) 2438 KTx recipients vs. 3229 waitlisted ESKD patients	15 (maximum)	≥70 years old	Deceased donors	Adjusted mortality risk at 4 years KTx vs. Waitlist: All DDKT: 0.6 (95% CI: 0.5–0.6) ECD recipients: 0.8 (95% CI: 0.6–0.9)
Savoye et al., 2007 [13]	France/National data (1996–2004) 2,099 KTx recipients vs. 746 waitlisted ESKD patients	2.9 (mean)	≥60 years old	Deceased donors	Adjusted mortality risk at 5 years Waitlist vs. KTx: All DDKT: 2.5 (95% CI: 2.0–3.2) SCD recipients: 3.8 (95% CI: 2.7–5.4) ECD recipients: 2.3 (95% CI 1.8–2.9)
Lloveras et al., 2014 [15]	Spain/Catalonian registry (1990–2010) 823 KTx recipients vs. 823 waitlisted ESKD patients	3.2 (median)	Overall: mean 62 years Subgroup ≥65 years old: 324 (39%) recipients	Deceased donors ≥65 years old	Adjusted mortality risk at 5 years Waitlist vs. KTx: All ages: 2.7 (95% CI: 2.2–3.2) Age 65–69: 2.2 (95% CI: 1.6–3.1) Age > 70: 1.9 (95% CI: 1.1–3.1)

Abbreviations: *CI*, confidence interval; *DDKT*, deceased donor kidney transplantation; *ECD*, expanded criteria donor; *ESKD*, end-stage kidney disease; *KTx*, kidney transplant; *SRTR*, Scientific Registry of Transplant Recipients; *U.S.*, United States; *USRDS*, United States Renal Data System

recipients [5,8,23–25]. The primary cause of allograft loss in older recipients is death with a functioning graft. Death with graft function is most commonly a result of cardiovascular disease, infection, or cancer [26–28]. Although older recipient age is an important risk factor for allograft failure, this is largely due to increased mortality, as death-censored survival analyses reveal comparable allograft survival among older and younger recipients [1,2,29,30]. In a series of Scottish transplant recipients, Oniscu et al. found equivalent 8-year death-censored graft survival regardless of recipient age [30]. Furthermore, two prospective studies suggest that rates of death-censored graft loss are lower in older adults due to the reduced incidence of acute rejection [31,32].

While the number of kidney transplants among older adults has been increasing, no specific recommendations have been formalized for the management of older kidney transplant recipients [33,34]. Prospective multicenter randomized controlled trials assessing immunosuppressive agents in older recipients are currently not available because older patients are often excluded from clinical trials [33,35]. Therefore, data on outcomes is generally derived from case series and retrospective registry–based analyses. This review considers management of immunosuppression for older kidney transplant recipients, with a focus on minimizing immunosuppression-related morbidity and mortality.

Immune Changes with Aging: Immunosenescence

Immunosenescence encompasses a series of aging-induced modifications in the immune system which are primarily characterized by dysfunctional immune responses and increased systemic inflammation termed as *inflamm-aging* [36–41]. Immunosenescence affects all immune compartments, with the most striking changes seen in the phenotypes and functions of CD4+ and CD8+ T cell components, and less frequently observed in components of the innate immune system [42–44]. Thymic involution plays a crucial role in T cell immunosenescence [45]. Patients age 60 years and older experience reductions in circulating naïve T cells, CD4 T cell receptor (TCR) excision circles, markers of thymic output, and TCR diversity [46]. The frequency of memory/effector T cells increases with age [47]. T cells downregulate the expression of the CD28 molecule with age, and subsets of CD4+/CD28− and CD8+/CD28− T cells emerge [48]. The downregulation of CD28 expression due to chronic immune activation of human T cells is one of the signatures of replicative senescence and has been associated with impaired vaccine responses in adults [49,50].

Immunosenescence leads to alteration in cellular immune function. Recently, Schaenman et al. assessed the T cell phenotype according to age by comparing 23 older (≥60 years)

and 37 matched younger patients (<60 years) in the first year after transplantation [42]. The investigators demonstrated a decrease in the frequency of naïve CD4+ and CD8+ T cells among older transplant recipients compared with the younger patients. In addition, older recipients demonstrated an increase in the frequency of terminally differentiated and senescent CD8+ T cells [42]. Among older patients with infection after transplantation, there was a significantly increased frequency of T cell immune senescence [42].

Antibody responses are also decreased with age in both mice and humans, leading to increased frequency and severity of infectious diseases and reduced protective effects of vaccination [51]. Not only does the production of high-affinity protective antibodies decrease with older age, the duration of protective immunity following immunization is also shortened [51]. The decreased ability of older individuals to produce high-affinity protective antibodies against infectious agents likely results from combined defects in T cells, B cells, and other immune cells. These changes in the adaptive immune system in older patients with immunosenescence contribute to impaired ability to respond to infection, vaccination, and tumor cells [42].

Immune reconstitution after lymphocyte-depleting treatments also differs with age. Lymphocyte-depleting agents, particularly rabbit anti-thymocyte globulin (rATG), carry the risk of impaired CD4+ T cell reconstitution after induction immunosuppresion [52,53]. Previous studies showed that this risk is age-dependent and older age causes a decline in the capacity of the adult immune system to regenerate CD4+ T cells after rATG [53,54]. In a study by Longuet et al., recipient age greater than 40 years and a low CD4+ T cell count at the time of transplantation were identified as risk factors for impaired CD4+ T cell reconstitution [52].

Older kidney transplant recipients also have a higher risk of post-transplant malignancies [55,56]. A single-center analysis of 1500 kidney transplant recipients found recipient age to be an independent predictor of post-transplant malignancies [57]. The investigators demonstrated a fivefold increase in the risk of malignancy among recipients ≥60 years compared to recipients <45 years [57]. Compared to recipients 18–34 years old, an analysis of United States Renal Data System (USRDS) and Medicare billing claims data demonstrated a threefold increase in the risk of cancers among recipients 50–64 years and a fivefold increase among recipients ≥65 years [58]. Thus, there is a concern that age-related immune dysfunction can increase the susceptibility of older adults to cancer [55]. While the risk of post-transplant malignancies has been associated with the use of induction therapy with T cell depleting agents [1, 59], a recent study using USRDS and Medicare billing claims data found that the use of rATG was associated with increased post-transplant malignancy risk only among younger recipients [60•], emphasizing an important

perspective that the risk of post-transplant malignancies among older recipients was not explained only by induction therapy with T cell depleting agents.

Inflamm-aging also results in chronic, low-grade, systemic inflammation characterized by a shift to the production of pro-inflammatory cytokines including IL-6, IL-1β, TNF-α, and IFN-γ, and reduction of the chemokine receptor expression and expression of several adhesion molecules [61,62]. High levels of age-associated pro-inflammatory markers are detected in the majority of older individuals, even in the absence of clinically active diseases [63–65]. This inflammatory status contributes to metabolic dysfunction and insulin resistance, and represents a significant risk factor for morbidity and mortality. The pro-inflammatory state has been implicated in the pathogenesis of several debilitating chronic diseases of older age including type 2 diabetes mellitus, osteoporosis, Alzheimer's disease, rheumatoid arthritis, and coronary heart disease. In older adults, malnutrition is also common and adversely affect T cell function contributing to a state of relative immunodeficiency [66].

Immunosenescence interferes with T cell function and differentiation, assessed by flow cytometry and T cell receptors. The resulting alterations in T cell phenotype modify both rejection and tolerance [67]. Future studies are required to assess the impacts of immunosenescence and inflamm-aging in older kidney transplant recipients on tolerance induction, rejection, infection, and malignancy. In addition, further work is needed to develop methods to optimally measure the levels of immune dysfunction in older transplant recipients to successfully prevent rejection without significantly increasing the risk of infection [68]. The ability to assess T cell maturation, immune senescence, and inflamm-aging by peripheral blood mononuclear cell flow cytometry in older kidney transplant recipients may offer the potential for risk stratification and individualization of immunosuppressive therapy to optimally balance risks of rejection and infection.

The reduced risk of acute cellular rejection is consistent with thymic involution and the limited T cell receptor repertoire observed with aging [69–71]. Additionally, humoral immune responses in older patients are altered, with increased memory responses and a skewed B cell repertoire which is more specialized to mount humoral immune responses [72–74]. Together with the reduced frequency of naïve T cells, these changes are associated with impaired host defense against tumors and infections, as well as with imparied vaccine responses [72,74–76]. In contrast, the heightened subclinical inflammation associated with *inflamm-aging* and increased reactivity of the innate immune system potentiates cardiovascular risk among older transplant recipients.

Most studies comparing older with younger transplant recipients have focused on T cell responses and have described reduced frequency of acute T cell–mediated rejections in older patients [70,72,77]. However, in the few studies that investigated antibody responses, a gradual decrease in incidence of donor-specific antibodies (DSA) has been correlated with increasing chronological age [78,79]. Older kidney transplant recipients have a lower risk of developing de novo DSA than pediatric recipients, demonstrating reduced humoral immune reactivity with increasing age [80]. Increasing fundamental knowledge of how aging is involved in the immune response to organ transplantation will inform age-tailored management strategies to improve health outcomes for older transplant recipients.

Age and the Pharmacology of Immunosuppressive Drugs

Aging is associated with altered drug pharmacokinetics, including absorption, distribution across body compartments, metabolism, and excretion [81••, 82–85]. After intestinal absorption, some drugs are transported back to the intestines via P-glycoprotein (P-gp), a cell transmembrane protein with reduced expression and activity with aging, resulting in alterations of peak medication plasma concentrations and bioavailability [82]. Furthermore, bioavailability can be influenced by decreased intestinal or hepatic first-pass metabolism with aging [86]. In addition, aging is associated with an increase in relative fat content of the body and a decrease in muscle mass [82], resulting in a larger volume of distribution of lipophilic drugs such as calcineurin inhibitors (CNIs) and mammalian target of rapamycin inhibitors (mTORis) [1,55,87].

Protein production declines with aging and protein binding is decreased by up to 15 to 25% in older compared to younger adults [88]. Reduction in protein binding increases free drug concentrations. Furthermore, there is a decrease in albumin, which binds acidic drugs, and an increase in alpha-1-acid glycoprotein (AGP), which binds basic drugs [89,90]. Tacrolimus (99%), sirolimus (91%), and mycophenolic acid (MPA) (up to 97%) are highly albumin-bound compounds [82]. Protein binding is especially important in the case of MPA, in which the free fraction is the active inhibitor of inosine monophosphate dehydrogenase. Hypoalbuminemia may lead to higher pharmacologic exposure to immunosuppressive medications, especially MPA [91].

Aging is also associated with reduced renal and hepatic clearance of pharmaceuticals. The reduced renal clearance of medications has been well described with aging [92–94]. Drug clearance via the hepatic cytochrome P450 (CYP450) enzyme decreases with age, resulting in higher plasma levels of CNIs, mTORis, and corticosteroids [95] [96–98]. Older kidney transplant recipients also frequently require polypharmacy to treat comorbid conditions, and these additional medications may incur drug-drug interactions with immunosuppressive agents (Table 2) [1,99].

Table 2 Age and impact of immunosuppressive medications in older kidney transplant recipients

Immunosuppressive agents	Altered drug pharmacokinetics	Impact of aging	Requirements and suggestions
Calcineurin inhibitors	Decrease in metabolism from CYP3A4 isozymes Reduced P-gp activity	Higher observed maximum concentration and area under the curve Decreased total body clearance	Require lower doses to obtain the same therapeutic levels
Mycophenolate	Hypoalbuminemia in older recipients can result in higher clearance of unbound MPA	Lower overall MPA exposure and trough concentrations	Require higher doses to achieve the same trough concentrations
mTOR inhibitors	No significant difference of drug clearance across age groups	Stable pharmacokinetic parameters	No significant dose adjustments
Corticosteroids	Clearance of corticosteroids decreases with aging	Enhanced exposure	Consider minimization of exposure

Abbreviations: *MPA*, mycophenolic acid; *mTOR*, mammalian target of rapamycin inhibitor; *P-gp*, P-glycoprotein

Calcineurin Inhibitors In a recent study evaluating the optimal dosing of CNIs in kidney transplant recipients >65 years, Jacobson et al. demonstrated that the normalized CNI trough concentrations were 50% greater among older recipients independent of the choice of CNI [100]. The investigators concluded that older recipients may require lower doses of CNIs to obtain the same therapeutic levels due to a decrease in metabolism from CYP3A4 isozymes and reduced P-gp activity, leading to enhanced bioavailability [81••,100]. David-Neto et al. assessed tacrolimus pharmacokinetics in 44 older kidney transplant recipients compared with 31 younger recipients [101]. Despite comparable tacrolimus trough concentrations, the older recipients had vastly different pharmacokinetics including higher observed maximum concentration (C_{max}) and area under the curve (AUC), a longer time to achieve the maximum concentration, and a decreased total body clearance. Consequently, a lower total dose of tacrolimus is needed to achieve comparable immunosuppressive effects in older patients. In a study of cyclosporine pharmacokinetics, the required daily dose of cyclosporine to maintain comparable target cyclosporine concentrations was significantly lower among kidney transplant recipients age 65 years and older compared to younger recipients [102]. In addition, cyclosporine clearance was decreased, and intracellular concentrations of cyclosporine in T lymphocytes were higher in older patients [102,103].

With regard to side effects, a study of older (age ≥ 55 years) kidney transplant recipient using USRDS data (1999–2011) found associations of CNI-free maintenance immunosuppression regimen with decreased risk of dementia (HR, 0.83; $P <$ 0.05), suggesting possible cognitive benefit of avoiding neurotoxic immunosuppression in recipients of this age group [104].

Mycophenolate Despite receiving similar doses of MPA, Romano et al. demonstrated lower overall MPA exposure and trough concentrations when comparing 44 older (63 ± 1 years) versus 31 younger (41 ± 5 years) kidney transplant recipients [105]. Given MPA is strongly bound to serum albumin, data from liver and kidney transplant recipients showed that there was a significant higher MPA dose requirement in patients with low serum albumin levels (<3.5 g/dL) compared with recipients who had normal serum albumin [106,107]. Hypoalbuminemia can result in higher clearance of unbound MPA. As a result, older recipients commonly require higher doses of MPA compared to younger patients to achieve the same trough concentrations.

mTOR Inhibitors Many studies evaluating mTORi pharmacokinetics included subgroup analyses of older patients and found no significant difference of drug clearance across age groups [82,108–111]. A recent study assessed the pharmacokinetics of everolimus in 16 older kidney transplant recipients receiving everolimus with low-dose tacrolimus and corticosteroids [112]. The investigators demonstrated that older patients had stable everolimus pharmacokinetic parameters without significant changes in dose or exposure during the first 6 months after kidney transplantation.

Corticosteroids Corticosteroids are bound to albumin and corticosteroid-binding globulin (CBG). The distribution characteristics of corticosteroids are dose-dependent and nonlinear plasma protein binding. Prednisolone's protein binding capability is decreased from 95 to 70% when higher doses are given [113]. The clearance of corticosteroids decreases with aging, resulting in enhanced exposure; however, the clinical impact of this finding requires further study [114,115].

Approach to Immunosuppression in Older Adults

Older transplant recipients comprise of a heterogeneous group and their response to immunosuppression may vary widely depending on many factors including genetic predisposition. Many biological factors such as sex, race, genetics, and other comorbidities also contribute to how older adults respond to immunosuppression regimens. Even if we define the "elderly" strictly by *chronological* age, younger and older individuals are likely to respond to immunosuppression differently. Biological age is likely a better predictor of how older recipients are likely to fare after transplant with certain immunosuppression regimens including immunosuppression efficacy and side effects. One of the tools that we use to determine biological age is frailty testing, such as Fried's frailty phenotype and Karnofsky Performance Score [116••]. Some laboratory tests now are able to estimate biological age and resulting immunosenescence which may assist in profiling older recipients. Unfortunately, large-scale studies that utilize frailty or laboratory tests to determine biological age as a tool to guide immunosuppression have not been performed, but are needed to assess the benefit of these tools.

Similarly, there are no large-scale, prospective randomized clinical trials performed specifically in older transplant recipients. In fact, the majority of immunosuppression trials exclude older patients or include only a small proportion of older participants, limiting generalizability. For example, there have been two pivotal, randomized clinical trials that compared rATG to basiliximab which led to U.S. Food and Drug Administration (FDA) approval for induction indication for rATG [59]. In these two studies, less than 10% of the participants were older than 65 years. Gill et al. [10] reported a retrospective study of induction immunosuppression in 14,820 older adults in the USA. The population was classified into 4 groups based on recipient and donor risk factors: (1) high-immunologic-risk recipients/high-risk donor, (2) high-immunologic-risk recipients/low-risk donor, (3) low-immunologic-risk recipients/high-risk donor, and (4) low-immunologic-risk recipients/low-risk donor. The authors demonstrated the use of IL2-receptor antibody (IL2rAb) was associated with an increased risk for acute rejection compared with rATG in the first 3 groups (HR 1.78, 95% CI 1.34–2.35;

HR 1.45, 95% CI 1.12–1.89, and HR 1.78, 95% CI 1.42–2.23), respectively. However, there was no difference in the risk of functional graft loss between the induction immunosuppression regimens. The same was observed in studies not specific to older adults; there was no significant difference in risk of acute rejection between IL2rAb and ATG in low-risk recipients/low-risk donors.

Based on the current data, the outcomes of induction immunosuppression in older adults are the same as in other populations: rATG decreases the risk of rejection and delayed graft function (DGF) and minimizes maintenance immunosuppression use without increasing complications. An approach to the choice of induction immunosuppression should consider both recipient and donor risk factors, as summarized in Tables 3 and 4. A tailored dose reduction of rATG induction in low-risk, non-sensitized recipients showed comparable outcomes of graft survival and rejection rate with typical dose recommendations of 1.5 mg/kg for up to 7 days [117]. This provides benefit among older recipients while reducing the complications.

To help address knowledge gaps using observational data, we examined associations of kidney transplant immunosuppression regimens with patient and graft survival in a retrospective cohort of older (≥ 65 years; *n* = 14,887) and younger (18–64 years; *n* = 51,475) adults using U.S. national transplant registry data (2005–2016) [118••]. We found that older transplant recipients were less likely to receive T cell depleting induction (rATG or alemtuzumab (ALEM)) with triple maintenance immunosuppression, rATG/ALEM + steroid avoidance, and mTORi-based treatment. However, older patients were more likely to receive IL2rAb + triple maintenance, IL2rAb + steroid avoidance, and cyclosporine-based regimens. Compared to older recipients treated with rATG/ALEM + triple maintenance, those who received rATG/ALEM + steroid avoidance and IL2rAb + steroid avoidance had lower risk of acute rejection, while cyclosporine-based immunosuppression was associated with borderline increased risk of acute rejection (Fig. 1). Compared to those who were treated with rATG/ALEM + triple maintenance, older recipients treated with Tac + antimetabolite avoidance, mTORi-based, and cyclosporine-based regimens had significantly (1.78-fold, 2.14-fold, and 1.78-fold, respectively) increased risks of death-censored graft failure. Further,

Table 3 Recipient and donor high-risk definitions

High-immunologic-risk recipients	Side effect risk considerations	Lower donor quality
Peak PRA > 80%	Cancer risk	Lower quality / higher KDPI
Historical or preexisting DSA	Infection risk	High DGF risk score
Repeat transplant	Metabolic risk	

Abbreviations: *DGF*, delayed graft function; *DSA*, donor specific antibody; *HLA*, human leukocyte antigen; *KDPI*, kidney donor profile index; *PRA*, panel reactive antibodies

Table 4 Immunosuppression strategies in older kidney transplant recipients, considering immunological risk, side effects, and donor quality

Immunologic risk	Side effects risk	Donor quality	Suggested immunosuppression regimen
High	Low	Either	rATG with Tac + MPA + steroids
High	High	Either	rATG with Tac + MPA + steroids
			Tailored maintenance regimen per side effects
Low	High	Low	IL2rAb or short course rATG with CNI minimization ± steroid withdrawal
Low	High	High	Short course of rATG or IL2rAb with both CNI minimization and steroid withdrawal
Low	Low	Low	Short course rATG or IL2rAb with delayed CNI or CNI minimization
Low	Low	High	IL2rAb with steroid withdrawal and CNI minimization

Abbreviations: *CNI*, calcineurin inhibitor; *IL2rAb*, interleukin-2 receptor antibody; *MPA*, mycophenolic acid; *rATG*, rabbit anti-thymocyte globulin; *TAC*, tacrolimus

we found that mTORi-based and cyclosporine-based regimens were associated with increased mortality (Fig. 1). Thus, these findings suggest that lower intensity immunosuppression regimens such as steroid-sparing may be beneficial for older kidney transplant recipients. Conversely, the use of mTORi and cyclosporine-based maintenance immunosuppression among older recipients should be discouraged or used cautiously due to higher risk of adverse outcomes.
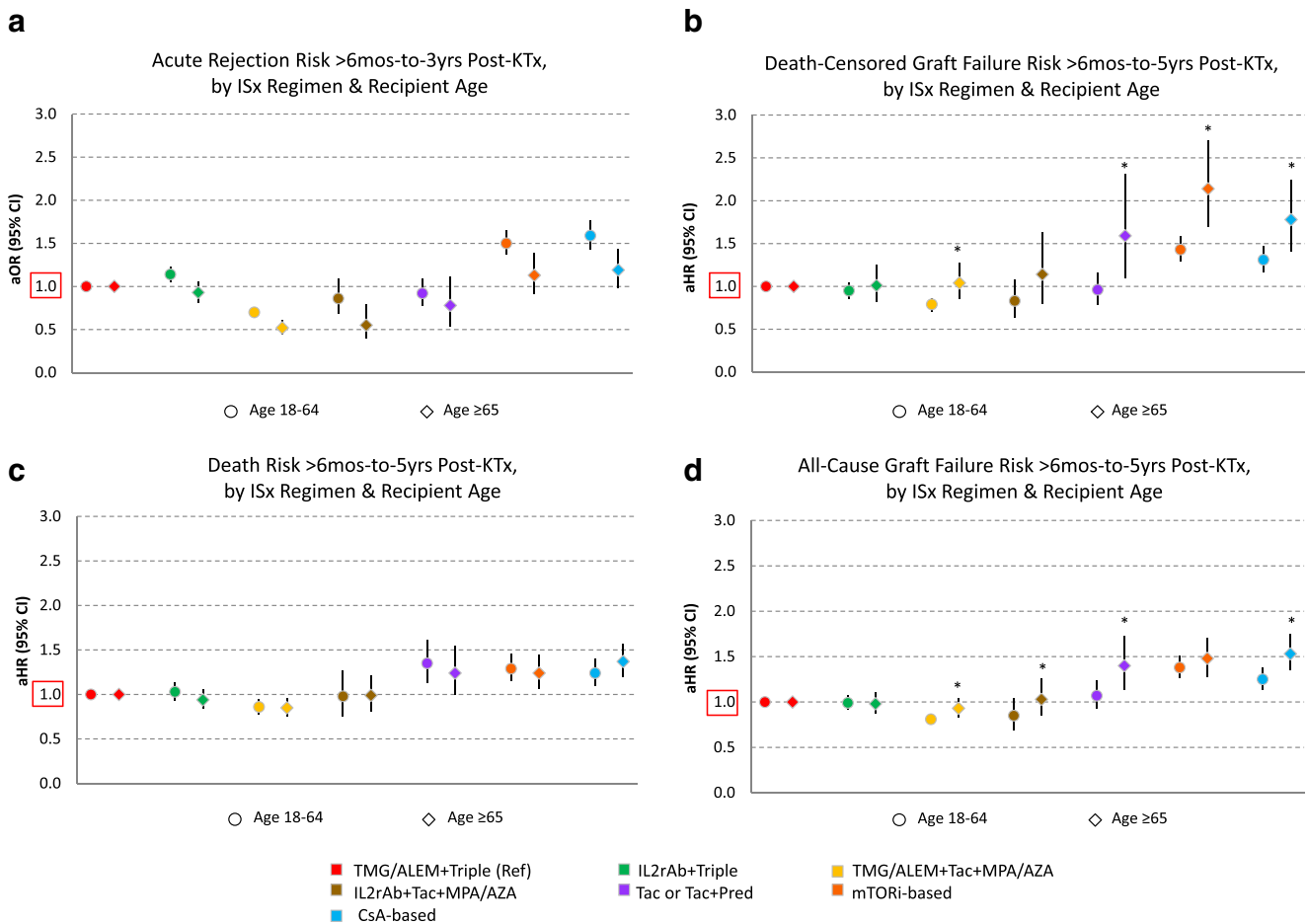
Fig. 1 Relative risks of **a** acute rejection, **b** death-censored graft failure, **c** death, and **d** all-cause graft failure according to early immunosuppression regimen and recipient age. Confidence intervals designate comparison of each regimen to the reference regimen, within age groups. *$P < 0.05$ for test of interaction of age group and regimen effects. Reproduced with permission from Lentine et al. [118••] and Wolters Kluwer

Future Investigations

To strengthen the evidence for tailored immunosuppression choice, ongoing research needs to define the balance of adequate immunosuppression, determined by the absence of rejection, with the risk of complications. In general, older recipients appear to have a lower risk of cellular rejection than younger patients and may require less intense immunosuppression. However, it is important to note that the consequences of rejection are likely to be more severe in older recipients. Furthermore, older recipients are more likely to receive higher KPDI kidneys which are at risk for DGF, which in turn increases the risk of rejection. Acute cellular rejection could lead to more severe and permanent damage in already compromised renal allografts. Older patients are also more likely to have adverse effects from maintenance immunosuppression and rejection treatments, including infection, cancer, post-transplant diabetes, and CNI-related nephrotoxicity. As such, recipient comorbidity, immunologic risk profile, and donor quality factors should all be taken into account when individualizing immunosuppression regimen. The initial immunosuppression plan should assess the need for and choice of induction agent, what combination of maintenance immunosuppression regimen will be used, and whether minimization of certain maintenance immunosuppression can be considered. During the course of transplant, maintenance immunosuppression regimen may need to be further adjusted when efficacy or side effects arise.

Based on these considerations, we can stratify older recipients according to lower versus higher numbers of comorbidities; classify immunologic risk as low versus high; and grade the donor quality as optimal versus less than optimal (Table 4). Recipients with a higher number of comorbidities, who will be receiving a living donor allograft, have no sensitizing events and have no DSA will be good candidates for a less intense maintenance immunosuppression. In contrast, older recipients with no comorbidities who are receiving a suboptimal deceased donor transplant and have DSA are likely to require more intense immunosuppression, both in the form of induction and maintenance therapy.

Conclusions

Aging is associated with altered pharmacodynamics, pharmacokinetics, and immune responses. While older recipients have a lower incidence of acute rejection, they face a significantly higher risk of allograft loss if they develop rejection. Personalization of immunosuppression management among older transplant recipients may be informed by consideration of recipient factors such as comorbidity burden, measures of biologic age, immunologic risk, measures of immunosenescence, and donor quality. Despite the growing number of older kidney transplant recipients, older adults continue to be under-represented in transplant clinical trials. To strengthen the evidence base for managing the care of older transplant recipients, ongoing research is needed, including robust, risk-adjusted analyses of national datasets combined with advocacy for inclusion of older adults in future prospective studies and clinical trials.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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