Frailty, Mycophenolate Reduction, and Graft Loss in Kidney Transplant Recipients

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Background. Mycophenolate mofetil (MMF) side effects often prompt dose reduction or discontinuation, and this MMF dose reduction (MDR) can lead to rejection and possibly graft loss. Unfortunately, little is known about what factors might cause or contribute to MDR. Frailty, a measure of physiologic reserve, is emerging as an important, novel domain of risk in kidney transplantation recipients. We hypothesized that frailty, an inflammatory phenotype, might be associated with MDR. **Methods.** We measured frailty (shrinking, weakness, exhaustion, low physical activity, and slowed walking speed), other patient and donor characteristics, longitudinal MMF doses, and graft loss in 525 kidney transplantation recipients. Time-to-MDR was quantified using an adjusted Cox proportional hazards model. **Results.** By 2 years after transplantation, 54% of frail recipients and 45% of nonfrail recipients experienced MDR; by 4 years, incidence was 67% and 51%. Frail recipients were 1.29 times (95% confidence interval [95% CI], 1.01–1.66; $P = 0.04$) more likely to experience MDR, as were deceased donor recipients (adjusted hazard ratio [aHR], 1.92; 95% CI, 1.44–2.54, $P < 0.001$) and older adults (age ≥ 65 vs <65; aHR, 1.47; 95% CI, 1.10–1.96, $P = 0.01$). Mycophenolate mofetil dose reduction was independently associated with a substantially increased risk of death-censored graft loss (aHR, 5.24; 95% CI, 1.97–13.98, $P = 0.001$). **Conclusion.** A better understanding of risk factors for MMF intolerance might help in planning alternate strategies to maintain adequate immunosuppression and prolong allograft survival.

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Mycophenolate mofetil (MMF) has become a mainstay of immunosuppression after kidney transplantation (KT) and had been shown to reduce acute rejection.[1] Although MMF is clinically effective, up to 60% to 70% of recipients will require an MMF dose reduction or discontinuation (MDR) in the first year after KT[2,3] because of dose-dependent adverse events, including gastrointestinal upset, hematologic complications, and concurrent infection.[4,5] Such alterations to the immunosuppression regimen can be associated with significant risk, including acute rejection and possibly graft loss.[2-4] Understanding factors associated with MDR will help identify patients that are at high risk of MMF intolerance so that alternate strategies can be developed to maintain adequate immunosuppression and to protect the allograft.

No studies to date have focused on identifying which KT recipients are at risk for MDR. One study lends tangential evidence to the possibility of a patient phenotype that is at higher risk for MDR: in a single-center study of 407 patients that sought to understand the association between MDR and early posttransplant outcomes, it was observed that the 29.6% of patients with delayed graft function (DGF) had a higher occurrence of diarrhea (presumably MMF associated) than the 16.3% patients with immediate allograft function; similarly, 15.6% of those with DGF and 6.1% of those without DGF had thrombocytopenia.[4] Other than this secondary finding, we are aware of no studies to date that have focused on identifying patient-level factors associated with MDR.

We hypothesized that frailty, a construct first described in gerontology[6] but more recently implicated in the pathophysiology of adverse posttransplant outcomes,[7-9] might be associated

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with MDR. Frailty is a measure of physiologic reserve[6] that has an inflammatory biological basis; the frailty phenotype has been associated with dysregulation of multiple physiologic systems, including the immune system.[10] Among community dwelling older adults, those who become frail are more likely to experience changes in their pharmacokinetic and pharmacodynamics response to drugs and are at higher risk of adverse drug reactions.[11-13] Furthermore, in this population, frailty is associated with increased use of prescription drugs[14,15] as well as lower average daily dose of medications for chronic conditions.[15] In posttransplant outcomes, the association with frailty and adverse outcomes has not been limited to older adults, but rather has been shown to extend across the age spectrum, likely because of the physiologic decline associated with end-stage organ disease.[7,8]

To better understand the relationship between frailty and MMF intolerance, as well as the relationship between MDR and posttransplant outcomes, we studied an established, single-center, prospective cohort of KT recipients in whom frailty, medication dosing, and graft survival were longitudinally captured.

MATERIALS AND METHODS

Study Design

This was a prospective, longitudinal study of 525 KT recipients at Johns Hopkins Hospital, Baltimore, Maryland, between December 2008 and November 2013. Frailty was measured at the time of KT, and MMF dose was followed longitudinally thereafter. Recipient and transplant factors (sex, age, race, BMI, recipient diabetes, time on dialysis, donor type, preemptive KT, previous transplant, donor age, HLA mismatches, use of induction therapy, and DGF) were abstracted from medical records, and ADL disability (needing assistance with at least one activity of daily living) was ascertained at the time of KT.[17]

Graft Loss

This study linked the single-center cohort to data from the Scientific Registry of Transplant Recipients (SRTR), a national registry of all solid organ transplants. The SRTR includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network, and has been described elsewhere. The Health Resources and Services Administration, U.S. Department of Health and Human Services, provided oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. As is standard with SRTR data, mortality and graft loss were augmented through linkage with the Social Security Death Master File, data from the Centers for Medicare and Medicaid Services, and waitlist data. Graft loss was defined as irreversible graft failure signified by return to long-term dialysis (ascertained from Centers for Medicare and Medicaid Services), listing for a KT (ascertained from SRTR), or retransplantation (ascertained from SRTR). Graft loss and death were also augmented through medical records. The Johns Hopkins Institutional Review Board approved the study.

Frailty

At admission for KT, frailty was measured as defined and validated by Fried et al.[6,18-27] and as we have previously validated in end stage renal disease and KT populations.[7,8,28,29] Frailty is a phenotype based on five components: shrinking (self-report of unintentional weight loss of more than 10 lbs in the past year based on dry weight), weakness (grip-strength below an established cutoff based on gender and BMI), exhaustion (self-report), low activity (kcal/week below an established cutoff), and slowed walking speed (walking time of 15 f. below an established cutoff by gender and height).[6] Each of the five components was scored as 0 or 1 representing the absence or presence of that component. The aggregate frailty score was calculated as the sum of the component scores (range, 0–5); nonfrail was defined as a score of 0 or 1, intermediately frail was defined as a score of 2, and frail was defined as a score of 3 or higher, as has been previously published.[28,29] In this study, we empirically combined the intermediately frail and frail groups (because both groups were associated with a similar risk of MDR) and refer to this group as frail throughout the article.

MMF Dose Reduction

The generic drug name, dose, schedule, start date, and end date were ascertained from medical and pharmacy records at the time of KT and every time there was a change in dosing. An MDR was defined as a decrease in the dose of mycophenolate mofetil (Cellcept) to a dose of less than 2000 mg per day or mycophenolic acid (Myfortic) to a dose of less than 1440 mg per day. Additionally, we considered a discontinuation of MMF (without a dose reduction) to be MDR. The physicians treating the participants enrolled in this study did not have access to study related measurements and were unaware of the participants' frailty status when deciding whether the participant needed an MDR.

Factors Associated with MDR

First, differences in recipient and transplant factors, stratified by ever experiencing an MDR, using a *t* test, Fisher exact test, or Kolmolgorov-Smirnoff test, as appropriate to the distribution of the variable being examined. Then, a Cox proportional hazards model, censored for mortality and graft loss, was used to identify recipient and transplant factors (including frailty) associated with time to first MDR. After exploring univariate associations of several recipient factors (age, race, sex, BMI, diabetes, time on dialysis, ADL disability, and frailty) and transplant factors (donor type, preemptive KT, history of previous KT, donor age, received induction therapy, number of HLA mismatches, length of stay for KT, and DGF) with MDR, we constructed a multivariate model empirically optimized for parsimony. We then tested for interactions of frailty with age, sex, race, and donor type, in the context of the Cox model, using a Wald test. Finally, we estimated the cumulative incidence of MDR, stratified by frailty status, age, race, sex, and donor type, using a Kaplan-Meier approach, censored for mortality and graft loss.

MDR and Graft Loss

The risk of death-censored graft loss associated with MDR was estimated using a multivariate Cox proportional hazards model. The MDR was treated as a time-varying exposure, which means that participants were classified as not having MDR from the date of KT until the date of the first MDR. Participants were then classified as having MDR until they experienced graft loss or were censored. Therefore, participants with MDR contributed time to both the no-MDR and MDR risk sets, switching risk sets on the day they

experienced MDR. This model was adjusted for frailty status at KT and the recipient and transplant factors that were associated with MDR. We tested for interactions of MDR with age, sex, race, frailty, and donor type, in the context of the Cox model, using a Wald test. We plotted the cumulative incidence of death-censored graft loss by MDR using a Kaplan-Meier approach, again treating MDR as time-varying.

As a sensitivity analyses, we adjusted both models (1. frailty and MDR as well as 2. MDR and death-censored graft loss) for post-KT eGFR as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation[30] to account for potential confounding by kidney function.

Statistical Analysis

For all analyses, a *P* value less than 0.05 was considered significant. All analyses were performed using STATA 13.0 (College Station, TX).

RESULTS

Study Population

Among 525 study participants, the mean age was 53.0 years (SD = 14.0), 39.8% were female, 38.5% were African American, and 44.4% were live donor recipients (Table 1). The prevalence of frailty at the time of KT was 19.5%, and the prevalence of intermediate frailty was 33.2% (hereafter, based empirically on associations with MDR, both groups are referred to as frail). Mycophenolate mofetil (Cellcept, Roche, Basel, Switzerland) was the most commonly used mycophenolate after KT, with less than 1% using mycophenolic acid (Myfortic, Novartis, Basel, Switzerland) as their initial MMF; the most common MMF dosing regimen initially after KT was 1,000 mg of mycophenolate mofetil (Cellcept) twice daily. The mean time of follow-up for MDR was 1.43 years (maximum 4.9 years).

MMF Dose Reduction

Over the course of the study, the cumulative incidence of MDR was 48.8%. The median time to the first MDR was 2.04 years. Of the 231 participants with a dose reduction of mycophenolate mofetil (Cellcept), the most likely total daily dose after the reduction was 1,000 mg (62%), and the second most common total daily dose reduction was 1,500 mg (29%); of the 25 participants with a dose reduction of mycophenolic acid (Myfortic), the most common total daily dose reduction was 1,080 mg (48%), and the second most common total daily dose reduction was 720 mg (36%).

Frailty and MDR

The incidence of MDR was greater for those who were frail than those who were nonfrail (log-rank $P = 0.02$) (Figure 1). Median time to an MDR was 3.77 years for those who were nonfrail, compared with 1.47 years for those who were frail. At 2 years, the incidence of MDR was 54% for those who were frail and 45% for those who were nonfrail; at 4 years, the corresponding incidences were 67% and 51% (Table 2). Compared to those who were nonfrail, those who were frail were 1.29 times (95% confidence interval [95% CI], 1.01–1.66; $P = 0.04$) more likely to experience MDR, even after accounting for multiple recipient and transplant factors (Table 3). Furthermore, when adjusted for post-KT estimated glomerular filtration rate (eGFR), the association between frailty and MDR remained statistically significant (hazard ratios, 1.29; 95% CI, 1.00–1.65; $P = 0.046$). The association of frailty and MDR was not modified by age (P for interaction = 0.9), by donor type (P for interaction = 0.2), by sex (P for interaction = 0.3), or by race (P for interaction = 0.2).

Other Factors Associated With MDR

Those with MDR were on average older (55.4 vs 50.7 years old, $P < 0.001$) and were more likely to have received a deceased donor kidney (63.7% vs 48.0%, $P < 0.001$) (Table 1). Additionally, women (43.0% vs 36.8%, $P = 0.2$) and those with lower BMI (27.1 vs 27.9 kg/m^2, $P = 0.09$) were more likely to experience MDR, although neither of these factors reached statistical significance. Activities of daily living (ADL) disability was not associated with MDR

TABLE 1.

Kidney transplant recipients, stratified by MDR

	Overall (n=525)	No MDR (n=269)	MDR (n=256)	*P*
Recipient factors				
Age, mean (SD)	53.0 [14.0]	50.7 [14.0]	55.4 [13.6]	<0.001
African American race, %	38.5	39.4	37.5	0.7
Female sex,	39.8	36.8	43.0	0.2
Body mass index, mean (SD), kg/m^2	27.5 (5.9)	27.9 [6.2]	27.1 [5.5]	0.09
Diabetes, %	17.9	19.0	16.8	0.6
Time on dialysis, mean (SD), yr	3.0 [4.0]	3.1 [4.0]	3.0 [4.0]	0.8
ADL disability	5.3	4.8	5.9	0.7
Transplant factors				
Deceased donor, %	55.6	48.0	63.7	<0.001
Preemptive KT, %	18.1	17.1	19.1	0.6
Previous KT, %	16.4	19.0	13.7	0.1
Donor age, mean (SD)	40.0 [14.9]	40.0 [14.4]	40.0 [15.3]	0.9
Received induction therapy, %	94.1	92.9	95.3	0.3
0 HLA mismatches, %	5.1	5.2	5.1	0.9
Delayed graft function, %	16.8	16.4	17.2	0.8

MDR was defined as a reduction in MMF immunosuppression to less than 2000 mg per day for mycophenolate mofetil (Cellcept) and less than 1440 mg per day for mycophenolic acid (Myfortic). Frailty was defined in two or more components (combining intermediately frail and frail)

SD, standard deviation; IQR, interquartile range; HLA, human leukocyte antigen; ADL, activities of daily living; MMF, mycophenolate mofetil.

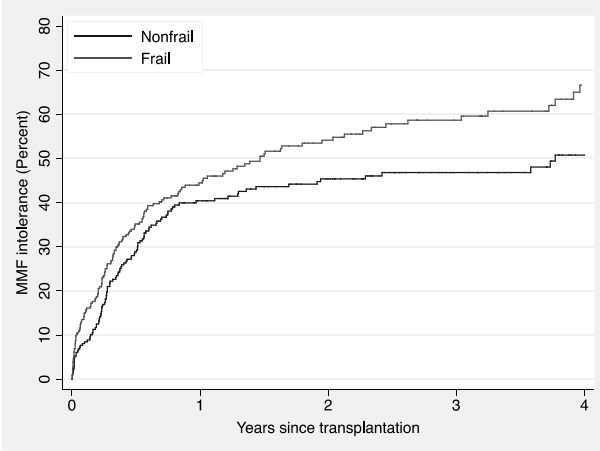

FIGURE 1. Cumulative Incidence of MDR By Frailty Status. MDR was defined as a reduction in MMF immunosuppression to less than 2000 mg per day for Mycophenolate mofetil (Cellcept) and less than 1440 mg per day for mycophenolic acid (Myfortic). Frailty was defined as a score of two or more components. Log-rank *P*=0.02. MMF, mycophenolate mofetil; MDR, MMF dose reduction.

(*P* = 0.7). At 2 years after KT, the incidence of MDR was higher for older adults (≥65 years old) (63% vs 46%), women (55% vs 47%), and deceased donor recipients (58% vs 40%). At 4 years, this trend persisted: older adults (74% vs 55%), women (63% vs 56%), and deceased donor recipients (66% vs 50%) (Table 2). In a multivariate model, older age (age, ≥65 vs <65) (adjusted hazard ratio [aHR] = 1.47, 95% CI, 1.10–1.96; *P* = 0.01), BMI (aHR: 0.87 per 5 kg/m^2 increase, 95% CI, 0.77–0.99; *P* = 0.03), and KT from a deceased donor (aHR, 1.92; 95% CI, 1.44–2.54; *P* < 0.001) were independently associated with MDR (Table 3).

MDR and Death-Censored Graft Loss

The incidence of death-censored graft loss was greater in KT recipients with MDR (Log-rank *P* = 0.003) (Figure 2). At 4 years, the incidence of death-censored graft loss was 5.3% for recipients without an MDR, compared with 11.9% for recipients with an MDR. Mycophenolate mofetil dose reduction was associated with 5.24 times (95% CI, 1.97–13.98; *P* = 0.001) higher risk of death-censored graft loss after adjusting for potential confounders. Furthermore, when adjusted for post-KT eGFR, the association between MDR and death-censored graft loss remained statistically significant (hazard ratios, 4.61, 95% CI, 1.72–12.41; *P* = 0.002). The association of MDR and death-censored graft loss was not modified by age (*P* for interaction = 0.4), by donor type (*P* for interaction = 0.2), by sex (*P* for interaction = 0.6), by race (*P* for interaction = 0.8), or by frailty (*P* for interaction = 0.5). Of the participants with MDR, those with graft loss were all prescribed mycophenolate mofetil (Cellcept); 15 recipients of 231 (6.5%) patients with MDR and taking mycophenolate mofetil (Cellcept) had graft loss.

TABLE 2.

MDR over time, stratified by frailty, age, race, sex, and donor type

	Years since KT		
1% (95% CI)	2% (95% CI)	4% (95% CI)	
Nonfrail (<2 components)	40 (34-47)	45 (39-52)	51 (44-58)
Frail (≥2 component)	44 (39-51)	54 (48-61)	67 (59-75)
Younger age (<65)	39 (34-44)	46 (41-52)	55 (48-61)
Older age (≥65)	56 (46-66)	63 (53-73)	74 (62-85)
Non–African American race	44 (38-50)	50 (44-56)	59 (52-66)
African American race	41 (34-51)	49 (42-57)	58 (49-67)
Females	46 (40-54)	55 (48-62)	63 (55-72)
Males	40 (35-46)	47 (41-53)	56 (49-64)
Deceased donor recipients	51 (45-57)	58 (52-64)	66 (59-73)
Live donor recipients	32 (27-39)	40 (33-47)	50 (41-58)

MDR was defined as a reduction in MMF immunosuppression to less than 2,000 mg per day for Mycophenolate mofetil (Cellcept) and less than 1440 mg per day for mycophenolic acid (Myfortic). The percent and 95% CI of MMF dose reduction by number of years since KT are presented below; each row in the table is a subgroup that represents a separate Kaplan-Meier analysis.
SD, standard deviation; KT, kidney transplantation; 95% CI, 95% confidence interval; MMF, mycophenolate mofetil.

TABLE 3.

Factors associated with MDR

	HR (95% CI) of MDR	*P*
Frailty (≥2 component)	1.29 (1.01-1.66)	0.04
Older age (≥65)	1.47 (1.10-1.96)	0.01
African American race	0.79 (0.60-1.04)	0.1
Female sex	1.26 (0.98-1.62)	0.07
Body mass index (5 kg/m^2)	0.87 (0.77-0.99)	0.03
Deceased donor	1.92 (1.44-2.54)	<0.001

The (HR) and 95% CI are from a single adjusted multivariate model. MDR was defined as a reduction in MMF immunosuppression to less than 2000 mg per day for mycophenolate mofetil (Cellcept) and less than 1440 mg per day for mycophenolic acid (Myfortic).
HR, hazard ratios; 95% CI, 95% confidence interval; MMF, mycophenolate mofetil; MDR, MMF dose reduction.

DISCUSSION

In this single-center, prospective, longitudinal study of 525 patients, frail KT recipients were 1.29 times more likely to experience MDR than their nonfrail counterparts, even after accounting for recipient and transplant factors. Recipients who were older had lower BMI or received a deceased donor kidney were also more likely to experience MDR. Importantly, MDR was associated with 5.24 times higher risk of death-censored graft loss.

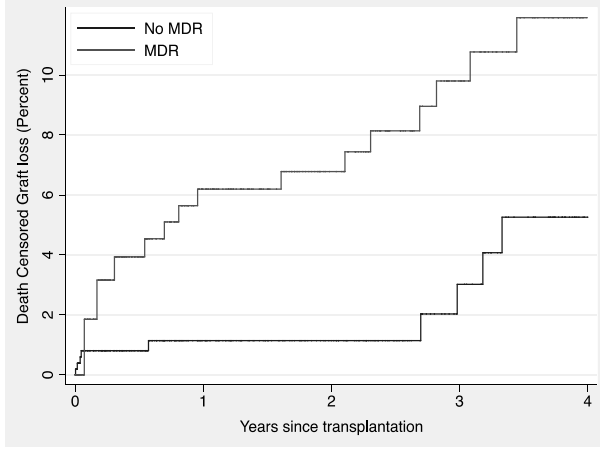

FIGURE 2. Death-censored graft loss by MDR. MDR is defined as a reduction in MMF immunosuppression to less than 2,000 mg per day for mycophenolate mofetil (Cellcept) and less than 1440 mg per day for mycophenolic acid (Myfortic). MDR was treated as time-varying. Log-rank *P*=0.003. MMF, mycophenolate mofetil; MDR, MMF dose reduction.

Frailty in KT recipients captures a unique domain of risk, namely, physiologic reserve. This decline in physiologic reserve leads to an increased vulnerability to stressors resulting from a dysregulation of multiple physiologic systems.[26,27] Immunosuppression use after transplantation represents a great stressor to KT recipients. It is possible that frail KT recipients lack the resiliency to withstand standard doses of MMF and, thus, require a dose reduction or discontinuation. Furthermore, through multiple physiologic pathways, those who require a dose reduction are at increased risk of graft loss.

Our findings that both older and frail recipients are at greater risk of MDR are consistent with previous evidence that frailty is associated with poor tolerance of medications in older adults. One study found that frail older men were more likely to be prescribed lower doses of allopurinol and ramipril.[15] They hypothesized that concerns about hypersensitivity of these two medications may lead to dose reductions in those who are frail; frail older men may have renal impairment, increasing the risk of hypersensitivity adverse drug reactions. In our study, the effect of frailty on MMF tolerance was not limited to older adults; rather, frailty increased the risk of MDR across the age spectrum, with age as a separate risk factor but not an effect modifier. This is consistent with previous posttransplant studies of high prevalence of frailty and strong evidence of a frailty effect even in younger transplant recipients.[7,8]

Two previous studies investigated the frequency of MDR and its association with outcomes in KT recipients.[2,3] One single-center study found that 70% of recipients had a change in MMF dose and that 3-year death-censored graft survival was lower in those with a change in MMF dose (76.3% vs 88.3%, $P = 0.003$).[2] The rate of MDR we observed may be lower than the rate observed in this single-center study because of the definition of MDR (a dose reduction vs any change in the dose of MMF), the timing of the study (2008–2012 vs 1995–2000), or different practices at each transplant center.[2] However, our rate of MDR was comparable to that observed in a more recent single-center study (59%).[3] We were able to extend these findings by studying MDR over a longer follow-up, investigating risk factors for MDR, including frailty, and demonstrating that MDR was independently associated with death-censored graft loss in a multivariate model.

Strengths of this study were the prospective measurement of a validated, objective frailty instrument, granular ascertainment of the recipient and transplant factors that were identified as predictors of MDR, and longitudinal ascertainment of MDR. The main limitation was the single-center study design, so direct inferences must be interpreted in the context of the demographics of our study population, which is somewhat older and more heavily represented by African Americans. That said, we did not identify any interactions between frailty and age, sex, donor type, or race, so the likelihood that this novel association is specific only to our population is low; in other words, the risk of biased inference is low because the effect of frailty was the same across factors that might have been different in our population than those of other centers. Additionally, it is unlikely that physicians changed the MMF dose because of a direct observation of frailty status. Although it may intuitively seem that frailty can be ascertained by physician observation, recent work by our group suggests quite the opposite: that the phenotype of frailty measured in this study represents an underlying vulnerability to stressors that is not always evident to the clinician. In fact, we have shown that measured and perceived frailty are very poorly correlated, with the agreement between measured and clinician-perceived frailty only slightly better than what would be expected by chance alone (64.1% observed agreement vs 52.9% expected agreement, $\kappa = 0.24$).[16]

In conclusion, we found that MDR is common after KT, and this reduction or discontinuation of mycophenolate is associated with increased risk of graft loss. Furthermore, we identified frailty as an independent risk factor for MDR; this novel measure of physiologic reserve, originally described in the geriatrics literature, was associated with MDR regardless of recipient age. A better understanding of which patients might not tolerate MMF would likely be helpful in planning alternate strategies to maintain adequate immunosuppression and protect the allograft. Recipients who are frail at the time of KT should be identified, monitored more closely for MMF adverse reactions which may necessitate a dose reduction or discontinuation, and possibly offered alternate immunosuppression approaches. Furthermore, close monitoring of these recipients may also reduce the risk of subsequent graft loss.

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