Article

Clinical and Economic Outcomes Associated with Medication Errors in Kidney Transplantation

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Abstract

Background and objectives Modern immunosuppressant regimens have significantly decreased acute rejection rates, but may have increased the risk of graft loss driven by adverse drug reactions (ADRs) and medication errors (MEs). The objectives of this study were to determine the incidence and risk factors for MEs and ADRs and determine the association between transplant outcomes and these events.

Design, setting, participants, & measurements This was a *post hoc* analysis of a prospective, randomized trial that included patients aged >18 years that received a solitary renal transplant at an academic medical center recruited between March 2009 and July 2011. Patients were divided into groups based on developing a clinical significant ME (CSME), defined as a significant ME that contributed to a hospital admission.

Results The mean study follow-up was 2.5±0.7 years. There were a total of 233 MEs and 327 ADRs in the 200 patients included in the analysis, with 64% of the cohort experiencing at least one ME and 87% experiencing an ADR; 23 patients (12%) experienced a CSME. Patients that experienced CSMEs had a trend toward more post-transplant readmissions (median 1 [interquartile range (IQR), 0–5] versus 0 [0–2]; P=0.06), higher costs for readmissions (median $18,091 [IQR, $3023–$56,268] versus $0 [$0–$15,991]; P<0.01), and overall length of stay (median 5.0 days [IQR, 2.0–14.0] versus 0.0 days [IQR, 0.0–5.5]; P<0.01) after the CSME event. CSME patients were also more likely to experience graft failure (22% versus 10%; P=0.05).

Conclusions Significant MEs commonly occur in renal transplant recipients and are associated with an increased risk of deleterious clinical outcomes, including subsequent hospital days, costs, and graft loss.
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Introduction

Kidney transplantation is considered the preferred option for patients with ESRD. As of 2007, there were >140,000 patients living in the United States with a functioning renal transplant allograft (1,2). Immunosuppression has significantly decreased acute rejection rates since the 1980s, with current 1-year acute rejection rates approximating 10%, compared with rates of roughly 30%–40% 3 decades prior (3). Despite this dramatic decrease, long-term graft survival remains largely unchanged. It is estimated that 3%–5% of allografts per year are lost to allograft nephropathy or death with a functioning graft (4). This was highlighted in a study by Meier-Kriesche et al. in which it was observed that immunosuppression has significantly decreased acute rejection rates but led to more graft loss driven by infection and overimmunosuppression (5). Contemporary immunosuppression regimens are highly effective at preventing rejections but carry the burdens of considerable toxicities coupled with exceedingly complex regimens. These attributes place a transplant patient at very high risk of developing adverse drug reactions (ADRs) and medication errors (MEs) (6–8).

Despite transplant patients being at very high risk for ADRs and MEs, there are limited studies analyzing the incidence, risk factors, and outcomes associated with these events. Friedman et al. demonstrated 149 MEs in 93 transplant recipients with 32% of these MEs resulting in an ADR (6). In an analysis of outpatient lung transplant recipients, 13% of all doses administered to patients were taken incorrectly (7). However, neither of these studies analyzed the direct causative effects of MEs and ADRs on long-term transplant outcomes. Taber et al. demonstrated that renal transplant recipients with medication-related problems (either MEs or ADRs) had higher rates of acute rejection, cytomegalovirus (CMV) infection, and 30-day readmissions. However, because of the retrospective design of this trial, only general associations could be inferred (8). Therefore, prospective studies are warranted to further define the incidence, severity, risk factors, and associated clinical outcomes with MEs in transplant recipients, with the long-term goals of preventing the occurrence and detrimental clinical sequelae that can occur as a result of these events. The purpose of this study was to determine the incidence, severity, risk factors, and clinical

outcomes associated with MEs and ADRs in renal transplant recipients receiving contemporary immunosuppression and post-transplant care through a *post hoc* analysis of a randomized controlled trial.

Materials and Methods

Study Design

This study was a *post hoc* analysis of a randomized controlled comparative efficacy study of two induction regimens in adult kidney transplant recipients (ClinicalTrials.gov NCT00859131). The primary aim of this analysis was to capture the incidence and severity of MEs within this prospectively monitored cohort of patients and to determine whether these events influenced the development of ADRs and clinical outcomes. For this analysis, MEs and ADRs were further categorized and analyzed from these records. Baseline recipient demographics, donor demographics, transplant characteristics, and clinical outcomes were captured and recorded as part of the original study in a prospective fashion. Clinical outcomes, which were also captured as part of the original study, included graft and patient survival rates, acute rejection rates, graft function, readmissions with cause, and infections. Hospitalization costs and length of stay (LOS) were also collected and analyzed. The *post hoc* data captured and analyzed included detailed socioeconomic information (education, detailed health insurance information), number of missed clinic and laboratory appointments, drug interactions, and the timing and severity of MEs and ADRs. As patients were enrolled and followed in a prospective investigational study, detailed information regarding medication regimens, side effects, and MEs were documented in the records by clinical coordinators and study personnel. These detailed records enabled investigators the ability to determine the incidence, severity, and timing of these events and link these data back to the clinical outcomes data that were captured as part of the original study. Data were collected on all patients up to March 2013, including additional clinical follow-up data.

Patients

This study included 200 patients between the ages of 18 and 75 years that received a solitary kidney transplant from March 2009 to July 2011. Patients were excluded if they had any substance abuse or psychiatric illness that was believed to interfere with communication, possessed a history of malignancy within 5 years (except basal or squamous cell carcinoma), or had an HLA identical living donor. All patients included in the prospective trial were included in this *post hoc* analysis.

Immunosuppressive and Anti-Infective Prophylactic Regimens

Patients were risk stratified and randomized to receive induction with thymoglobulin or an IL-2 receptor antagonist (IL-2RA). All patients were started on a maintenance immunosuppression regimen consisting of tacrolimus, mycophenolate mofetil, and corticosteroids. All patients received prophylactic antifungal therapy with nystatin for 30 days and sulfamethoxazole-trimethoprim for 90 days post-transplant for *Pneumocystis jiroveci* pneumonia prophylaxis. Patients received CMV prophylaxis with

valganciclovir or acyclovir for 90–180 days post-transplant depending on donor and recipient serologic status.

Definitions

MEs were captured and included in the analysis if it was documented by a healthcare provider (nurse, physician, or pharmacist) that a patient was taking a medication in a manner that was not intended. The type of ME was recorded and included patient-induced MEs, accessibility errors, prescription errors, and pharmacy errors. A severity for each of the MEs was assigned based on a previous validated ME severity scale (9). Please see Supplemental Table 1 for specific details regarding how the ME severity was classified. A clinically significant ME (CSME) was defined as a significant ME that reasonably contributed to a hospitalization, which was a similar definition used in previous studies (6–8). This was determined by evaluating the primary etiology for hospitalization and determining whether the ME likely contributed to this admission. For example, if a patient took too high a dose of mycophenolate mofetil and was admitted to the hospital for an infection or leukopenia, this was classified as a CSME.

ADRs were defined according to the World Health Organization, in which it describes an ADR as any response to a drug that is noxious and unintended. The severity of the ADR was defined according to the Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute (10). The CTCAE is a standardized classification system developed and validated to assess the frequency and severity of medication adverse effects. It was originally designed for cancer patients, but is now routinely utilized across multiple patient types in clinical research. Only ADRs that were considered to be significant according to the CTCAE criteria (grade≥3) were included in this analysis.

Acute rejection was defined as an elevation of serum creatinine of at least 20% above baseline or an absolute increase of >0.4 mg/dl with renal allograft biopsy showing at least grade 1A rejection by Banff 97 criteria or higher or treated borderline rejection (11). All patients were required to have biopsy confirmation of rejection episodes within 24 hours of onset of treatment for acute rejection. CMV infection was defined according to the most recent Kidney Disease Improving Global Outcomes guidelines (12). Infections were described as any diagnosed and treated infection and consisted of bacterial, viral, or fungal etiologies. Flulike illnesses, viral syndromes not requiring medical therapy, or nasopharyngitis were not included. We monitored for CMV infection by assessing signs and symptoms consistent with infection (fever, leukopenia, malaise, nausea/vomiting, and anorexia), coupled with conducting CMV PCR measurements monthly for the first year post-transplant after the discontinuation of valganciclovir prophylaxis. BK infection monitoring was conducted by measuring BK PCRs at months 1, 2, 3, 6, 9, 12, and 18 after transplantation. A BK PCR of >10,000 copies/ml led to a kidney biopsy to assess for BK nephropathy.

Statistical Analyses

Baseline demographic data were displayed using descriptive statistics (mean±SD for continuous data with normal distribution, median with interquartile ranges

[IQRs]) for continuous/ordinal data that were not normally distributed and percentages for categorical data) and compared between patient groups (CSME versus no CSME). Statistical comparisons between groups were conducted using the *t* test for normally distributed continuous data and the Mann–Whitney *U* test for continuous or ordinal data that were not normally distributed. Nominal data comparisons were conducted using the Pearson's chi-squared test. For nonparametric ordinal variables, a Mantel–Haenszel linear-by-linear association chi-squared analysis was performed. With regard to the analysis of readmissions, cost for readmissions, and LOS for readmissions, only the events that occurred after the CSME for this cohort, were included in the analysis. Kaplan–Meier curves were generated and the log-rank test was used for statistical comparisons of the time to graft loss based on the occurrence of a CSME and acute rejection episode. A *P* value <0.05 was considered statistically significant.

Results
Incidence and Severity of MEs and Association with ADRs
Two-hundred patients, transplanted from March 2009 to July 2011, were included and prospectively monitored in this analysis. The mean study follow-up was 2.5±0.7 years (IQR, 0.2–3.9 years). The total number of MEs identified in the study cohort was 233, with 64% of patients having at least one ME. Immunosuppressants were associated with 48% of the MEs when analyzed by medication class (Table 1). Of the MEs identified, 68% were due to patient-induced errors, 17% were related to pharmacy errors, and 15% were due to errors in prescribing. In addition, 128 patients (55%) experienced at least one significant ME based on Overhage and Lukes (9) criteria (score C or greater) and 28 patients (12%) developed a CSME that was a significant ME associated with a subsequent hospital admission. The MEs leading to the hospitalization in the CSME cohort occurred early after transplant (mean days to ME 60; median days to

ME 30 [IQR, 4–407 days]). The hospitalizations that occurred in relation to the ME in the CSME also occurred early after transplant (mean days to hospitalization 87; median days to hospitalization 68; IQR, 5–426 days). For 19 patients (83%) in the CMSE cohort, the hospitalization related to the ME was the first hospitalization after the transplant admission.

ADRs
During the follow-up period, there were a total of 327 significant ADRs (CTCAE grade≥3) in 173 patients (87% of the study cohort). Table 1 displays the type and frequency of these events. The most common ADRs were metabolic (hyperglycemia or new onset diabetes after transplantation, dyslipidemia, hyperuricemia), experienced by 42% of the cohort. This was followed by cytopenias (17%; leukopenia, anemia, or thrombocytopenia), opportunistic infections (17%; CMV, BK, other viruses, fungal), and gastrointestinal ADRs (15%; diarrhea, constipation, or dyspepsia). Patients that experienced at least one ME had a nonsignificantly higher odds of developing an ADR (90% versus 82%; *P*=0.13), with the predominant ADR differences seen in acute rejection (14% versus 7%; *P*=0.13) and neurotoxicities (8% versus 1%; *P*=0.05). Of the 23 patients that developed a CSME, all had at least one ADR (100% versus 85%; *P*=0.05), with cytopenias (43% versus 25%; *P*=0.08) and acute rejection (26% versus 9%; *P*=0.03) being the predominant ADR differences. In addition, the mean number of ADRs experienced was significantly higher in the CSME cohort (2.1±1.0 versus 1.6±1.1; *P*=0.03).

Risk Factors for CSME
Baseline risk factors associated with developing a CSME are displayed in Table 2. African-American race was different between cohorts (30% African American in the CSME group versus 52% in the non-CSME group; *P*<0.05). The use of IL-2RA induction therapy was associated with CSMEs (65% in the CSME group versus 47% in the non-CSME group; *P*<0.05). There were linear associations between level of education, total number of medications, and the development of a CSME. All patients received the same immunosuppression (tacrolimus, mycophenolate mofetil, and prednisone) and anti-infective prophylaxis (valganciclovir, sulfamethoxazole/trimethoprim, and nystatin). Over 90% of patients were receiving antihypertensives, the vast majority was receiving other cardiovascular risk factor medications (statins, antiplatelets, *etc*.), and approximately 40% were discharged from the hospital on medications to treat diabetes.

Table 2 also displays the post-transplant factors associated with the development of a CSME. Patients that had a CSME were more likely to be prescribed a triazole antifungal (30% versus 9%; *P*<0.01) or another interacting medication, including warfarin, amiodarone, or nonsteroidal anti-inflammatory drugs (17% versus 2%; *P*=0.03). In addition, cytopenias, nonopportunistic infections, and the occurrence of >4 MEs were all associated with the development of a CSME (*P*<0.05).

Outcomes Associated with CSME
The outcomes associated with the development of CSMEs are displayed in Table 3. The initial transplant event hospital cost and LOS were similar between the

Table 1. Frequency of MEs by drug class and ADRs by type	
Type of ME or ADR	Frequency (%)
ME by drug class	
Immunosuppressant	108 (48)
Other	38 (17)
Antihypertensive	27 (12)
Antibiotics	23 (10)
Not noted	15 (7)
Diabetes mellitus	10 (5)
NSAIDs	2 (1)
Gastrointestinal	48 (15)
ADRs by type	
Rejection	22 (7)
Opportunistic infection	54 (17)
Metabolic	136 (42)
Neurologic	11 (3)
Cytopenia	54 (17)
Dermatologic	2 (0.1)

ME, medication error; ADR, adverse drug reaction; NSAID, nonsteroidal anti-inflammatory drug.

Table 2. Baseline and post-transplant factors associated with developing a CSME

Characteristic	CSME Group (n=23)	Non-CSME Group (n=177)	P Value
Men	11 (48)	110 (62)	0.19
African-American race	7 (30)	92 (52)	0.05
Highest education level			0.13[a]
Elementary school	0 (0)	4 (2.3)	
High school	7 (30.4)	77 (43.5)	
Some college/technical college	9 (39.1)	44 (29.9)	
Bachelors degree or higher	6 (26.1)	36 (20.3)	
Primary insurance			0.18[a]
Medicare	20 (87)	127 (72)	
Medicaid	0 (0)	3 (1.7)	
Private	3 (13)	44 (24.9)	
Tricare	0 (0)	1 (0.6)	
Living donor	7 (30)	31 (18)	0.15
Standard criteria donor	14 (61)	128 (72)	0.26
Diabetes	8 (35)	55 (31)	0.72
Induction therapy with IL-2 receptor antagonist	15 (65)	83 (47)	0.04
Postoperative medications at discharge (n)			0.08[a]
5–9	3 (13)	31 (18)	
10–14	12 (52)	96 (54)	
>14	7 (30)	47 (26)	
Patient had >2 MEs	7 (30)	16 (9)	<0.01
Patient had >3 MEs	4 (17.4)	6 (4)	<0.01
Post-transplant triazole use	7 (30.4)	15 (8.5)	<0.01
Other drug interactions [b]	4 (17.4)	10 (5.6)	0.02
Cytopenias[c]	14 (60.9)	67 (37.9)	0.03
Nonopportunistic severe infection[d]	10 (43.5)	38 (21.5)	0.02
Missed >5 laboratory appointments	7 (30)	28 (16)	0.08

Data are n (%) unless otherwise stated. CSME, clinically significant medication error.
[a]Mantel–Haenszel linear-by-linear association chi-squared test (P<0.05).
[b]Other drug interaction: warfarin (75%), amiodarone, or NSAIDs, nonsteroidal anti-inflammatory drug.
[c]Cytopenias include severe leukopenia, anemia, or thrombocytopenia.
[d]Infections include pneumonia, urinary tract infection, or nasopharyngitis.

CSME and non-CSME groups. However, patients that developed a CSME were more likely to develop ADRs (2.1±1.0 versus 1.6±1.1 ADRs; P=0.03), had a trend toward more post-transplant readmissions (median 1 [IQR, 0–5] versus 0 [IQR, 0–2]; P=0.06), had higher costs associated with these readmissions (median $18,091 [IQR, $3023–$56,268] versus $0 [IQR, $0–$15,991]; P<0.01), and had an overall longer LOS during these readmissions (median 5.0 days [IQR, 2.0–14.0] versus 0.0 days [IQR, 0.0–5.5]; P<0.01). These data only include events that occurred after the CSME and the hospital admission associated with the CSME was not included in these comparisons. Five of the six (83%) acute rejections and 63% of the severe opportunistic infections that occurred in the CSME happened after the CSME event. Prior to the ME leading to the hospitalization (CSME), this cohort of patients had similar rates of clinical events to the control group. Figure 1 displays the Kaplan–Meier curve for graft survival based on the development of a CSME. Patients that developed a CSME were more likely to have subsequent graft failure compared with non-CSME patients (3-year graft failure rate: 22% for the CSME group versus 10% for the non-CSME group; P=0.05). Figure 1 also displays graft survival rates based on the development of acute rejection, demonstrating that the development of a CSME was more

strongly associated with graft loss compared with acute rejection (P=0.25).

Discussion

Modern immunosuppressant regimens utilized in transplantation are known to be highly effective, yet are flawed due to their complexity and high rates of ADRs (5). The results of this study demonstrate that MEs and ADRs occur in a majority of kidney transplant recipients and are usually caused by patient-related factors (*i.e.,* taking the wrong dose, the wrong drug, or a medication not prescribed). One in eight patients within this study had a significant ME that contributed to a hospitalization (CSME). On follow-up, after these CSMEs, this cohort of patients was more likely to have additional MEs, hospital readmissions, ADRs, and graft loss. To our knowledge, this is the first published study that specifically associates MEs and deleterious clinical outcomes in a prospectively monitored kidney transplant population. Kidney transplant patients are known to be at very high risk for MEs, and future interventional efforts are needed to reduce these events and associated clinical sequelae (6–8).

In the nontransplant population, MEs and ADRs are common and have serious consequences on patient

Table 3. Post-transplant outcomes associated with CSMEs

Characteristic	CSME Group (n=23)	Non-CSME Group (n=177)	P Value
Follow-up (yr)	2.4±0.9	2.5±0.8	0.36
Initial transplant hospitalization cost ($)	76,124 (74,951–84,583)	79,774 (74,625–86,178)	0.45
Initial transplant hospitalization LOS (d)	3.0 (3.0–4.0)	3.0 (3.0–3.0)	0.74
Post-transplant readmissions[a]	1.0 (0.0–5.0)	0.0 (0.0–2.0)	0.06
LOS of post-transplant readmissions (d)[a]	5.0 (2.0–14.0)	0.0 (0.0–5.5)	<0.01
Total costs of post-transplant readmissions ($)[a]	18,091 (3023–56,268)	0 (0–15,991)	<0.01
Patient survival at end of follow-up	100	95	0.27
Graft survival at end of follow-up	78	90	0.08
Acute rejection at end of follow-up	26	9	0.01
Chronic allograft nephropathy at end of follow-up	18	16	0.85
CMV syndrome or disease at end of follow-up	9	6	0.65
BK viremia or nephropathy at end of follow-up	13	10	0.67

Data are presented as the mean±SD, median (interquartile range), or percentage. LOS, length of stay; CMV, cytomegalovirus.
[a]Excluding the readmission associated with the CSME event.

outcomes. This was demonstrated in the landmark report by the Institute of Medicine, "To Err is Human" (13). The analysis revealed that MEs and the associated adverse drug events led to as many as 98,000 deaths per year in hospitalized patients. In addition, the Canadian Adverse Events Study found a 7.5% incidence rate for adverse events during hospitalization, extrapolating to roughly 185,000 hospitalizations being associated with an ADR with 70,000 of these adverse events found to be potentially preventable (14). In the study results presented here, MEs were identified in 64% of patients with 233 total errors identified in 200 patients. These event rates correspond to a previous analysis that found 149 errors in 93 patients (6). In addition, 12% of patients experienced a significant ME that was reasonably associated with a hospitalization. This is fairly similar to a previously conducted study that determined 37 (8%) of 476 patients developed a clinically significant medication-related problem that included errors associated with hospitalization, a clinic visit, or increased frequency of monitoring (8). In the analysis by Friedman *et al.*, errors leading to hospitalization or additional outpatient procedures occurred in 13% of the cohort (6). Thus, the previous literature analyzing MEs in transplantation, coupled with the data presented in this study, strongly suggests that these events are common, occurring in approximately one in eight patients, and are associated with deleterious clinical events, including graft loss.

Risk factors were evaluated in this cohort of patients to assist in the potential prediction of patients prone to developing MEs. This analysis discovered some interesting results that seem to contradict the findings of a previous analysis (8). One of the risk factors previously described was being of African-American race. The lack of an association in this trial may be due to the inclusion of patients that agreed to be enrolled in a randomized trial *via* the Hawthorne effect (patients modify behavior because they know they are being closely monitored and scrutinized). In addition, when evaluating education level, there appeared to be a slight trend toward patients with higher education levels being more likely to develop MEs (P=0.13). This might represent self-treatment by patients. Insurance

type was not shown to be a significant risk factor associated with a CSME; however, there appeared to be a numerical trend toward patients with Medicare (87% for the CSME group versus 72% for the non-CSME group) compared with private insurance (13% for the CSME group versus 25% for the non-CSME group) developing a ME (P=0.18). Induction with an IL-2RA was also associated with the development of a CSME (P<0.05). This finding could represent the aggressive upward titration of immunosuppressant medications by providers in patients that are known to have received less potent induction therapy. Because of the inconsistencies with risk factors seen in this cohort of patients, compared with previous studies, larger-scale studies are warranted to better discern the high-risk ME transplant patient phenotype.

Post-transplant characteristics associated with CSMEs included patients taking a medication known to interact with immunosuppressant regimens. These included triazoles, warfarin, and amiodarone. This association could be the result of a magnification of MEs causing clinical issues. The association of CSMEs and cytopenias may be a direct effect of the ME on the blood counts, or might represent the identification of patients at higher risk of developing clinical issues after experiencing a ME (select the patients that have lower reserves to recover from a ME).

The analysis of the clinical outcomes associated with a CSME presents many interesting results. Patients that developed a CSME had more post-transplant readmissions (2.4 versus 1.3; P=0.01), higher costs associated with these readmissions ($37,852 versus $15,978; P=0.01), and longer total LOS for readmissions (11 days versus 5 days; P=0.02). This provides further data that MEs and the resulting adverse effects may have significant financial and patient health implications. These findings concur with previous studies that adverse outcomes are associated with MEs and their resulting ADRs (6,8). There was also a statistically significant association with the number of ADRs and the occurrence of a CSME. This is similar to previous analyses that associated the occurrence of MEs and ADRs (6,7,15). A statistically significant association between the occurrence of graft loss and CSMEs was also identified.
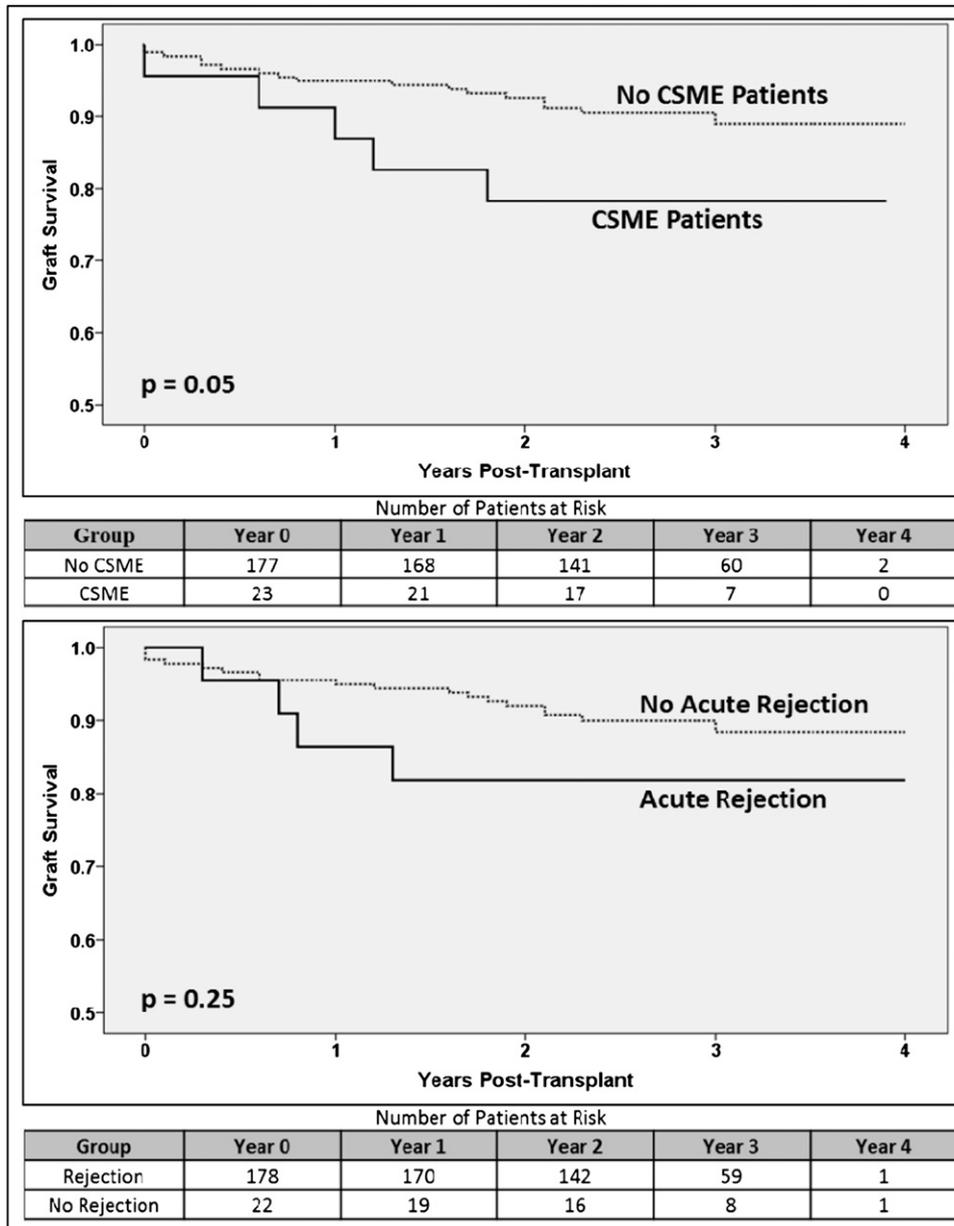
Figure 1. | **Kaplan–Meier survival curves for graft loss.** The top Kaplan–Meier analysis displays the graft survival curves for the CSME and non-CSME cohorts. The bottom Kaplan–Meier analysis displays the graft survival rates for those with and without acute rejection. The number of patients at risk for events during follow-up for each analysis is displayed below the corresponding survival curves. CSME, clinically significant medication error.

There was an approximate 15% reduction graft survival by 2 years after transplantation ($P=0.05$) in patients that developed a CSME. Notably, there was a limited association between graft survival and acute rejection, suggesting the etiologies for graft loss in patients that develop CSMEs are multifactorial, and not simply related to higher rates of acute rejection.

There are a number of limitations to this study that merit discussion. Although this was a prospective study, the analysis of MEs and ADRs was conducted in a *post hoc* fashion and relied on the accurate documentation by clinical and research coordinators in the medical record. Although the number and severity of these events were

considerable, if documentation was not complete or accurate, this study has the potential to underestimate these events. It is important to note that the documentation of MEs and ADRs did occur in a prospective fashion, during clinic visits, while grading the severity and the timing was the *post hoc* portion of this trial. Another potential limitation was the definition of a CSME. These events were defined as significant or severe MEs that reasonably contributed to a hospitalization. This definition was chosen by study investigators to be consistent with previous studies (6,8) and to discern differences in patients that have a ME compared with those that have a ME leading to a significant clinical issue. However, the use of CSMEs

to define the study cohort of interest may also select a higher-risk group of patients that were more prone to hospitalization, regardless of having a ME. Indeed, the higher rates of cytopenias, infections, and graft loss may partially be due to the lower reserves (higher disease acuity) in this group of patients. However, the higher total numbers of MEs in the CSME group argues against this as being the only reason for the differences seen in clinical outcomes. In addition, the ME leading to the CSME occurred very early after transplant, and the vast majority of deleterious clinical events and rehospitalizations occurred after the CSME. An additional limitation was the relatively small number of CSME patients in this analysis. This likely limited the power to detect a difference between CSME patients and the control group, particularly when identifying risk factors. In contrast with previously conducted trials, the use of a cohort of patients from a prospective randomized trial may have selected patients at lower risk for MEs, as it is known that patients enrolled in research trials, in general, have better clinical outcomes to those undergoing standard post-transplant care (16).

In summary, this analysis demonstrates that MEs are common in the renal transplant population; CSMEs are associated with the development of ADRs, hospitalization, and graft loss. In order to improve long-term outcomes in transplant recipients, future interventional studies are warranted to minimize the incidence and potential clinical consequences of MEs in this high-risk patient population.

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