Kidney Medicine

Kidney Transplantation, Immunosuppression and the Risk of Fracture: Clinical and Economic Implications

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Rationale & Objective: Disorders of bone and mineral metabolism frequently develop with advanced kidney disease, may be exacerbated by immunosuppression after kidney transplantation, and increase the risk of fractures.

Study Design: Retrospective database study.

Setting & Participants: Kidney-only transplant recipients aged ≥18 years from 2005 to 2016 in the United States captured in US Renal Data System records, which integrate Organ Procurement and Transplantation Network/United Network for Organ Sharing records with Medicare billing claims.

Exposures: Various immunosuppression regimens in the first 3 months after kidney transplantation.

Outcomes: The development of fractures, as ascertained using diagnostic codes on Medicare billing claims.

Analytical Approach: We used multivariable Cox regression with inverse propensity weighting to compare the incidence of fractures >3 months-to-3 years after kidney transplantation associated with various immunosuppression regimens compared to a reference regimen of antithymocyte globulin (TMG) or alemtuzumab (ALEM) with tacrolimus + mycophenolic acid + prednisone using inverse probability treatment weighting.

Results: Overall, fractures were identified in 7.5% of kidney transplant recipients (women, 8.8%; men, 6.7%; age < 55 years, 5.9%; age ≥ 55 years, 9.3%). In time-varying regression, experiencing a fracture was associated with a substantially increased risk of subsequent death within 3 months (adjusted hazard ratio [aHR], 3.06; 95% confidence interval [CI], 2.45-3.81). Fractures were also associated with increased Medicare spending (first year: $5,122; second year: $10,890; third year: $11,083; [$P$ < 0.001]). Induction with TMG or ALEM and the avoidance or early withdrawal of steroids significantly reduced the risk of fractures in younger (aHR, 0.63; 95% CI, 0.54-0.73) and older (aHR, 0.83; 95% CI, 0.74-0.94) patients. The avoidance or early withdrawal of steroids with any induction was associated with a reduced risk of fractures in women.

Limitations: This was a retrospective study which lacked data on immunosuppression levels.

Conclusions: Fractures after kidney transplantation are associated with significantly increased mortality risk and costs. The early avoidance or early withdrawal of steroids after induction with TMG or ALEM reduces the risk of fractures after kidney transplantation and should be considered for patients at high-risk of this complication, including older adults and women.

Visual Abstract included

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Chronic kidney disease-mineral and bone disorders (CKD-MBD) affect many patients who progress to chronic kidney failure and contribute to increased morbidity and even mortality.[1-3] CKD-MBD results in clinically evident osteoporosis in up to 66% of patients with kidney failure,[4,5] contributing to long-bone fractures, vertebral compression fractures, and other complications.[3,6,7] CKD-MBD is the outcome of chronic alternations in calcium or phosphorus metabolism, leading to hyperparathyroidism, alterations in the activity of fibroblastic growth factor-23, and impaired osteoblastic activity.[3-7]

Kidney transplantation has been conclusively demonstrated to offer the best treatment for chronic kidney failure, extending survival, improving the quality of life, and reducing life-time medical expenditures.[8-10] Unfortunately, there is historical evidence that immunosuppressive medications vital for kidney allograft survival contribute to further deterioration of bone health after kidney transplantation.[3,11-15] Although there are many factors that affect bone health, the long-term use of glucocorticoids after transplantation remains the key factor that exacerbates osteoporosis in patients with CKD-MBD who have undergone transplantation.[13,16] Immediately following kidney transplantation, there is rapid loss of bone mass because of decreased bone formation as a result of glucocorticoid therapy.[17] Bone mineral density has been shown to decrease by 4%-10% in the first 6 months after transplantation.[18] This reduction in bone density aligns with prior findings that up to 22.5% of kidney transplant recipients experienced a fracture within 5 years,[2,7,11,15,19-24] which is higher than the rates in the general population and in patients who require maintenance dialysis.[3,6,7] Post-transplantation fractures resulted in increased health care costs and up to a 60% increase in posttransplantation mortality.[2]

As patient survival following kidney transplantation has continued to improve, minimizing the impact of immunosuppression-associated comorbidities on patient

PLAIN-LANGUAGE SUMMARY

Disorders of bone and mineral metabolism often develop with advanced kidney disease and may have serious consequences in patients who have undergone transplantation and are taking immunosuppressive medications. Given that the selection of immunosuppression regimen is a potentially modifiable risk factor for complications after transplant, we assessed the associations of immunosuppression regimens with posttransplantation fractures using a linkage between a national transplant registry and Medicare claims data. Fractures were more common in older patients than in younger patients, and in women compared with men. The diagnosis of a fracture predicted a 3-fold increased risk of death and higher Medicare spending. We observed benefits of corticosteroid-sparing regimens with appropriate induction therapy on the posttransplantation risk of fractures in older and younger adults. These findings support consideration of the risk of nonimmune complications along with rejection risk when selecting immunosuppression regimens for kidney transplant recipients.

outcomes has become the focus of investigations.[25,26] Immunosuppression regimens are associated with clinically significant differences in the outcomes of kidney transplantation beyond rejection, graft failure, and mortality.[25,26] In a study of a national cohort of US recipients of kidney transplants, the selection of immunosuppression regimens was associated with statistically and clinically significant differences in the posttransplantation incidence of infection (pneumonia and sepsis), malignancy, and posttransplantation diabetes mellitus.[27,28] These associations varied by patient characteristics, including age, sex, and race. Therefore, tailoring immunosuppression based on an individual patient's clinical profile may be warranted to balance the efficacy of immunosuppression with morbidity after transplantation.

In the current study, we sought to examine the impact of the early selection of immunosuppression regimen on the incidence and sequelae of bone fractures in a contemporary sample of kidney transplant recipients. Using a national linkage of clinical registry data and health care claims data, we examined the incidence of fractures >3 months-to-3 years after kidney transplantation overall and among prespecified, higher-risk groups (older adults and women) with Medicare insurance coverage. This analysis uniquely assessed the impact of both the induction of immunosuppression and the selection of maintenance immunosuppression medications on the risk of clinically evident fractures.

METHODS

Data Source and Sampling

Study data were drawn from US Renal Data System records, which integrate Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) records with Medicare billing claims. The study identified kidney-only transplant recipients aged ≥18 years from 2005 to 2016 in the United States. The recipients were categorized as younger (<55 years) and older (≥55 years) adults. Recipient sex was determined based on the sex reported in the listing for kidney transplantation. Patients were selected for inclusion if they had Medicare as the primary payer at the time of transplantation and had Medicare-reimbursed prescriptions and fills for immunosuppression in the first 3 months after transplantation. This study was deemed as exempt from human subjects review by the Saint Louis University Institutional Review Board. Patients with primary insurance other than Medicare were excluded from this analysis.

Definition of Immunosuppression Regimens

We determined the use of induction agents based on center-reported data from the OPTN. We determined early immunosuppression regimens based on Medicare pharmacy claims for immunosuppression agents submitted within the first 3 months after transplantation and reimbursed through Part B or D benefits. Based on induction and maintenance immunosuppression regimens, we categorized the patients into 7 mutually exclusive study regimens, which are as follows (Fig S1):

1. Triple maintenance (tacrolimus [Tac] + mycophenolic acid/azathioprine + prednisone [Pred]), after T-cell–depleting induction: antithymocyte globulin (TMG) or alemtuzumab (ALEM) (reference regimen).
2. Triple maintenance after interleukin 2 receptor antibody (IL2rAb) induction: IL2rAb + triple therapy.
3. Steroid avoidance/withdrawal after T-cell-depleting induction: TMG or ALEM + no prednisone.
4. Steroid avoidance after IL2rAb induction: IL2rAb + no Pred.
5. Antimetabolite avoidance: tacrolimus [Tac] alone or Tac + Pred with any induction.
6. Mammalian target of rapamycin inhibitor (mTORi)-based regimens.
7. Cyclosporine A (CsA)-based regimens.

Outcome Measures

The primary outcome of interest was a clinically diagnosed fracture >3 months-to-3 years after kidney transplantation. We identified fractures using Medicare billings claims based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM, through September 2015), and the Tenth Revision (ICD-10-CM,

starting October 2015) diagnosis codes (250.x and E08-E13, respectively) that occurred or persisted >3 months-to-3 years after transplantation (Table S1). Mortality was identified using the transplant registry data. The cost of care was quantified based on aggregated Part A and B claims from discharge to the third year after transplantation.

Statistical Analysis

The clinical characteristics of the study sample were described as proportions. We grouped continuous variables into clinically relevant categories. Rather than imputing missing data, for the small number of absent values, we classified the missing data as "not reported" and included a missing category in the regression analyses. We compared the distributions of clinical characteristics according to immunosuppression regimen using the χ^2 test.

The cumulative incidence of fractures >3 months-to-3 years after kidney transplantation with each immunosuppression regimen was estimated using the Kaplan-Meier method, with the origin time for models at 3 months after transplantation (i.e., after the period of immunosuppression classification), which was chosen with the expectation that immunosuppression generally stabilizes by this point. The incidence of fractures with each immunosuppression regimen was compared to incidence with the reference regimen of TMG or ALEM + triple therapy using the log-rank test. We modeled the associations (adjusted hazard ratios [aHRs] and 95% confidence intervals [CIs]) between the selection of immunosuppression regimen and the development of fractures using the Cox proportional hazard analysis with inverse probability treatment weighting (IPTW). IPTW uses propensity weights to create "analytic" samples that are more similar and allow better estimation of the independent impact of immunosuppression regimen selection on the development of fractures. To construct the weights, we modeled the probability of development of a fracture, comparing each immunosuppression regimen with the reference regimen (TMG or ALEM + triple therapy) based on the patients' age, sex, race, number of human leukocyte antigen mismatches, panel-reactive antibody, and hepatitis C virus status; the age of donor; the type of donor (living or deceased, by Kidney Donor Profile Index (KDPI) level). The weights were stabilized; a robust sandwich estimator was used to prevent the underestimation of variance. Good balance was achieved for all confounders (standardized absolute mean difference <0.2 for all covariates and overall difference <0.1 for all models).

The patients were followed for up to 3 years after transplantation, death, or loss of Medicare coverage. We performed prespecified subgroup analyses based on age (<55 vs ≥55 years) and sex and investigated the potential interaction of immunosuppression regimen with age and sex on the incidence of fractures. We also explored the impact of fracture as a time-dependent exposure on the risk of subsequent mortality using multivariable, time-varying Cox regression, including adjustments for donor and recipient factors, per previous methods.[7,21] Based on exposure time, the risk of mortality associated with fractures after kidney transplantation was classified into within 3 months and >3 months after the diagnosis of a fracture. Analyses stratified by age and sex were included, as per previous methods.[7,21]

The marginal cost impact of fractures on costs in years 1, 2, and 3 after transplantation were computed using ordinary least squares regression as follows: $E(Y) = \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_k X_k$, where E(Y) is the Medicare payments within a period of interest, X_k is the value of a given predictor variable, and β_k is the marginal costs associated with a 1-unit change in a given variable after adjustment for other observed factors in the model. Thus, for binary variables such as fractures, the β_k parameters quantify the marginal costs associated with the diagnosis, adjusted for the recipient, donor, and transplant factors. Cost period models were also adjusted for other baseline factors, as previously described.[29-31] The costs of death were included because death may be a consequence of a fracture.

A P value of <0.05 was considered statistically significant. The management and analysis of data were performed using SAS, version 9.4 (SAS Institute Inc.).

RESULTS

Sample Characteristics and the Use of Immunosuppression Regimens

Among 193,984 kidney transplant recipients in the study period, 67,362 had Medicare insurance at the time of transplantation. The patients in the study sample were largely similar to those in the overall population who have undergone kidney transplantation: 31,740 (47.1%) were aged ≥55 years, 40,723 (60.5%) were men, 30,875 (45.8%) were White, 20,200 (30.0%) were African American, 22,668 (33.7%) had a body mass index (BMI) of ≥30 kg/m^2, and 51,462 (76.4%) received dialysis for >24 months before kidney transplantation (Table S2). The reference regimen (TMG or ALEM + triple therapy) was the most commonly used regimen (30,134; 44.7%), followed by the TMG or ALEM + no Pred (13,055; 19.4%), IL2rAb + triple therapy (10,836; 16.1%), mTORi-based (5,043; 7.5%), and CsA-based (4,707; 7.0%) regimens. IL2rAb + no Pred (1,553; 2.3%) and Tac alone or Tac + Pred with any induction (2,034; 3.0%) were rarely used (Table 1).

Clinical Correlates of Posttransplantation Fractures

The incidence of fractures >3 months-to-3 years after kidney transplantation was 7.5%, which varied by sex (women, 8.8%; men, 6.7%), age (<55 years, 5.9%; ≥55 years, 9.3%), and other characteristics (Table 2). After adjustment for other donor and recipient characteristics, the adjusted risk of fractures remained elevated for older patients (≥55 years: aHR, 1.26; 95% CI, 1.18-1.35) and women (aHR, 1.42; 95% CI, 1.33-1.52). Conversely, Black race (aHR, 0.54; 95% CI, 0.49-0.59), Hispanic

Table 1. Distributions of Baseline Kidney Transplant Recipient Traits, Donor Type, and Transplant Factors According to Early Immunosuppression Regimen Use (N = 67,362)

Characteristic	TMG or ALEM + Triple Therapy (Reference) n (%)	IL2rAb + Triple Therapy n (%)	TMG or ALEM + No Pred n (%)	IL2rAb + No Pred n (%)	Tac, Tac + Pred n (%)	mTORi-based n (%)	CsA-based n (%)
Age, y							
18-54	17,355 (57.6)	5,084 (46.9)	6,540 (50.1)	537 (34.6)	1,027 (50.5)	2,827 (56.1)	2,252 (47.8)
≥55	12,779 (42.4)	5,752 (53.1)	6,515 (49.9)	1,016 (65.4)	1,007 (49.5)	2,216 (43.9)	2,455 (52.2)
Sex							
Male	17,242 (57.2)	6,987 (64.5)	8,196 (62.8)	994 (64.0)	1,247 (61.3)	3,200 (63.5)	2,857 (60.7)
Female	12,892 (42.8)	3,849 (35.5)	4,859 (37.2)	559 (36.0)	787 (38.7)	1,843 (36.6)	1,850 (39.3)
Race							
White	12,208 (40.5)	5,525 (51.0)	6,212 (47.6)	911 (58.7)	1,061 (52.2)	2,535 (50.3)	2,423 (51.5)
African American	10,777 (35.8)	2,517 (23.2)	3,596 (27.6)	260 (16.7)	548 (26.9)	1,467 (29.1)	1,035 (22.0)
Hispanic	5,454 (18.1)	1,961 (18.1)	2,509 (19.2)	270 (17.4)	292 (14.4)	775 (15.4)	817 (17.4)
Other	1,695 (5.6)	833 (7.7)	738 (5.7)	112 (7.2)	133 (6.5)	266 (5.3)	432 (9.2)
Employment status							
Working	5,178 (17.2)	1,895 (17.5)	2,568 (19.7)	290 (18.7)	440 (21.6)	855 (17.0)	697 (14.8)
Not working	22,413 (74.4)	8,131 (75.0)	9,342 (71.6)	1,176 (75.7)	1,406 (69.1)	3,815 (75.7)	3,409 (72.4)
Not reported	2,543 (8.4)	810 (7.5)	1,145 (8.8)	87 (5.6)	188 (9.2)	373 (7.4)	601 (12.8)
Body mass index, kg/m^2							
<18.5	734 (2.4)	269 (2.5)	211 (1.6)	43 (2.8)	58 (2.9)	120 (2.4)	109 (2.3)
18.5-24.9	9,018 (29.9)	3,360 (31.0)	3,549 (27.2)	472 (30.4)	618 (30.4)	1,498 (29.7)	1,398 (29.7)
25.0-29.9	9,683 (32.1)	3,727 (34.4)	4,178 (32.0)	562 (36.2)	656 (32.3)	1,740 (34.5)	1,505 (32)
≥30.0	10,328 (34.3)	3,386 (31.3)	4,687 (35.9)	463 (29.8)	624 (30.7)	1,590 (31.5)	1,590 (33.8)
Not reported	371 (1.2)	94 (0.9)	430 (3.3)	13 (0.8)	78 (3.8)	95 (1.9)	105 (2.2)
Comorbid conditions							
Hypertension	9,531 (31.6)	3,495 (32.3)	4,267 (32.7)	530 (34.1)	652 (32.1)	1,834 (36.4)	1,593 (33.8)
Diabetes mellitus	10,246 (34.0)	4,106 (37.9)	5,155 (39.5)	665 (42.8)	761 (37.4)	1,790 (35.5)	1,892 (40.2)
Coronary artery disease	997 (3.3)	459 (4.2)	541 (4.1)	103 (6.6)	94 (4.6)	293 (5.8)	270 (5.7)
Cerebral vascular disease	159 (0.5)	75 (0.7)	113 (0.9)	12 (0.8)	7 (0.3)	51 (1.0)	50 (1.1)
Peripheral vascular disease	2,146 (7.1)	901 (8.3)	1,033 (7.9)	154 (9.9)	119 (5.9)	355 (7.0)	397 (8.4)
COPD	113 (0.4)	47 (0.4)	72 (0.6)	16 (1.0)	11 (0.5)	38 (0.8)	39 (0.8)
Hepatitis C positive	1,558 (5.2)	644 (5.9)	520 (4.0)	104 (6.7)	115 (5.7)	238 (4.7)	369 (7.8)
Kidney functional status, activities with:							
No assistance	26,057 (86.5)	8,948 (82.6)	11,741 (89.9)	1,321 (85.1)	1,706 (83.9)	3,900 (77.3)	3,935 (83.6)
Some assistance	2,860 (9.5)	1,118 (10.3)	781 (6.0)	130 (8.4)	129 (6.3)	842 (16.7)	418 (8.9)
Total assistance	523 (1.7)	233 (2.2)	303 (2.3)	24 (1.6)	22 (1.1)	72 (1.4)	74 (1.6)
Not reported	694 (2.3)	537 (5.0)	230 (1.8)	78 (5.0)	177 (8.7)	229 (4.5)	280 (6.0)

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Table 1 (Cont'd). Distributions of Baseline Kidney Transplant Recipient Traits, Donor Type, and Transplant Factors According to Early Immunosuppression Regimen Use (N = 67,362)

Characteristic	TMG or ALEM + Triple Therapy (Reference) n (%)	IL2rAb + Triple Therapy n (%)	TMG or ALEM + No Pred n (%)	IL2rAb + No Pred n (%)	Tac, Tac + Pred n (%)	mTORi-based n (%)	CsA-based n (%)
Cause of ESKD							
Hypertension	6,985 (23.2)	2,276 (21.0)	2,886 (22.1)	294 (18.9)	399 (19.6)	1,203 (23.9)	942 (20.0)
Diabetes mellitus	8,360 (27.7)	3,409 (31.5)	4,382 (33.6)	562 (36.2)	598 (29.4)	1,438 (28.5)	1,535 (32.6)
Glomerulonephritis	9,815 (32.6)	3,137 (29.0)	3,609 (27.6)	411 (26.5)	619 (30.4)	1,492 (29.6)	1,380 (29.3)
Polycystic kidney disease	2,202 (7.3)	841 (7.8)	1,128 (8.6)	111 (7.2)	179 (8.8)	437 (8.7)	352 (7.5)
Other	2,772 (9.2)	1,173 (10.8)	1,050 (8.0)	175 (11.3)	239 (11.8)	473 (9.4)	498 (10.6)
Duration of dialysis, mo							
None (pre-emptive)	1,163 (3.9)	913 (8.4)	899 (6.9)	182 (11.7)	173 (8.5)	309 (6.1)	379 (8.1)
>0-24	4,157 (13.8)	2,466 (22.8)	2,437 (18.7)	438 (28.2)	428 (21.0)	987 (19.6)	933 (19.8)
25-60	10,544 (35.0)	3,934 (36.3)	5,225 (40.0)	537 (34.6)	766 (37.7)	1,939 (38.5)	1,637 (34.8)
>60	14,264 (47.3)	3,518 (32.5)	4,487 (34.4)	394 (25.4)	663 (32.6)	1,806 (35.8)	1,748 (37.1)
Not reported	6 (0.0)	5 (0.1)	7 (0.1)	2 (0.1)	4 (0.2)	2 (0.0)	10 (0.2)
Most current PRA level, %							
<10	18,092 (60.0)	8,632 (79.7)	10,023 (76.8)	1,247 (80.3)	1,473 (72.4)	3,542 (70.2)	3,428 (72.8)
10-79	6,332 (21)	1,370 (12.6)	1,799 (13.8)	164 (10.6)	322 (15.8)	795 (15.8)	700 (14.9)
≥80	4,994 (16.6)	423 (3.9)	785 (6.0)	34 (2.2)	153 (7.5)	371 (7.4)	350 (7.4)
Not reported	716 (2.4)	411 (3.8)	448 (3.4)	108 (7.0)	86 (4.2)	335 (6.6)	229 (4.9)
HLA mismatches							
0 A, B, DR	1,831 (6.1)	818 (7.6)	791 (6.1)	237 (15.3)	153 (7.5)	350 (6.9)	409 (8.7)
0 DR	3,285 (10.9)	1,093 (10.1)	1,494 (11.4)	158 (10.2)	227 (11.2)	511 (10.1)	512 (10.9)
Other	25,018 (83.0)	8,925 (82.4)	10,770 (82.5)	1,158 (74.6)	1,654 (81.3)	4,182 (82.9)	3,786 (80.4)
Cold ischemia time, h							
≤12	11,398 (37.8)	5,137 (47.4)	4,999 (38.3)	736 (47.4)	811 (39.9)	2,126 (42.2)	1,862 (39.6)
13-24	12,749 (42.3)	3,917 (36.2)	4,769 (36.5)	486 (31.3)	757 (37.2)	1,902 (37.7)	1,764 (37.5)
25-36	3,919 (13.0)	1,056 (9.8)	1,670 (12.8)	118 (7.6)	237 (11.7)	568 (11.3)	543 (11.5)
≥37	897 (3.0)	163 (1.5)	678 (5.2)	25 (1.6)	60 (3.0)	147 (2.9)	102 (2.2)
Not reported	1,171 (3.9)	563 (5.2)	939 (7.2)	188 (12.1)	169 (8.3)	300 (6.0)	436 (9.3)
Previous organ transplant							
Yes	5,993 (19.9)	1,009 (9.3)	1,160 (8.9)	133 (8.6)	336 (16.5)	786 (15.6)	714 (15.2)
No	24,141 (80.1)	9,827 (90.7)	11,895 (91.1)	1,420 (91.4)	1,698 (83.5)	4,257 (84.4)	3,993 (84.8)
Donor type							
Living donor	5,301 (17.6)	3,137 (29.0)	3,425 (26.2)	600 (38.6)	490 (24.1)	1,184 (23.5)	1,193 (25.4)
Deceased, KDPI < 20	4,962 (16.5)	1,824 (16.8)	1,924 (14.7)	231 (14.9)	420 (20.7)	732 (14.5)	775 (16.5)
Deceased, KDPI 20-85	17,400 (57.7)	5,062 (46.7)	6,562 (50.3)	594 (38.3)	962 (47.3)	2,585 (51.3)	2,381 (50.6)

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Table 1 (Cont'd). Distributions of Baseline Kidney Transplant Recipient Traits, Donor Type, and Transplant Factors According to Early Immunosuppression Regimen Use (N = 67,362)

Characteristic	TMG or ALEM + Triple Therapy (Reference) n (%)	IL2rAb + Triple Therapy n (%)	TMG or ALEM + No Pred n (%)	IL2rAb + No Pred n (%)	Tac, Tac + Pred n (%)	mTORi-based n (%)	CsA-based n (%)
Deceased, KDPI > 85	2,471 (8.2)	813 (7.5)	1,144 (8.8)	128 (8.2)	162 (8.0)	542 (10.8)	358 (7.6)
Transplantation era							
2005-2008	6,402 (21.3)	2,929 (27)	3,722 (28.5)	584 (37.6)	875 (43.0)	2,206 (43.7)	2,209 (46.9)
2009-2012	11,692 (38.8)	4,220 (38.9)	5,278 (40.4)	644 (41.5)	726 (35.7)	1,691 (33.5)	1,628 (34.6)
2013-2016	12,040 (40.0)	3,687 (34.0)	4,055 (31.1)	325 (20.9)	433 (21.3)	1,146 (22.7)	870 (18.5)

Note: Data are presented as n (column %). $P < 0.05$ for the comparison of the distributions of immunosuppression regimens across all traits because of the large sample size. "Other race" includes Asian, Native American, Pacific Islander, and multiracial. Triple therapy includes tacrolimus + mycophenolic acid or azathioprine + prednisone.
Abbreviations: ALEM, alemtuzumab; COPD, chronic obstructive pulmonary disease; CsA, cyclosporine A; ESKD, end-stage kidney disease; HLA, human leukocyte antigen; IL2rAb, interleukin 2 receptor antibody; KDPI, kidney donor profile index; mTORi, mammalian target of rapamycin inhibitor; PRA, panel-reactive antibody; Pred, prednisone; Tac, tacrolimus; TMG, antithymocyte globulin.

ethnicity (aHR, 0.67; 95% CI, 0.61-0.74), other race (aHR, 0.55; 95% CI, 0.48-0.64), and elevated BMI >30 kg/m^2 (aHR, 0.90; 95% CI, 0.83-0.988) were protective against fracture risk.

Associations of Fracture With Mortality

Overall, mortality after kidney transplantation was significantly increased in patients who experienced a fracture >3 months-to-3 years after the kidney transplantation (Fig 1). The risk of death in patients diagnosed with a fracture within the first 3 months of diagnosis was >3-fold higher than that in patients without a fracture (aHR for death, 3.06; 95% CI, 2.45-3.81; Table 3). After 3 months, the risk of death remained elevated in patients with fractures (aHR, 1.68; 95% CI, 1.48-1.91). Other characteristics associated with the risk of death included older age (aHR, 1.03; 95% CI, 1.03-1.04; per year), female sex (aHR, 0.90; 95% CI, 0.87-0.93), Black race (aHR, 0.87; 95% CI, 0.83-0.90), Hispanic ethnicity (aHR, 0.68; 95% CI, 0.66-0.73), and other race (aHR, 0.71; 95% CI, 0.66-0.76). When the risk of death within 3 months was examined within subgroups, fractures were associated with a greater relative risk of death in men (*vs.* women) and older adults (vs. younger adults) (Figure 1; Table 3).

Impact of Fractures on Medicare Payments

After transplantation, the mean spending varied significantly according to the presence or absence of fracture diagnosis. Fractures within the first year resulted in a risk-adjusted incremental cost of care of $5,122 (Fig S2). In the second year after transplantation, a new fracture was associated with increased spending of $10,890, whereas patients with fractures in the prior year incurred $1,929 higher year 2 expenditures. In the third year after transplantation, new fractures were associated with incremental spending of $11,083, and prior fractures were associated with $1,844 higher year 3 Medicare payments. Other factors associated with increased spending included age, sex, cold ischemic time, kidney donor profile index, and diagnosis (Table S3).

Incidence of Fractures According to Immunosuppression Regimen, Age, and Sex

The choice of immunosuppression regimen significantly affects the incidence of fractures across all ages (Fig 2A) and both sexes (Fig 2B). Furthermore, the impact of immunosuppression varied among subgroups. Younger patients (<55 years) treated with TMG or ALEM + no Pred experienced significantly fewer fractures than those who received the reference immunosuppression regimen (TMG or ALEM + triple therapy; 4.0% vs 6.3%, respectively; $P < 0.0001$). No other regimen was associated with significantly lower rates, although the mTORi-based, CsA-based, and Tac + Pred regimens were all associated with a numerically greater incidence. In the multivariable, risk-adjusted analysis, both TMG or ALEM + no Pred (aHR, 0.63; 95% CI, 0.54-0.73) and IL2rAb + triple therapy (aHR, 0.81; 95% CI, 0.70-0.94) reduced the risk of fractures (Fig 2A).

Table 2. Cumulative Incidence of Fractures >3 Months-to-3 Years After Kidney Transplantation by Baseline Clinical Characteristics and Adjusted Correlates of Fracture Risk

Baseline Characteristic	Cumulative Incidence of Fractures >3 m-to-3 y After Kidney Transplantation % (95% CI)	Adjusted Correlates of Fracture Risk > 3 m-to-3 y After Kidney Transplantation aHR (95% CI)
Age, y		
18-54	5.9 (5.6-6.2)	Reference
≥55	9.3 (8.9-9.7)[a]	1.26 (1.18-1.35)[a]
Sex		
Male	6.7 (6.4-7.0)	Reference
Female	8.8 (8.4-9.2)[a]	1.42 (1.33-1.52)[a]
Race		
White	9.4 (9.0-9.8)	Reference
African American	5.4 (5.0-5.7)[a]	0.54 (0.49-0.59)[a]
Hispanic	6.7 (6.2-7.2)[a]	0.67 (0.61-0.74)[a]
Other	5.6 (4.9-6.5)[a]	0.55 (0.48-0.64)[a]
Employment status		
Working	5.6 (5.1-6.1)[a]	0.78 (0.71-0.86)[a]
Not working	8.1 (7.8-8.4)	Reference
Not reported	6.3 (5.6-7.0)[a]	0.84 (0.75-0.95)[b]
Body mass index, kg/m^2		
<18.5	7.9 (6.5-9.6)	1.10 (0.89-1.36)
18.5-24.9	7.4 (7.0-7.8)	Reference
25.0-29.9	7.5 (7.1-7.9)	0.94 (0.87-1.02)
≥30.0	7.7 (7.3-8.1)	0.90 (0.83-0.98)[b]
Not reported	6.4 (5.0-8.0)	0.71 (0.55-0.92)[b]
Comorbid conditions		
Hypertension	6.4 (6.0-6.7)[a]	0.87 (0.77-0.98)[b]
Diabetes mellitus	10.4 (9.9-10.8)[a]	1.22 (1.07-1.39)[b]
Coronary artery disease	8.9 (7.9-10.2)[b]	1.06 (0.90-1.24)
Cerebral vascular disease	9.4 (6.9-12.7)	1.08 (0.77-1.51)
Peripheral vascular disease	11.3 (10.3-12.3)[a]	1.25 (1.13-1.39)[a]
COPD	10.3 (7.3-14.4)	1.15 (0.79-1.66)
Hepatitis C positive	9.2 (8.2-10.4)[c]	1.30 (1.14-1.49)[a]
Kidney functional status, activities with:		
No assistance	7.1 (6.9-7.4)	Reference
Some assistance	9.7 (8.8-10.6)[a]	1.20 (1.09-1.33)[c]
Total assistance	8.9 (7.1-11)	1.16 (0.92-1.45)
Not reported	10.8 (9.4-12.3)[a]	1.44 (1.23-1.69)[a]
Cause of ESKD		
Hypertension	5.7 (5.3-6.2)	1.20 (1.04-1.38)[b]
Diabetes mellitus	11.0 (10.5-11.5)[a]	1.61 (1.40-1.86)[a]
Glomerulonephritis	5.6 (5.2-5.9)	Reference
Polycystic kidney disease	7.2 (6.5-8.1)[a]	1.11 (0.97-1.27)
Other	7.2 (6.5-8.0)[a]	1.09 (0.96-1.23)
Duration of dialysis, mo		
None (pre-emptive)	7.8 (7.0-8.8)	0.87 (0.74-1.01)
>0-24	8.4 (7.9-9.0)	Reference
25-60	7.6 (7.2-8.0)[b]	0.96 (0.88-1.05)
>60	6.9 (6.6-7.3)[a]	1.01 (0.92-1.12)
Not reported	15.0 (6.5-32.5)	1.73 (0.72-4.16)
Most current PRA level, %		
<10	7.4 (7.1-7.7)	Reference
10-79	7.8 (7.3-8.4)	1.02 (0.94-1.12)
≥80	6.7 (6.0-7.4)	0.87 (0.77-0.98)[b]
Not reported	9.8 (8.6-11.2)[a]	1.15 (0.98-1.34)

(Continued)

Table 2 (Cont'd). Cumulative Incidence of Fractures >3 Months-to-3 Years After Kidney Transplantation by Baseline Clinical Characteristics and Adjusted Correlates of Fracture Risk

Baseline Characteristic	Cumulative Incidence of Fractures >3 m-to-3 y After Kidney Transplantation % (95% CI)	Adjusted Correlates of Fracture Risk > 3 m-to-3 y After Kidney Transplantation aHR (95% CI)
HLA mismatches		
0 A, B, DR	8.6 (7.7-9.5)[b]	1.07 (0.95-1.2)
0 DR	7.4 (6.8-8.2)	1.02 (0.92-1.12)
Other	7.4 (7.2-7.7)	Reference
Cold ischemia time, h		
≤12	7.7 (7.4-8.1)	Reference
13-24	7.5 (7.1-7.8)	0.91 (0.84-0.99)[b]
25-36	7.5 (6.8-8.2)	0.92 (0.82-1.03)
≥37	7.0 (5.8-8.4)	0.85 (0.7-1.04)
Not reported	6.9 (6.0-7.8)	0.86 (0.75-1.00)[b]
Previous organ transplant		
Yes	7.9 (7.3-8.5)	1.18 (1.07-1.31)[b]
No	7.4 (7.2-7.7)	Reference
Donor type		
Living donor	7.1 (6.6-7.6)	0.84 (0.76-0.94)[b]
Deceased, KDPI < 20	7.3 (6.7-7.9)	0.95 (0.86-1.04)
Deceased, KDPI 20-85	7.4 (7.1-7.7)	Reference
Deceased, KDPI > 85	9.8 (8.9-10.7)[a]	1.17 (1.05-1.30)[b]
Transplantation era		
2005-2008	7.9 (7.5-8.3)	Reference
2009-2012	8.1 (7.8-8.5)	1.02 (0.95-1.10)
2013-2016	6.0 (5.6-6.5)[a]	0.73 (0.67-0.80)[a]

Note: "Other race" includes Asian, Native American, Pacific Islander, and multiracial.
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ESKD, end-stage kidney disease; HLA, human leukocyte antigen; KDPI, kidney donor profile index; PRA, panel-reactive antibody.
[a] $P < 0.0001$.
[b] $0.001 < P \leq 0.05$.
[c] $0.0001 \leq P < 0.001$.

Among older patients (≥55 years), those treated with TMG or ALEM + no Pred (7.4%) or IL2rAb + no Pred (8.7%) had lower rates of fractures than those treated with the reference immunosuppression regimen (9.0%; Fig 3A). The rates of fractures among older patients treated with Tac, Tac + Pred (11.3%), mTORi-based (12.1%), and CsA-based (11.7%) immunosuppression regimens were numerically higher. However, in the multivariable, risk-adjusted analyses, only those who received TMG or ALEM + no Pred had a statistically lower risk of fractures (aHR, 0.83; 95% CI, 0.74-0.94).

The impact of immunosuppression on the risk of fractures also differed by sex (Fig 3B). Women had lower rates of fractures when they were placed on the steroid-sparing regimens. Compared to the risk of fractures with TMG or ALEM + triple therapy, the risk of fractures was 32% lower (aHR, 0.68; 95% CI, 0.46-1.00) among women treated with IL2rAb + No Pred and 29% lower (aHR, 0.71; 95% CI, 0.62-0.82) among women placed on the TMG or ALEM + no Pred regimen. Conversely, only men treated with TMG or ALEM + no Pred had lower rates of fractures (aHR, 0.77; 95% CI, 0.68-0.87) compared to those who received the reference regimen, whereas men treated with Tac, Tac + Pred, CsA-based, or mTORi-based regimens had a statistically increased risk of fractures compared with those placed on the reference regimen.

DISCUSSION

Fractures can result in significant short- and long-term morbidity and mortality among kidney transplant recipients.[1-3,23] In this national analysis, older patients and women were particularly at risk, with almost 10% of older patients experiencing a fracture. Among patients with a fracture, the risk of death was tripled in the 3 months after the event, and medical spending increased dramatically following the episode and remained consistently higher than that for patients without fractures. Despite the evidence of the benefits of strategies for the minimization of immunosuppression, the most common immunosuppression regimen prescribed after kidney transplantation is still triple therapy (48.7% in those aged <55 years; 40% in those aged ≥55 years), exposing many kidney transplant recipients to the long-term risks of glucocorticoids. Compared with the reference group (treated with TMG or ALEM + triple therapy), the only group who experienced a lower incidence of fractures >3 months-to-3 years after kidney transplantation, irrespective of recipient age, were those who received TMG or ALEM + no Pred. Patients

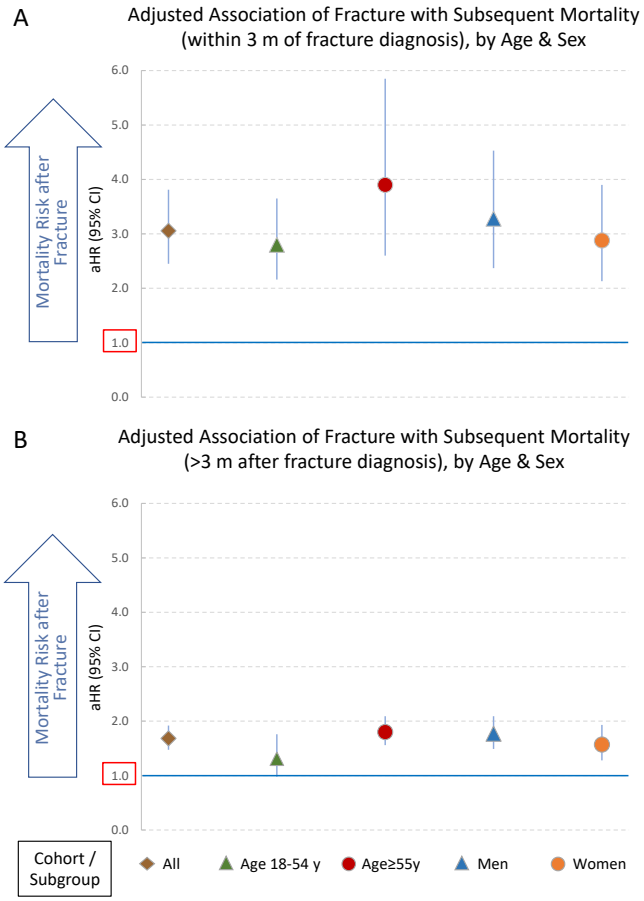

Figure 1. The adjusted risk of death following the diagnosis of a fracture >3 months-to-3 years after kidney transplantation. Effect estimates reflect the impact of the diagnosis of a fracture as a time-varying predictor of subsequent death, partitioned in exposure time (A) within 3 months and (B) ≥3 months after the diagnosis of fracture. Risk was stratified by age and sex. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; mo, month; y, year.

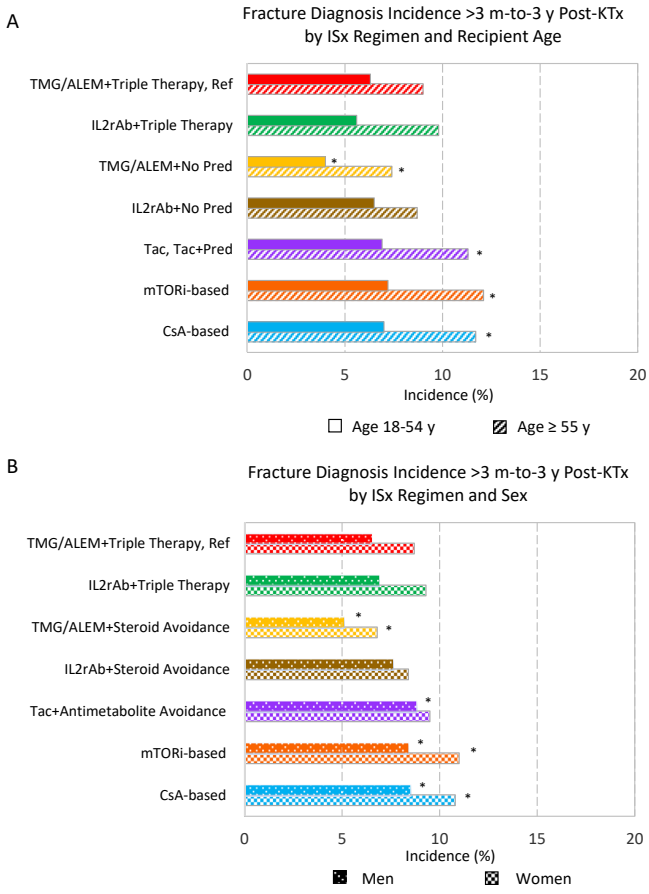

Figure 2. The incidence of the diagnosis of a fracture >3 months-to-3 years after kidney transplantation across immunosuppressive regimens, stratified by (A) age and (B) sex. Abbreviations: ALEM, alemtuzumab; CsA, cyclosporine A; IL2rAb, interleukin 2 receptor antibody; ISx, immunosuppression; KTx, kidney transplant; mo, month; mTORi, mammalian target of rapamycin inhibitor; Ref, reference; Tac, tacrolimus; TMG, antithymocyte globulin; y, year.

aged <55 years treated with IL2rAb + triple therapy and women placed on the IL2rAb + no Pred regimen also experienced lower risks of fractures. All other immunosuppression regimens were associated with equivalent or higher incidences of fractures.

Table 3. Mortality Risk Associated With Fracture >3 Months-to 3 Years After Kidney Transplantation Modeled as a Time-Varying Covariate, and Partitioned by Exposure Time Within 3 Months and >3 Months After Fracture Diagnosis

Sample Strata	aHR (95% CI) ≤3 m After Fracture	aHR (95% CI) >3 m After Fracture
All	3.06 (2.45-3.81)[a]	1.68 (1.48-1.92)[a]
Age 18-54 y	2.80 (2.16-3.65)[b]	1.31 (0.98-1.76)
Age ≥ 55 y	3.90 (2.60-5.85)[a]	1.80 (1.56-2.09)[a]
Men	3.28 (2.37-4.53)[c]	1.77 (1.49-2.09)[c]
Women	2.88 (2.13-3.90)[a]	1.57 (1.28-1.93)[a]

Note: The overall and stratified models are adjusted for all other baseline recipient, donor, and transplant factors (Table 1), including continuous age.
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.
[a]$0.001 < P \leq 0.05$.
[b]$P < 0.0001$.
[c]$0.0001 \leq P < 0.001$.

CKD-MBD is a systemic disorder characterized by abnormalities in the metabolism of calcium, phosphorus, parathyroid hormone, fibroblast growth factor-23, and vitamin D; abnormalities in bone turnover and mineralization; and extraskeletal calcifications. The retention of phosphate has long been thought to be the initial trigger for many of these components.[32] Secondary hyperparathyroidism, a major feature of CKD-MBD, occurs in response to the retention of phosphate, a decreased concentration of free ionized calcium, a decreased concentration of vitamin D, an increased concentration of fibroblastic growth factor-23, and reduced expression of vitamin D and calcium-sensing receptors.[33,34] In patients with advancing kidney disease, bone lesions are progressive and lead to complications such as fractures and bone pains, noted when patients undergo maintenance renal replacement therapies.[35] Posttransplantation bone disease is significantly different from the range of CKD-MBD seen

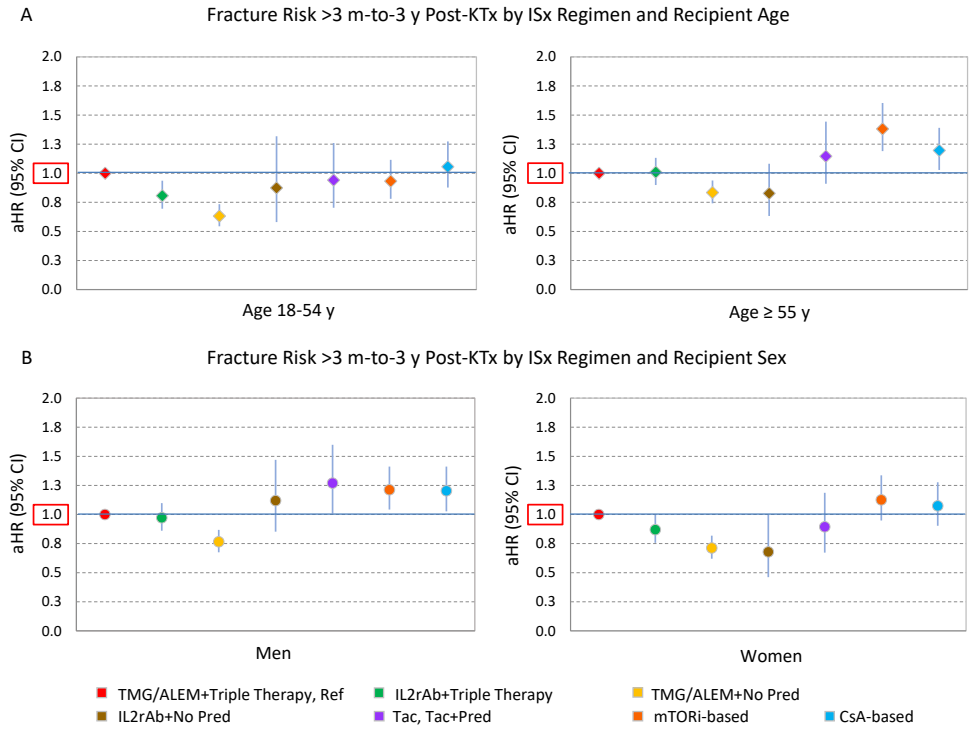

Figure 3. Adjusted associations of immunosuppressive regimens with the risk of a fracture >3 months-to-3 years after kidney transplantation stratified by (A) age and (B) sex. Interaction between immunosuppression and recipient age: interleukin 2 receptor antibody + triple therapy ($P = 0.006$), antithymocyte globulin or alemtuzumab + no prednisone ($P = 0.003$), and mammalian target of rapamycin inhibitor-based ($P = 0.003$) regimens. Interaction between immunosuppression and recipient gender: interleukin 2 receptor antibody + no prednisone regimen ($P = 0.04$). Abbreviations: aHR, adjusted hazard ratio; ALEM, alemtuzumab; CsA, cyclosporine A; CI, confidence interval; IL2rAb, interleukin 2 receptor antibody; ISx, immunosuppression; KTx, kidney transplant; m, month; mTORi, mammalian target of rapamycin inhibitor; Ref, reference; Tac, tacrolimus; TMG, antithymocyte globulin; y, year.

before transplantation and is characterized by changes in bone quality and density as well as mineral metabolism, which contribute to the increased risk of fractures.[36] Following successful kidney transplantation, several key changes in mineral metabolism occur. There is rapid loss of bone mass in the early posttransplantation period, which frequently affects the trabecular bone because of decreased bone formation as a result of glucocorticoid therapy.[17] The level of parathyroid hormone normalizes within 12 months after transplantation in 56.9% of patients,[37] and there are improvements in the levels of calcium, phosphorus, and 1,25-dihydroxy vitamin D, which are associated with the improvements of kidney function.[38] Despite these improvements, it is important to recognize that mineral homeostasis is complex and that bone remodeling continues after transplantation.[36] In a prospective cohort study of 27 kidney transplant recipients who consented to a bone biopsy while still receiving dialysis and another bone biopsy 2 years after transplantation, the rate of bone turnover declined after kidney transplantation.[39]

Previous studies have identified many risk factors for fractures among kidney transplant recipients, including female sex, older age, lower BMI, White race, diabetes, longer duration of dialysis, poor allograft function, persistent hyperparathyroidism, uremia, acidosis, and immunosuppression therapy, especially glucocorticoids.[12,20,22,40-44] Among these risk factors, older age is a strong and consistent risk factor for fractures after kidney transplantation,[11,12,20,22,40-44] as also demonstrated in our study. In the current study, we assessed the impact of various immunosuppression regimens on the risk of fractures and identified a significant reduction in the risk of fractures among older (≥55 years) adults who received the TMG or ALEM + no Pred regimen. The skeletal effects of glucocorticoids include decreases in the replication, differentiation, and life span of osteoblasts.[13,43,45] Additionally, glucocorticoids inhibit genes that encode type I collagen, osteocalcin, insulin-like growth factors, bone morphogenetic and other bone matrix proteins, transforming growth factor-beta, and the receptor activator for nuclear factor kappa B ligand.[46,47] These combined actions result in reduced bone formation and bone density, especially in the trabecular bone, and are related to cumulative steroid exposure.[13,17,48] Although the adverse effects of glucocorticoids on bone health among kidney transplant recipients have been clearly demonstrated, data on the effects of the early withdrawal or avoidance of steroids on preserved bone mass among patients who have undergone kidney transplantation are limited to several small studies,[49-52] and data on the risk of fractures have been

limited. The findings from our current study suggest protective effects of the early withdrawal or avoidance of steroids on the risk of fractures in all age and sex subgroups of kidney transplant recipients. Given recent evidence suggesting the beneficial effects of lower-intensity immunosuppression regimens (eg, early withdrawal or avoidance of steroids) on patient and graft survival among older kidney transplant recipients[53] and that older kidney transplant recipients are more susceptible to immunosuppression complications such as infection and malignancies,[54] the findings of our study also support the use of the early steroid withdrawal or avoidance for bone health among older kidney transplant recipients. Considering the conflicting and limited data on safety and clinical efficacy of treatments (including bisphosphonates, vitamin D, or denosumab) to reduce the risk of fractures after kidney transplantation,[55-57] the minimization of the risk of fractures with the early withdrawal or avoidance of steroids may provide an optimal strategy for older populations who have undergone kidney transplantation.

The effect of calcineurin inhibitors, which have become a mainstay of posttransplantation maintenance immunosuppression regimens, on bone metabolism is unclear. Calcineurin inhibitors have been suggested to stimulate the loss of bone mass independent of glucocorticoid therapy, with high-turnover bone metabolism noted in rat models.[58-61] However, results from human studies have not shown these effects.[13,43,45] Although the combination of calcineurin inhibitors and corticosteroids is associated with profound uncoupling of bone remodeling and rapid bone loss,[13,43,45] studies of kidney transplant recipients receiving CsA and a steroid-free regimen have not demonstrated significant bone loss.[7,62,63] In a small group of kidney transplant recipients followed for 1 year, those who received Tac and low doses of steroids had a slight net increase in the bone mineral density compared those who received CsA and normal doses of steroids, who experienced a decrease in bone mineral density.[64] Thus, these findings could have been confounded by the impact of glucocorticoids in these regimens. The effects of other immunosuppression agents have not been studied well. In rat models, the short-term use of mycophenolate mofetil did not result in decreased bone volume.[65] In humans, patients who received CsA showed the evidence of lesser bone turnover and bone resorption compared with those who received sirolimus.[66] Our study found an increased incidence of fractures with Tac, Tac + Pred, CsA-based, and mTORi-based regimens only in male kidney transplant recipients, and future studies evaluating underlying mechanisms are needed. The study identified a lower risk of fractures in younger patients and women treated with IL-2rAb + triple therapy than in those treated with TMG or ALEM + triple therapy. It is possible that these associations are driven by the clinical belief that these patients have less immunologic risk, allowing more rapid weaning of the total immunosuppression exposure.

Previous studies have shown that kidney transplant recipients who sustain a fracture have an increased risk of mortality compared with the general population.[1,23] Our analysis confirms that patients who are diagnosed with a fracture after kidney transplantation have a 3-fold increase in the risk of death during the 3 months after the event. These analyses could not determine the etiology of the increased mortality. It is possible that this association could be related to deterioration of health because of immobilization, the risk of death if fracture repair required surgery, or complications arising from the fractures themselves. Irrespective of the cause of death, it is imperative to recognize fractures as a factor that affects posttransplantation survival and that every measure possible is taken to prevent a fracture.

There are limitations to this study and its interpretation. First, bone health before transplantation plays a major role in the risk of fractures after transplantation. It is difficult to assess or classify the pretransplantation bone health status of kidney transplant recipients, especially in registry data.[32] Second, immunosuppression choice is highly influenced by center practices and protocols.[67] Because the US Renal Data System database does not provide center identifiers, we could not assess the impact of center on differences in the outcomes of immunosuppression. Third, the choice of immunosuppression regimen might have been affected by uncaptured risk factors in the database, such as prior rejection episodes, other donor characteristics, intolerance of standard medications, or social determinants of health. This analysis also focused on the early administration of immunosuppression (within 3 months). Patients who had fractures may have been administered steroids after the first 3 months of transplantation because of episodes of rejection. Lastly, our analysis did not differentiate among types of fractures. Fractures of the pelvis or hip, vertebra, and lower leg have been shown to be the most prevalent types of fractures based on Medicare data from patients receiving hemodialysis.[68] It is not possible to determine whether the relative risks and benefits of immunosuppression regimens differ by the location of fractures. However, regardless of the location, fractures identified using this analytic method were associated with clinically significant impacts on patient survival and spending. Despite these limitations, the inferences presented in this analysis reflect actual risks in real-world practice.

In summary, fractures after kidney transplantation negatively affect posttransplantation survival and healthcare costs. Immunosuppression plays an important role in determining the risk of a fracture after transplantation. The incidence of fractures >3 months-to-3 years after kidney transplantation is highest in older adults and women. TMG or ALEM + no Pred substantially reduced the risk of fractures in both higher and lower-risk groups. A strong consideration of the risks of complications such as fractures, along with the risk of rejection, is necessary when choosing the appropriate immunosuppressive regimen to optimize posttransplantation outcomes.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Patient flowchart.

Figure S2: Adjusted incremental cost of fracture occurring in the first, second, or third year posttransplant (in period) and incremental cost of patient care for patients who sustained fractures in prior periods.

Table S1: International Classification of Disease, Clinical Modification, Diagnosis Codes Used to Define Medical Diagnoses From Billing Claims Data.

Table S2: Characteristics of Patients in the Study Sample Compared to Kidney Transplant Recipients Not Included in the Cohort.

Table S3: Associations of Fracture >3 Months-to-3 Years After Kidney Transplantation and Other Clinical Factors With Costs After Transplant.

Table S4: Distributions of Baseline Patient, Donor, and Transplant Factors According to Early Immunosuppression Regimen Use Among Younger Adult Kidney Transplant Recipients (Age 18-54 Years; N = 35,622).

Table S5: Distributions of Baseline Patient, Donor, and Transplant Factors According to Early Immunosuppression Regimen Use Among Older Adult Kidney Transplant Recipients (Age ≥55 Years; N = 31,740).

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What are the clinical and economic implications of fractures in kidney transplant recipients?

Kidney Medicine

Methods

Retrospective database study

US Renal Data System & Medicare billing claims
2005 - 2016

N = 67,362 adult kidney transplant recipients (KTx) with Medicare insurance

Primary outcome: Fracture development
> 3months-to-3years after KTx

Results

Fracture risk (aHR, 95% CI)

Women (vs. men)		**1.42** (1.33, 1.52)
Age ≥ 55 (vs. < 55)		**1.26** (1.18, 1.35)
TMG/ALEM +early steroid withdrawal (vs. TMG/ALEM +triple therapy)	**Age < 55**	**0.63** (0.54, 0.73)
	Age ≥ 55	**0.83** (0.74, 0.94)

Mortality risk at ≤3 months after fracture: **3.06** (2.45, 3.81)

Medicare spending associated with fractures within:

1st year after KTx	**$5,122**
2nd year after KTx	**$10,890**
3rd year after KTx	**$11,082**

TMG – anti-thymocyte globulin; **ALEM –** alemtuzumab;
Triple therapy – tacrolimus + mycophenolic acid/azathioprine + prednisone

Conclusion: Fracture after KTx is associated with significantly increased fracture risk and costs. Early steroid withdrawal after induction with TMG/ALEM reduces the risk of fracture after KTx and should be considered for high-risk patients including older adults and women.

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