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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk factors for fracture in adult kidney transplant recipients

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Abstract

AIM: To determine the general and transplant-specific risk factors for fractures in kidney transplant recipients.

METHODS: We conducted a cohort study of all adults who received a kidney-only transplant (n = 2723) in Ontario, Canada between 2002 and 2009. We used multivariable Cox proportional hazards regression to determine general and transplant-specific risk factors for major fractures (proximal humerus, forearm, hip, and clinical vertebral). The final model was established using the backward elimination strategy, selecting risk factors with a P-value $\leqslant$ 0.2 and forcing recipient age and sex into the model. We also assessed risk factors for other fracture locations (excluding major fractures, and fractures involving the skull, hands or feet).

RESULTS: There were 132 major fractures in the follow-up (8.1 fractures per 1000 person-years). General risk factors associated with a greater risk of major fracture were older recipient age [adjusted hazard ratio (aHR) per 5-year increase 1.11, 95%CI: 1.03-1.19] and female sex (aHR = 1.81, 95%CI: 1.28-2.57). Transplant-specific risk factors associated with a greater risk of fracture included older donor age (5-year increase) (aHR = 1.09, 95%CI: 1.02-1.17) and end-stage renal disease (ESRD) caused by diabetes (aHR = 1.72, 95%CI: 1.09-2.72) or cystic kidney disease (aHR = 1.73, 95%CI: 1.08-2.78) (compared to glomerulonephritis as the reference cause). Risk factors across the two fracture locations were not consistent (major fracture locations *vs* other). Specifically, general risk factors associated with an increased risk of other fractures were diabetes and a fall with hospitalization prior to transplantation, while length of time on dialysis, and renal vascular disease and other causes of ESRD were the transplant-specific risk factors associated with a greater risk of other fractures.

CONCLUSION: Both general and transplant-specific risk factors were associated with a higher risk of fractures in kidney transplant recipients. Results can be used for clinical prognostication.

Key words: Fracture; Risk factors; Kidney transplant recipient; Prognostication; Cohort study

Core tip: We examined risk factors for major and other fractures in adult kidney transplant recipients. Increasing age and female sex were associated with an increased major fracture risk, while diabetes or cystic kidney disease as the cause of end-stage renal disease and increasing age of the kidney donor were the transplant-specific risk factors associated with an increased major fracture risk. Risk factors were variable across fracture locations (major *vs* other fractures). General and transplant-specific risk factors for fracture should be considered when assessing fracture risk in kidney transplant recipients. Different risk factors may need to be considered depending on the fracture location.

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INTRODUCTION

Kidney transplant recipients are at a higher risk of fracture compared to the general population[1-4]. Reasons for the increased fracture risk are multifactorial, and may include perturbations in bone and mineral metabolism that occur in renal bone disease, and the administration of glucocorticoids after transplantation[5]. However, the risk factors for fracture after transplant remain uncertain. In a recent systematic review many classical risk factors for fracture in the general population (*e.g.,* older age, female sex) were inconsistently associated with fractures in kidney transplant recipients[6]. Unlike the transplant population, risk factors for fracture in the general population are well-established and are included in the World Health Organization's (WHO) Fracture Risk Assessment tool (FRAX). FRAX is used to guide treatment decisions in the general population by incorporating age, sex, clinical risk factors (body mass index, parental hip fracture, glucocorticoid use, rheumatoid arthritis, smoking, alcohol intake $\geqslant$ 3 units per day), and hip bone mineral density (optional) to predict the 10-year probability of hip fracture or major osteoporotic fracture (proximal humerus, forearm, hip, or clinical vertebral)[7-9]. However, kidney transplant recipients may have different risk factors for fracture given the unique pathophysiology that underlies their bone disease[10]. For example, in a recent cohort study the only classical risk factor for fracture that reached statistical significance in kidney transplant recipients was high alcohol use[11]; however, this study had only 21 fracture events and may have had inadequate statistical power to identify other risk factors[11]. The same study also found that FRAX may be a useful tool to predict fracture in kidney transplant recipients (area under the receiver operating curve 0.62); however, the authors hypothesized that incorporating transplant-specific risk factors for fracture may further improve the performance of FRAX[11].

The WHO has called for a global strategy on fracture prevention and management[12]. Such strategies require an understanding of well-validated fracture risk factors and prediction tools so populations at high risk can be targeted for diagnosis, treatment, and therapeutic trials.

Given that risk factors for fracture in kidney transplant recipients have not been well-established, we conducted this study to determine general risk factors (*e.g.,* age, sex, previous fracture, previous fall) and transplant-specific risk factors (*e.g.,* length of time on dialysis prior to transplant) associated with major fractures (proximal humerus, forearm, hip, and clinical vertebral) in kidney transplant recipients. In an additional analysis we assessed risk factors for other fracture locations (excluding major fractures, and fractures involving the skull, hands or feet).

MATERIALS AND METHODS

Design and setting

We performed a population-based cohort study using healthcare databases held at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada. Ontario residents have universal access to hospital and physician services. These datasets were linked using unique encoded identifiers and analyzed at ICES. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada.

Data sources

We used several databases to obtain our study cohort, characteristics, risk factors, and outcome data. Information on all kidney transplant recipients who received their transplant in Ontario was provided by the Canadian Organ Replacement Register. Information on provincial physicians' billing claims was provided by the Ontario Health Insurance Plan database. The Canadian Institute for Health Information Discharge Abstract Database provided information on diagnostic and procedural codes during Ontario hospitalizations and information on emergency room visits was provided by the National Ambulatory Care Reporting System. The Ontario Registered Persons Database provided information on vital status and demographics.

Cohort

We identified all first-time kidney-only transplants in Ontario from April 1st, 2002 to December 31st, 2009, restricting to individuals $\geqslant$ 18 years of age at the transplant date. We selected April 1st, 2002 as our cohort entry date as this was when Canada changed the International Classification of Disease (ICD) system from version 9 to 10. The cohort entry date (index date) was the date an individual received their kidney transplant.

Risk factors

We assessed several general risk factors for fracture (*e.g.,* age, sex, and prior major fracture) which are incorporated in FRAX. We also assessed other general risk factors found to increase fracture risk in the non-transplant population, including: A fall with hospitalization in the year prior to transplantation, race/ethnicity, and diabetes (only type 1 diabetes is included in FRAX)[13-15]. We assessed several transplant-specific risk factors including: Length of time on dialysis prior to transplant (years), type of donor (living *vs* deceased), cause of end-stage renal disease [ESRD, *e.g.,* diabetes mellitus, glomerulonephritis, renal vascular disease, cystic kidney disease, or other (*i.e.,* any cause of ESRD not included in the aforementioned categories such as pyelonephritis)], pre-transplant dialysis modality (peritoneal, hemodialysis, or pre-emptive), and donor characteristics (age and sex).

Outcomes

We followed kidney transplant recipients from the date of transplant until first fracture, death, or end of follow-up (March 31st, 2013). We did not censor kidney transplant recipients if they returned to chronic dialysis or if they had another transplant during follow-up. Our primary outcome was major fractures which were defined as a composite of hip, forearm, proximal humerus, and clinical vertebral fractures. We chose to assess risk factors for major fractures with hospital presentation (emergency room visit or hospital admission) as these fracture locations are associated with excess morbidity and mortality in the general population[16-18]. We also assessed other fracture locations, defined as: Lower leg (ankle, tibia, fibula, patella), femoral shaft, rib/sternum/trunk, scapula, clavicle, and pelvis fractures. These fractures as a whole were considered the secondary outcome as they may be more common in kidney transplant recipients[10]. For example, in prior studies ankle fractures were common in kidney transplant recipients[1,19]. We included both high and low trauma fractures because, similar to low-trauma fractures, high-trauma fractures occur more commonly when an individual has compromised bone strength[20]. We identified fracture events using the 10th version of the ICD system. To increase accuracy, diagnosis codes for hip, forearm, and femoral shaft fractures had to be accompanied by procedural codes identified from hospital encounters and physician billing codes[21].

Statistical analysis

We compared differences in baseline characteristics of recipients with and without a fracture using the Mann Whitney *U* test for continuous variables and the chi-square test for categorical variables. We calculated the incidence rate of fracture (per 1000 person-years) censoring the observation period on the date of death, first fracture, or end of follow-up (March 31, 2013). We used the Cox proportional hazards model to assess effects of risk factors on the hazard of the first fracture. Prior to obtaining the adjusted hazard ratio (aHR) to quantify the effect of each risk factor, model assumptions such as the proportional hazards assumption and linearity of continuous factors (Martingale residuals) were assessed with a *P*-value < 0.05 used as criteria for a violation[22-24]. We used the backward elimination

Table 1 Characteristics of kidney transplant recipients classified by major fracture status[1] *n* (%)

	No fracture (*n* = 2591)	Major Fracture (*n* = 132)	*P*-value
General risk factors			
Age (yr)	50.5 (41-61)	56.5 (45-63)	0.01
Women	928 (35.8)	66 (48.5)	0.004
Race/ethnicity			0.40
White	1845 (71.2)	103 (78)	
Asian	208 (8.0)	8 (6.1)	
Black	198 (7.6)	7 (5.3)	
Other[2]	340 (13.1)	14 (10.6)	
Diabetes	673 (25.6)	40 (30.3)	0.27
Fall with hospitalization in the year prior to the transplant date	92 (3.6)	8 (6.1)	0.15
Major fracture prior to the transplant date[3]			
Transplant specific risk factors			
Length of time on dialysis prior to transplant (measured in years)[4]	2.8 (1.2-5.4)	2.7 (0.92-5.1)	0.56
Type of donor			0.47
Deceased (*vs* living)	1458 (56.3)	70 (53.0)	
Cause of end-stage renal disease[5]			0.004
Glomerulonephritis	951 (36.7)	39 (29.6)	
Cystic kidney disease	385 (14.9)	31 (23.5)	
Diabetes	560 (21.6)	37 (28.0)	
Other	695 (26.8)	25 (18.9)	
Pre-transplant dialysis modality[6]			0.99
Peritoneal dialysis	701 (27.1)	35 (26.5)	
Hemodialysis	1622 (62.6)	83 (62.9)	
Pre-emptive	268 (10.3)	14 (11.6)	
Donor characteristics			
Type of donor			0.47
Deceased (*vs* living)	1458 (56.3)	70 (53.0)	
Donor age (yr)	46 (36-54)	48 (41-55)	0.16
Donor sex			0.73
Women	1295 (50.0)	68 (51.5)	

Data are median (interquartile range) or *n* (%). [1]Major fracture events were comprised of forearm (*n* = 81), hip (*n* = 22), proximal humerus (*n* = 18), and clinical vertebral fractures (*n* = 13); [2]Other was defined as a composite of: Indian Sub-Continent, Pacific Islander, Aboriginal, Mid East/Arabian, Latin American, Other/Multiracial; [3]Due to the small number of recipients with a prior major fracture this risk factor was not able to be assessed; [4]Includes individuals who received a pre-emptive transplant where the time spent on dialysis was defined as 0 years; [5]Due to the small number of recipients with a major fracture who had renal vascular disease as the cause of their ESRD this category was combined into the other category; [6]We defined hemodialysis and peritoneal dialysis based on the modality the recipient first received. We defined pre-emptive transplant as no evidence of hemodialysis or peritoneal dialysis prior to transplant. ESRD: End-stage renal disease.

strategy to select risk factors that would be entered into the final model, with recipient age and sex forced into the model. To decrease the possibility of missing important risk factors for fracture post-transplant, a priori we chose a *P*-value of $\leqslant$ 0.2 to select variables for inclusion in the final model[25]. We assessed for multicollinearity among variables prior to entering variables into the backward elimination model. We found limited concern for multicollinearity, since all variance inflation factors were less than 2[26]. There were missing data for the following variables: Donor age (2.2%), donor sex (< 1%), cause of ESRD (11.6%), race (10.7%), and donor type (< 1%). We handled missing data by assigning values randomly selected from observed values with the exception of donor age for which we supplemented missing values with the median age. In the final model we interpreted two-sided *P*-values < 0.05 as statistically significant. We performed all analyses using Statistical Analysis Software, version 9.4 (www.sas.com). The statistical methods of this study were reviewed by a biostatistician, Guangyong Zou, PhD.

RESULTS

Incidence of fracture

Of the 2723 kidney transplant recipients the total follow-up was 16274 person-years (average 6 years), during which 402 (14.8%) died and 132 (4.8%) sustained a major fracture (8.1 fractures per 1000 person-years, 95%CI: 6.8-9.6).

Baseline characteristics

Recipients who sustained a major fracture in follow-up compared to recipients with no major fracture had a significantly higher median age (56.5 years *vs* 50.5 years), were more likely to be women (48.5% *vs* 35.8%), and were less likely to have glomerulonephritis as their cause of ESRD (29.6% *vs* 36.7%) (Table 1).

Univariable analysis

We found older recipient age and female recipient sex were the general risk factors associated with an increased risk of major fracture (Table 2). For example,

Table 2 Univariable and multivariable analysis of risk factors for major fracture in kidney transplant recipients

Risk factors	Univariable analysis HR (95%CI)	Multivariable analysis HR (95%CI)
Age (per 5 yr increase)	1.13 (1.06-1.21)	1.11 (1.03-1.19)
Sex		
Men	Reference	
Women	1.65 (1.18-2.33)	1.81 (1.28-2.57)
Race/ethnicity		
White	Reference	
Asian	0.72 (0.35-1.47)	
Black	0.65 (0.30-1.39)	
Other[1]	0.78 (0.44-1.36)	
Diabetes (*vs* none)	1.40 (0.96-2.02)	
Fall with hospitalization in the year prior to the transplant date (*vs* none)	2.00 (0.98-4.09)	1.72 (0.84-3.50)
Major fracture prior to the transplant date[2] (*vs* none)		
Length of time on dialysis prior to transplant (measured in years)[3]	1.06 (0.61-1.84)	
Type of donor		
Living	0.99 (0.70-1.39)	
Deceased	Reference	
Cause of end-stage renal disease[4]		
Glomerulonephritis	Reference	Reference
Cystic kidney disease	1.93 (1.20-3.08)	1.73 (1.08-2.78)
Diabetes	1.80 (1.15-2.82)	1.72 (1.09-2.72)
Other	0.92 (0.56-1.53)	0.88 (0.53-1.46)
Pre-transplant dialysis modality[5]		
Hemodialysis	Reference	
Peritoneal dialysis	0.99 (0.67-1.47)	
Pre-emptive	0.96 (0.54-1.68)	
Type of donor		
Living	0.99 (0.70-1.39)	
Deceased	Reference	
Donor age (per 5 yr increase)	1.11 (1.04-1.18)	1.09 (1.02-1.17)
Donor sex		
Men	Reference	
Women	1.03 (0.73-1.44)	

[1]Other was defined as a composite of: Indian Sub-Continent, Pacific Islander, Aboriginal, Mid East/Arabian, Latin American, Other/Multiracial; [2]Due to the small number of recipients with a prior major fracture this risk factor was not able to be assessed; [3]Includes individuals who received a pre-emptive transplant where the time spent on dialysis was defined as 0 years; [4]Due to the small number of recipients with a major fracture who had renal vascular disease as the cause of their ESRD this category was combined into the other category; [5]We defined hemodialysis and peritoneal dialysis based on the modality the recipient first received. We defined pre-emptive transplant as no evidence of hemodialysis or peritoneal dialysis prior to transplant. ESRD: End-stage renal disease; HR: Hazard ratio.

female recipients had almost a two-fold greater risk of major fracture (HR = 1.65, 95%CI: 1.18-2.33). Due to the small number of recipients with a prior major fracture this risk factor was not able to be assessed. Regarding transplant-specific risk factors, cystic kidney disease (HR = 1.93, 95%CI: 1.20-3.08) and diabetes (HR = 1.80, 95%CI: 1.15-2.82) as the cause of ESRD (compared to glomerulonephritis as the reference cause) were both associated with a higher risk of major fracture. Each 5-year increase in donor age was also associated with a greater risk of major fracture (HR = 1.11, 95%CI: 1.04-1.18).

Multivariable analysis

In the multivariable model, older recipient age (5-year increase) (aHR = 1.11, 95%CI: 1.03-1.19) and female recipient sex (aHR = 1.81, 95%CI: 1.28-2.57) were the general risk factors associated with a greater risk of major fracture (Table 2). Regarding transplant-specific risk factors diabetes (aHR = 1.72, 95%CI: 1.09-2.72) and cystic kidney disease (aHR = 1.73, 95%CI: 1.08-2.78) as the cause of ESRD (compared to glomerulonephritis as the reference cause), and older donor age (5-year increase) (aHR = 1.09, 95%CI: 1.02-1.17) were associated with a greater risk of major fracture.

Other fractures

When we assessed other fracture events (excluding the major fractures, and skull, hands, or feet) kidney transplant recipients had 141 fractures (8.7 fractures per 1000 person-years, 95%CI: 7.3-10.2). Recipients with *vs* without such fractures were significantly more likely to have diabetes (40.4% *vs* 25.4%) and were more likely to have had a fall with hospitalization in the year prior to transplant (7.1% *vs* 3.5%) (Table 3). In the multivariable model we found diabetes and a fall with hospitalization prior to transplantation were the general risk factors associated with an increased risk of fracture, while length of time on dialysis, and renal

Table 3 Characteristics of kidney transplant recipients classified by other fractures status[3] *n* (%)

	No fracture (*n* = 2582)	Other fracture (*n* = 141)	*P*-value
General risk factors			
Age (yr)	52 (42-61)	54 (44-61)	0.18
Women	944 (36.6)	48 (34.0)	0.55
Race/ethnicity			0.33
White	1838 (71.2)	110 (78.0)	
Asian	208 (8.1)	8 (5.7)	
Black	198 (7.8)	7 (5.0)	
Other[1]	338 (13.1)	16 (11.4)	
Diabetes	656 (25.4)	57 (40.4)	< 0.001
Fall with hospitalization in the year prior to the transplant index	90 (3.5)	10 (7.1)	0.03
Major fracture prior to the transplant date[5]	69 (2.7)	13 (9.2)	< 0.001
Transplant specific risk factors			
Length of time on dialysis prior to transplant (measured in years)[2]	2.7 (1.1-5.4)	3.0 (1.7-5.3)	0.068
Type of donor			
Deceased	1439 (55.7)	89 (63.1)	0.09
Cause of end-stage renal disease			0.003
Glomerulonephritis	958 (37.1)	32 (22.7)	
Cystic kidney disease	397 (15.4)	19 (13.5)	
Diabetes	555 (21.5)	42 (29.8)	
Renal vascular disease	294 (11.4)	23 (16.3)	
Other	378 (14.6)	25 (17.7)	
Pre-transplant dialysis modality[4]			0.09
Peritoneal dialysis	694 (26.7)	42 (29.8)	
Hemodialysis	1613 (62.5)	92 (65.3)	
Pre-emptive	275 (10.7)	7 (5.0)	
Donor characteristics			
Type of donor			
Deceased	1439 (55.7)	89 (63.1)	0.09
Donor age (yr)	46 (36-54)	48 (40-54)	0.13
Donor sex			
Women	1298 (50.3)	65 (46.1)	0.33

Data are median (interquartile range) or *n* (%). [1]Other was defined as a composite of: Indian Sub-Continent, Pacific Islander, Aboriginal, Mid East/Arabian, Latin American, Other/Multiracial; [2]Includes individuals who received a pre-emptive transplant where the time spent on dialysis was defined as 0 years; [3]Other fracture events were comprised of pelvis (*n* = 15), ankle (*n* = 37), patella (*n* = 8), tibia/fibula (*n* = 37), rib/sternum (*n* = 34), and other (femoral shaft, scapula, clavicle; *n* = 16); [4]We defined hemodialysis and peritoneal dialysis based on the modality the recipient first received. We defined pre-emptive transplant as no evidence of hemodialysis or peritoneal dialysis prior to transplant; [5]Prior major fracture had to occur from 1991 to cohort entry (date of transplant).

vascular disease and other causes of ESRD were the transplant-specific risk factors associated with a greater risk of other fractures (Table 4).

DISCUSSION

Similar to the general population, we found increasing recipient age and female sex were associated with an increased major fracture risk in kidney transplant recipients. Unique to the kidney transplant population, we also found diabetes or cystic kidney disease as the cause of ESRD and increasing age of the kidney donor were associated with a significantly increased major fracture risk. However, risk factors were not consistent across fracture locations with increasing age and female sex not associated with an increased other fracture risk. Our findings suggest that both general and transplant-specific risk factors for fracture should be considered by clinicians when assessing fracture risk in kidney transplant recipients. However, different risk factors may need to be taken into account when considering different fracture locations.

We previously published a study of 321 kidney transplant recipients from Manitoba, Canada and found that FRAX was able to modestly predict fracture and may be a useful tool for clinicians to use to help guide treatment decisions; the area under the receiver operating curve value was 0.62 and there was concordance in the observed *vs* predicted 10-year major osteoporotic fracture probability (6.3% *vs* 5.6%, respectively)[11]. However, the number of major osteoporotic fracture events was small (*n* = 21), with correspondingly wide 95%CIs[11]. We hypothesized that a fracture prediction tool incorporating both general and transplant-specific risk factors may improve fracture prediction[11]. However, model updating may not be needed as the absolute fracture rate found in the current study was lower than previously reported, similar to other recently conducted studies[27,28]. Moreover, the strength of the transplant-specific risk factors was only moderate. Additionally, the large sample size needed to update a model and the reasonable performance of the original FRAX model in kidney transplant recipients further suggests model updating may not be needed. However,

Table 4 Univariable and multivariable analysis of risk factors for other fracture in kidney transplant recipients

Risk factor	Univariable analysis HR (95%CI)	Multivariable analysis HR (95%CI)
Age (per 5 yr increase)	1.09 (1.02-1.17)	1.03 (0.96-1.10)
Sex		
Men	Reference	
Women	0.99 (0.63-1.26)	0.97 (0.68-1.39)
Race/ethnicity		
White	Reference	
Asian	0.67 (0.33-1.37)	0.67 (0.32-1.39)
Black	0.59 (0.27-1.26)	0.47 (0.21-1.02)
Other[1]	0.82 (0.49-1.39)	0.73 (0.43-1.26)
Diabetes (*vs* none)	2.2 (1.57-3.08)	2.19 (1.38-3.49)
Fall with hospitalization in the year prior to the transplant date (*vs* none)	2.37 (1.25-4.52)	2.05 (1.07-3.93)
Length of time on dialysis prior to transplant (measured in years)[2]	1.06 (1.00-1.12)	1.07 (1.01-1.14)
Type of donor		
Living	Reference	
Deceased	0.67 (0.47-0.92)	
Cause of end-stage renal disease		
Glomerulonephritis	Reference	Reference
Cystic kidney disease	1.4 (0.8-2.47)	1.35 (0.76-2.39)
Diabetes	2.47 (1.56-3.91)	1.40 (0.78-2.49)
Renal vascular disease	2.40 (1.41-4.10)	2.11 (1.22-3.65)
Other	2.04 (1.21-3.44)	2.03 (1.20-3.45)
Pre-transplant dialysis modality[3]		
Hemodialysis	Reference	
Peritoneal dialysis	1.06 (0.74-1.53)	
Pre-emptive	0.43 (0.2-0.92)	
Donor age (per 5 yr increase)	1.07 (1.01-1.14)	1.06 (0.99-1.12)
Donor sex		
Men	Reference	
Women	0.83 (0.6-1.16)	

[1]Other was defined as a composite of: Indian Sub-Continent, Pacific Islander, Aboriginal, Mid East/Arabian, Latin American, Other/Multiracial; [2]Includes individuals who received a pre-emptive transplant where the time spent on dialysis was defined as 0 years; [3]We defined hemodialysis and peritoneal dialysis based on the modality they first received. We defined pre-emptive transplant as no evidence of hemodialysis or peritoneal dialysis prior to transplant.

to gain a more complete understanding of fracture risk, it is likely important for clinicians to consider some transplant-specific risk factors (*e.g.,* cause of ESRD) in isolation, when assessing fracture risk. Future research should assess other potential transplant-specific risk factors (unavailable in our current analyses), including: Change in body mass index after transplantation (weight changes found to increase fracture risk in the general population) and fibroblast growth factor 23 (suppresses mineralization of the bone matrix)[29,30].

We found that risk factors for fracture may vary across fracture locations. For example, there were different risk factors for fracture between our two fracture classifications (major fracture locations *vs* other fracture locations). A possible explanation for this finding is that in the kidney transplant population risk factors for fractures are site specific. For example, similar to what some studies have found in the general population, in our study increasing recipient age and female recipient sex were both associated with an increased major fracture risk[31-33]. However, increasing recipient age and female sex were not associated with an increased risk of other fractures. This provides a potential explanation for the results of a previous systematic review which found risk factors for fracture in kidney transplant recipients were inconsistent; studies in the review included different fracture locations[6]. However, we cannot discount the possibility that the differences in risk factors across fracture locations found in this study were the result of a type Ⅱ error. Future studies with larger sample sizes should assess site-specific risk factors for fractures (*e.g.,* ankle) in kidney transplant recipients.

Of concern, several of the risk factors for fracture identified in this study are becoming more common in recent eras of kidney transplant recipients. For example, we found diabetes as the cause of ESRD and older recipient age were significant risk factors for major fractures. The number of recipients with diabetes and the average recipient age has been increasing[34,35]. Similar to results found in a previous study[36], increasing donor age was also associated with an increased risk of major fracture. This is concerning as there has been an increase in the number of recipients receiving a kidney from older donors[37,38]. It is important to note that donor age may only be a surrogate measure for recipient age, with kidneys from older donors often being allocated to older recipients. Nevertheless, the increase in the aforementioned risk factors may have important implications for fracture risk in future recipients.

Unfortunately, none of the risk factors for major

fractures found in this study are easily modifiable. However, a hospitalized fall in the year prior to transplant was a significant risk factor for other fractures; falls are potentially modifiable through the use of fall prevention programs[39-41]. This is an important finding given the commonality of falls in kidney transplant recipients with over 10% of women recipients aged ⩾ 50 years sustaining a fall with hospitalization in the first 3-years after transplant[4]. The paucity of modifiable risk factors is concerning as one of the best ways to prevent fractures in the general population is to provide therapy (*e.g.,* bisphosphonates); the efficacy of these therapies in kidney transplant recipients is unclear[42]. However, given that not many recipients sustained a fracture the lack of modifiable risk factors may be less of a concern.

Limitations of the study are noted. First, we were unable to assess drug use (*e.g.,* glucocorticoids) as a potential risk factor for fracture; drug information in our databases was only available for a minority of kidney transplant recipients; therefore, our sample size would have been decreased, limiting statistical power. It is important to note that a previous study found that kidney transplant recipients who received early corticosteroid withdrawal had a 1.6% reduction in fracture compared to recipients who received standard corticosteroid based immunosuppression[43]. Future studies should explore this further, including measuring glucocorticoid use as a continuous variable and assessing the impact of reduced dose on fracture risk, with a consideration given to the impact this may have on long-term immunological outcomes (*e.g.*, graft loss)[44]. Second, we were unable to assess several risk factors, such as body mass index and estimated glomerular filtration rate, due to a high proportion of missingness (> 50%). Third, the small number of fracture events may have limited statistical power and increased concerns about the validity of the model. However, we selected a liberal *P*-value in our backward elimination analysis to ensure we were not excluding potentially important variables. Additionally, it is unlikely there were type Ⅰ errors given there were at least 10 events per variable[45]. Finally, due to the small number of fracture events we were also not able to assess several of the other risk factors included in the FRAX algorithm (*e.g.*, rheumatoid arthritis). Last, the generalizability of these results to other races/ethnic groups may be limited as the majority (72%) of our sample was White.

Both general and transplant-specific risk factors for fracture should be considered by clinicians when assessing fracture risk in this unique patient population; however, risk factors may be variable across fracture locations. Future studies with larger sample sizes should assess the ability of other transplant-specific risk factors to predict fracture.

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COMMENTS

Background

Compared to the general population kidney transplant recipients are at an increased risk of fracture due to a multitude of factors, including: Chronic kidney disease-mineral and bone disorder and glucocorticoid administration post-transplant. However, risk factors for fracture are not well-established in the kidney transplant population. An understanding of risk factors for fracture is important to target high risk recipients for treatment and therapeutic trials.

Research frontiers

To determine the general and transplant-specific risk factors for fractures in kidney transplant recipients.

Innovations and breakthroughs

General and transplant-specific risk factors for fracture should be considered by clinicians when assessing fracture risk in kidney transplant recipients. However, different risk factors may need to be taken into account when considering different fracture locations. Unfortunately, none of the risk factors for major fractures found in this study are easily modifiable. However, a hospitalized fall in the year prior to transplant was a significant risk factor for other fractures; falls are potentially modifiable through the use of fall prevention programs. This is an important finding given the commonality of falls in kidney transplant recipients.

Applications

The risk factors for fracture identified in this study are useful for clinical prognostication.

Terminology

Major fractures were defined as a composite of hip, forearm, proximal humerus, and clinical vertebral fractures. Other fracture locations were defined as a composite of lower leg (ankle, tibia, fibula, patella), femoral shaft, rib/sternum/trunk, scapula, clavicle, and pelvis fractures.

Peer-review

This is a well written study on an important topic in transplantation as the risk of

bone fractures after transplantation. The statistical analysis is well conducted.

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