Fractures in Kidney Transplant Recipients: A comparative study between England and New York State

Running Head: **Fractures after Kidney Transplantation**

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Abstract

Objectives

Fractures are associated with high morbidity and are a major concern to kidney transplant recipients. There has not been any comparative analysis conducted between countries in the contemporary era to inform future international prevention trials.

Materials and Methods

Data were obtained from the Hospital Episode Statistics and the Statewide Planning and Research Cooperative databases on all adult kidney transplants performed in England and New York State respectively (2003-2013) and on post-transplant fracture-related hospitalization (2003-2014).

Results

In total, 18,493 English and 11,602 New York State kidney transplant recipients were included. Overall, 637 (3.4%) English and 398 (3.4%) New York State recipients sustained a fracture giving an unadjusted event rate of 7.0 and 5.9 per 1000 years respectively (P=0.948). A total of 147 (0.8%) English and 101 (0.9%) New York State recipients sustained a hip fracture, giving an unadjusted event rate of 1.6 and 1.5 per 1000 years respectively (P=0.480). There were no differences in the cumulative incidence of all fractures or hip fractures. One-year mortality after any fracture (9% and 11%) or after a hip fracture (15% and 17%) was not different between cohorts.

Conclusions

Contemporaneous English and New York State kidney transplant recipients have very similar fracture rates and mortality post-fracture.

Key words: Kidney transplant, fracture, mortality, epidemiology

Introduction

Bone disease is a major fear for kidney transplant recipients, ranking high on a list of patient concerns[1]. Kidney transplant recipients have a higher fracture risk than the general population[2-10]. This increased risk has been attributed to changes in bone mineral metabolism as a consequence of impaired renal function and the prolonged use of high dose glucocorticoids. However, most studies were done before 2000[11], have had only short-term follow-up and demonstrate large inter-study variability in fracture rates[11].

Hip fractures are common, costly, require hospitalization, and are associated with poor outcomes[12, 13]. In the general population mortality rates after hip fracture have changed little over the past 30 years despite surgical and medical advances[14-16]. Hip fracture rates vary widely across countries and are higher in the United States of America (USA) than in Canada; with both these countries reporting higher fracture rates than England[13, 17-19]. Ethnicity is also associated with hip fractures; people of black ethnicity consistently sustain lower fracture rates than whites[18].

Recent studies from England and Ontario Province, Canada in contemporary cohorts have shown that hip fracture rates in kidney transplant recipients are lower than have been historically reported[20, 21]. These studies suggest that any future trial on fracture prevention would need to be international because of the low overall numbers involved.

A better understanding of fracture incidence in kidney transplant recipients and comparisons between countries remains important for estimating sample size requirements for potential future fracture prevention trials and gaining a better understanding of whether systematic differences in the population demographics and healthcare systems and whether the background rate of fracture in the general population may be contributing to fracture rates

and post-fracture outcomes, including mortality. To our knowledge, no comparative analysis of fracture rates has ever been conducted between countries in the contemporary era. We therefore conducted this study to provide estimates of incidence rates of all fractures and hip fractures requiring hospitalization in all adult kidney transplant recipients from England and New York State (NYS), USA. We also examined 1-year mortality rates post-fracture and causes of death.

Materials and Methods

Study Population

We performed a retrospective cohort study of all kidney-alone transplants performed in adults (aged greater than 18 at time of transplantation) in England and NYS between January 2003 and December 2013. Patients were followed up until December 2014 allowing all patients the potential to have at least 1 year of follow-up. We collected patient demographics that included age, gender, ethnicity, and medical co-morbidities at the time of transplantation.

Data Sources

For patients transplanted in England, data was obtained from Hospital Episodes Statistics (HES), an administrative database containing all admissions to National Health Service hospitals in England. Data was extracted utilizing codes on procedural classifications (Office of Population Censuses and Surveys Classification of Interventions and Procedures, 4th revision (OPCS-4) and medical classifications (World Health Organization International Classification of Diseases, 10th revision (ICD-10)).[20] Mortality (including cause of death) was determined by linkage to the Office of National Statistics (ONS)[20].

For patients transplanted in New York State, data was extracted from the Statewide Planning and Research Cooperative (SPARCS), a comprehensive all-payer administrative database

with information on all admissions to non-federal hospitals in New York State. Data was extracted utilizing codes on medical classifications (World Health Organization International Classification of Diseases, 9th revision (ICD-9)) and procedural classifications (ICD-9 Procedure Codes) and medical classifications.[16] Mortality was determined using a linkage to the NYS Department of Vital Statistics and New York City Department of Vital Statistics[16].

Both HES and SPARCS databases have previously been used to study the incidence of fractures[16, 20, 22, 23]. Only pseudoanonymized data was available for analysis. As such, this study did not require institutional review board approval.

Outcomes

Patients who after renal transplantation were readmitted to hospital in England with a fracture ICD-10 code (S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T07, T10, T12) and in New York State with a fracture ICD-9 code (800-829) were flagged. Hip fractures were defined as ICD-10 codes S72.0-S72.2 and ICD-9 code 820. Data on fractures occurring before transplantation were also collected and analyzed as a potential risk factor for post-transplantation fracture. Mortality within 1 year of a fracture was also collected.

Statistical Analyses

Differences between groups were compared using chi-square tests for categorical variables and Mann-Whitney tests for continuous variables. We defined 1-year, 3-year, 5-year and 10-year cumulative incidence of fracture as the proportion of kidney transplant recipients who sustained a fracture within the respective period of follow-up; no fracture could occur in follow-up if the recipient died before fracture. We calculated the 1-year, 3-year, 5-year and 10-year incidence rates of fracture (defined as the rate per 1000 patient-years of follow-up;

censoring at the time of death or fracture in follow-up). Results are presented for the entire cohorts and by gender (male versus female) and age (<50 versus ≥ 50 years) at the time of transplantation. The age cut-off was chosen for several reasons, namely that the median age of participants was 50 years, the average age of menopause is approximately 50 years[24, 25] and fracture risk increases after the menopause[26], and previous research has found kidney transplant recipients older than 50 years to have an increased fracture risk[10]. Our analyses were also performed to be as much as possible directly comparable to a recent analysis performed on a contemporaneous cohort of kidney transplant recipients from Ontario, Canada[21].

Time-to-fracture outcomes were analyzed with the Cox's proportional hazards model and the log-rank test. All variables used in the analyses had <5% of the values missing and were therefore treated as missing at random with case-wise deletion. Results are presented as Hazard Ratios (HR) with 95% confidence intervals (95% CI). Mortality in the year following a fracture was analyzed using logistic regression analysis. Variables included in the models were age, gender, ethnicity, history of fracture before transplantation and available medical comorbidities, including history of myocardial infarction, peripheral vascular disease, cerebrovascular disease, congestive cardiac failure, pulmonary disease, cancer, liver disease and diabetes mellitus. Results are presented as the Odds Ratio (OR) with 95% CI. Analyses were performed using Stata statistical software (V14, Statacorp, LP, Texas, USA). A P value of <0.05 was considered statistically significant.

Results

We studied 18,493 adults from England and 11,602 adults from NYS who received a kidney transplant from January 2003 to December 2013. Recipients were followed up until December 2014, giving a total of 90,655 patient-years (median 5 years, range 0-12 years)

follow-up for English recipients and 67,743 patient-years (median 6 years, range 0-12 years) follow-up for NYS recipients. The baseline characteristics of both cohorts are described in Table 1. Recipients from NYS were older (51 (interquartile range (IQR) 41-61 years) vs. 48 (IQR 38-58) years; P<0.001), more likely to be of black ethnicity (23% vs. 7%; P<0.001) and more likely to be diabetic (38% vs. 15%; P<0.001). Recipients from NYS also had increased pre-transplant cardiovascular morbidity than English recipients with a higher incidence of myocardial infarction, heart failure, peripheral vascular disease and cerebrovascular disease (P<0.001 for all). English recipients were more likely to have been diagnosed with pulmonary disease than NYS recipients (12% vs. 0.6%: P<0.001) and more likely to have sustained a fracture before transplantation (3.1% vs. 2.5%; P=0.002).

All fracture risk

In total 637 (3.4%) English kidney transplant recipients sustained any fracture during the follow-up period with 34 (0.2%) recipients sustaining two fractures, 9 (0.1%) recipients sustaining three and 8 (0.04%) recipients sustaining four or more fractures. In total 398 (3.4%) NYS kidney transplant recipients sustained any fracture during the follow-up period with 76 (0.7%) recipients subsequently sustaining two fractures, 10 (0.1%) recipients sustaining three and 8 (0.1%) recipients sustaining four or more fractures. There were no differences in the proportions of recipients in both cohorts sustaining any fracture or more than one fracture. The unadjusted event rate for any fracture was 7.0 per 1000 patient years for the English cohort and 5.9 per 1000 years for the NYS cohort (P=0.948). Overall, there were no differences between the groups in the proportion of recipients admitted with lower limb, upper limb, trunk or skull fractures.

The 1-year, 3-year, 5-year and 10-year cumulative incidence and incidence rate of any fracture are presented in Table 2 and according to age and gender in Supplementary Table 1.

For both English and NYS recipients, women over 50 had the highest rates of fracture at all time-points. There were no differences between the English and NYS cohorts in the cumulative incidence or incidence rates at any time point when taken as a whole (Table 2; Figure 1) or in any of the sub-groups (Supplementary Table 1).

Parameters associated with sustaining any fracture for both English of NYS recipients are presented in Table 3A. Increasing age, female gender, white ethnicity, pre-transplantation diabetes mellitus and having sustained a fracture pre-transplant were associated with sustaining a fracture post-transplantation in both groups. When all recipients were combined, being a NYS kidney transplant recipient was not associated with an increased fracture risk (HR 1.03, 95% CI 0.89 – 1.18; P=0.699) compared to an English recipient. This joint analysis made no material difference to the relationship between the other parameters and fracture risk (Supplementary Table 2).

Hip fracture risk

In total 147 (0.8%) English and 101 (0.9%) NYS kidney transplant recipients sustained a hip fracture during the study period (P=0.480), giving a crude all fracture incidence rate of 1.6 per 1000 patient years and 1.5 per 1000 patient years respectively. The 1-year, 3-year, 5-year and 10-year cumulative incidence and incidence rate of hip fracture are presented in Table 4 and according to age and gender in Supplementary Table 3. For both the English and NYS cohorts, women over 50 years of age had the highest rates of fracture at all time points. There were no differences between the English and NYS cohorts in the cumulative incidence or incidence rates at any time point when taken as a whole (Table 4; Figure 1) or in any of the sub-groups (Supplementary Table 3). The 10-year cumulative incidence rate for women over 50 was 3.26% (95% CI 1.70-6.2) for English recipients and 2.62% (95% CI 1.37-4.97) for NYS recipients, with no difference between the groups (P=0.210).

Variables associated with sustaining a hip fracture in both English and NYS cohorts are presented in Table 3B. Factors associated with hip fracture were similar to those associated with sustaining any fracture, except that black ethnicity was not associated with a lower rate of fracture in English recipients and having sustained a fracture pre-transplantation was not associated with a greater risk of hip fracture in NYS recipients. When both cohorts were combined, being a NYS kidney transplant recipient was not associated with an increased hip fracture risk (HR 0.90, 95% CI 0.67-1.20; P=0.473: Supplementary Table 4) compared to an English patient. In this combined analysis black ethnicity was associated with a reduced hip fracture risk (HR 0.42, 95% CI 0.25-0.71; P=0.001) and having sustained a fracture before transplantation was associated with an increased hip fracture risk (HR 2.48, 95% CI 1.49-4.14; P<0.001).

One-year mortality post fracture

Within 1 year of sustaining any fracture 55 (9%) English and 43 (11%) NYS recipients had died (P=0.246). Within 1 year of sustaining a hip fracture 22 (15%) English and 17 (17%) NYS recipients had died (P=0.692). In both univariable and multivariable analyses, being an English or NYS kidney transplant recipient was not associated with an increased 1-year mortality after any fracture (OR 1.11, 95% CI 0.69-1.79; P=0.655: Supplementary Table 5) or hip fracture (OR 0.92, 95% CI 0.47-1.82; P=0.819: Supplementary Table 6).

Causes of death were only available for the English kidney transplant recipients; of the 55 deceased no cause of death was reported more than 5 times, which prevents us from showing the data for reasons of privacy.

Discussion

We have found that all fracture rates requiring hospitalization and hip fracture rates in kidney transplant recipients with different baseline demographics from two very different health care systems, England and NYS, are not different at 1, 3, 5 and 10 years post-transplantation. Furthermore, we have shown that the 1-year mortality after any fracture or hip fracture is the same across both cohorts. These findings have important implications for future studies aimed at reducing the rate of fractures in kidney transplant recipients, as well as reducing the high mortality associated with fractures.

Our finding that fracture rates requiring hospitalization, and especially hip fracture rates, are the same in England as in NYS is perhaps unexpected given the differences in demographics between the two populations. Recipients from NYS were older and a larger proportion were diabetic than English recipients. These demographics are consistent with the known differences in the end-stage renal disease populations between England and the US[27, 28]. However, whereas black ethnicity is known to be associated with a significantly lower rate of fractures compared to white ethnicity[18, 20], older age[29-32] and being diabetic[20, 33] are associated with an increased risk. Thus it appears that these risk factors potentially cancel each other out across the overall population.

A recent study from Ontario reported fracture rates in kidney transplant recipients from Ontario over a similar time period has reported similar fracture rates to our study[21]. They reported a 3-year cumulative hip fracture rate of 0.4% (95% CI 0.3-0.7), which is identical to the rates we found in both the English and NYS recipients of 0.4% with very similar confidence intervals (95% CI 0.3-0.6) for both. Furthermore, they reported a 10-year cumulative incidence rate for hip fractures of 1.7% (95% CI 1.2-2.3). Although the rates we report for England and NYS were slightly lower at 1.4% (95% CI 1.0-2.0) and 1.4% (0.9-2.0)

respectively, the confidence intervals are wide, given the much lower numbers of patients with this length of follow-up, and overlap considerably.

Thus it appears that the rates of hip fractures in kidney transplant recipients are virtually identical in three distinct populations England, NYS and Ontario. This is perhaps unanticipated given that hip fracture rates vary greatly in the general population across countries. The US population has significantly higher rates than the Canadian population, which in turn has a higher rate than that reported in England[13, 17-19]. These differences are considerable; a recent study reported that Canadian women had a 30% lower rate of hip fractures compared to US women[19]. Our finding of virtually identical hip fracture rates in kidney transplant recipients from England and NYS, which are effectively the same as those seen in Ontario, suggests a commonality of risk factors in these groups that do not necessarily reflect the underlying prevalence of risk factors in their respective general populations.

Our study is also consistent with the recently published report on kidney transplant recipients from Ontario[21] in that only women aged over 50 years were a high risk group for fracture as defined by a hip fracture rate greater than 3% at 10 years[26, 34]. This patient group should be considered a priority for measures designed to prevent fractures post-transplantation or indeed as the preferred high-risk group for a future study of fracture prevention. However, it should be noted that in both our study and in the Canadian study, the total at risk population was very low (n=696 and n=354 respectively).

Several studies have documented a high mortality rate after hip fractures in the general population[35-39]. In our previous study we reported a mortality of 16% within 1 year of a hip fracture in an English kidney transplant recipient population,[20] which was higher than previously reported rates from the US[4, 40]. This appeared to be consistent with reports that

mortality in the general population was also lower in the US than England[41]. Differences in healthcare systems between the two countries including the timing of interventions and length of hospital stay had been postulated to affect survival[42]. In this current study, however, we have found that mortality after any fracture requiring hospitalization and after a hip fracture in both the English and NYS recipient were very similar with no differences detected.

Although rates of acute myocardial infarction are high post-hip fracture[43] the cause of mortality and associated comorbid conditions vary widely with no clear pattern in the general population[44]. In this study, we were only able to examine the causes of death in the English population (NYS data on cause of death was not available). However, like reports from the general population, we were unable to identify either associated comorbidities or a particular cause or group of causes for death, suggesting that, other than preventing the fracture in the first place, a wide approach is required to lower mortality.

Our study has a number of strengths as well as limitations. We were able to include all patients transplanted in England and NYS. Loss to follow-up would only have happened if the recipient left the country or state. As is often done, we used administrative data to ascertain comorbidities despite the fact that there are problems with under-reporting of diagnosis codes for many conditions and this may vary systematically across healthcare systems[45-47]. We reported higher rates of cardiovascular co-morbidities in NYS kidney transplant recipients compared to their English counterparts. A significant proportion of this could perhaps be explained by the much higher incidence of diabetes in NYS recipients (entirely consistent with what is known about the US dialysis population), as well as their higher median age. It may also be caused by a systematic bias in reporting, which may also be the most likely explanation for the higher reported rates of chronic pulmonary disease we

found in the English cohort. Nevertheless, the presence of these comorbidities does not appear to be associated with fracture incidence rates in either populations when studied separately or in combination. Like many other studies in this field we did not have creatinine values to determine the degree to which the transplant recipients had CKD. We only had access to recipients transplanted in NYS. Whether our results from NYS could be generalizable to other statewide populations in the USA is unknown. Overall, we are reassured of the robustness of our data given the high concordance of fracture incidence rates and associated mortality we found between the English and NYS recipient populations. In addition, our 3-year and 10-year cumulative incidence of hip fractures for both the English and NYS recipients are very similar to a recent report from Ontario, Canada, providing further substantiation to our data[21].

In conclusion, our results show comparable rates for fractures requiring hospitalization and for hip fractures in English and NYS kidney transplant recipients. We have also demonstrated a high mortality rate in both populations 1 year after a fracture requiring hospitalization and especially after a hip fracture. No single cause or group of causes for the excess mortality nor associated co-morbid conditions were identified, suggesting a wide range of measures would be required to reduce this mortality, other than preventing fractures in the first place.

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Table 1: Baseline characteristics of kidney transplant recipients from England and New York State

	England (n=18,493)	**New York State (n=11,602)**	***P* value**
Age (years)	48 (38-58)	51 (41-61)	<0.001
Women	7123 (39%)	4569 (39%)	0.14
Ethnicity			
White	14508 (78%)	6202 (53%)	<0.001
Black	1215 (7%)	2660 (23%)	
Other	2770 (15%)	2740 (24%)	
Co-morbidities			
Myocardial infarction	1148 (6%)	1375 (12%)	<0.001
Cerebrovascular disease	803 (4%)	859 (7%)	<0.001
Congestive Heart Failure	924 (5%)	2587 (22%)	<0.001
Peripheral vascular disease	1020 (6%)	920 (8%)	<0.001
Diabetes mellitus	2781 (15%)	4462 (38%)	<0.001
Liver disease	86 (0.5%)	213 (2%)	<0.001
Pulmonary disease	2170 (12%)	68 (0.6%)	<0.001
Previous Cancer	696 (4%)	452 (4%)	0.56
Previous fracture	566 (3%)	286 (2%)	0.002

Data are medians (interquartile range) or n (%).

Table 2. One-year, three-year, five-year and ten-year cumulative incidence and incidence rates of all fractures requiring hospitalization in England and New York State*

	Cumulative Incidence, % (95% Confidence Intervals)			**Incidence Rate per 1000 patient years (95% Confidence Intervals)**		
	England	**NYS**	***P value***	**England**	**NYS**	***P value***
One-year (n=29,898)	0.74% (0.63-0.88)	0.66% (0.53-0.83)	0.488	7.44 (6.28-8.81)	6.73 (5.38-8.42)	0.50
Three-year (n=23,729)	1.96% (1.74-2.21)	1.76% (1.51-2.05)	0.265	6.62 (5.87-7.46)	5.93 (5.09-6.91)	0.27
Five-year (n=17,810)	3.16% (2.83-3.53)	2.87% (2.51-3.28)	0.273	6.43 (5.75-7.19)	5.83 (5.10-6.67)	0.27
Ten-year (n=4,103)	7.40% (6.34-8.62)	5.94% (4.92-7.16)	0.096	7.52 (6.41-8.82)	6.14 (5.07-7.45)	0.11

*Cumulative incidence defined as the proportion of kidney transplant recipients who sustained any fracture within the follow-up period: no fracture could occur if the kidney transplant recipient died before fracture. Incidence rate defined as the rate per 1000 patient years of follow-up; censoring at the time of death or fracture in follow-up.

NYS, New York State

Table 3. Adjusted associations between kidney transplant recipient demographics and co-morbidities with the cumulative incidence of all fractures requiring hospitalization(A) and hip fractures (B).

A: All fractures requiring hospitalization*

		England		New York State	
Variable		**Hazard Ratio (95% Confidence Intervals)**	**P value**	**Hazard Ratio (95% Confidence Intervals)**	**P value**
Age	18 to 49	1	-	1	-
	50 to 69	1.46 (1.21-1.75)	<0.001	1.36 (1.06-1.76)	0.02
	70 and over	2.51 (1.71-3.70)	<0.001	2.07 (1.43-3.00)	<0.001
Gender	Male	1	-	1	-
	Female	1.47 (1.23-1.75)	<0.001	1.27 (1.01-1.59)	0.04
Ethnicity	White	1	-	1	-
	Black	0.58 (0.37-0.91)	0.019	0.63 (0.47-0.85)	0.002
	Other	0.64 (0.48-0.85)	0.003	0.67 (0.50-0.91)	0.009
Pre-transplantation diabetes mellitus		2.16 (1.75-2.66)	<0.001	1.95 (1.54-2.46)	<0.001
Previous Fractures		2.09 (1.41-3.08)	<0.001	1.97 (1.18-3.29)	0.009

B: Hip fractures*

Variable		England		New York State	
		Hazard Ratio (95% Confidence Intervals)	**P value**	**Hazard Ratio (95% Confidence Intervals)**	**P value**
Age	18 to 49	1	-	1	-
	50 to 69	4.00 (2.52-6.34)	<0.001	3.28 (1.71-6.28)	<0.001
	70 and over	8.95 (4.34-18.44)	<0.001	7.48 (3.46-16.20)	<0.001
Gender	Male	1	-	1	-
	Female	1.89 (1.28-2.78)	0.001	1.03 (0.63-1.67)	0.91
Ethnicity	White	1	-	1	-
	Black	0.70 (0.29-1.73)	0.445	0.40 (0.20-0.81)	0.01
	Other	0.27 (0.11-0.68)	0.005	0.34 (0.15-0.74)	0.007
Pre-transplantation diabetes mellitus		2.70 (1.76-4.13)	<0.001	1.73 (1.07-2.81)	0.03
Previous Fractures		3.04 (1.52-6.09)	0.002	0.62 (0.08-4.47)	0.63

*Models adjusted for; age, gender, ethnicity, history of myocardial infarction, peripheral vascular disease, cerebrovascular disease, congestive

cardiac failure, pulmonary disease, diabetes mellitus and previous fractures.

Table 4. One-year, three-year, five-year and ten-year cumulative incidence and incidence rates of hip fractures*

	Cumulative incidence, % (95% Confidence Intervals)			**Incidence Rate per 1000 patient years (95% Confidence Intervals)**		
	England	**NYS**	***P value***	**England**	**NYS**	***P value***
One-year (n=29,898)	0.23% (0.17-0.31)	0.16% (0.10-0.25)	0.162	2.33 (1.72-3.15)	1.57 (0.99-2.49)	0.16
Three-year (n=23,729)	0.42% (0.33-0.55)	0.42% (0.30-0.57)	0.899	1.43 (1.10-1.85)	1.39 (1.02-1.91)	0.91
Five-year (n=17,810)	0.67% (0.52-0.85)	0.68% (0.51-0.89)	0.924	1.34 (1.05-1.71)	1.37 (1.04-1.80)	0.98
Ten-year (n=4,103)	1.39% (0.96-2.01)	1.62% (1.12-2.33)	0.532	1.36 (0.94-1.97)	1.63 (1.13-2.36)	0.50

NYS, New York State

*Cumulative incidence defined as the proportion of kidney transplant recipients who sustained a hip fracture within the specified period of follow-up: no hip fracture could occur if follow-up if the kidney transplant recipient died before hip fracture. Incidence rate defined as the rate per 1000 patient years of follow-up; censoring at the time of death or fracture in follow-up.

Figure Legend

Figure 1. Cumulative incidence of all fractures requiring hospitalization and hip fractures in adult kidney transplant recipients in England and New York State (NYS). There were no differences in all fracture (P=0.257 by the log-rank test) and hip fracture (P=0.094 by the log-rank test) rates between the two populations.