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Peptic ulcer disease and Pulmonary disease are Associated with Risk of Periprosthetic Fracture after Primary Total Knee Arthroplasty

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Abstract

Objective—To assess the association of specific comorbidities with periprosthetic fractures after primary total knee replacement (TKA)

Methods—We used the prospectively collected data in the Mayo Clinic Total Joint Registry from 1989-2008 on all patients who had undergone primary TKA. The outcome of interest was postoperative periprosthetic fractures during the follow-up. Main predictors of interest were comorbidities grouped from the validated Deyo-Charlson index. Multivariable-adjusted Cox regression analyses adjusted for gender, age, body mass index (BMI), American Society of Anesthesiology (ASA) class, operative diagnosis and implant fixation. Hazard ratios and 95% confidence intervals were calculated.

Results—We included 17,633 primary TKAs with a mean follow-up of 6.3 years. The mean age was 68 years, 55% were women and mean BMI was 31. There were 188 postoperative periprosthetic fractures on postoperative day one or later; 162 fractures (86%) occurred postoperative day 90 day or later. In multivariable analyses that simultaneously adjusted for all comorbidities and other variables (age, gender, BMI, ASA, operative diagnosis, cement status), two conditions were significantly associated with increased hazard of postoperative periprosthetic fractures: peptic ulcer disease, hazard ratio of 1.87 (95% confidence interval:1.28, 2.75; p=0.0014); and chronic obstructive pulmonary disease (COPD) hazard ratio of 1.62 (95% confidence interval:1.10, 2.40; p=0.02).

Conclusions—Peptic ulcer disease and COPD are associated with higher risk of periprosthetic fractures after primary TKA. This may be related to the disease or their treatments, which needs further study. Identification of specific risk factor may allow for implementation of intervention strategies to reduce this risk.

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Keywords

Total knee arthroplasty; total knee replacement; periprosthetic fracture; predictors; risk factors; comorbidity; Primary TKA

Introduction

Total knee replacement (TKA) is the most common joint replacement procedure. Approximately 0.5 million procedures are performed annually in the U.S. and the procedure volume is projected to increase 6-fold by 2030 (1). Periprosthetic fracture is associated with higher morbidity (2) and mortality (3-4). A better understanding of risk factors for periprosthetic fractures after TKA can provide guidance regarding potential intervention for risk modification or modifiable risk factors to improve outcomes.

Studies of periprosthetic fractures after TKA have identified risk factors. Risk factors assessed previously include corticosteroid use (5-7), demographics such as female gender and age >70 years (8) and underlying diagnosis such as inflammatory arthritis (5-7, 9) and previous revision arthroplasty (9-10). In two small studies of 26 and 14 fractures, osteoporosis was suspected to be a risk factor for periprosthetic fractures (9-10); a cadaveric biomechanical study had similar findings (11). Most of the previous studies focused on demographics and underlying diagnosis leading to TKA, which are unmodifiable. To our knowledge, only two small studies focused on osteoporosis (9-10). None of the previously published studies have examined any other comorbidity as a (potentially modifiable) risk factor for periprosthetic fractures after TKA.

Our objective was to examine whether medical comorbidities were associated with a higher risk of periprosthetic fractures after primary TKA in a large cohort of patients who were prospectively followed in an institutional joint registry.

Methods

Study Cohort

We used the prospectively collected data in Total Joint Registry at the Mayo Clinic, Rochester, MN. The Mayo Clinic Total Joint Registry, details described elsewhere (12) (13), captures demographic, clinical and implant-related information for each patient undergoing joint replacement surgery at the Mayo Clinic. Each patient is followed prospectively clinically in the total joint registry and important postoperative outcomes including revision, infection, fracture and patient-reported outcomes are captured. Several previous studies have examined periprosthetic fractures using this prospective registry (14-18), that collects data from local medical records. Standardized rigorous follow-up protocols are followed for the total joint registry for collection of these and other patient-reported outcomes. For patients failing to return for regular clinic follow-up visits, a letter is sent to patients inquiring about complications related to index arthroplasty including periprosthetic fractures, infections and additional surgeries or procedures, in addition to other questions. In some cases, where both approaches (clinic follow-up and mailed questionnaire) are not successful, trained staff personnel administer contact the patients by telephone and inquire about post-arthroplasty complications (and other outcomes). In addition, medical records from other health care facilities (including radiographs) are obtained for patients with report of complications including fractures, infection and any other surgery on the index joint, who don't return for follow-up to the Mayo Clinic. For this study, we included a cohort of all patients who had undergone primary TKA, from 1989-2008. We chose this time-period since key variables for available for this entire period, allowing us to adjust the analyses for important factors.

Outcome of interest

The outcome of interest was periprosthetic fracture at postoperative day one or later. We did not include intraoperative fractures since their etiology is different from postoperative fractures. We chose not to include periprosthetic fractures on postoperative day zero, since these could not be definitely distinguished from intraoperative fractures due to lack of availability of exact time of fracture and performance of multiple surgeries related to complications on postoperative day zero in some patients with fractures, as well as for other complications. Thus, our cohort selection approach was specific and conservative. The documentation of periprosthetic fracture in the Mayo Clinic total joint registry came from two key components of patient's medical records, the operating room report and/or orthopedic surgeon's clinical note that indicated the occurrence of fracture post-TKA in patient's medical records. In an occasional instance, fractures that were patient-reported (on mailed questionnaire or during telephone conversation) and subsequently confirmed by an orthopedic surgeon's documentation of a periprosthetic fracture in the letter correspondence to the patient (based on review of outside medical records, operating room reports and radiographic studies, obtained as a clinical protocol for all post-arthroplasty complications), was considered consistent with an occurrence of periprosthetic fracture. Thus, the data regarding periprosthetic fractures in the registry came from patient medical records. Patients were followed from the day of their index primary TKA to the time of occurrence of postoperative periprosthetic fracture or death, whichever occurred earlier."

Predictor variables and definitions

The main predictors of interest in our study were medical comorbidities, grouped from the well-known comorbidity measure, the Deyo-Charlson index. Data regarding the presence of Deyo-Charlson comorbidities was obtained from the Mayo Clinic electronic health care records, where data on Deyo-Charlson comorbidities is available for this study period. It is a valid measure of comorbidity, assessed as a cumulative weighted score of several comorbidities (19-20). The comorbidities were grouped into 10 categories as follows: cardiac disease (myocardial infarction, congestive heart failure); peripheral vascular disease; cerebrovascular disease (cerebrovascular disease, hemiplegia); moderate-severe renal disease; peptic ulcer disease; chronic obstructive pulmonary disease; diabetes (with or without organ damage); connective tissue disease; cancer (leukemia, lymphoma, any other tumor, metastatic solid tumor); other (dementia, liver disease, AIDS).

Statistical Analyses

We used univariate Cox proportional hazards regression analyses to examine the association of each of the Deyo-Charlson comorbidities and periprosthetic fracture. We performed multivariable-adjusted Cox regression analyses that simultaneously adjusted for the following important variables (known or suspected to be associated with periprosthetic fracture risk). These included gender, age (≤60, 61-70, 71-80 and >80 years), body mass index as per WHO classification (<25, 25-29.9,30-39.9, ≥40) (21), American Society of Anesthesiology (ASA) Physical Status score class (1, 2, 3, 4) (22-23), operative diagnosis (osteoarthritis, rheumatoid arthritis, other) and implant fixation (cemented/hybrid, uncemented). Hazard ratios (HR) and 95% confidence interval (CI) are presented.

Results

Demographic and clinical characteristics of patients are shown in table 1. 17,633 primary TKAs were included in the study with a mean follow-up of 6.3 years. The mean age was 68 years, mean BMI was 31, 27% had bilateral procedures and 55% were women. There were 188 postoperative periprosthetic fractures on postoperative day one or later, of which 162 fractures (86%) occurred 90 days or later after index TKA.

In univariate analyses, peptic ulcer disease, chronic obstructive pulmonary disease (COPD) and other diagnoses (dementia, liver disease, AIDS) were each associated with a higher risk of periprosthetic fractures (Table 2).

In multivariable analyses that simultaneously adjusted for all comorbidities and other variables (age, gender, BMI, ASA, operative diagnosis, cement status), only peptic ulcer disease and COPD were significantly independently associated with a higher risk of periprosthetic fracture with respective hazard ratios of 1.87 (95% confidence interval: 1.28, 2.75; p=0.0014) and 1.62 (95% confidence interval: 1.10, 2.40; p=0.02) (Table 2). Other diagnoses (dementia, liver disease, AIDS) were not significantly associated with risk of periprosthetic fractures after multivariable adjustment.

Sensitivity analyses were performed by entering only significant comorbidities from the univariate analyses into multivariable-adjusted analyses, which did not alter the significance of associations and only changed their magnitude minimally (Table 2). Another sensitivity analysis adjusting the main multivariable model additionally for bilaterality did not have any meaningful effect on the associations: peptic ulcer disease, odds ratio 1.87 (1.27, 2.75) and COPD, odds ratio 1.63 (1.10, 2.40).

Discussion

In this study, we found that presence of two diseases was associated with an increased risk of postoperative periprosthetic fractures. Peptic ulcer disease increased the risk of periprosthetic fracture by 87% and COPD increased the risk by 62%. This increased risk is significant both statistically and clinically. One key finding to be kept in mind is the robustness of these estimates. For both conditions, the estimates were attenuated only slightly from the univariate models to multivariable-adjusted regression models (adjusted for 16 variables simultaneously). Both conditions were also common in our patient cohort undergoing primary TKA (10% and 13% patients). These findings are important and novel and deserve further discussion.

The observation of association of peptic ulcer disease and periprosthetic fractures leads to additional interesting hypotheses that need to be tested in future studies. Is this association due to peptic ulcer disease? Or is it treatment-related (proton-pump inhibitors versus other therapies)? Emerging evidence in cohorts of postmenopausal women suggests a consistently increased risk of fragility fractures in patients using proton-pump inhibitors (24-26), while it is unclear whether histamine-2 receptor blockers are associated with higher or lower fracture risk (24, 26). It remains to be seen whether these observations made for postmenopausal fragility fractures are true for patients undergoing TKA. These hypotheses need to be tested in TKA patients with periprosthetic fractures in future studies.

The association of COPD with periprosthetic fracture risk is not surprising considering that corticosteroids (inhaled, oral and parenteral) are used not uncommonly in patients with COPD. Some evidence exists in the non-arthroplasty literature regarding similar risks. COPD duration and severity and the use of inhaled corticosteroids were associated with increased risk of vertebral fractures (27-29). The lack of availability of medication data in total joint registry limited us from performing additional analyses to investigate whether use of corticosteroids was the underlying reason for the association of COPD with periprosthetic fractures. Studies to examine these hypotheses in a different dataset that provides data on medication use in TKA cohorts are underway to determine the exact nature of this association.

How do these findings help surgeons and patients? Our study examined several diseases as potential predictors of periprosthetic fractures and found that only two comorbidities were

associated independently with the risk. The knowledge gained from our study can be incorporated in patient-surgeon discussions regarding this increased risk in patients with peptic ulcer disease or COPD. These findings should also stimulate research into why these associations exist and further research into mechanisms of these associations.

These findings must be interpreted considering study limitations. Misclassification bias for comorbidity is possible, since we used electronically captured diagnoses. This may have biased some estimates towards the null, meaning that we may have missed some significant associations. Thus, our estimates are likely conservative. We may have missed periprosthetic fractures in some patients due to loss to follow-up, despite intensive efforts by dedicated total joint registry staff, and thus the cumulative incidence estimates may be conservative. However, as described earlier, dedicated registry staff makes every attempt to follow each patient prospectively for these outcomes. Another limitation is the inability to control for osteoporosis, an important confounder of association of other comorbidities and fracture risk. The study was not designed to examine operation-technique related factors and postoperative physical activity, covariates that may impact the observed associations. Studies are needed to address if after adjustment for these and other factors, the associations noted in our study hold true. Both loss to follow-up (underreporting of fractures in some patients not reachable through clinic, mail and phone contact) and misclassification of comorbidity and fractures due to capture from medical records (rather than a re-review and validation) likely biased our estimates towards null, making these estimates conservative, where the real associations may be even more impressive. However, there is a rigorous protocol to follow all post-arthroplasty patients for complications, the diagnosis of periprosthetic fractures were based on medical records including the operating room report, an orthopedic surgeon's clinical note and/or review of outside records or radiographic films in all cases, and Deyo-Charlson comorbidities have been systematically captured in Mayo databases since 1994, a key reason for choosing this time-period for study. These procedures minimize these biases. Selection bias is unlikely to have impacted these results, since the sample consisted of every patient who underwent TKA and provided permission for use of their medical records (>98% of all patients seen at Mayo Clinic provide permission for use of data for research).

Our study has several strengths including use of prospectively collected data from the total joint registry and a large sample size allowing for meaningful analyses. Another strength is the use of multivariable adjusted analyses, that control for multiple important demographic, clinical and implant factors. Our estimates were robust, and showed minor attenuation when adjusted for several variables in multivariable analyses.

In summary, the presence of peptic ulcer disease and chronic obstructive pulmonary disease were associated with higher risk of postoperative periprosthetic fractures after primary TKA. The increase in risk was both statistically and clinically significant indicating by almost doubling of the risk. Surgeons should consider discussing this risk with patients prior to the surgery, considering that both conditions are common in patients undergoing TKA. Future studies should examine whether these associations are related to the disease (peptic ulcer disease or chronic pulmonary disease) or the treatments used for these conditions (proton-pump inhibitors, H2-blockers, corticosteroids etc.).

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IRB approval: This study was approved by the Mayo Clinic Institutional Review Board and all investigations were conducted in conformity with ethical principles of research.

"The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government."

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Significance and Innovation

1. Presence of peptic ulcer disease is associated with twice the risk of periprosthetic fractures after primary TKA.
2. Chronic obstructive pulmonary disease leads to 1.6-times higher risk of periprosthetic fractures after primary TKA.
3. Intervention strategies targeting better preoperative comorbidity management may lead to reduction of risk of periprosthetic fractures after primary TKA.

Table 1

Demographic Features of Study Cohort

	Primary TKA (n=17,633)
	Mean (standard deviation) or n (%)
Mean Follow-up in years	6.3 (4.7)
Male /Female	7,852 (45%)/9,781 (55%)
Unilateral/bilateral	12,914 (73%)/4,719 (27%)
Age at Surgery in years	68.4 (10.0)
Age Category	
≤60 years	3352 (19%)
61-70 years	6206 (35.2%)
71-80 years	6493 (36.8%)
>80 years	1582 (9%)
Body Mass Index (BMI) in kg/m^2	31.2 (6.15)
BMI Category, kg/m^2	
Missing	67 (0.4%)
Normal, < 25.0	2,362 (13.4%)
Overweight, 25-29.9	5,961 (33.9%)
Obese, 30-39.9	7,710 (43.9%)
Morbidly obese, ≥40.0	1,533 (8.7%)
ASAScore	
Missing	67 (0.4%)
1	291 (1.7%)
2	9,614 (54.7%)
3	7,544 (42.9%)
4	117 (0.7%)
Deyo-Charlson Index Group	
Heart disease	1794 (10.2%)
Peripheral vascular disease	1106 (6.3%)
Cerebrovascular disease	1678 (3.6%)
Moderate-severe Renal disease	1320 (7.5%)
Peptic ulcer disease	1721 (9.8%)
Chronic Obstructive Pulmonary disease	2228 (12.6%)
Diabetes	2217 (12.6%)
Connective tissue disease	1596 (9.1%)
Cancer	2925 (16.6%)
Other (dementia, liver disease, AIDS)	1173 (6.7%)
Operative Diagnosis (Primary)	
Osteoarthritis	16372 (92.8%)
Rheumatoid/inflammatory arthritis	657 (3.7%)
Other[a]	604 (3.4%)
Implant Fixation	

	Primary TKA (n=17,633)
	Mean (standard deviation) or n (%)
Uncemented	1555 (8.8%)
Cemented or hybrid*	16078 (91.2%)

[a]Other diagnoses included genu varum, genu valgum, hemophilia, paget's disease, failed previous disease including arthrodesis, failed previous osteotomy, failed previous patellectomy, Chacot arthropathy, chondromalacia, pigmented villonodular synovitis etc.

ASA, American Society of Anesthesiologists

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Table 2

Univariate and Multivariable-adjusted Hazard of Postoperative Periprosthetic fracture following Primary Total Knee Replacement (TKA)

Variable	Total (n=17633)	Periprosthet ic fractures (n=188)	Univariate Hazard Ratio (95% CI)	Multivariable Hazard [a] Ratio (95% CI)	Multivariable Hazard Ratio (95% CI) [b]
Heart Disease (MI, CHF)			p=0.419	p=0.96	
No	15839	168 (1%)	1.00 (ref)	1.00 (ref)	
Yes	1794	20 (1%)	1.21 (0.76, 1.93)	1.01 (0.61, 1.67)	
Peripheral Vascular Disease			p=0.16	p=0.48	
No	16527	174 (1%)	1.00 (ref)	1.00 (ref)	
Yes	1106	14 (1%)	1.48 (0.86, 2.55)	1.23 (0.69, 2.19)	
Cereberovascular disease (including hemiplegia)			p=0.693	p=0.73	
No	15955	171 (1%)	1.00 (ref)	1.00 (ref)	
Yes	1678	17 (1%)	1.11 (0.67, 1.82)	0.91 (0.53, 1.55)	
Moderate-severe Renal Disease			**p=0.037**	p=0.13	P=0.11
No	16313	170 (1%)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	1320	18 (1%)	1.68 (1.03, 2.73)	1.49 (0.89, 2.49)	1.51 (0.92, 2.49)
Peptic Ulcer Disease			**p<0.001**	**p=0.0014**	**P=0.0011**
No	15912	154 (1%)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	1721	34 (2%)	2.08 (1.43, 3.02)	1.87 (1.28, 2.75)	1.88 (1.29, 2.75)
Chronic Obstructive Pulmonary Disease (COPD)			**p=0.002**	**p=0.02**	**P=0.01**
No	15405	154 (1%)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	2228	34 (2%)	1.78 (1.22, 2.57)	1.62 (1.10, 2.40)	1.62 (1.11, 2.39)
Diabetes (with or without organ damage)			p=0.161	p=0.24	
No	15416	163 (1%)	1.00 (ref)	1.00 (ref)	
Yes	2217	25 (1%)	1.35 (0.89, 2.06)	1.30 (0.84, 2.03)	
Other (dementia, liver disease, AIDS)			**p=0.042**	p=0.07	P=0.13
No	16460	171 (1%)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	1173	17 (1%)	1.68 (1.02, 2.77)	1.64 (0.96, 2.81)	1.48 (0.89, 2.46)
Connective tissue Disease			p=0.056	p=0.55	
No	16037	161 (1%)	1.00 (ref)	1.00 (ref)	
Yes	1596	27 (2%)	1.49 (0.99, 2.24)	1.17 (0.69, 1.99)	
Cancer			p=0.785	p=0.17	

Variable	Total (n=17633)	Periprosthet ic fractures (n=188)	Univariate Hazard Ratio (95% CI)	Multivariable Hazard [a] Ratio (95% CI)	Multivariable Hazard Ratio (95% CI) [b]
No	14708	161 (1%)	1.00 (ref)	1.00 (ref)	
Yes	2925	27 (1%)	0.94 (0.63, 1.42)	0.73 (0.47, 1.15)	

[a] Multivariable model simultaneously adjusted for all variables including age, gender, ASA class, BMI, operative diagnosis, implant fixation (cement status) and each Deyo-Charlson comorbidity category; 17,499 of the 17,633 TKAs were available for the multivariable analyses

[b] Multivariable model adjusted only for comorbidities significant in univariate analyses with p-value <0.05

Ref, reference category