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Rheumatoid Arthritis vs Osteoarthritis in Patients Receiving Total Knee Arthroplasty: Perioperative Outcomes

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Abstract

There is a paucity of data available on perioperative outcomes of patients undergoing total knee arthroplasty (TKA) for rheumatoid arthritis (RA). We determined differences in demographics and risk for perioperative adverse events between patients suffering from osteoarthritis (OA) versus RA using a population-based approach. Of 351,103 entries for patients who underwent TKA, 3.4% had a diagnosis of RA. RA patients were on average younger [RA: **64.3** years vs OA: **66.6** years; p<0.001] and more likely female [RA: **79.2**% vs OA: **63.2**%; P<0. 001]. The unadjusted rates of mortality and most major perioperative adverse events were similar in both groups, with the exception of infection [RA: **4.5**% vs. OA: **3.8**%; P<0.001]. RA was not associated with increased adjusted odds for combined adverse events.

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Keywords

Osteoarthritis; Rheumatoid Arthritis; Arthroplasty; Knee; Outcomes Research

Introduction

Most patients undergo total knee arthroplasty (TKA) for progressive bone and joint destruction evoked by osteoarthritis (OA). However, patients suffering from rheumatoid arthritis (RA) frequently develop involvement of the knee joint during the course of their disease[22, 31]. Despite advances in treatment, knee replacement can eventually be indicated in a subgroup of patients. The multisystem disease characteristics of RA were previously identified as a risk factor for adverse outcomes in a surgical setting[38, 39]. Immunological processes leading to gradual destruction of various tissues throughout the body – including lung, heart and great vessels – increased patients' risk to incur various cardiopulmonary adverse events. Patients suffering from RA were shown to have higher rates of cardiac morbidity[37], pulmonary disease[35] and, historically, higher mortality rate after surgery. However, treatment strategies for RA underwent significant evolution before and around the turn of the century. The widespread and extensive use of potent disease-modifying drugs (DMARDs) ultimately obviated surgical treatment in a substantial number of patients and improved overall health, outcome and survival of RA patients[7]. While the immunosuppressive medication is frequently discontinued in the perioperative phase, long-term treatment decreases the tissue destruction process and might therefore beneficially influence the perioperative risk. Yet, little is known on how these temporal changes impact on surgical outcome in patients still in need of knee arthroplasty. Existing literature is frequently limited by inclusion of older data[49], restriction to few outcomes of interest[20, 33], or by inclusion of heterogeneous populations, such as patients suffering from a variety of different autoimmune conditions or undergoing different forms of orthopedic surgery[10, 20, 38]. In this study we sought to study perioperative outcomes of patients undergoing TKA with or without a diagnosis of RA with the goal to 1) identify the prevalence of RA in patients undergoing TKA, 2) compare their demographics to those being operated on for OA, and 3) determine differences in rates of and adjusted risk for perioperative adverse events, mortality and various other outcomes. We hypothesized that, despite their higher comorbidity burden, patients suffering from RA are not subject to an increased risk of perioperative adverse events, compared to those undergoing their surgery for sole OA.

Materials and Methods

We obtained data files for the time period between years 2006 and 2010 from Premier Perspective, Inc. (Charlotte, NC)[36]. Data included in this proprietary administrative discharge database, containing information from approximately 400 acute care hospitals in the United States, is fully de-identified and compliant with the Health Insurance Portability and Accountability Act (HIPAA)[44]. As all coding sources included are associated with billing and accounting operations, data contributors are incentivized to ensure accuracy of the data. Moreover, all data undergoes quality assurance cross-checks by the vendor, along with a rigorous seven-step integrity validation process before processing in the premier data warehouse. This project was exempted from review by our Institutional Review Board.

Study sample, demographic variables, comorbidities, adverse events

The database was queried for entries of patients receiving primary knee arthroplasty, utilizing the International Classification of Diseases-9th revision-Clinical Modification

(ICD-9-CM) procedure code (81.54). The results were subdivided by concomitant diagnosis of osteoarthritis (715.x) or rheumatoid arthritis (714.×) and analyzed with regard to patient and health care-related characteristics (age, sex, race, admission type, hospital size, hospital location, hospital teaching status and type of anesthesia (general, neuraxial, combined neuraxial-general, unknown)). The prevalence of individual preexisting comorbidities, including myocardial infarction, peripheral vascular disease, cerebrovascular disease, COPD, uncomplicated diabetes, complicated diabetes, renal disease and cancer, as well as an overall comorbidity burden was assessed and compared between groups utilizing the method described by Deyo et al[9]. The Deyo adaptation of the Charlson comorbidity index is frequently used to provide a numeric measurement of the patient's comorbidity load. In principle, each comorbidity is numerically weighed according to its severity and subsequently added up to an overall score. Higher scores are known to directly correlate with a higher risk of adverse outcomes. Patients were categorized into one of four groups according to their Deyo score (0, 1, 2, >=3).

Occurrences of major adverse events, mechanical ventilation and blood product transfusion were identified using ICD-9-CM codes and/or billing codes (see Appendix 1). Major adverse events included were pulmonary embolism, deep vein thrombosis, cerebrovascular event, pulmonary compromise, sepsis, cardiac adverse events other than myocardial infarction, acute myocardial infarction, pneumonia, all other infections, acute renal failure, gastrointestinal adverse events and mortality. The incidence of 30-day mortality includes hospital mortality and readmission within 30 days leading to death. Moreover, length of stay and cost of hospitalization were determined and compared between groups. For the regression analysis, length and cost of hospitalization were dichotomized based on the 75th percentile to accommodate skewness of the data; values exceeding this cut-off were defined as prolonged hospital stay or increased hospital costs, respectively, based on statistical and clinical judgment. A sensitivity analysis using various other cut-offs (including the median) yielded similar results.

Statistical analysis

All statistical analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC). The weighting procedure developed by CMS and made available by Premier was utilized to derive nationally representative estimates from the available data[36]. To facilitate analysis of weighted data, the SAS procedures SURVEYMEANS, SURVEYFREQ, SURVEYREG and SURVEYLOGISTIC were utilized to descriptive analyses and modeling efforts.

Univariate Analysis

Weighted means and percentages were described for continuous and categorical variables, respectively, by type of arthritis. For variables that had a skewed distribution, median and interquartile range was estimated. For continuous variables, 95% confidence intervals (CI) were shown as a measure of variability. Chi-Square test was performed to evaluate the association of two categorical variables. Two-sample T-test or Wilcoxon Ranked sum test were used to compare means or medians for a continuous variable between two groups. Percentage of missing data of variables was also determined.

Multivariate regression analysis

Binary outcomes of incidence of major adverse events (as defined above), mechanical ventilation, use of blood product transfusion, prolonged length of hospital stay and increased hospital costs (as defined above) were analyzed . All variables that were considered clinically important or variables with p-values < 0.20 in the univariate analysis were included in the final multivariate analysis. For each outcome, logistic regression was used to evaluate its association with the type of arthritis while adjusting for age, sex, race, admission

type, type of anesthesia, hospital size, hospital teaching status, hospital location and individual comorbidities mentioned above. `Missing' data was included as separate category in each analysis. Adjusted odds ratios, 95% CI and p-values were reported. The conventional threshold of statistical significance (i.e., two-sided p-value <0.05) was used to determine significance of variables. 95% CIs of estimates were to provide readers additional information on the significance of the findings. A test of model discrimination using the C-statistic and a test of model calibration using the Hosmer-Lemeshow (H-L) test were performed for each model[17].

Results

351,103 entries for patients receiving TKA between 2006 and 2010 were found. Of those, 3.4% (n=11,755) patients had a diagnosis of RA. Patient and healthcare related parameters for both groups are listed in Table 1.

Patients with RA as the underlying pathology for arthroplasty were on average younger than those in the OA group [RA: 64.34 years (95 % C.I.=(64.12,64.57)) vs OA: 66.64 years (95 % C.I.=(66.60,66.68)); p<0.001], and the proportion of female patients was higher [RA: 79.2% vs OA: 63.2%; P<0.001]. More patients in the OA group underwent their surgery under neuraxial anesthesia [RA: 7.6% neuraxial, 53.9% general, 11.2% neuraxial+general, 27.3% unknown; OA: 8.8% neuraxial, 52.3% general, 10.4% neuraxial+general, 29.0% unknown]. In Table 2, prevalence rates of individual comorbidities are listed. Patients with a diagnosis of RA had a significantly higher prevalence of chronic obstructive pulmonary disease, but a lower incidence of diabetes mellitus. Missing data of race, admission type and type of anesthesia were approximately 19.0%, 0.5% and 26.0%, respectively.

With regard to adverse events, only the rate of infections was higher in the RA group [RA: 4.5% vs. OA: 3.8%; P<0.001]. All other adverse events occurred at similar rates in both groups, except for non-myocardial infarction cardiac adverse events, acute renal failure and gastrointestinal adverse events, which occurred more frequently in the OA group. Furthermore, the combined rate of adverse events was higher in the OA group [RA: 11.3% vs. OA: 12.5%; P=0.0003]. 30-day mortality tended to be lower in the RA group, but without reaching statistical significance.

However, patients in the RA group received blood product transfusions significantly more frequently [RA: 23.3% vs. OA: 16.6%; P<0.001], had longer mean lengths of hospitalization [RA: 3.60 (95 % C.I.=(3.56;3.63)) days vs. OA: 3.51 (95 % C.I.=(3.50;3.52)) days; P<0.001] as well as higher hospital cost [RA: 16,678 (C.I, 16,497 to 16,859) USD vs OA: 16,188 (95% C.I., 16,150 to 16,226); P<0.001] There was no difference in the requirement for mechanical ventilation between groups.

Similarly, for the RA group, the multivariate logistic regression yielded no increased adjusted odds for cumulative adverse events [OR=0.98 (CI 0.92;1.05); P=0.63] or mechanical ventilation [OR=0.91 (CI 0.70;1.19); P=0.49], but increased adjusted odds for blood product transfusion [OR=1.51 (CI 1.44;1.59); P<0.001], prolonged hospitalization [OR=1.10 (CI 1.05;1.15); P<0.001] and increased cost of hospitalization [OR=1.16 (CI 1.11;1.21); P<0.001] (exceeding the 75th percentile).

The C-statistics were 0.6, 0.7, 0.6, 0.6, 0.6 for cumulative adverse events, mechanical ventilation, transfusion, prolonged hospitalization, and increased hospital costs, respectively. The moderate C-statistics may be explained by higher homogeneity of the sample for these outcomes, and thus may not represent inadequate discrimination[26]. The H-L test showed significant p-values for all models except mechanical ventilation. However, the H–L test was previously shown to not perform well with large sample sizes[21].

Discussion

In this study, we compared patients receiving TKA based on the underlying pathology of RA versus OA. RA patients were more frequently female and younger, but carried a higher comorbidity burden. In our cohort, the only major perioperative adverse events that occurred more frequently in RA patients were infections other than sepsis or pneumonia. All other adverse events either occurred at a similar rate in both groups, or even more often in OA patients. Neither in-hospital nor 30 day mortality differed between groups. After adjustment for covariates, the risk for major adverse events was equal in both groups. However, the adjusted risk for blood product transfusion, increased length of stay and cost of hospitalization remained significantly higher in RA patients.

Our findings of female predominance and younger age among RA patients are consistent with the available literature[7]. Furthermore, patients with a diagnosis of RA had a higher comorbidity burden and were particularly more likely to have a diagnosis of chronic pulmonary disease. Lung involvement is a well-described systemic manifestation of RA[35], along with other organ systems affected by the disease[15]. Moreover, smoking has been identified as a risk factor for development and exacerbation of RA[19]. Despite this higher prevalence of conditions potentially predisposing RA patients to adverse perioperative outcomes, rates and risk for most adverse events were not higher in our sample, except for infections. Of note, while the incidence of postoperative infections in general was higher in the RA group, no difference was seen in rates of sepsis and pneumonia.

On the one hand, the increased risk of infection in RA patients may be attributable to decreased immune system response brought about by the disease itself, or by its immunosuppressive treatment[6]. Pharmacological agents used in RA have been suspected to provoke postsurgical infectious consequences, particularly glucocorticoids and immunosuppressive DMARDs[2, 8]. Controversy exists on the question whether treatment with biologics increases the risk for prosthetic joint infections and leads to impaired wound healing[4, 10, 43]. Even though different biologic agents act by similar mechanisms, there probably is considerable variability in their comparative side effect profile[45, 48]. In a perioperative setting, the long-term antirheumatic therapy should be adjusted to reach a desirable balance between avoidance of both infection and exacerbation of RA. Unfortunately, literature and appropriate recommendations on how to attain this goal remain sparse[16, 29]. Unfortunately, we have no information on therapy in this study.

On the other hand, aggressive treatment with TNFi and MTX has been associated with a lower incidence of cardiac events in RA patients[14, 30]. In a recent study including more than 7 million patients undergoing different types of surgery, Yazdanyar et al found no differences in the incidence of cardiovascular adverse events or mortality among patients with a diagnosis of RA, compared to those without[50]. Furthermore, RA patients in our sample had higher rates of chronic pulmonary disease and underwent TKA under general anesthesia more frequently than OA patients. Lung disease and general anesthesia is a potentially worrisome combination, with a reported 4- to 8-fold increase in risk for postoperative pulmonary adverse events among the general population[24]. Yet, the rate of these pulmonary adverse events remained unchanged across groups, and the regression did not yield different odds for postoperative mechanical ventilation. The reasons for this finding have to remain speculative, but it is feasible that advances and better understanding of the pathophysiology of perioperative lung injury may have reduced these events in RA patients to approximate those seen in the general population. It is tempting to speculate that current therapeutic norms for RA while decreasing the prevalence of cardiac disease have enriched the population of RA arthroplasty cases with the less treatment responsive smokers who are more likely to have underlying pulmonary disease. Moreover, general anesthesia

requiring tracheal intubation can pose significant difficulties and risks in patients suffering from rheumatoid arthritis-related cervical spine instability[1, 18].

Surprisingly, three adverse events occurred more frequently in the OA group in terms of crude incidence: non-myocardial infarction cardiac adverse events, acute renal failure and gastrointestinal adverse events. Several explanations for this seemingly counterintuitive finding come to mind. Patients in the OA group were on average older and more frequently male, and thus more prone to adverse events independently of comorbid conditions. Furthermore, OA patients had a higher prevalence of diabetes mellitus. Advanced age, male gender as well as presence of metabolic syndrome-related comorbidities have previously reported to be associated with higher rates of adverse events among joint arthroplasty patients[13, 25]. However, after adjustment for these and other covariates, the overall perioperative adverse event risk was equal among RA and OA patients. Reasons for this finding may include the fact that RA patients as a group may receive higher levels of attention from clinicians and from a wider range of professions during preparation for surgery and their hospital stay. RA patients were more likely to receive their surgery in larger teaching hospitals, which may have contributed to improved outcomes. Additionally, rheumatologists are frequently involved in the care of those patients in addition to the "regular" perioperative team. These factors may have enhanced the attentiveness and timely treatment of impending adverse events previously identified as an effective measure to prevent perioperative adverse outcomes and reduce mortality[12].

Mortality outcomes were not different between RA and OA patients, which is consistent with most recent studies focusing on short-term mortality after lower extremity joint arthroplasty [5, 10, 39, 47]. The risk for requiring a blood transfusion was about 50% higher for RA patients in our cohort compared to OA patients; similar observations have previously been published for total hip and shoulder arthroplasty [23, 40]. The increased requirement for blood product substitution is believed to partly relate to iron deficiency anemia caused by chronic non-steroidal analgesic use, anemia of chronic disease and bone marrow depression due to medications, all of which are common in RA patients [3, 34]. Moreover, the increases in length of stay and hospital costs, lower rate of discharges to home and increased adjusted risk for prolonged and more expensive hospitalization we observed are consistent with previous reports [11, 20, 27]. Likely, these heightened requirements for healthcare resources in RA patients relate to slower rehabilitation due to multiple joint involvement, as well as the increasingly multidisciplinary care these patients receive.

Our study has several limitations, most of which are inherent to the retrospective analysis of discharge databases. First, post-discharge events (except 30-day mortality), including readmissions, are not captured and can therefore not be taken into consideration. Secondly, we do not have information about medication administered or taken by the patients. Thus, we are not able to make assertions about adequacy and adjustment of antirheumatic and analgesic medication in the perioperative period. Similarly, intraoperative events like anesthetic adverse events and blood loss cannot be taken into consideration. However, the evaluation of outcomes likely represents a "real-world settings" as it represents data collected form various types of practices and non-protocolized environments. Furthermore, the accuracy of RA diagnoses within administrative databases has been questioned previously [46]. Identification of RA patients by diagnosis code alone has yielded a relatively low positive predictive value in a recent study by Ng et al [32]. However, we believe that performance of knee arthroplasty increases the likelihood that an existing diagnosis of RA in a patient is relevant, and thus the co-existence of the respective codes increases the accuracy of identification. We identified adverse events and comorbidities using ICD-9-CM codes (see Appendix 1). Despite a rigorous seven-step quality check performed by the vendor of the database, there is a possibility that inconsistencies and coding errors occurred. The

potential influence exerted by this effect is presumably low because the whole data collection process is exposed to the same coding bias, thus affecting both groups equally. Finally, there is considerable controversy about the ideal measures of model calibration and discrimination [41]. While it is necessary to use some measure of model performance in both categories of calibration and discrimination, overt reliance on any particular measure or a related cutoff (e.g., 0.7 for c-statistic and p-value <0.05 for L-H test) should be avoided [26].

In conclusion, apart from a moderately increased rate of infection, there is no increase in risk for perioperative adverse events and mortality detectible for patients with RA undergoing total knee arthroplasty, despite their higher comorbidity burden when compared to OA patients. RA patients are more prone to receive blood product transfusions postoperatively. Appropriate blood loss and transfusion management should be deliberated in due time in patients suffering from RA, including shed blood retransfusion, preparation of autologous blood as well as preoperative injection of epoetin [28, 42]. The finding of increased requirement for health care resources may in part pertain to the more thorough preparation for surgery that RA patients receive. Improvements in the medical therapy for RA might also account for the equally low perioperative risk profile to some extent. However, further research is warranted to provide scientific evidence for this relation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

presents patient demographics and health-care system related parameters, grouped by underlying disease (rheumatoid arthritis vs. osteoarthritis).

Characteristics				
Variable	**Category**	**Rheumatoid Arthritis**	**Osteoarthritis**	**p-value**
N=		11,755	339,348	-
% of Total		3.4	96.7	-
Average Comorbidity Index	(CI)	1.58 (1.56;1.60)	0.63 (0.62;0.63)	<0.001
Deyo Comorbidity Index Categories (%)	**0**	1.4	54.3	<0.001
	1	50.8	27.5	
	2	26.8	10.2	
	>/=3	21.0	8.0	
Average Age	(years) (CI)	64.34 (64.12;64.57)	66.64 (66.60;66.68)	
Age Group	**</=44**	4.3	1.5	<0.001
	45–54	14.1	11.2	
	55–64	30.4	28.6	
	65–74	31.4	33.9	
	>/=75	19.8	24.7	
Gender	**Female**	79.2	63.2	<0.001
	Male	20.8	36.8	
Race	**White**	66.6	71.0	<0.001
	Black	9.6	6.3	
	Other	4.5	2.9	
	Unknown	19.3	19.8	
Admission Type	**Emergent**	2.0	1.6	0.001
	Urgent	3.5	3.9	
	Routine	94.1	94.1	
	Other	0.1	0.1	
	Unknown	0.3	0.4	
Hospital Size (Bed number)	**</=299**	34.2	36.8	<0.001
	300–499	44.1	43.0	
	>/=500	21.7	20.2	
Hospital Location	**Rural**	4.8	4.9	0.40
	Urban	95.3	95.1	
Hospital Teaching Status	**Non-Teaching**	77.9	79.1	<0.001
	Teaching	22.1	20.9	
Patient discharged to	**Home**	58.8	63.1	<0.001
	Rehabilitation Facility / Other	41.2	36.8	
Type of Anesthesia	**Neuraxial Anesthesia**	7.6	8.3	<0.001
	General Anesthesia	53.9	52.3	

Characteristics				
Variable	**Category**	**Rheumatoid Arthritis**	**Osteoarthritis**	**p-value**
	Neuraxial + General	11.2	10.4	
	Unknown	27.3	29.0	

Table 2

details the prevalence of pre-existing comorbidities among patients.

Comorbidities			
	Rheumatoid Arthritis (%)	**Osteoarthritis (%)**	**p-value**
Myocardial Infarction	3.2	3.6	0.052
Peripheral Vascular Disease	1.8	1.6	0.31
Cerebrovascular Disease	0.2	0.2	0.73
COPD	17.6	14.2	<0.001
Uncomplicated diabetes mellitus	17.4	19.6	<0.001
Complicated diabetes mellitus	1.2	1.2	0.86
Renal disease	<0.1	<0.1	0.73
Cancer	1.5	1.5	0.86

Table 3

lists are the incidences of adverse events, use of blood product transfusion and mechanical ventilation as well as mean length of stay and hospital costs, grouped by underlying pathology.

	Rheumatoid Arthritis	Osteoarthritis	p-Value
Cumulative Adverse events	11.3	12.5	<0.001
In-Hospital Mortality (%)	0.1	0.1	0.49
30-day mortality (%)	0.1	0.1	0.25
Pulmonary Embolism (%)	0.4	0.5	0.23
Deep Vein Thrombosis (%)	0.6	0.6	0.94
Cerebrovascular Event (%)	0.1	0.1	0.30
Pulmonary Compromise (%)	0.6	0.6	0.92
Sepsis	0.1	0.1	0.58
Cardiac (non myocardial infarction) (%)	4.7	6.4	<0.001
Acute Myocardial Infarction (%)	0.2	0.2	0.15
Pneumonia (%)	0.8	0.8	0.97
All Infections (%)	4.5	3.8	<0.001
Acute Renal Failure (%)	1.1	1.4	0.021
Gastrointestinal Adverse event (%)	0.5	0.7	0.010
Blood product transfusion (%)	23.3	16.6	<0.001
Mechanical Ventilation (%)	0.6	0.7	0.27
Length of stay (days) (mean (CI))	3.60 (3.56;3.63)	3.51 (3.50;3.52)	<0.001
Hospital costs (USD) (mean (CI))	16,678 (16,497;16,859)	16,188 (16,150,16,226)	<0.001

Table 4

presents results from the multivariate regression, odds rations and 95% Wald confidence limits

Multivariate Regression: Rheumatoid Arthritis vs. Osteoarthritis (Reference)				
Effect	**Adjusted Odds Ratio**	**95% Confidence Limit**		**P-Value**
Cumulative Adverse events	0.98	0.92	1.05	0.63
Mechanical Ventilation	0.91	0.70	1.19	0.49
Blood Product Transfusion	1.51	1.44	1.59	<0.001
Prolonged Hospitalization	1.10	1.05	1.15	<0.001
Increased Cost of Hospitalization	1.16	1.11	1.21	<0.001

Reference = 1 (Osteoarthritis). Cumulative adverse event occurrence is defined by occurrence of any of the following: pulmonary embolism, deep venous thrombosis, cerebrovascular event, pulmonary compromise, sepsis, cardiac adverse events including myocardial infarction, pneumonia, all other infections, acute renal failure, gastrointestinal adverse events and in-hospital mortality