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Age alone is not a risk factor for periprosthetic joint infection

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SUMMARY

Background: It is not known whether age alone or the increased comorbidities in older patients are responsible for the higher rate of periprosthetic joint infection (PJI) in older patients.

Aim: To test the hypothesis that age alone is not a risk factor for PJI after total joint arthroplasty.

Methods: This retrospective study included the review of 23,966 patients undergoing primary total hip and knee arthroplasty between January 1st, 2010 and December 31st, 2016 at a single institution. Patients who developed PJI, as defined by International Consensus Meeting criteria, were identified. All enrolled patients were divided into three groups that included patients aged <65 years ($N = 12,761$), 65–74 years ($N = 6850$) and ≥75 years ($N = 4355$). Using multivariate analysis and propensity score matching analysis, the possible association between age and PJI was examined.

Findings: The incidence of PJI in the entire cohort was 0.72% (171 out of 23,966). Multivariate analysis adjusting for all variables, except age, demonstrated that, compared to the patients aged <65 years, there was no statistically significant difference in the rate of PJI for patients aged 65–74 years (odds ratio: 0.89; 95% confidence interval: 0.55–1.42; $P = 0.62$) or for patients aged ≥75 years (0.69; 0.36–1.32; $P = 0.26$).

Conclusion: When adjusting for confounding variables, age alone is not a risk factor for PJI. Studies evaluating the influence of age on the incidence of PJI should take into account the other confounding variables that contribute to PJI.

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Introduction

Periprosthetic joint infection (PJI), though relatively rare at 1%, is a devastating complication of total hip arthroplasty (THA) and total knee arthroplasty (TKA) [1,2]. The consequences of PJI are correlated with poor clinical outcomes, including increased mortality, as these patients often require multiple operations and a prolonged period of rehabilitation [3]. Management of PJI also places a massive economic burden on society [4,5]. In recent years more effort has been invested to understand risk factors that lead to PJI while seeking more effective preventive strategies [6–9].

Total joint arthroplasty (TJA) is a rewarding surgical procedure that is also offered to older patients [10]. The influence of age on the rate of PJI remains controversial. Some studies

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Table I
Demographic data of enrolled patients

Variable	Age group (years)			*P*-value
	<65 (*N* = 12,761)	65–74 (*N* = 6850)	≥75 (*N* = 4355)	
Body mass index	31.0 ± 6.1	30.0 ± 5.5	27.8 ± 4.9	<0.001
Operation time	79.2 ± 33.9	76.4 ± 31.1	71.1 ± 27.3	<0.001
Length of stay	2.7 ± 1.8	3.0 ± 2.1	3.6 ± 2.7	<0.001
Average CCI by age	2.3 ± 1.1	3.8 ± 1.1	4.9 ± 1.1	<0.001
Sex				<0.001
Male	6356 (49.8%)	2737 (40.0%)	1583 (36.3%)	
Female	6405 (50.2%)	4113 (60.0%)	2772 (63.7%)	
Type of surgery				<0.001
Total hip arthroplasty	7111 (55.7%)	3065 (44.7%)	2116 (48.6%)	
Total knee arthroplasty	5650 (44.3%)	3785 (55.3%)	2239 (51.4%)	
Transfusion	435 (3.4%)	390 (5.7%)	387 (8.9%)	<0.001
Alcohol abuse	6 (0.0%)	2 (0.0%)	0	0.451
Smoking	4668 (42.4%)	2698 (46.2%)	1441 (40.0%)	<0.001
Drug abuse	28 (0.2%)	5 (0.1%)	0	<0.001
Diabetes	1402 (11.0%)	1223 (17.9%)	667 (15.3%)	<0.001
Chronic renal failure	100 (0.8%)	120 (1.8%)	142 (3.3%)	<0.001
Chronic heart failure	100 (0.8%)	155 (2.3%)	168 (3.9%)	<0.001
Coagulopathy	126 (1.0%)	59 (0.9%)	56 (1.3%)	0.086
Chronic pulmonary disease	1408 (11.0%)	880 (12.8%)	456 (10.5%)	<0.001
Liver disease	136 (1.1%)	57 (0.8%)	17 (0.4%)	<0.001
Depression	1497 (11.7%)	740 (10.8%)	375 (8.6%)	<0.001
Malignancy	95 (0.7%)	96 (1.4%)	68 (1.6%)	<0.001
Hypertension	5774 (45.2%)	4153 (60.6%)	2788 (64.0%)	<0.001
Hypothyroidism	1277 (10.0%)	979 (14.3%)	786 (18.0%)	<0.001
AIDS	10 (0.1%)	6 (0.1%)	0	0.127
Deficiency anaemia	1578 (12.4%)	619 (9.0%)	449 (10.3%)	<0.001

CCI, Charlson comorbidity index; AIDS, acquired immune deficiency syndrome.
The number of periprosthetic joint infections, body mass index, operation time, length of stay, and average CCI by age are shown as mean ± SD.

have proposed that older patients are at higher risk of PJI [1,11], whereas others have not found age to play a role in causing PJI [12–16]. One of the main issues related to age and PJI relates to the fact that older patients are more likely to suffer medical comorbidities and/or be immunocompromised, which may be responsible for the higher rate of PJI in the elderly. Thus, for age to be an independent risk factor for PJI, the influence of other confounding variables needs to be separated out.

This study was designed to examine the hypothesis that age alone is not a risk factor for PJI.

Methods

This investigational protocol was conducted with the approval of our institutional ethical committee. A retrospective single institutional review was performed of patients undergoing primary THA or TKA between January 1st, 2010 and December 31st, 2016 and reached a one-year minimum follow-up. Patients with inflammatory arthritis and osteonecrosis of the femoral head were excluded. Patients who developed PJI, as defined by the International Consensus Meeting in 2013, within one year of index arthroplasty were identified [17]. Patients who developed PJI were identified from a cross-reference query with a biannually maintained institutional PJI database of PJIs that fulfilled Musculoskeletal Infection Society criteria [17]. A manual chart review was then performed to verify data.

Detailed demographic data including gender, age, body mass index (BMI), the length of hospital stay (LOS), operative time, type of surgery (THA or TKA), blood transfusion data as well as data pertinent to other variables were collected. The Charlson comorbidity index (CCI) of the patients, taking into account age and comorbidities such as alcohol abuse, smoking, drug abuse, diabetes mellitus, chronic renal failure, chronic

Table II
Bivariate and multivariate analyses of the association between age and developing periprosthetic joint infection

Age (years)	Non-adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
≤64	Reference		Reference	
65–74	0.99 (0.70–1.40)	0.96	0.89 (0.55–1.42)	0.62
≥75	0.84 (0.55–1.29)	0.43	0.69 (0.36–1.32)	0.26

OR, odds ratio; CI, confidence interval.

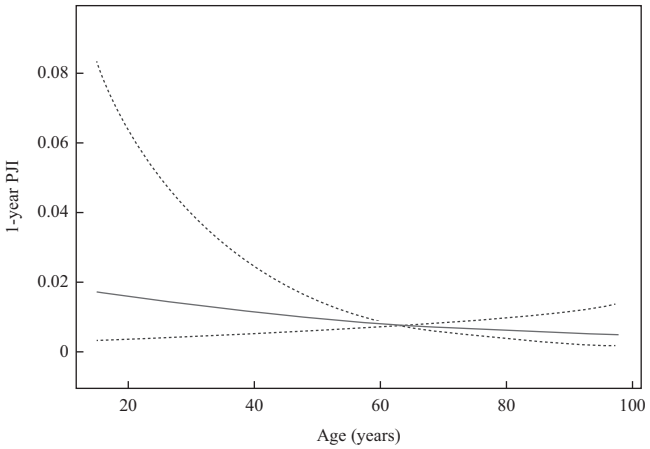

Figure 1. Adjusted smoothing spline plot for relationship between age and developing periprosthetic joint infection (PJI).

heart failure, coagulopathy, chronic pulmonary disease (CPD), liver disease, depression, malignancy, hypertension, hypothyroidism, acquired immunodeficiency syndrome (AIDS), and deficiency anaemia, was determined.

For the purpose of this study and to be able to perform meaningful analyses, the patients were divided into three groups based on age: <65, 65–74, and ≥75 years. By using bivariate and multivariate analyses with logistic regression, unadjusted and adjusted odds ratio (OR) were calculated in order to investigate the association between age and development of PJI. Furthermore, adjusted smoothing spline plots were generated to assess the shape of the relationship between age as continuous variable and development of PJI.

A set of sensitivity analysis using propensity score matching (PSM) was performed to validate the findings. PJI patients were matched with non-PJI patients using 1:10 nearest-neighbour matching, without replacement within a caliper width of 0.05. Variables chosen for matching included sex, BMI, operation time, LOS, CCI by age, type of surgery, transfusion, alcohol abuse, smoking, drug abuse, diabetes, chronic renal failure, chronic heart failure, coagulopathy, CPD, liver disease, depression, malignancy, hypertension, hypothyroidism, AIDS, deficiency anaemia. A standardized mean difference (SMD) for each variable was examined after PSM. Finally, bivariate analysis was conducted to identify the relationship between age and development of PJI in this matched cohort.

Statistical analysis

All the statistical analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solution, Inc., Boston, MA, USA). Categorical variables were presented as frequencies and percentages, and continuous variables as means and standard deviation. The patient demographics were compared among groups using analysis of variance (ANOVA) or Kruskal–Wallis test for

Table III
Demographic data after propensity score matching

Variables	Non-PJI ($N = 1570$)	PJI ($N = 157$)	Standardized mean difference	*P*-value
Body mass index	32.1 ± 6.1	32.1 ± 6.8	0.0065	0.9350
Operation time	89.2 ± 41.9	89.7 ± 44.8	0.0110	0.8928
Length of stay	3.27 ± 3.10	3.27 ± 2.07	0.0022	0.9819
Average CCI by age	3.52 ± 1.77	3.48 ± 1.55	0.0261	0.7672
Sex			0.0104	0.9690
Male	948 (60.4%)	94 (59.9%)		
Female	622 (39.6%)	63 (40.1%)		
Type of surgery			0.0166	0.9090
Total hip arthroplasty	753 (48%)	74 (47.1%)		
Total knee arthroplasty	817 (52%)	83 (52.9%)		
Transfusion	140 (8.9%)	13 (8.3%)	0.0227	0.9041
Alcohol abuse	0	0	–	–
Smoking	747 (47.6%)	76 (48.4%)	0.0166	0.9090
Drug abuse	12 (0.8%)	1 (0.6%)	0.0153	1.0000
Diabetes	389 (24.8%)	37 (23.6%)	0.0283	0.8116
Chronic renal failure	58 (3.7%)	6 (3.8%)	0.0067	1.0000
Chronic heart failure	76 (4.8%)	7 (4.5%)	0.0182	0.9858
Coagulopathy	33 (2.1%)	4 (2.5%)	0.0296	0.9372
Chronic pulmonary disease	185 (11.8%)	20 (12.7%)	0.0291	0.8231
Liver disease	86 (5.5%)	10 (6.4%)	0.0378	0.7777
Depression	269 (17.1%)	27 (17.2%)	0.0017	1.0000
Malignancy	27 (1.7%)	2 (1.3%)	0.0367	0.9292
Hypertension	1107 (70.5%)	108 (68.8%)	0.0374	0.7202
Hypothyroidism	213 (13.6%)	21 (13.4%)	0.0056	1.0000
AIDS	0	0	–	–
Deficiency anaemia	162 (10.3%)	16 (10.2%)	0.0042	1.0000

PJI, periprosthetic joint infection; CCI, Charlson comorbidity index; AIDS, acquired immune deficiency syndrome.
The number of periprosthetic joint infections, body mass index, operation time, length of stay, and average CCI by age are shown as mean ± SD.

Table IV
Bivariate analyses of the association between age and developing periprosthetic joint infection after propensity score matching

Age (years)	OR (95% CI)	*P*-value
≤64	Reference	–
65–74	1.00 (0.69–1.45)	1.00
≥75	0.90 (0.56–1.43)	0.66

OR, odds ratio; CI, confidence interval.

continuous variables and χ^2-test or Fisher exact test for categorical variables. Bivariate and multivariate analyses with a logistic regression model were performed to identify the association between age as both continuous and categorical (aged <65, 65–74, and ≥75 years) variables and the development of PJI. $P < 0.05$ was considered significant.

Results

The study included 23,966 patients undergoing primary TJA. Among the cohort 12,761 patients were aged <65 years, 6850 patients were aged 65–74 years, and 4355 patients were aged ≥75 years (Table I). There was a statistically significant difference in the incidence of major comorbidities and demographics between the groups.

Out of the entire group, 172 patients developed PJI within one year of index arthroplasty, accounting for a PJI rate of 0.72% (172 out of 23,966). The rate of PJI among the different age groups was not significantly different. The mean incidence of PJI was 0.74% (94 out of 12,761) in patients aged <65 years, 0.73% (50/6,850) among the cohort of patients aged 65–74 years, and 0.64% (28/4355) among patients aged ≥75 years. The results of bivariate and multivariate analyses are shown in Table II. Bivariate analyses in all non-adjusted variables revealed that there was no statistically significant difference in patients aged 65–74 years (odds ratio (OR): 0.99; 95% CI: 0.70–1.40; $P = 0.96$) and in patients aged ≥75 years (OR: 0.84; 95% CI: 0.55–1.29; $P = 0.43$) compared with patients aged <65 years. Multivariate analyses also showed that there was no statistically significant difference in the rate of PJI between the three different age groups. Furthermore, the adjusted smoothing spline plot for relationship between age and PJI indicated that age alone had no association with PJI, as the relationship was non-linear (Figure 1).

The patient demographic after PSM is shown in Table III. The PSM yielded 157 PJI patients and 1570 non-PJI patients with comparable baselines (all SMDs <0.05). There was no significant difference in all variables between non-PJI and PJI groups. The quality of propensity score matching was considered well balanced. In this PSM cohort, bivariate analyses showed that there was no significant difference in patients aged 65–74 years (OR: 1.00; 95% CI: 0.69–1.45; $P = 1.00$) and patients aged ≥75 years (OR: 0.90; 95% CI: 0.56–1.43; $P = 0.66$) compared with patients aged <65 years (Table IV).

Discussion

The improvement in life expectancy has led to many elderly active people with arthritis of joints who may need TJA [10]. Therefore, the number of TJAs continues to increase across the globe, as does the number of patients who develop PJI. Our understanding of PJI continues to improve as the risk factors for this complication after TJA are identified [6–9]. One issue that remains is the influence of age on PJI. Some studies have suggested that age is a risk factor for PJI [1,11], whereas other studies have refuted this [12–16]. Bozic *et al.* investigated the risk factors for PJI in a case–control multicentre study and concluded that age alone was not a risk factor [12]. Kunutsor *et al.* performed a systematic review that included 66 observational studies, concluding that age had no direct influence on the rate of PJI [14]. On the other hand, some studies reported that age was the risk factor for developing PJI after TJA. Ridgeway *et al.* investigated the major risk factor for developing PJI after hemiarthroplasty, primary THA, and revision THA in a multicentre study [1]. They concluded that patients aged 75–79 years and >80 years had a 1.56- and 1.66-fold increased risk for PJI, respectively, compared with patients aged <65 years [1]. Also, Wu *et al.* investigated the risk factor for PJI after primary THA and TKA in Chinese patients in a case–control study [11]. They observed that patients aged 65–75 years had a 3.36-fold increased risk of PJI, compared with patients aged between 45 and 65 years [11]. Based on the available studies, the relationship between age and PJI remains conflicting and unknown.

The current study was designed to overcome the shortfalls of prior studies, namely controlling for important variables when assessing the relationship between age and PJI. The collected data were subjected to bivariate or multivariate analyses and then all variables were adjusted using propensity score matching. Additionally, adjusted smoothing spline plot examining the relationship between age and PJI revealed that age as continuous variable was non-linear. The aforementioned analysis allows us to dispel the notion that age alone is a risk factor for PJI.

There were some limitations to this study. First, the study was retrospective in nature and the accuracy of the collected data depended on the details of the information recorded in our database. Second, this study was from a single institution, with a relatively small number of PJI patients, limiting its generalizability. The number of PJI patients was relatively small compared to that of a multicentre study although a large number of primary THAs was included in our study. Third, the three groups were not exactly equal in terms of some of the important variables being examined. The latter issues were the reason for us conducting propensity score matching analysis in order to control for many confounding factors and the potential for selection bias.

Despite the aforementioned limitations, the study reached its intended goal of examining the relationship between age and PJI. This finding may be useful for orthopaedic surgeons in their discussion of risks with patients. It may also help future research investigations in the field of PJI.

In conclusion, this study found that age alone is not a risk factor for PJI when adjusting for confounding variables. Studies evaluating the influence of age on the incidence of PJI should take into account the other confounding variables that contribute to PJI. Our result may be useful for orthopaedic surgeons in their discussion of risks with patients.

Conflict of interest statement
None declared.

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