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Which patient-related factors are linked to superficial surgical site infection and the progression into a periprosthetic joint infection after elective primary total joint arthroplasty?
A cross-sectional study on 1,291 patients

Running title: Which patient-related factors are linked to superficial surgical site infection and the progression in to a periprosthetic joint infection?

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Declarations

None of the authors have any conflict of interest to declare.

Ethics approval

The study design was reviewed and approved by the Human Research Ethics Committee in Uppsala, Sweden, Nr: 2019-01425.

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Abstract

Objectives: The incidence of superficial surgical site infection (SSSI) may increase the risk of periprosthetic joint infection (PJI). The objective of this study is to identify patient-related risk factors associated with SSSI and investigate their correlation with the progression of PJI. **Design:** 1,291 primary elective hip and knee prostheses were included. Patients were interviewed ≥3 months after surgery to answer questions about the postoperative period, including any occurrences of SSSI. The diagnosed PJI was determined by an orthopaedic surgeon and a specialist in infectious diseases. All patients with PJI underwent revision surgery. **Setting:** This study was performed at Uppsala Univerity Hospital, Uppsala.

Participants: 1,184 patients and 1,314 joints were included. Because of bilateral surgery during the same operative session, 23 joints were excluded due to an increased risk of infection.

Primary and secondary outcome measures: Which of the patient-related risk factors; joint, age, sex, the American Society of Anaesthesiologists classification (ASA), body mass index (BMI), smoking, diabetes and rheumatic disease associated with 1) superficial surgical site infection and 2) the progress in to a periprosthetic joint infection.

Results: 7.0% of the patients developed an SSSI and 26.7% of those progressed to a PJI. Factors found with increased adjusted risk ratio (aRR) for SSSI were: knee surgery (1.9; 95% confidence interval CI: 1.2 – 3.1), age ≥65 years (1.7; 95% CI: 1.1 – 2.8) and BMI ≥35 (2.3; 95% CI: 1.2 – 4.2). Male patients showed a significant risk of developing PJI after SSSI, with a RR of 3.3 (95% CI: 1.1 – 10.5).

Conclusions: Patients developing SSSI have a great risk on progress to PJI. Older obese patients considered for elective primary total knee arthroplasty seem to have an increased risk of developing SSSI and male gender is the most significant risk factor to progress from SSSI into PJI.

Strengths and limitations of this study

Strengths

- Large cohort size (n=1291)
- Meticulous follow-up of each patient
- Exclusively includes patients with primary elective joint surgery

Limitations

- Retrospective study design
- Small number of infections leading to the risk of a type II error.

Keywords

Periprosthetic joint infection (PJI), superficial surgical site infection (SSSI), total joint arthroplasty, risk factors.

Introduction

Infection after TJA can be defined as either superficial involving skin or subcutaneous tissue only (a superficial surgical site infection, SSSI) or deep (periprosthetic joint infection, PJI) with deep soft tissue involvement (e.g., fascial and muscle layers) and the prosthesis. The incidence of SSSI after TJA can vary from 1 to 10% (1, 2) and may increase the risk of PJI by up to 35 times (3). The frequency of PJI ranges between 1 and 5% (4-7). Patient-related risk factors, such as obesity, RA, smoking, male sex, age, alcohol abuse, American Society of Anaesthesiologists (ASA) classification >2 and diabetes mellitus (DM) (8-16), have been described as risk factors for PJI. In clinical practice priority should be to identify patients at high risk for SSSI and PJI, aiming for patient optimisation and the opportunity to manage modifiable risk factors since it is essential to seize any opportunity to optimise all prerequisites for the best achievable surgical outcome. Our primary objectives were to 1) determine which patient-related factors are linked to superficial surgical site infection (SSSI) and 2) investigate the progression in to a deep periprosthetic joint infection (PJI). Our study aims to (i) identify patient-related risk factors associated with SSSI and (ii) investigate their correlation with the progression of PJI.

Methods

Study design

This cross-sectional study of primary elective prostheses in hip or knee joints included patients in a national project designed to lower the incidence of hospital-related infections (17). Patients included in this study were treated at Uppsala Univerity hospital from November 2008 to December 2012, and interviewed ≥3 months after surgery to answer questions about the postoperative period. The patients' records were reviewed to determine whether there had been any documentation of difficulties with wound-healing or whether antibiotics were prescribed to treat an infection related to arthroplasty surgery.

In a retrospective review of patient records selected patients fulfilled the criteria for PJI (18), but those criteria had not been used at diagnosis. Patient records were reviewed for patient-related risk factors while a local arthroplasty register was used to obtain perioperative information about whether revision surgery had been necessary due to persistent PJI. Follow-up was a minimum of 5 years.

This study was limited to patient-related risk factors associated with developing an SSSI and focused on those factors that might be possible to avoid or optimise preoperatively.

Consent for publication was considered in the application to the Human Research Ethics Committee. However, no consent, verbal or written was needed, due to the retrospective study design. The study design was reviewed and approved by the Human Research Ethics Committee (Dnr: 2019-01425).

Patient and Public Involvement

Patients or the public were not involved in the development of the research question, outcome measures, the design, conduct, reporting, or dissemination plans of our research. The results of this study will not be seprately dissiminated to study participants.

Study population

1,184 patients and 1,314 joints were included. Because of bilateral surgery during the same operative session, 23 joints were excluded due to an increased risk of infection. 1,291 surgeries (815 hips, 476 knees) were included.

Only cemented components were used in all knees. Hip prostheses were cemented, cementless or hybrids. In all cemented prostheses antibiotic-loaded cement with gentamycin was applied. All patients received systemic pre- and perioperative antibiotic prophylaxis in accordance with national guidelines (cloxacillin, and in the case of penicillin allergy, clindamycin).

Statistics

Descriptive statistics were used to summarise and report demographic characteristics.

Confounders

Such patient-related factors as joint, sex, age, BMI, RA, ASA classification, smoking and DM were considered clinically relevant confounders in the correlation between arthroplasty surgery and SSSI or PJI.

These specific patient-related variables have previously been linked to exposure and outcome and are not considered in the causal pathway between potential risk factors and outcome (Figure 1).

Some of the relevant confounders were analysed as categorical variables: ASA classification: <3 or ≥3, BMI: <35 or ≥35 and Age: <65 years or ≥65 years.

Patients with DM included both type 1 and 2 (drug- or diet-treated). In an initial analysis logistic regression was performed, entering all covariates as singular variables. Crude risk ratios (RRs) for SSSI and PJI were calculated for each variable with 95% confidence intervals (95% CIs). In the next step the covariates were entered in the regression model, with RRs mutually adjusted for all covariates. Adjusted RRs (aRRs) for each covariate were calculated for the occurrence of SSSI or PJI and any progression of SSSI in to PJI.

All statistical analyses were performed using SPSS (version 26.0) and p-values ≤ 0.05 were considered statistically significant.

Results

The total number of surgeries for prosthetic hip or knee joints was 1,291. 90 knee joints (7.0%) developed an SSSI and 24 (1.9%) a PJI. Of the 90 joints with SSSI, 24 (26.7%) progressed to a PJI (Figure 2).

In the hip cohort (815) 41 joints (5.0%) developed an SSSI, and 9 (1.1%) a PJI. In the knee cohort (476), 49 joints ((10.0%) developed an SSSI and 15 (3.2%) a PJI (Table 1).

Table 1. Number of postoperative infections

Variable	SSSI	PJI
Total cohort (1291)	90 (7.0 %)	24 (1.9%)
Hip (815)	41 (5.0 %)	9 (1.1%)
Knee (476)	49 (10.3 %)	15 (3.2%)

SSSI (superficial surgical site infection), PJI (periprosthetic joint infection).

Demographic characteristics of the cohorts are outlined in Table 2.

Table 2. Demographic characteristics

Variable	Total cohort	Hip cohort	Knee cohort	Range
	n = 1291	n = 815 (63%)	n = 476 (37%)	
Mean age (year)	63	61	65	18–96
Age				
<65	729 (56%)	479 (59%)	250 (53%)	
≥65	562 (44%)	336 (41%)	226 (47%)	
ASA-class[a]				
≤2	1048 (82%)	679 (85%)	369 (79%)	
≥3	225 (18%)	125 (15%)	100 (21%)	
Mean Body mass index	28	27	29	14–51
BMI[b]				
<35	1145 (90%)	743 (92%)	402 (86%)	
≥35	130 (10%)	63 (8%)	67 (14%)	
Gender				
Woman	731 (57%)	421 (52%)	310 (65%)	
Man	560 (43%)	394 (48%)	166 (35%)	
Smoking[c]				
No	1141 (90%)	716 (90 %)	425 (90%)	
Yes	129 (10%)	84 (10%)	45 (10%)	
Diabetes[a]				
No	1145 (90%)	731 (91%)	414 (88%)	
Yes	128 (10%)	73 (9%)	55 (12%)	
Rheumatological disease[d]				
No	1052 (88%)	689 (91%)	363 (83%)	
Yes	139 (12%)	67 (9 %)	72 (17%)	

ASA (American Society of Anaesthesiologists), BMI (Body mass index).

[a] missing data in 18 cases
[b] missing data in 16 cases
[c] missing data in 21 cases
[d] missing data in 100 cases

Risk factors for SSSI

Risk factors with a significant crude RR for developing SSSI were knee surgery (2.2; 95% CI: 1.4 – 3.3), age ≥65 years (1.7; 95% CI: 1.1 – 2.6), ASA classification ≥3 (2.3; 95% CI: 1.4 – 3.7), BMI ≥35 (2.4; 95% CI: 1.4 – 4.2) and rheumatic disease (1.9; 95% CI: 1.1 – 3.4). Adjusting for all covariates, factors with significant aRRs for SSSI were knee surgery (1.9; 95% CI 1.2 – 3.1), age ≥65 years (1.7; 95% CI: 1.1 – 2.8) and BMI ≥35 (2.3; 95% CI: 1.2 – 4.2) (Table 3).

Table 3. Risk ratio (RR) for SSSI

No SSSI	1201 (93%)				
SSSI	90 (7%)				
Variable	**SSSI**	**Crude RR (95 % CI)**	**P-value**	**Adjusted RR (95 % CI)**	**P-value**
Joint					
Hip	41 (45%)				
Knee	49 (55%)	2,2 (1,4 – 3,3)	**0,000**	1,9 (1,2 – 3,1)	**0.005**
Age					
<65	40 (44%)				
≥65	50 (56%)	1,7 (1,1 – 2,6)	**0,018**	1,7 (1,1 – 2,8)	**0,024**
ASA class[a]					
≤ 2	61 (69%)				
≥ 3	28 (31%)	2,3 (1,4 – 3,7)	**0,001**	1,6 (0,9 – 2,7)	0,069
Body mass index					
<35	72 (80%)				
≥35	18 (20%)	2,4 (1,4 – 4,2)	**0,002**	2,3 (1,2 – 4,2)	**0,010**
Gender					
Woman	49 (54%)				
Men	41 (46%)	1,1 (0,7 - 1,7)	0,666	1,4 (0,9 – 2,2)	0,206
Smoking[a]					
No	80 (90%)				
Yes	9 (10%)	1,0 (0,5 - 2,0)	0,988	1,1 (0,5 – 2,4)	0,836
Diabetes[a]					
No	76 (85%)				
Yes	13 (15%)	1,6 (0,9 – 3,0)	0,142	1,2 (0,6 – 2,3)	0,606
Rheumatological disease[b]					
No	68 (81%)				
Yes	16 (19%)	1,9 (1,1 – 3,4)	**0,031**	1,7 (0,9 – 3,2)	0,077

SSSI (superficial surgical site infection), ASA (American Society of Anaesthesiologists), CI (confidence interval)
[a] missing data in 1 case
[b] missing data in 6 cases

Risk factors for PJI

Risk factors with a significant crude RR for the development of PJI were knee surgery, ASA classification ≥3 and BMI ≥35. Factors with significant aRRs for PJI were knee surgery (2.6; 95%

CI: 1.1 – 6.4), ASA classification ≥3 (3.2; 95% CI: 1.3 – 7.9), BMI ≥35 (3.0; 95% CI: 1.2 – 4.2) and male sex (3.0; 95% CI: 1.2 – 7.5) (Table 4).

Table 4. Risk ratio (RR) for PJI

No PJI	1267 (98,1%)				
PJI	24 (1,9%)				
Variable	**PJI**	**Crude RR (95 % CI)**	**P-value**	**Adjusted RR (95 % CI)**	**P-value**
Joint					
Hip	9 (38%)				
Knee	15 (63%)	2,9 (1,3 – 6,7)	**0,012**	2,6 (1,1 – 6,4)	**0,033**
Age					
<65	12 (50%)				
≥65	12 (50%)	1,3 (0,6 – 2,9)	0,520	1,0 (0,4 – 2,5)	0,941
ASA class					
≤ 2	12 (50%)				
≥ 3	12 (50%)	4,9 (2,2 – 11,0)	**0,000**	3,2 (1,3 – 7,9)	**0,010**
Body Mass Index					
<35	17 (71%)				
≥35	7 (29%)	3,8 (1,5 – 9,3)	**0,004**	3,0 (1,2 – 4,2)	**0,032**
Gender					
Woman	9 (38%)				
Men	15 (62%)	2,2 (0,9 – 5,1)	0,063	3,0 (1,2 – 7,5)	**0,016**
Smoking					
No	23 (96%)				
Yes	1 (4%)	0,4 (0,1 – 2,8)	0,345	2,2 (0,3 – 16,8)	0,448
Diabetes					
No	19 (79%)				
Yes	5 (21%)	2,4 (0,9 – 6,6)	0,086	1,4 (0,5 – 4,0)	0,544
Rheumatological disease					
No	19 (79%)				
Yes	5 (21%)	2,0 (0,7 – 5,5)	0,166	1,9 (0,6 – 5,5)	0,259

SSSI (superficial surgical site infection), PJI (periprosthetic joint infection), ASA (American Society of Anaesthesiologists)
CI (confidence interval)

Risk factors for PJI in patients with SSSI

In the group of patients with SSSI the only significant risk factor for progression to PJI was male sex, with an aRR of 3.3 (95% CI: 1.1 – 10.5) (Table 5).

Table 5. Risk ratio (RR) for PJI in patients with SSSI

SSSI - no PJI	66 (73%)				
SSSI - PJI	24 (27%)				
Variable	**PJI**	**Crude RR (95 % CI)**	**P-value**	**Adjusted RR (95 % CI)**	**P-value**
Joint					
Hip	9 (37%)				
Knee	15 (63%)	1,6 (0,6 – 4,1	0,357	1,5 (0,5 – 4,4)	0,462
Age					
<65	12 (50%)				
≥65	12 (50%)	1,4 (0,5 – 3,5)	0,523	1,6 (0,6 – 4,9)	0,376
ASA-class					
≤ 2	12 (50%)				
≥ 3	12 (50%)	3,0 (1,1 – 8,2)	**0,025**	3,1 (1,0 – 10,0)	0,051
Body Mass Index					
<35	17 (71%)				
≥35	7 (29%)	2,1 (0,7 – 6,1)	0,195	2,0 (0,5 – 8,1)	0,316
Gender					
Woman	9 (37%)				
Men	15 (63%)	2,6 (1,0 – 6,7)	0,055	3,3 (1,1 – 10,5)	**0,041**
Smoking					
No	23 (96%)				
Yes	1 (4%)	3,2 (0,4 – 27,0)	0,282	0,3 (0,4 – 39,5)	0,230
Diabetes					
No	19 (79%)				
Yes	5 (21%)	1,9 (0,6 – 6,4)	0,317	1,6 (0,3 – 7,5)	0,556
Rheumatological disease					
No	19 (79%)				
Yes	5 (21%)	0,9 (0,3 – 2,8)	0,792	1,2 (0,3 – 5,1)	0,780

SSSI (superficial surgical site infection), PJI (periprosthetic joint infection), ASA (American Society of Anaesthesiologists)
CI (confidence interval)

Discussion

This study shows that knee surgery, age >65 years and obesitas are independent risk factors for the development of SSSI. Superficial wound complications were associated with PJI in 24% of the cases, and male sex was a significant factor in the progression into PJI. A recent meta-analysis, showed that male sex was a risk factor for PJI development, especially after total knee arthroplasty (TKA) supports these results (19). The link between male sex and PJI may be attributed to some contributing behavioural factors, including smoking, diet, hygiene and alcohol consumption, but the reasons behind this are not clear. Sex-related differences in immune response due to bacteria (e.g., Staphylococcus aureus and Pseudomonas aeruginosa) have been reported. In addition, septicaemia and bacteraemia occur more frequently in males than females (20), but whether it will or will not this affect the development of SSSI or PJI has yet to be investigated.

Patients with knee prostheses have shown a higher rate of PJI and are known to be in greater need of revision surgery than patients with hip prostheses (6, 9, 12, 19). There is less soft tissue around the knee than around the hip, meaning a shorter distance between skin and joint. Blood circulation around the knee area is more exposed to impact than the hip area and the perfusion is easier to disturb.

Age was a significant risk factor for SSSI in our study, which is congruent with results from a large (n=1,000 patients) retrospective study (1). An elderly patient may have pre-existing medical conditions and fragile skin that can impair wound healing and cause SSSI.

A high ASA classification posed a significant risk factor for developing PJI and SSSI in the univariate analysis but not after adjusting for the other covariates. The correlation between a high ASA classification and infection after surgery may be explained because the ASA classification encapsulates several other known risk factors (e.g., smoking, DM and obesity). Each of these risk factors has been independently associated with a higher risk of surgical site infection resulting from tissue hypoperfusion and subsequent impaired immunological function (13, 21).

Excess weight/obesity is a known risk factor for osteoarthritis, TJA and PJI (22). Multiple medical comorbidities, including DM type II, hypertension and cardiovascular diseases, are usually associated

with obesity, affecting patients' BMI and ASA classification (23-25). In this study BMI ≥ 35 was a risk factor for SSSI and PJI. The association between BMI and postoperative wound complications may be explained by prolonged or more complicated arthroplasty surgery (26) and protracted postoperative wound drainage (27). The present results are in line with large register-based studies. Sayed-Noor et al. observed that the risk of reoperation within 2 to 5 years increased in patients with higher BMI classification (I-III) (28). In another study with 19,000 patients by Shohat et al. noted that the BMI cut-off threshold was associated with an increased risk of PJI (29). No threshold for PJI was observed (29), although a higher BMI classification was linked to an increased risk of PJI.

The rate of SSSI (7.0%) and PJI (1.9%) in this study is consistent with international studies showing levels of SSSI ranging from 1-10% (1, 30) and PJI ranging from 0.2-2.23% (5, 6, 8).

Two major strengths of this study are cohort size (n=1291) and the meticulous follow-up of each patient. This thorough postoperative follow-up confirms that the number of recorded incidents of SSSI is accurate, and the follow-up time of 5 years is sufficient to reveal any potential cases of PJI. Similar studies have presented larger cohorts but only on registers (31, 32) or shorter follow-ups (1, 2, 31). Our study exclusively includes patients with primary elective joint surgery to minimise the influence of other risk factors concatenated with the initial trauma (hip fractures) or extended impact on the tissue (revision surgery). This inclusion criterion is an additional strength of the study given that the rate of PJI is known to be higher after trauma and revision surgery (33).

A potential limitation is the retrospective nature of the study design. Therefore, there may be inaccuracies or misinterpretations of information received from medical records. Another limitation is that SSSI is not culture-verified but determined by medical assessment, reflecting clinical reality. As in infection-related research in general in which a small number of infections is a major challenge, this study may have failed to detect a link between a potential risk factor and postoperative infection due to a type II error. A larger cohort would have been desirable.

Conclusion

In conclusion, this study demonstrates that patients developing SSSI after primary elective hip or knee arthroplasty have a great risk to progress into PJI. Older (≥65 years) obese patients seem to have an increased risk of developing SSSI. Male gender is a significant patient-related risk factor to progress from SSSI into PJI.

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Availability of data and materials

The dataset generated and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests in this work.

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Authors' contributions

Both authors (HE, SL) made substantial contributions to conception and design of the study and in acquisition, analysis and interpretation of data. Both authors (HE, SL) have been involved in drafting the manuscript and given final approval of the version to be published. Both authors (HE, SL) have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abbreviations

Superficial surgical site infection: SSSI; Periprosthetic joint infection: PJI; Total joint arthroplasty: TJA; Total hip arthroplasty: THA; Total knee arthroplasty: TKA; Body mass index: BMI; American Society of Anaesthesiologists classification: ASA classification; Rheumatologic disease: RA; Diabetes mellitus: DM; Adjusted RR: aRR.

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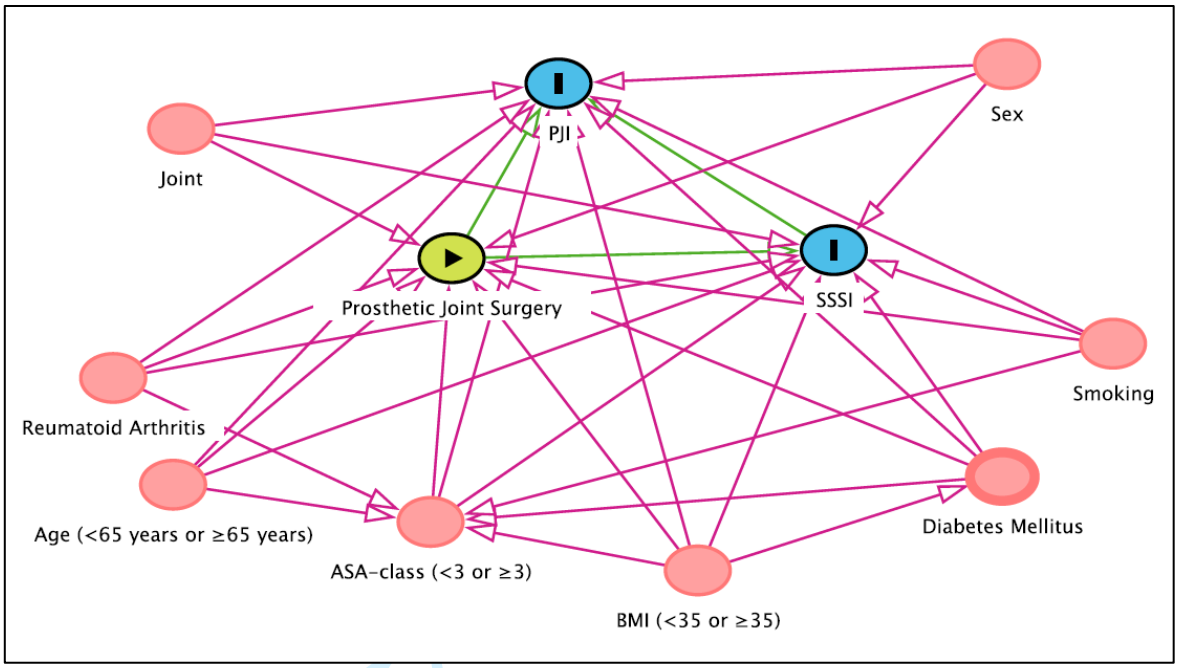
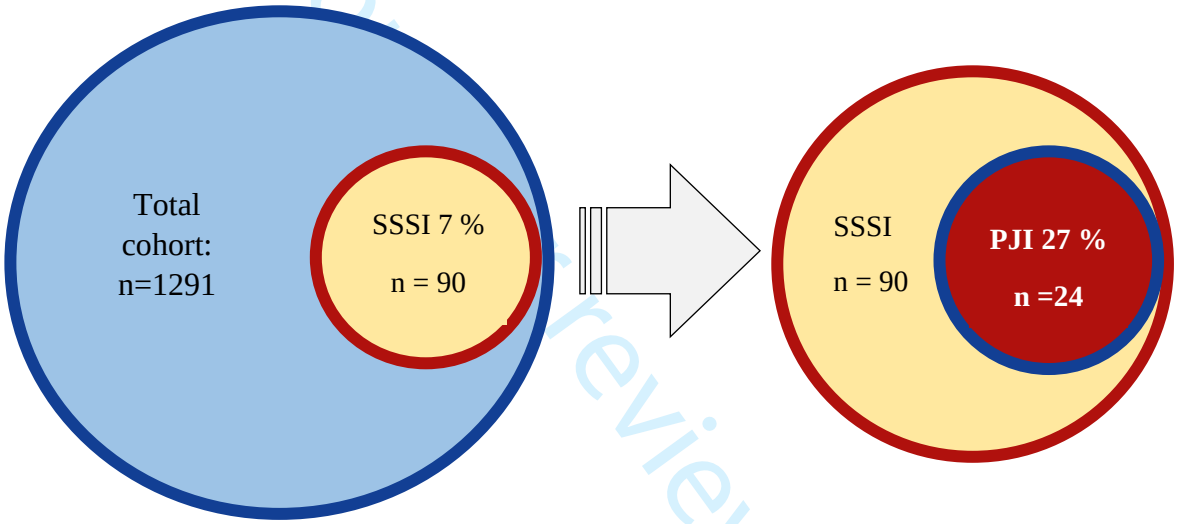
Figure legends

Figure 1. Directed acyclic graph for selecting confounders.

The circle with an arrow indicates the exposure; the circles with an (I) illustrate outcomes; and the circles without text indicate confounders used in the statistical model.

Figure 2. Proportion of SSSI and PJI in the total cohort.





STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*na*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	na
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	na
		(*e*) Describe any sensitivity analyses	na
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Patient-related factors associated with superficial surgical site infection and the progression into a periprosthetic joint infection after elective primary total joint arthroplasty: a single-centre, retrospective study in Sweden

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Patient-related factors associated with superficial surgical site infection and the progression into a periprosthetic joint infection after elective primary total joint arthroplasty: a single-centre, retrospective study in Sweden

Running title: Patient-related factors associated with superficial surgical site infection and the progression into a periprosthetic joint infection after elective primary total joint arthroplasty

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Declarations

None of the authors have any conflict of interest to declare.

Ethics approval

The study design was reviewed and approved by the Human Research Ethics Committee in Uppsala, Sweden, Nr: 2019-01425.

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Abstract

Objectives: The incidence of superficial surgical site infection (SSSI) may increase the risk of periprosthetic joint infection (PJI). The objective of this study is to identify patient-related risk factors associated with SSSI and investigate their correlation with the progression of PJI. **Design:** In this retrospective study 1,191 elective hip and knee prostheses were included. Patients were interviewed ≥3 months after surgery to answer questions about the postoperative period. Patients' records were reviewed to determine whether there had been any documentation of difficulties with wound-healing or antibiotics were prescribed to treat an infection related to arthroplasty surgery. Diagnosed PJI was determined by an orthopaedic surgeon in consultation with a consultant in infectious diseases. **Setting:** This study was performed at Uppsala University Hospital.

Participants: 1,191 joints were included of which, 433 were knees and 758 hips. **Primary and secondary outcome measures:** Which of the patient-related risk factors; joint, age, sex, the American Society of Anaesthesiologists (ASA) classification body mass index (BMI), smoking, diabetes and rheumatic disease associated with 1) superficial surgical site infection and 2) the progress into periprosthetic joint infection.

Results: 84 (7%) of the total cohort developed an SSSI, of which 24 (29%) progressed to a PJI. Factors found with increased adjusted risk ratio (aRR) for SSSI were: knee surgery (1.7; 95% CI: 1.1 – 2.7), age ≥65 years (1.7; 95% CI: 1.1 – 2.8), BMI≥30 (1.9; 95% CI: 1.0 – 3.4) and ASA classification ≥3 (1.7; 95% CI: 1.0 – 2.9). The factor with significant aRR for progression from SSSI to PJI was ASA classification ≥3 (3.3; 95% CI: 1.0 – 10.3).

Conclusions: Patients developing SSSI have a great risk of progress into PJI. Older obese patients with high ASA classification considered for elective total knee arthroplasty seem to have an increased risk of developing SSSI. Patients with a high ASA classification have the highest risk of progressing from SSSI into PJI.

Strengths and limitations of this study

- Strengths of this study are a large cohort size (n=1191)
- Meticulous follow-up of each patient and exclusive inclusion of patients with primary elective arthroplasty surgery on hip or knee.
- Limitations of this study are the retrospective study design, small number of infections leading to a potential risk of a type II error.

Keywords

Periprosthetic joint infection (PJI), superficial surgical site infection (SSSI), total joint arthroplasty (TJA), risk factors.

Introduction

Infection after TJA can be defined as either superficial involving skin or subcutaneous tissue only (a superficial surgical site infection, SSSI) or deep (periprosthetic joint infection, PJI) with deep soft tissue involvement (e.g., fascial and muscle layers) and the prosthesis. The incidence of SSSI after TJA can vary from 1 to 10% (1-3) and may increase the risk of subsequent PJI by up to 35 times (3). The frequency of PJI ranges between 1 and 5% (4-7). Patient-related risk factors, such as obesity, rheumatoid arthritis (RA), smoking, male sex, age, alcohol abuse, American Society of Anaesthesiologists (ASA) classification >2 and diabetes mellitus (DM) (8-15), have been described as risk factors for PJI but not confirmed as risk factors for SSSI. In clinical practice priority should be to identify patients at high risk for SSSI and PJI, aiming for patient optimisation and the opportunity to manage modifiable risk factors since it is essential to seize any opportunity to optimise all prerequisites for the best achievable surgical outcome. Our primary objectives were to 1) determine which patient-related factors are linked to SSSI and 2) investigate the progression into a PJI.

Methods

Study design

This retrospective study of primary elective prostheses in hip or knee joints included patients in a national project designed to lower the incidence of hospital-related infections (16). Patients included in this study were treated at Uppsala University hospital from November 2008 to December 2012, and interviewed ≥3 months after surgery to answer questions about the postoperative period. The patients' records were reviewed to determine whether there had been any documentation of difficulties with wound-healing or whether antibiotics were prescribed to treat an infection related to arthroplasty surgery. An orthopedic consultant reviewed all information from the patients' records (recorded from general practitioners or orthopedic consultants) including possible wound healing problems or antibiotic prescription due to suspected postoperative infection. This information and the results of the patient interview were taken under consideration in order to determine the occurrence of SSSI. The diagnosed PJI was determined by a consultant orthopaedic surgeon in consultation with a consultant in infectious diseases. In a retrospective review of patient records selected patients fulfilled the criteria for PJI (17), but those criteria had not been used at diagnosis. Patient records were reviewed for patient-related risk factors while a local arthroplasty register was used to obtain perioperative information about whether revision surgery had been necessary due to persistent PJI. Follow-up was a minimum of 5 years.

This study was limited to patient-related risk factors associated with developing an SSSI and focused on those factors that might be possible to avoid or optimise preoperatively.

Consent for publication was considered in the application to the Human Research Ethics Committee. However, no consent, verbal or written was needed, due to the retrospective study design. The study design was reviewed and approved by the Human Research Ethics Committee (Dnr: 2019-01425).

Patient and Public Involvement

Patients or the public were not involved in the development of the research question, outcome measures, the design, conduct, reporting, or dissemination plans of our research. The results of this study will not be separately disseminated to study participants.

Study population

1,191 joints were included, of which 664 were men, 527 women, 433 were knees and 758 hips. Only cemented components were used in all knees. Hip prostheses were cemented, cementless or hybrids. In all cemented prostheses antibiotic-loaded cement with gentamycin was applied. All patients received systemic pre- and perioperative antibiotic prophylaxis in accordance with national guidelines (cloxacillin, and in the case of penicillin allergy, clindamycin).

Confounders

Such patient-related factors as joint, sex, age, BMI, RA, ASA classification, smoking and DM were considered clinically relevant confounders in the correlation between arthroplasty surgery and SSSI or PJI. These specific patient-related variables have previously been linked to exposure and outcome and are not considered in the causal pathway between potential risk factors and outcome (Figure 1). Relevant confounders were analysed as categorical variables: ASA classification: <3 or ≥ 3, for BMI the WHO (World Health Organization)-classification was used and divided into the following groups: BMI<25 (under- and normal weight), $25 \leq$BMI<30 (overweight) and BMI≥ 30 (obesity class I-III), and Age: <65 years or ≥ 65 years. Patients with DM included both type 1 and 2 (drug- or diet-treated).

Statistics

Descriptive statistics were used to summarise and report demographic characteristics.

In an initial analysis logistic regression was performed, entering all covariates as singular variables. Crude risk ratios (RRs) for SSSI and PJI were calculated for each variable with 95% confidence intervals (95% CIs). In the next step, the covariates were entered into the regression model, with RRs mutually adjusted for all covariates. Adjusted RRs (aRRs) for each covariate were calculated for the occurrence of SSSI or PJI and any progression of SSSI into PJI.

All statistical analyses were performed using SPSS (version 26.0) and p-values ≤ 0.05 were considered statistically significant.

Results

The total number of surgeries for prosthetic hip or knee joints was 1,191. 84 joints (7%) developed an SSSI and 24 (2%) a PJI. Of the 84 joints with SSSI, 24 (29%) progressed to a PJI (Figure 2).

In the hip cohort (758) 40 joints (5%) developed an SSSI, and 11 (2%) a PJI. In the knee cohort (433), 44 joints (10%) developed an SSSI and 13 (3%) a PJI (Table 1).

Table 1. Number of postoperative infections

Variable	SSSI	PJI
Total cohort (1191)	84 (7.1%)	24 (2.0%)
Hip (758)	40 (5.3%)	11 (1.5%)
Knee (433)	44 (10.4%)	13 (3.1%)

SSSI (superficial surgical site infection), PJI (periprosthetic joint infection).

Demographic characteristics of the cohorts are outlined in Table 2.

Table 2. Demographic characteristics

Variable	Total cohort	Hip	Knee	Range
	n = 1191	n = 758 (64%)	n = 433 (36%)	
Mean age (year)	63	61	65	18–96
Age				
<65	673 (56%)	447 (59%)	226 (52%)	
≥65	518 (44%)	331 (41%)	207 (48%)	
ASA-class[a]				
≤2	964 (81%)	631 (84%)	333 (78%)	
≥3	210 (18%)	117 (16%)	93 (22%)	
Mean Body mass index	28	27	29	14–51
BMI				
BMI<25[b]	356 (30%)	259 (34%)	97 (22%)	
25≤BMI<30	474 (40%)	307 (41%)	167 (39%)	
BMI≥30	361 (30%)	192 (25%)	169 (39%)	
Sex				
Woman	664 (56%)	387 (51%)	277 (64%)	
Man	527 (44%)	371 (49%)	156 (36%)	
Smoking[c]				
No	1064 (90%)	673 (89%)	391 (90%)	
Yes	122 (10%)	81 (11%)	41 (10%)	
Diabetes				
No	1067 (90%)	686 (91%)	381 (88%)	
Yes	124 (10%)	72 (9%)	52 (12%)	
Rheumatological disease				
No	1052 (88%)	690 (91%)	362 (84%)	
Yes	139 (12%)	68 (9%)	71 (16%)	

ASA (American Society of Anaesthesiologists), BMI (Body mass index).

[a] missing data in 17 cases
[b] underweight 17 cases (BMI under 18.5)
[c] missing data in 5 cases

Risk factors for SSSI

Risk factors with a significant crude RR for developing SSSI were knee surgery (2.0; 95% CI: 1.3 – 3.2), age ≥65 years (1.8; 95% CI: 1.2 – 2.8), ASA classification ≥3 (2.4; 95% CI: 1.5 – 3.8) and rheumatic disease (1.9; 95% CI: 1.1 – 3.3). Adjusting for all covariates, factors with significant aRRs for SSSI were knee surgery (1.7; 95% CI 1.1 – 2.7), age ≥65 years (1.7; 95% CI: 1.1 – 2.8), ASA classification ≥3 (1.7; 95% CI: 1.0 – 2.9) and BMI≥30 (1.9; 95% CI: 1.0 – 3.4) (Table 3).

Table 3. Risk ratio (RR) for SSSI

No SSSI	1107 (9%)
SSSI	84 (7%)

Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
Joint				
Hip	ref		ref	
Knee	2.0 (1.3 -3.2)	**0.002**	1.7 (1.1 – 2.7)	**0.022**
Age				
<65	ref		ref	
≥65	1.8 (1.2 – 2.8)	**0.010**	1.7 (1.1 – 2.8)	**0.024**
ASA class[a]				
≤ 2	ref		ref	
≥ 3	2.4 (1.5 – 3.8)	**0.001**	1.7 (1.0 – 2.9)	**0.038**
Body mass index				
BMI<25	ref		ref	
25≤BMI<30	1.4 (0.8 – 2.2)	0.211	1.1 (0.6 – 2.0)	0.780
BMI≥30	2.3 (0.9 – 5.5)	0.075	1.9 (1.0 – 3.4)	**0.045**
Sex				
Woman	ref		ref	
Men	1.1 (0.7 – 1.7)	0.677	1.1 (0.8 – 2.1)	0.298
Smoking[b]				
No	ref		ref	
Yes	1.1 (0.5 – 2.3)	0.811	1.1 (0.5 – 2.3)	0.841
Diabetes				
No	ref		ref	
Yes	1.6 (0.9 – 3.1)	0.118	1.1 (0.6 – 2.2)	0.753
Rheumatological disease				
No	ref		ref	
Yes	1.9 (1.1 – 3.3)	**0.031**	1.7 (0.9 – 3.1)	0.089

ASA (American Society of Anaesthesiologists), BMI (Body mass index).

[a] missing data in 17 cases

[b] missing data in 5 cases

Risk factors for PJI

The only risk factor with a significant crude RR for the development of PJI was ASA classification ≥3 (4.8; 95% CI: 2.1 – 10.9). Factors with significant aRRs for PJI were ASA classification ≥3 (3.8; 95% CI: 1.6 – 9.1), and male sex (2.8; 95% CI: 1.2 – 6.9) (Supplementary table 1).

Risk factors for PJI in patients with SSSI

In the group of patients with SSSI, the only risk factor with a significant crude RR for the development of PJI was ASA classification ≥3 (3.0; 95% CI: 1.1 – 8.1). The adjusted relative risk shown for ASA classification was (3.3; 95% CI: 1.0 – 10.3) (Table 4).

Table 4. Risk ratio (RR) for PJI in patients with SSSI

SSSI - no PJI	60 (71%)
SSSI - PJI	24 (29%)

Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
Joint				
Hip	ref		ref	
Knee	1.1 (0.4 – 2.9)	0.836	1.3 (0.4 – 3.6)	0.663
Age				
<65	ref		ref	
≥65	1.5 (0.6 – 3.9)	0.404	2.0 (0.7 – 6.2)	0.212
ASA-class				
≤ 2	ref		ref	
≥ 3	3.0 (1.1 – 8.1)	**0.030**	3.3 (1.0 – 10.3)	**0.044**
Body Mass Index				
BMI<25	ref		ref	
25≤BMI<30	1.7 (0.6 – 5.0)	0.309	2.3 (0.5 – 9.6)	0.264
BMI≥30	1.2 (0.5 – 3.1)	0.728	1.8 (0.5 – 7.1)	0.411
Sex				
Woman	ref		ref	
Men	2.5 (0.9 – 6.6)	0.065	2.8 (0.9 – 8.3)	0.064
Smoking				
No	ref		ref	
Yes	4.9 (0.5 – 51.1)	0.188	5.3 (0.5 – 54.4)	0.160
Diabetes				
No	ref		ref	
Yes	0.6 (0.2 – 2.0)	0.394	1.3 (0.3 – 5.7)	0.774
Rheumatological disease				
No	ref		ref	
Yes	1.2 (0.4 – 3.8)	0.792	1.1 (0.3 – 4.7)	0.883

ASA (American Society of Anaesthesiologists), BMI (Body mass index).

Discussion

Identifying, mitigating, and optimising amenable risk factors for SSSI and PJI is a highly desirable approach for prevention of this devastating complication. The results of our study is relevant and offer new insight concerning the relationship between patient-related risk factors for SSSI and their correlation to the risk of PJI development. The risk and consequences of PJI after TJA is well described earlier (2, 5, 12). Further, the occurrence of SSSI is shown to increase the risk of subsequent PJI by up to 35 times (3). However, factors affecting the progression of SSSI into PJI have not been presented before. Identification and optimisation of risk factors for SSSI may decrease the risk of subsequent PJI.

Patient related risk factors for superficial surgical site infection

This study shows that knee surgery, age >65 years, a high ASA classification and obesity are independent risk factors for the development of SSSI after elective primary joint arthroplasty.

Knee surgery seems to be a risk factor for developing SSSI after elective primary arthroplasty. Earlier studies have shown patients with knee prostheses to have a higher risk of PJI and to be in greater need of revision surgery than patients with hip prostheses (6, 8, 11, 18). Since there is less soft tissue around the knee than around the hip, meaning a shorter distance between skin and joint it is reasonable that the risk for superficial infection also is increased. The blood circulation around the knee area is more exposed to impact than the hip area and the perfusion is easier to disturb. Increased tourniquet time has been identified as an individual risk factor for deep infection and impaired wound healing and prolonged wound discharge after total knee arthroplasty (1), but this analysis is excluded from this study due to lack of this information.

Age as a significant risk factor for SSSI shown in this study is congruent with results from a large (n=1,000) retrospective study (1) by Caroll et al. Elderly patients may have pre-existing medical conditions and fragile skin that can impair wound healing and cause SSSI.

The correlation between a high ASA classification and infection after surgery may be explained due to that the ASA classification encapsulates several other known risk factors (e.g., smoking, DM and

obesity). These risk factors have been independently associated with a higher risk of surgical site infection resulting from tissue hypoperfusion and subsequent impaired immunological function (12). In our study, obese patients have 1.9 times higher risk to develop SSSI after primary elective arthroplasty. Shohat et al. reported in a study including 19,000 patients that the risk for infection increases with higher BMI levels, though no threshold for PJI was observed (19). Our results are also in line with another large register-based study by Sayed-Noor et al. which observed that the risk of reoperation within 2 to 5 years increased in patients with higher BMI classification (obesity class I-III) (20). The association between BMI and postoperative wound complications may be explained by linked comorbidities such as DM type II (21), prolonged or more complicated arthroplasty surgery (22) and protracted postoperative wound drainage (23). Further, it has been proposed that although overweight and obese patients may not be calorie deficient, they may often be micronutrient and protein deficient (24-27). Thus can, malnutrition paradoxically be associated with increasing BMI. Patients with preoperative malnutrition are shown to have higher rates of comorbidities (congestive heart failure, previous cardiac surgery, hypertension, dyspnea, chronic obstructive pulmonary disease, renal disease requiring dialysis, stroke, diabetes, chronic corticosteroid use, bleeding disorders) (28). Higher rates of surgical site infection after total joint arthroplasty are shown in patients with hypoalbuminemia (29).

It has been described that RA is a risk factor on developing PJI after TJA. A systematic review by Kong et al. presented a significant odds ratio for PJI in RA patients with a THA of 1.75 (95% CI: 1.49 – 2.06) (11) and an odds ratio of 1.34 (95% CI: 1.18 – 1.52) in patients with a TKA. We found that RA had a significant crude RR for the development of SSSI after primary TJA. The risk was 1.7 times higher for RA patients than in patients without RA when adjusting for all covariates and was close to a statistically significance (Table 3). The significance of the association between RA and SSSI may be missed out in this analysis, due to the small number of infections and type II statistical error.

Patient related risk factors for development of deep surgical site infection

We found that superficial wound complications were associated with the development of PJI in 29%, and high ASA classification was the factor shown to be significant (3.3 times higher than patients with ASA<3) in the progression into PJI. ASA classification is a crude estimate of a patient's medical condition and has been associated with the risk of PJI in numerous previous reports (10, 11). Blanco et al. report a 15-fold odds ratio (95% CI: 6.54–35.80) for PJI in patients with ASA classification ≥3 and another study by Panula et al. presented a hazard ratio of 3.2 (95% CI: 2.0–5.1) for the same ASA classification (30).

In our analysis male sex was close to a significant risk factor for progression from SSSI into PJI both as singular variable and after adjustment for all covariates (2.8 times higher risk for men than women). A recent meta-analysis showed that male sex was a risk factor for PJI development, especially after total knee arthroplasty (TKA) (18). The link between male sex and PJI may be attributed to some contributing behavioural factors, including smoking, diet, hygiene and alcohol consumption, but the reasons behind this are not clear. Sex-related differences in immune response due to bacteria (e.g., Staphylococcus aureus and Pseudomonas aeruginosa) have been reported. In addition, septicaemia and bacteraemia occur more frequently in males than females (21), but whether it will or will not affect the development of SSSI or PJI has yet to be investigated. The absence of statistically significance for male sex as a risk factor of developing PJI after SSSI can depend on the total number of infected patients including in our study.

Prevention of postoperative infection

The rate of SSSI (7%) and PJI (2%) in this study is consistent with international studies showing levels of SSSI ranging from 1-10% (1, 31) and PJI ranging from 0.2-2.23% (5-7). This work is focused on patient-related factors with a possible effect on the occurrence of SSSI or PJI after elective primary TJA. There are several other factors related to the surgery such as operation time, intraoperative blood loss, number of door openings, discipline in the operating room, antibiotic-prophylaxis used, surgeon's experience, that can affect the overall risk for postoperative infection, but

those are not included in this current analysis. With the challenging complication of PJI and its major burden on patients (32) and health systems (33), prevention through the implementation of effective strategies is the first and best strategy and should be a priority. Identifying high-risk patients planning to undergo arthroplasty surgery and providing interventions, when possible, by modifying these risk factors, might form the basis of PJI prevention strategies in the future.

Strengths

Two major strengths of this study are the large cohort size (n=1191) and the meticulous follow-up of each patient. This thorough postoperative follow-up confirms that the number of recorded incidents of SSSI is accurate, and the follow-up time of 5 years (mean 7.3; range: 5.1-9.2) years is sufficient to reveal any potential cases of PJI. Similar studies have presented larger cohorts but only on registers (32, 34) or shorter follow-ups (1, 2, 34).

Additionally, our study exclusively includes patients with primary elective joint surgery to minimise the influence of other risk factors concatenated with the initial trauma (hip fractures) or extended impact on the tissue (revision surgery). This inclusion criterion is an additional strength of the study given that the rate of PJI is known to be higher after trauma and revision surgery (35). According to preoperative screening routines in our hospital patients with a history of excessive use of alcohol, IV drug use, poor oral hygiene or other medical conditions or medications that compromise immunity referred to our unit for primary arthroplasty are excluded from surgery or already rehabilitated before surgery.

Limitations

A potential limitation is the retrospective nature of our study design. Therefore, there may be inaccuracies or misinterpretations of information received from medical records. However, all patients included in this study were interviewed in person to answer questions about the postoperative period and the information was in that way verified.

Another limitation is that SSSI is not culture-verified but determined by a consultant orthopaedic surgeon which reflects the clinical reality. Cultures taken at a superficial infection can be misleading

and classified as contamination, even if a possibility of a clinical significance of skin flora found in cultures recently has been raised (36).

As in infection-related research in general in which a small number of infections is a major challenge, this study may have failed to detect a link between a potential risk factor and postoperative infection due to a type II error.

Conclusion

In conclusion, this study demonstrates that patients developing SSSI after primary elective hip or knee arthroplasty have a great risk to progress into PJI. Older obese patients with high ASA classification seem to have an increased risk of developing SSSI. A high ASA classification significantly affects the progression from SSSI into PJI.

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Availability of data and materials

The dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests in this work.

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Authors' contributions

Both authors (HE, SL) made substantial contributions to conception and design of the study and to acquisition, analysis and interpretation of data. Both authors (HE, SL) have been involved in drafting the manuscript and given final approval of the version to be published. Both authors (HE, SL) have participated sufficiently in the work to take public responsibility

for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abbreviations

Superficial surgical site infection: SSSI; Periprosthetic joint infection: PJI; Total joint arthroplasty: TJA; Total hip arthroplasty: THA; Total knee arthroplasty: TKA; Body mass index: BMI; American Society of Anaesthesiologists classification: ASA classification; Rheumatologic disease: RA; Diabetes mellitus: DM; Adjusted RR: aRR.

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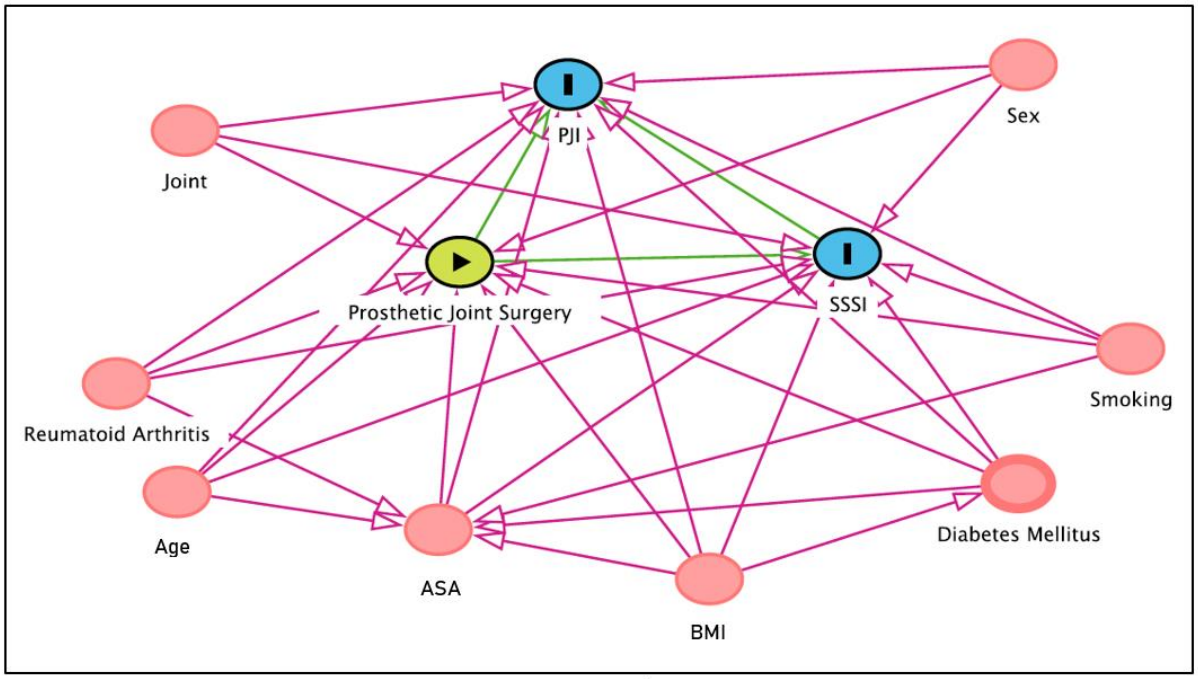
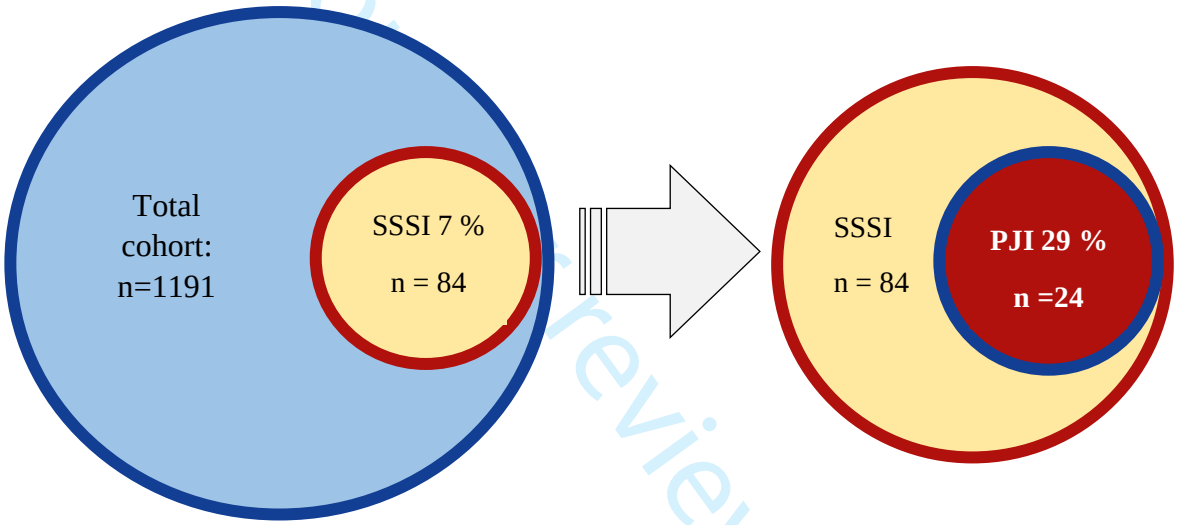
Figure legends

Figure 1. Directed acyclic graph for selecting confounders.

The circle with an arrow indicates the exposure; the circles with an (I) illustrate outcomes; and the circles without text indicate confounders used in the statistical model.

Figure 2. Proportion of SSSI and PJI in the total cohort





Supplementary table 1. Risk ratio (RR) for PJI

SSSI - no PJI	1167 (98%)
SSSI - PJI	24 (2%)

Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
Joint				
Hip	ref		ref	
Knee	2.1 (0.9 – 4.7)	0.073	2.0 (0.8 – 4.8)	0.112
Age				
<65	ref		ref	
≥65	1.3 (0.6 – 2.9)	0.517	1.1 (0.5 – 2.7)	0.781
ASA-class[a]				
≤ 2	ref		ref	
≥ 3	4.8 (2.1 – 10.9)	**0.000**	3.8 (1.6 – 9.1)	**0.003**
Body Mass Index				
BMI<25	ref		ref	
25≤BMI<30	2.0 (0.8 – 5.1)	0.142	1.9 (0.6 – 5.9)	0.271
BMI≥30	1.9 (0.9 – 4.4)	0.110	1.2 (0.4 – 3.3)	0.772
Sex				
Woman	ref		ref	
Men	2.1 (0.9 – 4.9)	0.075	2.8 (1.2 – 6.9)	**0.022**
Smoking[b]				
No	ref		ref	
Yes	2.7 (0.4 – 20.0)	0.338	2.5 (0.3 – 19.0)	0.379
Diabetes				
No	ref		ref	
Yes	2.3 (0.9 – 6.3)	0.101	1.4 (0.5 – 4.1)	0.543
Rheumatological disease				
No	ref		ref	
Yes	2.0 (0.8 -5.5)	0.166	1.8 (0.6 – 5.2)	0.294

ASA (American Society of Anaesthesiologists), BMI (Body mass index).

[a] missing data in 17 cases
[b] missing data in 5 cases

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*na*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	na
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	na
		(*e*) Describe any sensitivity analyses	na
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Patient-related factors associated with superficial surgical site infection and progression to a periprosthetic joint infection after elective primary total joint arthroplasty: a single-centre, retrospective study in Sweden

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Patient-related factors associated with superficial surgical site infection and progression to a periprosthetic joint infection after elective primary total joint arthroplasty: a single-centre, retrospective study in Sweden

Running title: Patient-related factors associated with superficial surgical site infection and the progression to a periprosthetic joint infection after elective primary total joint arthroplasty

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Abstract

Objectives: Superficial surgical site infection (SSSI) may increase the risk of serious complications such as periprosthetic joint infection (PJI). This study aims to identify patient-related risk factors associated with SSSI and investigate their correlation with the progression of PJI.

Design: In this retrospective study 1,191 elective hip and knee prostheses were included. Patients were interviewed 3-5 months after surgery to answer questions about the postoperative period. Patient records were reviewed to determine whether there had been any documentation of wound-healing difficulties or whether antibiotics were prescribed to treat an infection related to arthroplasty surgery.

Setting: Uppsala University Hospital, patients treated between November 2008 to December 2012.

Participants: The study population comprised 433 knees and 758 hips.

Outcome measures: We studied patient-related risk factors (joint, age, sex, the American Society of Anesthesiologists (ASA) classification, body mass index (BMI), smoking, diabetes and rheumatic disease) to determine whether they were associated with 1) SSSI and 2) the progress from SSSI to PJI.

Results: 84 (7%) patients of the total cohort developed SSSI. This infection progressed to a PJI in 24 (29%) of the patients. Factors with increased adjusted risk ratios (aRRs) for SSSIs were knee surgery (1.7; 95% confidence interval, CI: 1.1 – 2.7), age ≥65 years (1.7; 95% CI: 1.1 – 2.8), BMI ≥30 (1.9; 95% CI: 1.0 – 3.4) and ASA classification ≥3 (1.7; 95% CI: 1.0 – 2.9). ASA classification ≥3 was the only factor showing a significant progression from SSSI to PJI (aRR=3.3; 95% CI: 1.0 – 10.3).

Conclusions: The risk of progressing from a SSSI to a PJI is high. Older patients, patients with obesity, and those with a high ASA classification considered for elective total knee arthroplasty seem to have an increased risk of developing SSSI. Patients with a high ASA classification seem to have an increased risk of progressing from SSSI to PJI.

Strengths and limitations of this study

- Strengths of this study include the large cohort size (n=1,191) and careful follow-up of each patient.
- Exclusive inclusion of patients with primary elective arthroplasty surgery on the hip or knee.
- Limitations of this study include the retrospective study design and the small number of infections, leading to a potential risk of a type II error.

Keywords

Periprosthetic joint infection (PJI), superficial surgical site infection (SSSI), total joint arthroplasty (TJA), risk factors.

Introduction

Infection after total joint arthroplasty (TJA) can be defined as either superficial involving skin or subcutaneous tissue only (a superficial surgical site infection, SSSI) or deep (periprosthetic joint infection, PJI) with deep soft tissue involvement (e.g., fascial and muscle layers) and the prosthesis. The incidence of SSSI after TJA can vary from 1 to 10% (1, 2, 3) and may increase the risk of subsequent PJI by 35-fold (3). The frequency of PJI ranges between 1 and 5% (4-7). Patient-related risk factors, such as obesity, rheumatoid arthritis (RA), smoking, male sex, age, alcohol abuse, American Society of Anesthesiologists (ASA) classification >2 and diabetes mellitus (DM) (8-16), have been described as risk factors for PJI but not confirmed as risk factors for SSSI. In clinical practice priority should be to identify high-risk patients for SSSI and PJI, aiming for optimal patient outcomes and the opportunity to manage modifiable risk factors. It is essential to seize any possibility to optimise all prerequisites for the best achievable surgical outcome. Thus, we sought to 1) determine which patient-related factors are linked to SSSI and 2) investigate the progression from SSSI to PJI.

Methods

Study design

This retrospective study of primary elective prostheses in hip or knee joints included patients in a national project designed to reduce the incidence of hospital-related infections (17). The study patients were treated at Uppsala University Hospital from November 2008 to December 2012 and interviewed 3-5 months after surgery to answer questions about the postoperative period. Patient medical records were reviewed to determine whether there had been any documentation of difficulties with wound healing or whether antibiotics were prescribed to treat an infection related to hip or knee arthroplasty. An orthopaedic consultant reviewed all information from patient records (recorded from general practitioners or orthopaedic consultants), including possible wound healing complications or antibiotic prescriptions due to suspected postoperative infection. This information and the results of the patient interview were used to determine the occurrence of SSSI. The diagnosis of PJI was made by a consultant orthopaedic surgeon in consultation with a consultant in infectious diseases. In a retrospective review of patient records selected patients met the criteria for PJI (18), but those criteria were not used at the time of diagnosis. Patient records were reviewed for patient-related risk factors, and a local arthroplasty register was used to obtain information about revision surgery that had been necessary due to persistent PJI. This study was limited to patient-related risk factors associated with the development of SSSI and focused on factors that may be avoidable or preoperatively optimised.

Consent for publication was considered in the application to the Human Research Ethics Committee. Because this was a retrospective study, no consent (written or verbal) was needed for this work. The study design was reviewed and approved by the Human Research Ethics Committee (Dnr: 2019-01425).

Study population

The study population comprised 664 men, 527 women and the study material included 1,191 joints (433 knees, 758 hips). Hip prostheses were cemented, cementless or hybrids. Only cemented

components were used in all knees. In all cemented prostheses antibiotic-loaded cement with gentamycin was applied. All patients received systemic pre- and perioperative antibiotic prophylaxis in accordance with national guidelines (cloxacillin, and in the case of penicillin allergy, clindamycin).

Confounders

Patient-related factors (e.g., joint, sex, age, body mass index (BMI), RA, ASA classification, smoking, DM) were considered clinically relevant for the association between arthroplasty and SSSI or PJI. These specific patient-related variables have previously been linked to exposure and outcome and are not considered in the causal pathway between potential risk factors and outcome (Figure 1). Relevant confounders were analysed as categorical variables: ASA classification (<3 or ≥3), age (<65 years or ≥65 years) and DM (patients with DM included both type 1 and 2, drug- or diet-related). For BMI, the WHO (World Health Organisation) classification was used and divided into the following groups: BMI <25 (under and normal weight), 25 ≤BMI<30 (overweight) and BMI ≥30 (obesity class I-III).

Statistics

Descriptive statistics were used to summarise and report demographic characteristics.

In an initial analysis logistic regression was performed, entering covariates as single variables. Crude risk ratios (RRs) for SSSI and PJI were calculated for each variable with 95% confidence intervals (95% CIs). The covariates were entered into the regression model in the next step, with RRs mutually adjusted for all covariates. An adjusted RR (aRR) for each covariate was calculated for the occurrence of SSSI or PJI and any progression of SSSI to PJI.

All statistical analyses were performed using SPSS (version 26.0) and p-values ≤0.05 were considered significant.

Patient and public involvement

Patients or the public were not involved in developing the research questions, outcome measures, the design, conduct, reporting or dissemination plans of our research. The results of this study will not be distributed separately to study participants.

Results

The number of surgeries for prosthetic hip or knee joints was 1,191. 84 joints (7%) developed an SSSI and 24 (2%) a PJI. Of the 84 joints with SSSI, 24 (29%) progressed to a PJI (Figure 2).

In the hip cohort (758) 40 joints (5%) developed an SSSI and 11 (2%) a PJI. In the knee cohort (433) 44 joints (10%) developed an SSSI and 13 (3%) a PJI (Table 1).

Table 1. Number of postoperative infections

Variable	SSSI	PJI
Total cohort (1,191)	84 (7.1%)	24 (2.0%)
Hip (758)	40 (5.3%)	11 (1.5%)
Knee (433)	44 (10.4%)	13 (3.1%)

SSSI (superficial surgical site infection), PJI (periprosthetic joint infection).

Demographic characteristics of the cohorts are outlined in Table 2.

Table 2. Cohort demographic characteristics

Variable	Total cohort	Hip	Knee	Range
	n = 1.191	n = 758 (64%)	n = 433 (36%)	
Mean age (year)	63	61	65	18–96
Age				
<65	673 (56%)	447 (59%)	226 (52%)	
≥65	518 (44%)	331 (41%)	207 (48%)	
ASA-class				
≤2	964 (81%)	631 (84%)	333 (78%)	
≥3	210 (18%)	117 (16%)	93 (22%)	
Mean BMI	28	27	29	14–51
BMI				
BMI <25[b]	356 (30%)	259 (34%)	97 (22%)	
25≤BMI<30	474 (40%)	307 (41%)	167 (39%)	
BMI ≥30	361 (30%)	192 (25%)	169 (39%)	
Sex				
Women	664 (56%)	387 (51%)	277 (64%)	
Men	527 (44%)	371 (49%)	156 (36%)	
Smoking[c]				
No	1064 (90%)	673 (89%)	391 (90%)	
Yes	122 (10%)	81 (11%)	41 (10%)	
Diabetes				
No	1067 (90%)	686 (91%)	381 (88%)	
Yes	124 (10%)	72 (9%)	52 (12%)	
Rheumatological disease				
No	1052 (88%)	690 (91%)	362 (84%)	

Yes	139 (12%)	68 (9%)	71 (16%)

ASA (American Society of Anesthesiologists), BMI (body mass index).

[a] missing data in 17 cases
[b] underweight 17 cases (BMI <18.5)
[c] missing data in 5 cases

Risk factors for SSSI

Risk factors with a significant crude RR for developing SSSI were knee surgery (RR=2.0; 95% CI: 1.3 – 3.2), age ≥65 years (RR=1.8; 95% CI: 1.2 – 2.8), ASA classification ≥3 (RR=2.4; 95% CI: 1.5 – 3.8) and rheumatic disease (RR=1.9; 95% CI: 1.1 – 3.3). Adjusting for all covariates, factors with significant aRRs for SSSI were knee surgery (aRR=1.7; 95% CI 1.1 – 2.7), age ≥65 years (aRR=1.7; 95% CI: 1.1 – 2.8), ASA classification ≥3 (aRR=1.7; 95% CI: 1.0 – 2.9) and BMI ≥30 (aRR=1.9; 95% CI: 1.0 – 3.4) (Table 3).

Table 3. Risk ratio (RR) for SSSI

No SSSI	1107 (9%)
SSSI	84 (7%)

Variable	**Crude RR (95 % CI)**	**P-value**	**Adjusted RR (95 % CI)**	**P-value**
Joint				
Hip	ref		ref	
Knee	2.0 (1.3 -3.2)	**0.002**	1.7 (1.1 – 2.7)	**0.022**
Age				
<65	ref		ref	
≥65	1.8 (1.2 – 2.8)	**0.010**	1.7 (1.1 – 2.8)	**0.024**
ASA class[a]				
≤ 2	ref		ref	
≥ 3	2.4 (1.5 – 3.8)	**0.001**	1.7 (1.0 – 2.9)	**0.038**
BMI				
BMI <25	ref		ref	
25≤BMI<30	1.4 (0.8 – 2.2)	0.211	1.1 (0.6 – 2.0)	0.780
BM I≥30	2.3 (0.9 – 5.5)	0.075	1.9 (1.0 – 3.4)	**0.045**
Sex				
Women	ref		ref	
Men	1.1 (0.7 – 1.7)	0.677	1.1 (0.8 – 2.1)	0.298
Smoking[b]				
No	ref		ref	
Yes	1.1 (0.5 – 2.3)	0.811	1.1 (0.5 – 2.3)	0.841
Diabetes				
No	ref		ref	
Yes	1.6 (0.9 – 3.1)	0.118	1.1 (0.6 – 2.2)	0.753
Rheumatological disease				
No	ref		ref	
Yes	1.9 (1.1 – 3.3)	**0.031**	1.7 (0.9 – 3.1)	0.089

ASA (American Society of Anesthesiologists), BMI (body mass index).

[a] missing data in 17 cases
[b] missing data in 5 cases

Risk factors for PJI

The only risk factor with a significant crude RR for the development of PJI was ASA classification ≥3 (RR=4.8; 95% CI: 2.1 – 10.9). Factors with significant aRRs for PJI were ASA classification ≥3 (aRR=3.8; 95% CI: 1.6 – 9.1) and male sex (aRR=2.8; 95% CI: 1.2 – 6.9) (Supplementary Table 1).

Risk factors for PJI in patients with SSSI

The only risk factor with a significant crude RR for the development of PJI in the SSSI group was ASA classification ≥3 (RR=3.0; 95% CI: 1.1 – 8.1). The aRR shown for ASA classification was 3.3 (95% CI: 1.0 – 10.3) (Table 4).

Table 4. Risk ratio (RR) for PJI in patients with SSSI

SSSI – no progression to PJI	60 (71%)
SSSI – progression to PJI	24 (29%)

Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
Joint				
Hip	ref		ref	
Knee	1.1 (0.4 – 2.9)	0.836	1.3 (0.4 – 3.6)	0.663
Age				
<65	ref		ref	
≥65	1.5 (0.6 – 3.9)	0.404	2.0 (0.7 – 6.2)	0.212
ASA class				
≤ 2	ref		ref	
≥ 3	3.0 (1.1 – 8.1)	**0.030**	3.3 (1.0 – 10.3)	**0.044**
BMI				
BMI <25	ref		ref	
25≤BMI<30	1.7 (0.6 – 5.0)	0.309	2.3 (0.5 – 9.6)	0.264
BMI ≥30	1.2 (0.5 – 3.1)	0.728	1.8 (0.5 – 7.1)	0.411
Sex				
Women	ref		ref	
Men	2.5 (0.9 – 6.6)	0.065	2.8 (0.9 – 8.3)	0.064
Smoking				
No	ref		ref	
Yes	4.9 (0.5 – 51.1)	0.188	5.3 (0.5 – 54.4)	0.160
Diabetes				
No	ref		ref	
Yes	0.6 (0.2 – 2.0)	0.394	1.3 (0.3 – 5.7)	0.774
Rheumatological disease				
No	ref		ref	
Yes	1.2 (0.4 – 3.8)	0.792	1.1 (0.3 – 4.7)	0.883

ASA (American Society of Anesthesiologists), BMI (body mass index).

Discussion

Identifying, mitigating and optimising risk factors for SSSI and PJI is a desirable approach to prevent this devastating complication. The results of our study are relevant and provide new insight into the relationship between patient-related risk factors for SSSI and their association with the risk of PJI development. The risk and consequences of PJI after TJA have been described elsewhere (2, 5, 12). It has been reported that the occurrence of SSSI increases the risk of PJI by up to 35 times (3). However, factors affecting the progression from SSSI to PJI have not been investigated. Identifying and optimising risk factors for SSSI may decrease the risk of PJI.

Patient-related risk factors for superficial surgical site infection

This study shows that knee surgery, age >65 years, a high ASA classification (≥3) and obesity (BMI >30) are independent risk factors for developing SSSI after elective primary joint arthroplasty.

Knee surgery seems to be a risk factor for developing SSSI after elective primary arthroplasty. Studies have shown that patients with knee prostheses have a higher risk of PJI and are in greater need of revision surgery than patients with hip prostheses (6, 9, 12, 19). Because there is less soft tissue around the knee than around the hip, meaning a shorter distance between skin and joint, the risk of superficial infection is also increased. Blood circulation around the knee area is more exposed to impact than the hip area and perfusion is more easily disturbed. Increased tourniquet time has been identified as an individual risk factor for deep infection, impaired wound healing and prolonged wound discharge after total knee arthroplasty (TKA) (1). However, due to a lack of data, this analysis could not be included in this study.

Our finding that age is a significant risk factor for SSSI is congruent with the results from a large (n=1,000) retrospective study (1). Older patients (≥65 years) may have pre-existing medical conditions and fragile skin that could impair wound healing, making them more susceptible to SSSI. The correlation between a high ASA score and infection after surgery can be explained because the ASA classification encapsulates several other known risk factors (e.g., smoking, DM, obesity). These

risk factors have been independently associated with a higher risk of surgical site infection due to tissue hypoperfusion and subsequent impaired immunological function (13).

Our obese patients have a 1.9 times higher risk of SSSI after primary elective arthroplasty. Shohat et al. reported in a study including 19,000 patients that the risk for infection increases with higher BMI levels, although no BMI threshold was observed (20). Our results align with another large register-based study that reported an increased risk of reoperation in patients with higher BMI classification (obesity class I-III) (21). The association between BMI and postoperative wound complications may be explained by linked comorbidities (e.g., DM type II) (22), prolonged or more complicated arthroplasty surgery (23) and protracted postoperative wound drainage (24). It has also been suggested that, although overweight and obese patients may not be calorie deficient, they are often micronutrient and protein deficient (25-28). Thus, malnutrition can be linked to increased BMI. Patients with preoperative malnutrition have higher rates of comorbidities (congestive heart failure, previous cardiac surgery, hypertension, dyspnoea, chronic obstructive pulmonary disease, renal disease requiring dialysis, stroke, diabetes, chronic corticosteroid use, bleeding disorders) (29). Higher rates of surgical site infection after TJA are shown in patients with hypoalbuminemia (30).

It has been described that RA is a risk factor for developing PJI after TJA. A systematic review presented a significant odds ratio (OR) for PJI in RA patients with a THA of 1.75 (95% CI: 1.49 – 2.06) (12) and an OR of 1.34 (95% CI: 1.18 – 1.52) in patients with a TKA. We found that RA had a significant crude RR for developing SSSI after primary TJA. The risk was 1.7 times higher for patients with RA than those without RA when adjusting for all covariates, although this risk difference was not statistically significant (Table 3). The significance of the association between RA and SSSI may have gone undetected in this analysis because of the small number of infections and type II statistical error.

Patient-related risk factors for the development of deep surgical site infection

We found that superficial wound complications were associated with developing PJI in 29% of our patients, with high ASA classification (3.3 times higher than patients with ASA <3) a determining factor in the progression from SSSI to PJI. ASA classification is a crude estimate of a patient's medical condition and a high score has been associated with the risk of PJI in numerous reports (11, 12). For instance, Blanco et al. reported a 15-fold OR (95% CI: 6.54–35.80) for PJI in patients with ASA classification ≥3 and Panula et al. presented an HR of 3.2 (95% CI: 2.0–5.1) for the same ASA classification (31).

A recent meta-analysis showed that male sex was a risk factor for PJI development, especially after TKA (19). In our analysis male sex was close to a significant risk factor for progression from SSSI into PJI, both as a single variable and after adjustment for all covariates (2.8 times higher risk for men than women). The link between male sex and PJI may be attributed to certain contributing behavioural factors, including smoking, diet, hygiene and alcohol consumption, but the underlying reasons for this are unclear. Sex-related differences in immune response due to bacteria (e.g., Staphylococcus aureus and Pseudomonas aeruginosa) have been reported. In addition, septicaemia and bacteraemia occur more frequently in males than females (32), but whether they will affect the development of SSSI or PJI has yet to be determined. The absence of statistical significance for male sex as a risk factor of developing PJI after SSSI can depend on the total number of infected patients in our study.

Prevention of postoperative infection

The rate of SSSI (7%) and PJI (2%) in this study is consistent with international studies showing levels of SSSI ranging from 1-10% (1, 33) and PJI ranging from 0.2-2.23% (5, 6, 8). The present work is focused on patient-related factors with a possible effect on the occurrence of SSSI or PJI after elective primary TJA. Several other factors related to the surgery (e.g., operation time, intraoperative blood loss, number of door openings, discipline in the operating room, antibiotic-prophylaxis used, surgeon's experience) may affect the risk of postoperative infection. However, those factors are not included in our analysis. With the challenging complexity of PJI and its heavy burden on patients

(34) and healthcare systems (35), prevention through effective strategies is the first and best approach and should be prioritized. Identifying high-risk patients planning to undergo arthroplasty surgery and providing interventions when possible by modifying these risk factors might form the basis of PJI prevention strategies in the future.

Strengths

Two major strengths of this study are the large sample size (n=1,191) and the meticulous follow-up of each patient. This thorough postoperative follow-up confirms that the number of recorded incidents of SSSI is accurate, and the follow-up time of 5 (mean 7.3; range 5.1-9.2) years is sufficient to reveal potential cases of PJI. Similar studies have presented larger cohorts but only on registers (36, 37) or shorter follow-ups (1, 2, 36).

Additionally, our study includes patients with primary elective joint surgery to minimise the influence of other risk factors connected to the initial trauma (hip fractures) or extended impact on the tissue (revision surgery). This inclusion criterion is an additional strength of the study given that the rate of PJI is known to be higher after trauma and revision surgery (38). According to preoperative screening routines in our hospital, patients with a history of excessive alcohol use, intravenous drug use, poor oral hygiene or other medical conditions or medications that compromise immunity are excluded from surgery or rehabilitated before surgery.

Limitations

A potential limitation is the retrospective nature of our study design. Therefore, there may be inaccuracies or misinterpretations of information retrieved from medical records. All our patients, however, were interviewed in person to answer questions about the postoperative period. Thus, the information from medical reports was verified.

Another limitation is that SSSI is not culture-verified but determined by a consultant orthopaedic surgeon that reflects the clinical reality. Cultures of a superficial infection can be misleading, which can be classified as contamination, even if a possibility of a clinical significance of skin flora found in cultures has recently been reported (39).

As in infection-related research in general, where a small number of infections are a major challenge, this study may have failed to detect an association between a potential risk factor and postoperative infection due to a type II error.

Conclusion

In conclusion, this study demonstrates that older obese patients with a high ASA classification may have an increased risk of developing SSSI. Patients developing SSSI after primary elective hip or knee arthroplasty have a high risk of progressing into PJI and a high ASA classification significantly affects the progression from SSSI to PJI.

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Ethics approval

The study design was reviewed and approved by the Human Research Ethics Committee in Uppsala, Sweden, Nr: 2019-01425.

Data availability statement

The dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests in this work.

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Contributors

Both authors (HE, SL) contributed substantially to the conception and design of the study and acquisition, analysis and interpretation of data. Both authors (HE, SL) have been involved in drafting the manuscript and given final approval of the version to be published. Both authors (HE, SL) have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abbreviations

Superficial surgical site infection: SSSI; Periprosthetic joint infection: PJI; Total joint arthroplasty: TJA; Total hip arthroplasty: THA; Total knee arthroplasty: TKA; Body mass index: BMI; American

Society of Anesthesiologists classification: ASA classification; Rheumatologic disease: RA; Diabetes mellitus: DM; Risk ratios RR; Adjusted RR: aRR.

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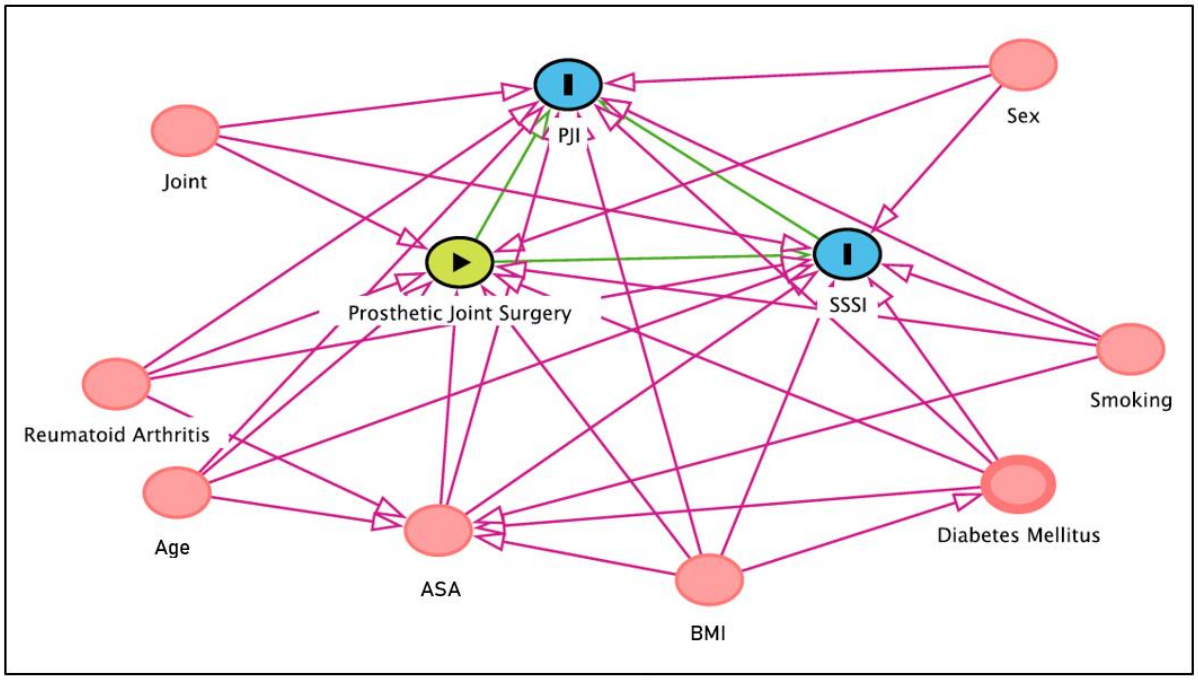
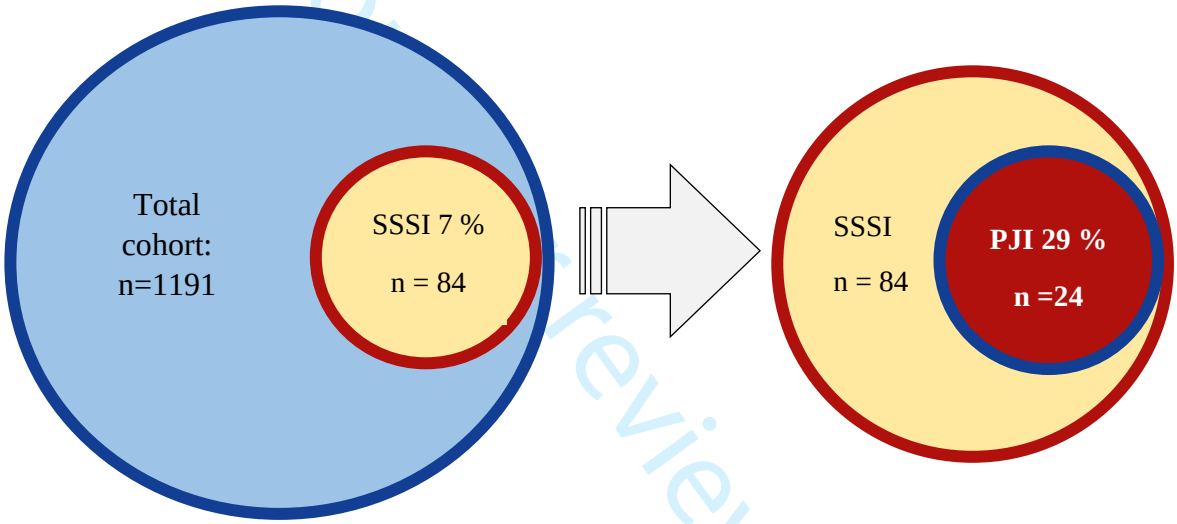
Figure legends

Figure 1. Directed acyclic graph for the selection of confounders

The circle with an arrow indicates the exposure, the circles with an (I) illustrate outcomes and the circles without text indicate confounders used in the statistical model.

Figure 2. Proportion of SSSI and PJI in the total cohort





Supplementary Table 1. Risk ratio (RR) for PJI

SSSI - no PJI	1167 (98%)
SSSI - PJI	24 (2%)

Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
Joint				
Hip	ref		ref	
Knee	2.1 (0.9 – 4.7)	0.073	2.0 (0.8 – 4.8)	0.112
Age				
<65	ref		ref	
≥65	1.3 (0.6 – 2.9)	0.517	1.1 (0.5 – 2.7)	0.781
ASA-class[a]				
≤ 2	ref		ref	
≥ 3	4.8 (2.1 – 10.9)	**0.000**	3.8 (1.6 – 9.1)	**0.003**
BMI				
BMI<25	ref		ref	
25≤BMI<30	2.0 (0.8 – 5.1)	0.142	1.9 (0.6 – 5.9)	0.271
BMI≥30	1.9 (0.9 – 4.4)	0.110	1.2 (0.4 – 3.3)	0.772
Sex				
Woman	ref		ref	
Men	2.1 (0.9 – 4.9)	0.075	2.8 (1.2 – 6.9)	**0.022**
Smoking[b]				
No	ref		ref	
Yes	2.7 (0.4 – 20.0)	0.338	2.5 (0.3 – 19.0)	0.379
Diabetes				
No	ref		ref	
Yes	2.3 (0.9 – 6.3)	0.101	1.4 (0.5 – 4.1)	0.543
Rheumatological disease				
No	ref		ref	
Yes	2.0 (0.8 -5.5)	0.166	1.8 (0.6 – 5.2)	0.294

ASA (American Society of Anaesthesiologists), BMI (Body mass index).

[a] missing data in 17 cases
[b] missing data in 5 cases

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*na*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	na
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	na
		(*e*) Describe any sensitivity analyses	na
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.