Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Preoperative and perioperative risk factors, and risk score development for prosthetic joint infection due to *Staphylococcus aureus*: a multinational matched case-control study

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ARTICLE INFO

Article history:
Received 20 February 2022
Received in revised form
1 May 2022
Accepted 8 May 2022
Available online xxx

Editor: M. Paul

ABSTRACT

Objectives: We aim to identify the preoperative and perioperative risk factors associated with post-surgical *Staphylococcus aureus* prosthetic joint infections (PJI) and to develop and validate risk-scoring systems, to allow a better identification of high-risk patients for more efficient targeted interventions.
Methods: We performed a multicenter matched case-control study of patients who underwent a primary hip and knee arthroplasty from 2014 to 2016. Two multivariable models by logistic regression were performed, one for the preoperative and one for perioperative variables; predictive scores also were developed and validated in an external cohort.

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https://doi.org/10.1016/j.cmi.2022.05.010
1198-743X/Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases.

Keywords:
Prosthetic joint infection
Arthroplasty
Staphylococcus aureus
Risk factors
Case-control study
Multinational study

Results: In total, 130 cases and 386 controls were included. The variables independently associated with *S. aureus*-PJI in the preoperative period were (adjusted OR; 95% CI): body mass index >30 kg/m^2 (3.0; 1.9 to 4.8), resident in a long-term care facility (2.8; 1.05 to 7.5), fracture as reason for arthroplasty (2.7; 1.4 to 5.03), skin disorders (2.5; 0.9 to 7.04), previous surgery in the index joint (2.4; 1.3 to 4.4), male sex (1.9; 1.2 to 2.9) and American Society of Anesthesiologists index score 3 to 4 (1.8; 1.2 to 2.9). The area under the receiver operating characteristic curve was 0.73 (95% CI 0.68 to 0.78). In perioperative model, the risk factors were the previous ones plus surgical antibiotic prophylaxis administered out of the first 60 minutes before incision (5.9; 2.1 to 16.2), wound drainage for >72 hours after arthroplasty (4.5; 1.9 to 19.4) and use of metal bearing material versus ceramic (1.9; 1.1 to 3.3). The area under the receiver operating characteristic curve was 0.78 (95% CI 0.72 to 0.83). The predictive scores developed were validated in the external cohort.
Discussion: Predictive scores for *S. aureus*-PJI were developed and validated; this information would be useful for implementation of specific preventive measures. **Reinaldo Espindola, Clin Microbiol Infect 2022;▪:1**

Introduction

Staphylococcus aureus is the leading cause of surgical site infections (SSI) after arthroplasty [1] and prosthetic joint infections (PJI) [2]. In addition, treatment of *S. aureus* PJI (SA-PJI) is associated with high-risk of failure [3]. Most SA-PJI are acquired during surgery; therefore, interventions aimed at preventing these infections during the surgical intervention have been studied, mostly using mupirocin-based preoperative decontamination strategies. However, logistic barriers preclude the implementation of universal screening colonization before surgery in many hospitals, and universal decolonization may increase the risk of disseminating mupirocin-resistance [4]. Other preventive strategies of *S. aureus* infections are under development, including vaccines and monoclonal antibodies [5,6].

Because of the barriers in implementation and cost issues, identifying the patients who would most benefit from preventive strategies to reduce the risk of SA-PJI is important.

In addition, this would help a more efficient design of randomized trial testing innovative prevention strategies by including the patients at higher risk. The risk factors for PJI have been extensively studied [7–11] but, to the best of our knowledge, there are no studies specifically addressing the risk factors for SA-PJI. On the other hand, most studies on PJI risk factors focused on total arthroplasties; however, hip hemiarthroplasties are being increasingly performed, and therefore it is important to obtain information about these procedures. Finally, early diagnosis of SA-PJI is important to provide timely management of these infections [3] in order to improve their outcomes; therefore, identifying the patients that may need a closer follow-up after arthroplasty would also be helpful.

The objective of this study was to identify the preoperative and perioperative risk factors associated with postsurgical SA-PJI in patients undergoing a hip and knee primary arthroplasty and to develop and validate risk-scoring systems, to allow a better identification of high-risk patients in whom targeted interventions and trials would be more efficient.

Materials and methods

Study design, sites, and period

To identify the risk factors and develop the scores, a multicenter, multinational, matched case-control study of adult patients who underwent hip and knee arthroplasty in 19 hospitals between 1 January 2014 and 31 December 2016 was performed. The participating sites, located in six European countries (Spain, Italy, France, Germany, United Kingdom, and The Netherlands), were selected on the base of their research experience in PJI and ability to collect the predefined data using the CLIN-Net research network (https://www.combacte.com/about/clin-net/). The study protocol was registered at clinicaltrials.gov (NCT03826108). The scores were validated using data from a previously collected prospective cohort study in three Spanish sites including all patients who underwent hip/knee arthroplasty between March 2013 and February 2015 (validation cohort); the features of the cohort had been previously published [11].

Patients, study variables, and procedures

In the case-control study, all patients who underwent a hip or knee (total or partial) primary arthroplasty during the study period were eligible and identified by consulting the surgical registries at each participating hospital. Those who developed a microbiologically-confirmed PJI due to *S. aureus* (see below) during the first year after surgery were selected as cases. Microbiological and local surveillance SSI databases were also checked. For each case, three patients without PJI were selected as controls, matched by hospital, joint of arthroplasty (knee/hip), and surgery date (the nearest to the surgery date of the corresponding case). The matching variables were selected to control the potential confounding effect of the sites, surgeon teams, season and joint; matching for other variables was not performed to avoid overmatching and to investigate them as risk factors. An additional control group formed by patients with PJI caused by other pathogens was not included because the specific target for novel preventive measures was only SA-PJI.

PJI were diagnosed according to standard criteria [12] and were considered as caused by *S. aureus* if this organism was isolated from ≥1 joint aspirate samples, ≥2 periprosthetic tissue samples, and/or blood cultures without any other evident source of infection. The microbiology laboratories of the participating hospitals used standard procedures for bacterial identification and susceptibility testing.

Potential risk factors for SA-PJI were selected according to previous studies [7–11] and additional hypotheses developed by the project team (Tables 1 and 2); exposure to these variables was assessed at two time points: in the preoperative evaluation of the patients (preoperative variables) and in the first week after surgery (preoperative plus perioperative variables). Standard definitions were used; we defined skin disorder as a history of dermatitis or ≥2 episodes of cellulitis requiring treatment with antibiotics, or the presence of partial thickness loss of skin over legs or back with open ulcers.

Please cite this article as: Espindola R et al., Preoperative and perioperative risk factors, and risk score development for prosthetic joint infection due to *Staphylococcus aureus*: a multinational matched case-control study, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2022.05.010

Table 1
Univariable analysis of preoperative risk factors for *S. aureus*-prosthetic joint infection

Variable	Cases $n = 130$	Controls $n = 386$	OR (95% CI)	p value
Age (median; IQR)	73 (59.7–81.0)	70 (62.0–78.0)	—	0.316
Male sex	66 (50.8)	150 (38.9)	1.6 (1.1–2.4)	0.018
Born abroad	2 (1.5)	8 (2.1)	0.7 (0.1–3.5)	0.700
Body mass index (median; IQR)	31.2 (25.6–35.0)	27.8 (24.7–31.2)		<0.001
Resident in LTCF	13 (10.0)	9 (2.3)	4.6 (1.9–11.2)	<0.001
Current smoking	20/124 (16.1)	42/368 (11.4)	1.5 (0.8–2.6)	0.171
Heavy alcohol consumption	5/115 (4.3)	9/369 (2.4)	1.8 (0.6-5.5)	0.286
Rheumatoid arthritis	1 (0.8)	12 (3.1)	0.2 (0.03–1.9)	0.141
Other arthropathy[a]	4 (3.0)	18 (4.6)	0.64 (0.2–1.9)	0.439
Functional status before arthroplasty:	$n = 125$	$n = 370$		
Walk without help	71 (54.6)	259 (67.1)	Ref.	—
Walk with a crutch	31 (23.8)	80 (20.7)	1.4 (0.9–2.3)	0.167
Walk with two crutches	7 (5.4)	9 (2.3)	2.8 (1.0–7.9)	0.046
Unable to walk	16 (12.3)	22 (5.7)	2.6 (1.3–5.3)	0.006
Immunosuppression[b]	7 (5.4)	19 (4.9)	1.1(0.4–2.7)	0.835
Previous joint infection (not due to *S. aureus*)	2 (1.5)	1 (0.3)	6.0 (0.5–66.9)	0.097
Previous joint surgery[c]	24 (18.5)	40 (10.4)	1.9 (1.2–3.4)	0.015
Previous intra-articular steroids injection (3 months)	9 (6.9)	23 (6.0)	1.2 (0.5–2.6)	0.693
Anticoagulation	17 (13.1)	29 (7.5)	1.8 (1.0–3.5)	0.054
Skin disorders[d]	9 (6.9)	9 (2.3)	3.1 (1.2–8.0)	0.014
Depression	24 (18.5)	52 (13.5)	1.4 (0.8–2.5)	0.165
Hypertension	83 (64.3)	219 (56.9)	1.4 (0.9–2.0)	0.149
Preoperative *S. aureus* infection	0	0	—	—
S. aureus colonization screening performed	46 (35.4)	158 (41.1)	0.8 (0.5–1.2)	0.246
S. aureus positive on screening	6/46 (13.0)	17/158 (10.8)	1.2 (0.5–3.4)	0.660
Decolonization treatment	35/129 (27.1)	109/382 (28.6)	0.9 (0.6–1.4)	0.747
Reason for arthroplasty:				
Osteoarthritis	84 (64.6)	304 (78.8)	Ref.	
Fracture	35 (26.9)	53 (13.7)	2.4 (1.5–3.9)	<0.000
Osteonecrosis	5 (3.8)	12 (3.1)	1.5 (0.5–4.4)	0.452
Rheumatoid arthritis	1 (0.8)	5 (1.3)	0.7 (0.1–6.3)	0.769
Dysplasia	2 (1.5)	10 (2.6)	0.7 (0.1–3.4)	0.680
Septic arthritis	1 (0.8)	0 (0)	—	—
Tumor	2 (1.5)	2 (0.5)	3.6 (0.5–26.1)	0.202
Type of arthroplasty:				
THA	50 (38.5)	193 (50.0)	Ref.	—
PHA	28 (21.5)	42 (10.9)	2.6 (1.4–4.5)	0.001
TKA	50 (38.5)	145 (37.6)	1.3 (0.8–2.0)	0.213
PKA	2 (1.5)	6 (1.6)	1.3 (0.2–6.6)	0.674
Charlson comorbidities				
Myocardial infarction	17 (13.1)	36 (9.4) $n = 384$	1.4 (0.8–2.7)	0.230
Chronic heart failure	17 (13.1)	28 (7.3)	1.9 (1.0–3.6)	0.042
Peripheral vascular disease	7 (5.4) $n = 129$	10 (2.6)	2.1 (0.8–5.8)	0.119
Cerebrovascular disease	8 (6.2)	21 (5.4)	1.1 (0.5–2.6)	0.760
Hemiplegia	3 (2.3)	3 (0.8)	3.0 (0.6–15.1)	0.159
Chronic pulmonary disease	30 (23.1)	49 (12.7)	2.0 (1.2–3.4)	0.004
Diabetes mellitus	30 (23.1)	68 (17.6)	1.4 (0.9–2.3)	0.170
Diabetes with organ damage	3 (2.3)	8 (2.1)	1.1 (0.3–4.3)	0.872
Renal disease	5 (3.8)	8 (2.1)	1.9 (0.6–5.9)	0.264
Mild chronic liver disease	3 (2.3)	6 (1.6)	1.5 (0.4–6.1)	0.570
Moderate-severe liver disease	2 (1.5)	3 (0.8)	2.0 (0.3–12.0)	0.443
Gastric or peptic ulcer	2 (1.6) $n = 129$	14 (3.6)	0.4 (0.1–1.9)	0.239
Solid tumor	8 (6.2)	11 (2.8)	2.2 (0.9–5.7)	0.084
Lymphoma	2 (1.5)	2 (0.5)	3.0 (0.4–21.5)	0.251
Leukemia	0	2 (0.5)	—	0.411
Dementia	12 (9.3) $n = 129$	12 (3.1)	3.2 (1.4–7.3)	0.004
Rheumatic/connective tissue disease	11 (8.5)	30 (7.8)	1.1 (0.5–2.2)	0.801
HIV infection	0	1 (0.3)	—	0.561
Charlson index:				
0	45 (34.6)	189 (49)	Ref.	
1-2	58 (44.6)	158 (40.9)	1.5 (1–2.4)	0.055
3-4	18 (13.8)	36 (9.3)	2.1 (1.1–4)	0.026
≥5	9 (6.9)	3 (0.8)	12.6 (3.3–48.4)	<0.001

(*continued on next page*)

Please cite this article as: Espindola R et al., Preoperative and perioperative risk factors, and risk score development for prosthetic joint infection due to *Staphylococcus aureus*: a multinational matched case-control study, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2022.05.010

Table 1 (*continued*)

Variable	Cases $n = 130$	Controls $n = 386$	OR (95% CI)	p value
ASA index:				
1	7 (5.4)	54 (14)	Ref.	
2	58 (44.6)	219 (56.7)	2 (0.9–4.7)	0.095
3	60 (46.2)	108 (28)	4.3 (1.8–10)	0.001
4	5 (3.8)	5 (1.3)	7.7 (1.8–33.5)	0.006

Data for cases and controls are expressed as number of cases (%) except where specified. The denominator is specified when there are missing cases.
ASA, American Society of Anesthesiologists index; LTCF, Long-term care facility; PHA, partial hip arthroplasty; PKA, partial knee arthroplasty; THA, total hip arthroplasty; TKA, total knee arthroplasty.

[a] Other arthropathies: Cases: one gout arthropathy, two hip dysplasias, one Perthes disease. Controls: one hemophilic arthropathy, nine hip dysplasias, five osteonecrosis, one Perthes disease, two psoriatic arthropathies.

[b] Immunosuppression (defined as HIV patients with <200 CD4 cells/mm^3, use of steroids >5 mg of prednisone or equivalent >2 weeks during the last 2 months, biologic immunosuppressive therapy up to 4 weeks before the procedure, cancer chemotherapy during previous 3 months, radiotherapy during previous 3 months, splenectomy): Cases: one use of steroids, two biologic therapy, three chemotherapy, one radiotherapy. Controls: one HIV, four use of steroids, eight biologic therapy, two chemotherapy, two radiotherapy, two splenectomies.

[c] Previous joint surgery: Cases: nine arthroscopies, three joint resurfacing, five osteotomies, four fracture treatment, three open meniscectomies. Controls: 21 arthroscopies, 2 dysplasia treatment, 2 forages, 2 joint resurfacing, 5 osteotomies, 2 biopsies, 4 fracture treatment, 1 meniscectomy, 1 patellectomy.

[d] Skin disorders: defined as a history of dermatitis, two or more episodes of cellulitis requiring treatment with antibiotics, or the presence of partial thickness loss of skin over legs or back with open ulcers.

The data were collected by trained local investigators and entered in an anonymized electronic case report form; the quality of the data was remotely monitored for missing values and coherence. The study was approved by the Ethics Boards at each site according to local regulations that waived the need to obtain informed consent due to the retrospective nature of the study except in French hospitals, where it was required.

The validation cohort (briefly described in Table S4) was an external prospective PJI cohort collected in three Spanish hospitals before the current cohort, one of them participating in the present

Table 2
Univariable analysis of perioperative risk factors for *S. aureus*-prosthetic joint infection

Variable	Cases $n = 130$	Controls $n = 386$	OR (95% CI)	p value
Days of hospitalization before surgery (median; IQR)	1 (0–1.0)	0 (0–1.0)	—	0.251
Duration of surgery in minutes (median; IQR)	89 (70.0–110.0); ($n = 120$)	82 (65.0–103.0); ($n = 355$)	—	0.146
NNIS score 1-2 (vs 0)	68/120 (56.7)	125/355 (35.2)	2.4 (1.6–3.7)	<0.001
Days of drain tube in situ (median; IQR)	1 (1.0–2.0); ($n = 108$)	1 (1.0–2.0); ($n = 331$)	—	0.318
Days of urine catheter in situ (median; IQR)	0 (0–2.0) ($n = 116$)	0 (0–1.0) ($n = 334$)	—	0.133
Days of vascular catheter in situ (median; IQR)	3 (2.0–5.0) ($n = 98$)	2.5 (2.0–5.0) ($n = 302$)	—	0.160
Glycopeptide vs beta-lactam prophylaxis	6/128 (4.7)	4/378 (1.1)	4.6 (1.3–16.6)	0.011
Timing of antibiotic prophylaxis:	$n = 119$	$n = 351$		
<60 min before incision	108 (90.8)	341 (97.2)	Ref.	—
>60 min before incision	5 (4.2)	5 (1.4)	3.2 (0.9–11.1)	0.073
After incision	6 (5.0)	5 (1.4)	3.8 (1.1–12.6)	0.030
Prophylaxis, out of 60 min before incision	11/119 (9.2)	10/351 (2.8)	3.9 (1.6–9.6)	0.007
Prophylaxis, repeated dose	70/117 (59.8)	195/366 (53.3)	1.3 (0.8–2.0)	0.215
Hyperglycemia before surgery	4/72 (5.6)	12/169 (7.1)	0.7 (0.2–2.5)	0.659
Hyperglycemia after surgery	10/64 (15.6)	18/188 (9.6)	1.7 (0.8–4.0)	0.183
Use of bone cement	86/130 (66.2)	219/378 (57.9)	1.4 (0.9–2.1)	0.099
Cement with antibiotic	47/81 (58.0)	105/207 (50.7)	1.3 (0.8–2.2)	0.260
Bearing material, metal vs ceramic	88/117 (75.2)	195/346 (56.4)	2.3 (1.5–3.8)	<0.001
General anesthesia	55/127 (43.3)	156/384 (40.6)	1.1 (0.7–1.7)	0.595
Red cells transfusion	20/130 (15.4)	34/384 (8.9)	1.9 (1.1–3.4)	0.036
Invasive procedure during hospitalization[a]	1 (0.8)	3 (0.8)	0.9 (0.1–9.6)	0.993
Superficial surgical site infection	4 (3.1)	0	—	0.001
Distant infection during hospitalization[b]	8 (6.2)	17 (4.4)	1.4 (0.6–3.4)	0.422
Anticoagulation after surgery	116 (89.2)	347 (89.9)	—	0.954
Wound dehiscence	4 (3.1)	1 (0.3)	—	0.015
Drainage from the wound >72 hours	23 (17.7)	12 (3.1)	6.7 (3.2–13.9)	<0.001

Data for cases and controls are expressed as number of cases (%) except where specified. The denominator is specified when there are missing cases.
IQR, interquartile range; NNIS, National Nosocomial Infections Surveillance.

[a] Invasive procedure during hospitalization: Cases: one coronary angiography. Controls: one upper endoscopy, two intra-articular catheters.

[b] Distant infections during hospitalization: Cases: one skin infection, two urinary tract infections, five pneumonias, one *Clostridioides difficile* infection (one case had two distant infections). Controls: one skin infection, eight urinary tract infections, four pneumonias, two phlebitis, one pharyngitis, one *C. difficile* infection.

Please cite this article as: Espindola R et al., Preoperative and perioperative risk factors, and risk score development for prosthetic joint infection due to *Staphylococcus aureus*: a multinational matched case-control study, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2022.05.010

Table 3
Multivariable model of preoperative factors for *S. aureus*-prosthetic joint infection and assignment of scores based on regression coefficients. The analysis of the subgroup of patients without fracture is added.

Variable	β	Adjusted OR (95% CI)	p value	Score
All patients[a]				
Male sex	0.62	1.9 (1.2–2.9)	0.005	2
Body mass index >30	1.10	3.0 (1.9–4.8)	<0.001	4
Resident in LTCF	1.03	2.8 (1.05–7.5)	0.040	3
ASA score 3–4	0.62	1.8 (1.2–2.9)	0.009	2
Previous joint surgery	0.88	2.4 (1.3–4.4)	0.005	3
Skin disorder	0.92	2.5 (0.9–7.04)	0.077	3
Fracture (hip/knee)	0.99	2.7 (1.4–5.03)	0.003	3
Patients without fracture[b]				
Male sex	0.58	1.8 (1.1–2.9)	0.020	2
Body mass index >30	0.88	2.4 (1.5–3.9)	0.001	3
Resident in LTCF	2.11	8.3 (0.8–84.7)	0.074	7
ASA score 3–4	0.64	1.9 (1.1–3.2)	0.016	2
Previous joint surgery	0.84	2.3 (1.2–4.3)	0.008	3
Skin disorder	1.06	2.9 (0.9–9.3)	0.073	4

ASA, American Society of Anesthesiologists index; LTCF, long-term care facilities.
[a] Area under the receiver operating characteristic curve of the model: 0.73 (95% CI: 0.68–0.78); Calibration: for Hosmer-Lemeshow test p = 0.769.
[b] Area under the receiver operating characteristic curve of the model: 0.72 (95% CI: 0.66–0.78); Calibration: for Hosmer-Lemeshow test p = 0.329.

cohort [11]. Cases of SA-PJI were selected from the overall validation cohort. The same definition for SA-PJI was used; patients were followed for 12 months after surgery. The same variables were collected, except for bearing material.

Statistical analysis

Using the ene3.0 software (available at https://sct.uab.cat/estadistica/es/content/software-de-interes), we estimated that inclusion of 111 cases and 333 controls would allow the identification of risk factors with an OR ≥2 for a 20% exposure rate among controls (frequent for key risk factors in previous studies [9,10]), with a β error ≤20% and two-sided α < 0.05.

To investigate the risk factors, two models were constructed: a preoperative and a perioperative model. The univariable association of each factor with SA-PJI were studied by using McNemar and Mann-Whitney U tests for qualitative and quantitative variables, respectively; those with a p value < 0.15 were considered for inclusion in multivariable models, developed by conditional logistic regression. Collinearity and effect-modifying interactions between variables were also assessed. The variables in each model were selected using a manual stepwise backward procedure; all variables with p < 0.10 were kept. Weighted scores for each variable were calculated by dividing each regression coefficient by one-half of the smallest coefficient and rounding to the nearest integer. The predictive ability of the models and score systems were examined by calculating their area under the receiver operating characteristic (AUROC) curves with 95% confidence interval (CI). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for different break points and the scores obtained were then applied to the validation cohort. The analyses were performed using IBM SPSS 23.0.

Results

Overall, 130 cases and 386 controls were included (for 4 cases, one selected control was excluded because of lack of data). The median number of cases per site was 7 (interquartile range 5 to 9). The median age of patients was 71 years (interquartile range 61 to 78) and 216 (41.9%) were males. Overall, 313 (60.7%) patients underwent a hip arthroplasty (total, 243 (77.6%); partial, 70 (22.4%)) and 203 (39.3%) underwent a knee arthroplasty (total, 195 (96.1%); partial 8 (3.9%)). The diagnosis of infection among the cases was made within the first 90 days after arthroplasty in 122 (93.8%) patients. Bacteremia occurred in 25 (19.2%) cases; a methicillin-resistant *S. aureus* was isolated in 29 (22.3%) patients.

In the univariate analysis, the variables associated with SA-PJI in the preoperative period (namely, collected in the evaluation prior arthroplasty) are shown in Table 1. Variables associated with SA-PJI in the perioperative period (namely, collected in the first week after arthroplasty) are shown in Table 2.

The multivariable models are shown in Tables 3 and 4. The variables independently associated with SA-PJI in the preoperative model were male sex, body mass index >30, being resident in a long-term care facility (LTCF), American Society of Anesthesiologists index (ASA) score 3 to 4, previous surgery in the index joint, skin disorders, and fracture as reason for arthroplasty. The model

Table 4
Multivariable model of perioperative risk factors for *S. aureus*-prosthetic joint infection and assignment of scores based on regression coefficients. The analysis of the subgroup of patients without fracture is added.

Variable	β	Adjusted OR (95% CI)	p value	Score
All patients[a]				
Male sex	0.65	1.9 (1.1–3.2)	0.013	2
Body mass index >30	0.89	2.4 (1.4–4.1)	0.001	3
Resident in LTCF	1.39	4.0 (1.0–16.2)	0.050	4
ASA score 3-4	0.77	2.1 (1.3–3.7)	0.005	2
Previous joint surgery	0.95	2.6 (1.3–5.3)	0.009	3
Fracture (hip/knee)	1.14	3.1 (1.5–6.7)	0.003	4
Antibiotic prophylaxis out of the 60-minute period before incision	1.78	5.9 (2.1–16.2)	0.001	6
Metal bearing (vs ceramic)	0.64	1.9 (1.1–3.3)	0.025	2
Wound drainage >72 hours	1.50	4.5 (1.9–10.4)	<0.001	5
Patients without fracture[b]				
Male sex	0.63	1.9 (1.1–3.3)	0.028	2
Body mass index >30	0.76	2.1 (1.2–3.8)	0.010	2
Resident in LTCF	2.22	9.2 (0.7–120.2)	0.089	7
ASA score 3–4	0.80	2.2 (1.2–4.0)	0.008	2
Previous joint surgery	0.92	2.5 (1.2–5.2)	0.014	3
Antibiotic prophylaxis out of the 60 minute period before incision	1.85	6.3 (2.2–18.4)	0.001	6
Metal bearing (vs ceramic)	0.61	1.8 (1.03–3.3)	0.039	2
Wound drainage >72 hours	1.49	4.4 (1.8–10.9)	0.001	5

ASA, American Society of Anesthesiologists index; BMI, Body mass index; LTCF, long-term care facilities.
[a] Area under the receiver operating characteristic curve of the model: 0.78 (95% CI: 0.72–0.83); Calibration: for Hosmer-Lemeshow test p = 0.418.
[b] Area under the receiver operating characteristic curve of the model: 0.76 (95% CI: 0.70–0.82). Calibration: for Hosmer-Lemeshow test p = 0.531.

Please cite this article as: Espindola R et al., Preoperative and perioperative risk factors, and risk score development for prosthetic joint infection due to *Staphylococcus aureus*: a multinational matched case-control study, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2022.05.010

with these variables showed a moderate prediction ability, with an AUROC curve of 0.73 (95% CI, 0.68 to 0.78) for observed data (Fig. S1A). The score-based prediction rule (Table 3) showed the same AUROC curve (0.73 (95% CI, 0.68 to 0.78)). When the score was applied to the validation cohort, the AUROC curve was 0.76 (95% CI, 0.68 to 0.83; Fig. S2A). The sensitivity, specificity, PPV, and NPV for different breakpoints of the score are listed in Table 5.

The variables independently associated with SA-PJI in the perioperative model were the same except for the exclusion of skin disorders and the addition of surgical antibiotic prophylaxis (SAP) administered out of the 60-minute period before incision, use of metal-bearing material, and drainage from the wound >72 hours after surgery. The AUROC curve for this model was 0.78 (95% CI: 0.72 to 0.83), also showing a moderate prediction ability (Fig. S1B). The score-based prediction rule (Table 4) showed an AUROC curve of 0.77 (95% CI, 0.72 to 0.81), and when was applied to the validation cohort, the AUROC curve was 0.79 (95% CI, 0.71 to 0.86; Fig. S2B). The sensitivity, specificity, PPV, and NPV for different breakpoints of the score are listed in Table 5.

When patients in whom the arthroplasty was performed because of a fracture were excluded, the models were similar (univariable analyses are shown in Tables S2 and S3, and multivariable models on Tables 3 and 4).

Discussion

This multinational case-control study identified several risk factors for SA-PJI after all types of primary hip and knee arthroplasty. We developed two multivariable models with a scoring system and externally validated: one including only preoperative variables, which would be useful for assessing the risk when evaluating the patients before surgery and eventually identifying those for which target preventive intervention or inclusion in randomized trials would be more efficient, and another including perioperative variables, which would be useful to identify which patients would need a closer postsurgery follow-up for an early diagnosis and treatment of infection.

Because the control group was formed by patients who did not develop PJI, some of the risk factors found might not be specific for *S. aureus*; in fact, some of them had been also identified as risk factor for all-cause PJI. While this reflects the importance of *S. aureus* as an aetiological agent of PJI, we think the risk estimations provided for each variable in this study are useful from the perspective of our objective as they would be more accurate for *S. aureus*. Interestingly, some of the risk factors found are associated with *S. aureus* colonization in the general population, including male sex, obesity, and skin disorders [13–17]. It could be argued that it is better to just perform universal screening for *S. aureus* colonization before surgery; however, in this study, reflecting real-life conditions, only around half of the patients were screened for *S. aureus,* and 28% were decolonized. This on one side limited the statistical power to estimate the influence of these factors but on the other side reflects that implementation of universal screening is complex. We think the above variables might be in fact proxies for *S. aureus* colonization and could be used to identify high-risk patients when universal screening is not feasible, or even to select patients for screening. In addition to *S. aureus* colonization, some of these variables may add other reasons for an increased risk also related to *S. aureus*, e.g. dosing of SAP (which is mostly targeting staphylococci) in obese patients might be more frequently suboptimal [18], and skin disorders may jeopardize appropriate hygiene and skin decolonization measures.

We also found the ASA score, a universally accepted risk classification for adverse events during surgery based on the underlying comorbidities, to be a risk factor. While recognized as a risk factor for PJI caused by any pathogen [10], it may also be associated with *S. aureus* colonization because of increased healthcare contact of patients with higher ASA. From a practical perspective, this is a useful marker because it is usually integrated in the preanesthetic assessment. Although we excluded patients with a revision arthroplasty, which is frequently performed for a previous infection [11], we also found previous surgery in the index joint to be associated with increased risk of SA-PJI; this was not unexpected because previous surgery-associated fibrosis and tissue damage may reduce the bacterial load needed to cause an infection. Similarly, fracture as a reason for arthroplasty may facilitate infection beyond its potential association with comorbidities, in relation to soft tissue damage and hematoma [19,20]; also, surgery for fracture may be more frequently performed without the appropriate preventive preparation. Interestingly, the risk factors in the subgroup of patients without fracture were similar to those in the overall population.

Regarding the perioperative factors, we found SAP administered out of the 60-minute period before incision increased the risk. The association found in this study may be higher than when analyzing all-cause PJI because the antibiotics used for SAP primarily target staphylococci. This is in line with the results of a meta-analysis that showed that administration of SAP >120 minutes before incision or after incision is associated with a higher risk of SSIs [21]. The use of metal instead of ceramics bearing was also found to increase the risk of SA-PJI in our study. The lower surface roughness (which is classically associated with a lower bacterial adhesion [22]) and hydrophilicity (which has also been found to decrease *S. aureus* adherence compered to hydrophobic surfaces [23]) of ceramic bearings might explain this finding. However, a meta-analysis in total hip arthroplasty could not find an association of bearing surfaces with different risk of infection for PJI caused by any pathogen [24], and therefore the association of type of bearing with SA-PJI needs further studies. Finally, wound drainage >72 hours after surgery was previously associated with PJI [11]; while purulent drainage is indicative of SSI, prolonged wound serous-type drainage is frequently self-limited. Our data suggest that these patients should be closely followed with a high suspicion of PJI if any sign or symptom appear.

This study has some limitations. The sample size may have been insufficient to detect some risk factors, particularly in some

Table 5
Proportion of patients, Sensitivity, Specificity, PPV, and NPV for different break points according to the score predicting *S. aureus*-prosthetic joint infection in the ARTHR-IS case-control cohort and in the validation cohort at preoperative and perioperative evaluation

ARTHR-IS cohort						Validation cohort					
Preoperative model	**Proportion of patients**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Preoperative model**	**Proportion of patients**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Score ≥4	60.1%	83.1%	47.7%	1.6%	99.6%	Score ≥4	59%	75%	41.2%	1.3%	99.4%
Score ≥8	16.3%	33.8%	89.6%	3.1%	99.2%	Score ≥8	10.2%	33.3%	89.9%	3.3%	99.2%
Perioperative model	**Proportion of patients**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Perioperative model**	**Proportion of patients**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Score ≥4	66.7%	85.4%	39.6%	0.1%	99.6%	Score ≥4	50%	77.7%	50.3%	1.6%	99.5%
Score ≥8	23.4%	33.8%	89.6%	3.2%	99.2%	Score ≥8	10.1%	33.3%	90.1%	3.3%	99.2%

ARTHR-IS, Arthroplasties' Infections due to *Staphylococcus aureus*; NPV, negative predictive value; PPV, positive predictive value.

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subgroups of patients, such as early and late SA-PJI, or infections caused by methicillin-resistant S. *aureus*. Also, its retrospective nature limited the type of variables to collect. The model's prediction was moderate, possibly because *S. aureus* colonization status was available only for about a third of patients, and we were not able to collect the individual measures of patient preparation before surgery. However, this represents the available data in real practice, and the high NPV allows us to rule out SA-PJI in the absence of any risk factors described. Some strengths include the multinational nature of the study, the reflection of real-life conditions, the fact that specifically SA-PJI were investigated in two different moments of patient care, and the validation in an external cohort.

In conclusion, this study provided real-life data on the risk factors for postsurgical SA-PJI after primary hip and knee arthroplasty in European countries. These data would be useful to identify high-risk patients for specific preventive interventions and design of randomized trials and to identify the patients who would need a closer postsurgery follow-up for an early diagnosis and treatment of infection.

Transparency declaration

RE, NB, IM, ST, NR, JH, LS, OM, MS, CS, JK, MCF, MP, IM, RE-S, CA, CB, F-AD, W-YL, JL-T, JP, JU, JR-B, and MDDT declare not to have no conflicts of interest. VV, EC, MP, and FB are employees of the GSK group of companies and have nonfinancial interest to declare. VV, MP, and FB hold shares in the GSK group of companies. FB holds pending and issued patents on *Staphylococcus aureus* vaccine formulations. RE, LS, OM, EE-S, JL-T, JP, JR-B, and MDDT are members of the Spanish Network for Research in Infectious Diseases (REIPI), supported by Plan Nacional de I + D + i 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Ciencia, Innovación y Universidades, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0001; 0002; 0005; 0009; 0011; 0015), co-financed by European Development Regional Fund "A way to achieve Europe," Operative Program Intelligence Growth 2014-2020. GlaxoSmithKline Biologicals SA was provided the opportunity to review a version of this manuscript for factual accuracy; authors are solely responsible for final content and interpretation.

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement No. 115523, COMBACTE-NET consortium (European Union FP7/2007–2013 and GlaxoSmithKline Biologicals SA, as EFPIA partner).

Author contributions

JRB and MDDT contributed equally as senior authors of the study. RE, VV, JR-B, and MDDT contributed to the conception and design of the study, analysis and interpretation of data, and drafting the article. NB, IM, ST, NR, JH, LS, OM, MS, CS, JK, MCF, MP, IM, RE-S, CA, CB, F-AD, W-YL, JL-T, JP, and JU contributed to the acquisition of data and revising the article. EC, MP, and FB participated in the analysis and interpretation of data and revision the article. All authors gave their final approval of the version to be submitted.

Acknowledgements

Many researchers at each institution have helped to make this study possible. We are deeply indebted to the following collaborators and members of the ARTHR-IS group: Nienke Cuperus and Giuseppe Manfré (Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands) collaborated in the selection process of the participating centers. Eleonora Zamparini (Policlinico Sant'Orsola-Malpighi, University of Bologna, Bologna, Italy), Stéphanie Verhagen (Department of Orthopaedic Surgery & Trauma, Máxima MC, Eindhoven, the Netherlands), Juan P. Horcajada, Joan Gómez Junyent, and Albert Alier (Hospital del Mar, Institut Hospital del Mar d'Investigacions Mèdiques, Universitat Pompeu Fabra, Barcelona, Spain), Laura Soldevila (Servicio Enfermedades Infecciosas Hospital Universitari Bellvitge. IDIBELL, Barcelona, Spain), Miranda van Rijen and Jannie Romme (Amphia Hospital, Breda, Netherlands), Juliane Ankert (Jena University Hospital, Jena, Germany), Celia Whitehouse and Adrian Jones (Norfolk and Norwich University Hospital, Norwich, UK), Javier Cobo and Javier Moreno (Hospital Universitario Ramón y Cajal, Madrid, Spain), Anne Meheut (Centre Hospitalier Universitaire de Rennes, Rennes, France), Claire Gledel (Orthopedic surgery department, Croix Rousse Hospital, Lyon, France), Pauline Perreau (Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France), Remco J.A. van Wensen (Department of Orthopaedic Surgery & Trauma, Catharina Hospital, Eindhoven, the Netherland), and Gabriella Lindergard (North Manchester General Hospital, Manchester, UK) collaborated in the data collection.

We also appreciate the collaboration of the authors of the publication of the cohort of patients with prosthetic joint infection where it has been possible to validate the results of this work: Cecilia Peñas (at the time of publication, Infectious Diseases Unit, Hospital Universitario Virgen Macarena, Sevilla, Spain); Ana Conde Albarracín (Orthopedic and Traumatology Unit, Hospital Universitario Virgen Macarena, Sevilla, Spain); Julián Palomino (Infectious Diseases Unit, Hospital Universitario Virgen del Rocío, Sevilla, Spain); Francisco Brun (at the time of publication, Internal Medicine Unit, Hospital Universitario Puerta del Mar, Cádiz, Spain); Santiago Sánchez (at the time of publication, Orthopedic and Traumatology Unit, Hospital Universitario Puerta del Mar, Cádiz, Spain).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.05.010.

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