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Periprosthetic Joint Infection and Concomitant Sepsis: Unveiling Clinical Manifestations, Risk Factors, and Patient Outcomes

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ABSTRACT

Background: This study investigated the epidemiology, risk factors, and outcomes of sepsis, a life-threatening complication, in the context of periprosthetic joint infections (PJIs) of the hip and knee.
Methods: Sepsis was determined using the sepsis-1 criteria. The cohort with PJI and sepsis was compared to patients who had PJI without sepsis. Analyzed risk factors were patient characteristics, microbiological findings, and comorbidities. Outcome parameters were mortality, length of hospital stay, and intensive care unit stay. Among 108 PJIs (48 hips and 60 knees), 40.6% met the sepsis criteria.
Results: In hip PJI, the sepsis group had a higher Charlson Comorbidity Index (4.0 versus 1.0; $P \leq 0.001$) with *Staphylococcus aureus* infections more common in septic cases (9 of 17 versus 6 of 31; $P = 0.04$). Renal (odds ratio (OR) 16.9; $P \leq 0.001$) and cardiac (OR 12.5; $P = 0.02$) disease increased sepsis risk. Sepsis correlated with prolonged hospital stays (54 versus 24 days; $P = 0.002$) and increased mortality (23.5 versus 3.2%; $P = 0.047$). In knee PJI cases, septic patients had more *Staphylococcus aureus* PJI (14 of 28 versus 8 of 32; $P = 0.04$). Atrial fibrillation (OR 3.3; $P = 0.04$) and renal disease (OR 4.0; $P = 0.02$) were associated with sepsis. Sepsis cases had longer hospital stays (48 versus 29.5 days; $P = 0.01$) and higher intensive care unit admissions (67.9 versus 34.4%; $P = 0.02$). In-hospital mortality was 10-fold higher in the sepsis cohort (25.0 versus 3.3%; OR 10.3, $P = 0.02$).
Conclusions: In a considerable number of patients, PJI can lead to a septic course associated with increased mortality. This underscores the need for close monitoring to prevent overlooking these patients' deteriorating clinical conditions. Timely interventions, akin to the "every hour counts" approach in sepsis management, might help reduce morbidity and mortality in these patients.

The global incidence of arthroplasty procedures has been steadily increasing, making them one of the most common orthopaedic interventions worldwide [1,2]. Despite their high success rates, periprosthetic joint infections (PJIs) remain among the most frequent, important, and challenging complications associated with these procedures [3–5]. The clinical presentation of PJI can vary widely, ranging from a painful joint to severe systemic manifestations, including sepsis [6,7]. Sepsis is a dysregulated host response to infection, leading to widespread inflammation and organ dysfunction; crude mortality rates range from 10 to > 40% [6]. The individual risk of mortality depends on the site of infection and the infecting pathogen, host factors such as age and comorbidities, and the promptness and efficacy of therapy [8–11].

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Data Availability Statement: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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The consequences of PJI and its various treatment options, ranging from (debridement, antibiotics, and implant retention (DAIR) to staged surgical procedures and even amputation, have been well investigated in terms of quality of life, necessary revision rates, and mortality [12–15]. However, there is a paucity of studies specifically investigating the subgroup of patients who have sepsis. Understanding the differences between patients who do and do not have sepsis in the context of PJI is essential for improving outcomes and guiding clinical management. Therefore, this study aimed to investigate: (1) the proportions of PJI patients who have concomitant sepsis; (2) risk factors for sepsis; and (3) mortalities and outcomes in the cohort suffering from PJI and sepsis.

Methods

Patient Identification

A single-center retrospective cohort study of patients treated for PJI was conducted (Figure 1). Patients presented either to the clinic's emergency department or our outpatient clinic. The inclusion period was defined from January 1, 2017, to December 31, 2020. Eligible patients aged 18 years or older were selected from our electronic patient data management system by the International Classification of Disease 10 diagnosis "T84.5 Infection and inflammatory reaction due to internal joint prosthesis." Only the patients who had a PJI of the hip or knee were included. To define PJI in this study, the criteria established by the European Bone and Joint Infection Society in 2021 were used [16].

The confirmatory criteria for PJI used in this cohort include the following:

(1) Presence of a sinus tract communicating with the prosthesis or visualization of the prosthesis.
(2) Microbiological findings such as ≥ two positive cultures with the same microorganism from synovial fluid or periprosthetic tissue; or sonication fluid results showing > 50 colony-forming units/ml of any organism.
(3) Histological evidence showing the presence of ≥ five neutrophils in ≥ five high-power fields at 400x magnification, or the presence of visible microorganisms.

Tests for synovial biomarkers such as alpha-defensin were not routinely performed and therefore not considered as a confirmatory criterion.

The diagnosis of sepsis was established according to the "sepsis-1" definition by the consensus conference in 1991, which required at least two positive systemic inflammatory response syndrome (SIRS) criteria [17]. The SIRS criteria are (1) abnormal body temperature, indicated by a fever above 38.0°C (100.4°F) or hypothermia below 36.0°C (96.8°F); (2) tachycardia, with a heart rate exceeding 90 beats per minute; (3) tachypnea, characterized by a respiratory rate over 20 breaths per minute or a reduced partial pressure of carbon dioxide in arterial blood (PaCO2) below 32 mm Hg; (4) abnormal white blood cell count, featuring either an elevation (> 12,000 cells/mm^3) or a reduction in total white blood cell count (< 4,000 cells/mm^3), or the presence of more than 10% immature (band) forms in the blood [17].

Patient Characteristics and Outcome Parameters

Patient characteristics, including sex, age, body mass index (BMI), and Charlson Comorbidity Index (CCI), were retrospectively evaluated by reviewing electronic medical records. Clinical data consisted of the affected joint, duration of symptoms (classified as acute if ≤ 3 weeks or chronic if > 3 weeks), hematogenous infection route (determined by signs of infection occurring ≥ 3 months postsurgery), number and type of surgical procedures performed on the affected joint (DAIR, one-stage exchange, 2-stage exchange, and multiple-stage exchange), laboratory findings (C-reactive protein (CRP), leukocyte count, and procalcitonin (PCT) levels), and microbiological findings (joint aspiration, intraoperative tissue samples, and blood cultures). For risk analysis, pre-existing conditions such as diabetes mellitus, coronary heart disease, a history of myocardial infarction, congestive heart failure, atrial fibrillation, peripheral artery disease, apoplexy, dementia, chronic obstructive pulmonary disease, liver disease, cancer, rheumatic disease, and kidney disease were taken into consideration. Additionally, concurrent infections encompassed endocarditis, pneumonia, upper respiratory tract infection, urinary tract infection, and oral or dental infections at the time of presentation.

The primary outcome was in-hospital mortality, and the number of operations performed, length of hospital stay, intensive care

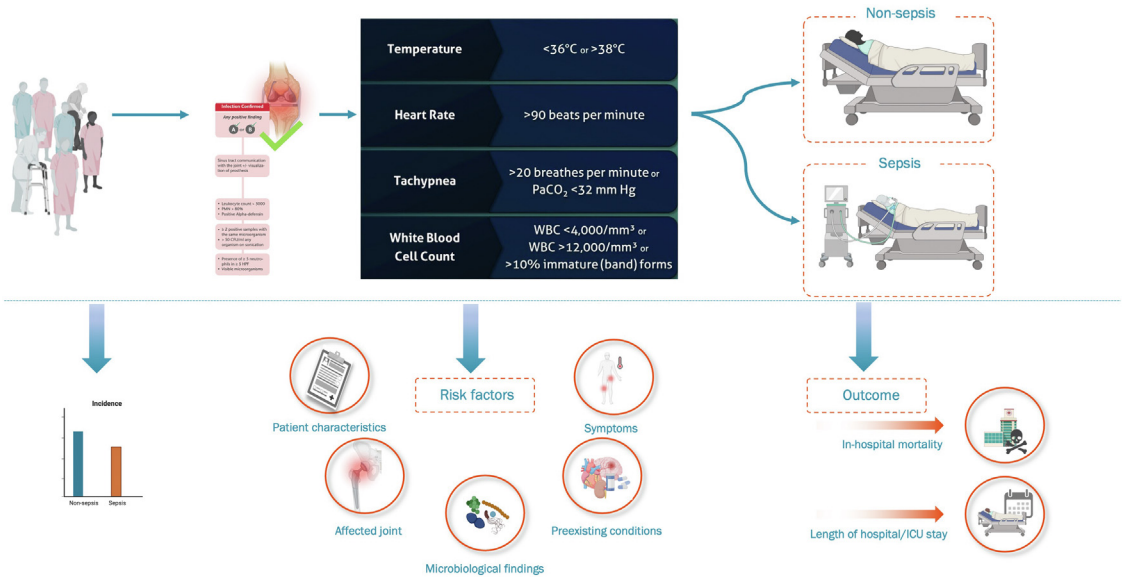

Figure 1. Overview of the study design: periprosthetic joint infection confirmation followed European Bone and Joint Infection Society criteria, and subsequent sepsis screening utilized systemic inflammatory response syndrome criteria. The incidence of sepsis was determined, and risk factors were explored based on patient characteristics, the affected joint, microbiological findings, medical history, and symptoms. Outcome parameters were in-hospital mortality and length of intensive care unit and overall hospital stay.

Table 1
Baseline Characteristics of Patients With Periprosthetic Joint Infection of the Hip in the Nonsepsis and Sepsis Cohort.

Characteristics	Nonsepsis (n = 31)	Sepsis (n = 17)	*P* Value
Men (%)	15 (48.4)	10 (58.8)	0.49
Age (years)	73.0 (37.0 to 94.0)	77.5 (58.0 to 87.0)	0.39
BMI (range)	29.0 (17.6 to 43.5)	28.3 (21.6 to 48.8)	0.55
Acute PJI (duration of symptoms ≤3 weeks) (%)	20 (64.5)	9 (52.9)	0.43
Chronic PJI (duration of symptoms >3 weeks) (%)	11 (35.5)	8 (47.1)	0.43
Hematogenous PJI (≥3 months postsurgery) (%)	20 (76.9)	6 (35.3)	0.052
Synchronous PJI (%)	4 (12.9)	4 (23.5)	0.48
Charlson Comorbidity Index	1.0 (0 to 6.0)	4.0 (0 to 7.0)	**≤0.001**

P-value numbers marked in bold indicate significance ($P < 0.05$).
BMI, body mass index; PJI, periprosthetic joint infection.

unit (ICU) admission, and length of ICU stay were secondary outcome parameters. Length of hospitalization was reported as the cumulative length of hospitalization for treatment of PJI, which may have included multiple hospitalizations (e.g., if a patient was discharged before reimplantation).

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University Hospital Regensburg (file number 20-1680-101, 25 March 2021).

Data Analyses

Frequencies were reported in numerical values and percentages. Continuous parameters were checked for normal distribution using Shapiro-Wilk tests, and equality of variances was measured using Levene tests. Non-normally distributed data were compared using Mann-Whitney *U* tests and presented as median values with ranges. The comparison of categorical variables was conducted using the *Chi*-square tests and Fisher's exact tests, as appropriate. First, univariate logistic regression was used to explore the relationship between categorical variables and severity, with results presented as odds ratios (ORs) and 95% confidence intervals (CIs). In the second step, significant categorical risk factors were incorporated into a multivariate logistic model to assess their combined effects, accounting for interactions and potential multicollinearity. The significance level was set at $P \leq 0.05$. Statistical analysis employed IBM Statistical Package for Social Sciences Statistics software (version 24.0, IBM Corp., Armonk, New York) and GraphPad Prism 9.4.1 (GraphPad Software, San Diego, California).

Demographic Data

In total, 101 patients who had confirmed PJI and available data on SIRS criteria were eligible. The PJI patients were classified as nonsepsis (n = 60) and sepsis (n = 41) cohorts. Overall, 108 PJIs were recorded, with 48 PJIs involving the hip and 60 PJIs involving the knee.

Among patients who had a hip PJI, 17 (35.4%) were in the sepsis cohort. There was no statistically significant difference between the groups in terms of sex distribution or age. However, there was a significant difference in CCI between the cohorts ($P \leq 0.001$), with the sepsis cohort having a higher CCI (Table 1). Other factors, such as BMI, duration of symptoms, and the distribution of hematogenous or synchronous PJI, showed no significant differences.

A septic course was recorded in 28 (46.6%) of the patients who had a knee PJI. When comparing septic and nonseptic PJI of the knee, there were no significant differences in terms of sex, age, BMI, acute versus chronic PJI, hematogenous PJI, synchronous PJI, or CCI (Table 2).

Results

Periprosthetic Joint Infection of the hip

Diagnostic Findings

In the nonsepsis hip PJI cohort, the median CRP level at admission was 77.0 mg/L, while the sepsis cohort had a significantly higher median CRP of 130.0 mg/L ($P = 0.017$) (Table 3). The median PCT level at admission was 0.07 ng/mL in the nonsepsis cohort and 0.8 ng/mL in the sepsis cohort; however, this difference was not statistically significant ($P = 0.09$). The leukocyte count at admission was 8,000.0/μL in the nonsepsis group and 7,000.0/μL in the sepsis

Table 2
Baseline Characteristics of Patients With PJI of the Knee in the Nonsepsis and Sepsis Cohort.

Characteristics	Nonsepsis (n = 32)	Sepsis (n = 28)	*P* Value
Men (%)	17 (53.1)	15 (53.6)	0.97
Age (years)	76.5 (41.0 to 91.0)	78.0 (53.0 to 91.0)	0.77
BMI (range)	29.7 (20.5 to 58.6)	28.3 (15.6 to 51.4)	0.51
Acute PJI (duration of symptoms ≤3 weeks) (%)	19 (59.4)	19 (76.9)	0.34
Chronic PJI (duration of symptoms >3 weeks) (%)	13 (40.6)	9 (32.1)	0.50
Hematogenous PJI (≥3 months postsurgery) (%)	25 (78.1)	20 (71.4)	0.55
Synchronous PJI (%)	3 (9.4)	6 (21.4)	0.19
Charlson Comorbidity Index (range)	3.0 (0 to 9.0)	3.0 (0 to 7.0)	0.14

BMI, body mass index; PJI, periprosthetic joint infection.

Table 3
Diagnostic Findings in Nonsepsis and Sepsis Patients With Periprosthetic Joint Infections of the Hip.

Diagnostic Findings	Nonsepsis (n = 31)	Sepsis (n = 17)	*P* Value
Systemic			
CRP at admission	77.0 (0.7 to 107.0) mg/L	130.0 (13.0 to 468.0) mg/L	**0.017**
PCT at admission[a]	0.07 (0.05 to 3.2) ng/mL	0.8 (0.05 to 62.8) ng/mL	0.09
Leukocyte count/μL at admission	8,000.0 (6,000.0 to 15,000.0)/μL	7,000.0 (1,000.0 to 14,000.0)/μL	0.14
Blood culture positive (%)	4 of 14 (28.6)	10 of 15 (66.7)	**0.04**
Identical pathogen in blood culture and intraoperative sample (%)	2 of 4 (50.0)	5 of 10 (50.0)	1.00
Local			
Culture-positive aspiration fluid (%)	17 (54.8)	13 (81.3)	0.07
Positive culture of deep tissue samples (%)	19 (61.3)	14 (82.4)	0.13

P-value numbers marked in bold indicate significance ($P < 0.05$).
CRP, C-reactive protein; PCT, procalcitonin; PJI, periprosthetic joint infection.
[a] Data available in 24 patients.

group ($P = 0.14$). Blood cultures were positive in 28.6% of cases in the nonsepsis cohort compared to 66.7% in the sepsis cohort ($P = 0.04$). The same pathogen was identified in both blood culture and aspiration fluid or tissue samples in 50.0% of cases in both groups. No significant difference was observed in the rate of culture-positive aspiration fluid ($P = 0.07$) or tissue samples ($P = 0.13$) between the 2 cohorts (Table 3).

Pathogens

Table 4 summarizes the microbiological findings from blood cultures and tissue samples of PJI of the hip. Methicillin-sensitive *Staphylococcus aureus* (MSSA) was significantly more common in the sepsis cohort for both tissue samples (47.1 versus 19.4%, $P = 0.04$) and blood cultures (41.2 versus 9.7%, $P = 0.02$). Coagulase-negative staphylococci, especially *Staphylococcus epidermidis*, were more prevalent in nonseptic cases (61.2 versus 29.4%, $P = 0.03$) (Figure 2A). Polymicrobial infections were more frequently observed in the blood cultures of the sepsis cohort, although this result was not statistically significant ($P = 0.08$).

Surgical Procedures

In the nonsepsis hip PJI group, DAIR were performed in 38.7% of patients, compared to 29.4% in the sepsis group ($P = 0.51$). A one-stage exchange was performed in 16.1% of nonsepsis patients but was not applied in the sepsis group ($P = 0.15$). A 2-stage exchange was slightly more common in the nonsepsis group (12.9%) compared to the sepsis group (5.9%) without significant differences between both cohorts ($P = 0.64$). Multistage exchanges were more frequent in the sepsis group (52.9%) than in the nonsepsis group (29.0%), though this difference was not statistically significant ($P = 0.10$). A small percentage of patients had no surgery or had unknown surgical status in both groups (3.2% in nonsepsis, 11.8% in sepsis; $P = 0.99$).

Risk Factors

The CCI was significantly higher in the sepsis group than in the nonsepsis group (median CCI 4.0 versus 1.0, $P = 0.001$), with an increased CCI score associated with a higher risk for sepsis (OR 2.0, 95% CI: 1.3 to 3.1). In univariate logistic regression analysis (Table 5), kidney disease was the strongest risk factor for sepsis (76.5% in sepsis versus 16.1% in nonsepsis, $P \leq 0.001$; OR 16.9, 95% CI: 3.9 to 73.8). Myocardial infarction and coronary heart disease were also more common in the sepsis group (both 29.4 versus 3.2%, $P = 0.02$; OR 12.5, 95% CI: 1.3 to 118.5). Pneumonia was more frequent in the sepsis cohort (41.2 versus 6.5%, $P = 0.006$; OR 10.2, 95% CI: 1.8 to 57.1). In multivariate analysis, kidney disease ($P = 0.02$, OR 10.2, 95% CI: 1.5 to 68.1) and coronary heart disease or myocardial infarction (both $P = 0.047$ OR; 13.7, 95% CI: 1.0 to 180.2) remained significant predictors of sepsis development, while pneumonia did not retain significance ($P = 0.38$).

Table 4
Isolated Microorganisms in Tissue Samples and Blood Cultures in Patients With Periprosthetic Joint Infections of the Hip.

Pathogen	Pathogen in PJI			Pathogen in Blood Cultures		
	Nonsepsis	sepsis	*P* value	Nonsepsis	sepsis	*P* Value
Staphylococcus aureus (%)	6 (19.4)	9 (52.9)	**0.02**	3 (9.7)	7 (41.2)	**0.02**
MSSA (%)	6 (19.4)	8 (47.1)	**0.04**	3 (9.7)	7 (41.2)	**0.02**
MRSA (%)	0	1 (5.9)	0.35	0	0	-
Coagulase-negative staphylococci (%)	19 (61.2)	5 (29.4)	**0.03**	1 (3.2)	1 (5.9)	1.00
Staphylococcus epidermidis (%)	13 (41.9)	2 (11.8)	**0.050**	1 (3.2)	1 (5.9)	1.00
Other Staphylococcus species (%)	6 (19.4)	3 (17.6)	1.00	0	0	0
Streptococci (%)	2 (6.5)	4 (23.5)	0.17	1 (3.2)	1 (5.9)	1.00
Enterococci (%)	5 (16.1)	1 (5.9)	0.40	0	0	-
Gram-negative bacteria (%)	6 (19.4)	3 (33.3)	1.00	0	2 (11.8)	0.12
Anaerobic bacteria (%)	0	0	-	0	0	-
Other (%)	3 (9.7)	0	0.54	0	0	-
Fungi (%)	1 (3.2)	1 (5.9)	1.0	0	1 (5.9)	0.35
Polymicrobial (%)	10 (32.3)	6 (35.4)	1.00	1 (3.2)	3 (17.7)	0.08

P-value numbers marked in bold indicate significance ($P < 0.05$).
PJI, periprosthetic joint infection; MSSA, Methicillin-sensitive *Staphylococcus aureus*; MRSA, Methicillin-resistant *Staphylococcus aureus*.

Outcome

There was one death (3.2%) in the nonsepsis cohort, while the sepsis of hip PJI had a significantly higher mortality of 4 cases (23.5%) ($P = 0.047$, OR = 9.2; 95% CI 0.9 to 90.8). The median length of hospital stay was 24.0 days in the nonsepsis patients compared to 54.0 days in sepsis patients ($P = 0.002$). There were 8 patients (25.8%) from the nonsepsis cohort who were admitted to the ICU during the hospital stay, compared to 12 patients (70.6%) in the sepsis cohort ($P = 0.005$). The OR for ICU admission was 6.9 (95% CI of 2.1 to 11.9) for septic patients who had a significantly longer length of ICU stay ($P \leq 0.001$) (Table 6).

Periprosthetic Joint Infection of the Knee

Diagnostic Findings

In the nonsepsis knee PJI cohort, the median CRP level at admission was 115.0 mg/L, compared to a significantly higher CRP level of 157.0 mg/L in the sepsis cohort ($P = 0.009$) (Table 7). The median PCT level was 0.14 ng/mL in the nonsepsis cohort and 0.76 ng/mL in the sepsis cohort ($P = 0.01$). In nonseptic cases, 5.6% of the blood cultures were positive, while 55.6% of the sepsis cases were culture positive ($P \leq 0.001$). Culture-positive aspiration fluid was observed in 59.4% of the nonsepsis cohort, compared to a higher proportion of 85.7% in the sepsis cohort ($P = 0.02$) in accordance

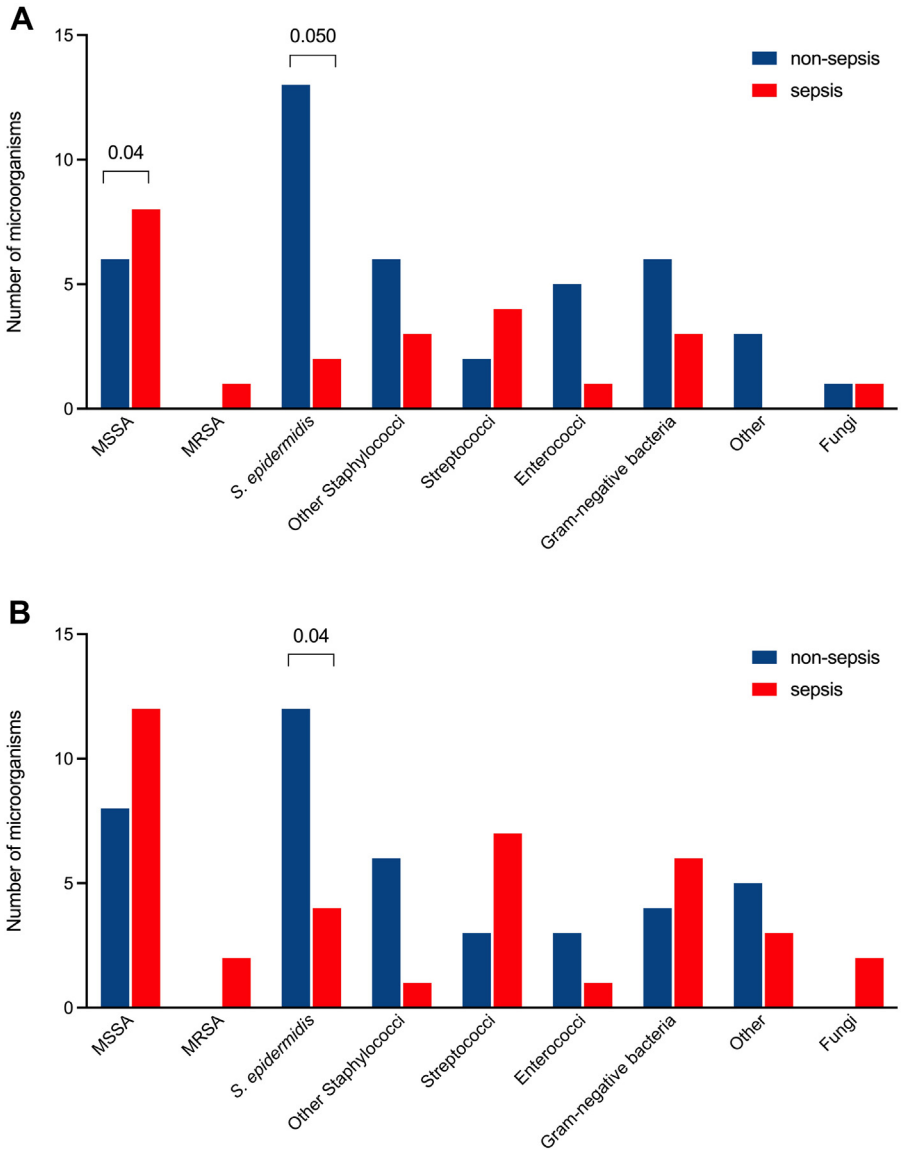

Figure 2. Distribution of causative pathogens of PJIs divided by PJI of the hip (A) and the knee (B) in the nonsepsis and sepsis cohort. MSSA, Methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; PJI, periprosthetic joint infection.

Table 5
Potential Risk Factors for the Onset of Concomitant Sepsis in Periprosthetic Joint Infections of the Hip.

Characteristics	Nonsepsis (n = 31)	Sepsis (n = 17)	*P* Value	OR (95% CI)
Men (%)	15 (48.4)	10 (58.8)	0.49	1.5 (0.5 to 5.0)
Age (years)	73.0 (37.0 to 94.0)	77.5 (58.0 to 87.0)	0.38	1.0 (0.97 to 1.1)
BMI (range)	29.0 (17.6 to 43.5)	28.3 (21.6 to 48.8)	0.53	1.0 (0.9 to 1.)
Charlson Comorbidity Index	1.0 (0 to 6.0)	4.0 (0 to 7.0)	**0.001**	2.0 (1.3 to 3.1)
Coronary heart disease (%)	1 (3.2)	5 (29.4)	**0.02**	12.5 (1.3 to 118.5)
Myocardial infarction (%)	1 (3.2)	5 (29.4)	**0.02**	12.5 (1.3 to 118.5)
Congestive heart failure (%)	4 (12.9)	5 (29.4)	0.25	2.8 (0.6 to 12.4)
Atrial fibrillation (%)	6 (19.4)	6 (35.3)	0.94	1.1 (0.3 to 4.3)
Peripheral artery disease (%)	7 (22.6)	4 (23.5)	0.63	0.76 (0.3 to 2.3)
Apoplex (%)	1 (3.2)	2 (1.8)	0.54	4.0 (0.4 to 47.7)
Dementia (%)	4 (12.9)	2 (11.8)	1.00	0.9 (0.2 to 5.5)
COPD (%)	3 (9.7)	0	0.54	0.6 (0.5 to 0.78)
Liver disease (%)	5 (16.1)	3 (17.6)	1.00	1.1 (0.2 to 5.4)
Cancer (%)	4 (12.9)	5 (29.4)	0.25	2.8 (0.6 to 12.4)
Rheumatic disease (%)	2 (6.5)	2 (11.8)	0.61	1.9 (0.3 to 15.2)
Kidney disease (%)	5 (16.1)	13 (76.5)	**≤0.001**	16.9 (3.9 to 73.8)
Diabetes mellitus (%)	5 (16.1)	7 (41.2)	0.06	3.6 (0.9 to 14.2)
Urinary tract infection (%)	5 (16.1)	2 (11.8)	1.00	0.7 (0.2 to 4.0)
Oral and dental infection (%)	1 (3.2)	0	1.00	0.6 (0.5 to 0.8)
Upper respiratory tract infection (%)	1 (3.2)	1 (5.9)	1.00	1.8 (0.1 to 32.0)
Pneumonia (%)	2 (6.5)	7 (41.2)	**0.006**	10.2 (1.8 to 57.1)
Endocarditis (%)	0	2 (11.8)	0.12	0.33 (0.22 to 0.5)

P-value numbers marked in bold indicate significance ($P < 0.05$).
BMI, body mass index; COPD, chronic obstructive pulmonary disease; CI, confidence interval; OR, odds ratio.

with an increased rate of culture-positive deep tissue samples in septic knee PJI cases ($P = 0.02$) (Table 7).

Pathogens

Table 8 summarizes microbiological findings from blood cultures and tissue samples from PJI of the knee. *Staphylococcus aureus* was significantly more common in the sepsis cohort ($P = 0.04$). Like in hip PJI, coagulase-negative staphylococci were more prevalent in nonseptic cases ($P = 0.003$). The microbiological findings of blood cultures revealed that MSSA ($P \leq 0.001$) and coagulase-negative staphylococci ($P = 0.04$) were more common in the septic cohort. No significant differences were found in tissue samples or blood cultures for streptococci, enterococci, gram-negative bacteria, or fungi (Figure 2B). Additionally, there was no increased incidence of polymicrobial PJI in the sepsis cohort.

Surgical Procedures

In knee PJI, DAIR was performed in 34.4% of nonsepsis patients and 32.1% of sepsis patients ($P = 0.85$). A one-stage exchange was conducted in 12.5% of nonsepsis cases and in none of the sepsis cases ($P = 0.11$). Two-stage exchanges were performed in 25.0% of nonsepsis cases and 14.3% of sepsis cases ($P = 0.35$). Multistage exchanges, however, were significantly more common in the sepsis group (46.4%) compared to the nonsepsis group (18.8%) ($P = 0.02$). In three non-sepsis and two sepsis cases, either no surgery was performed or no information regarding the surgical treatment could be retrieved.

Risk Factors

In knee PJI, CCI, sex, or age demonstrated no significant difference between the two groups. In univariate logistic regression analysis, kidney disease showed the strongest association with sepsis ($P = 0.02$, OR 4.0, 95% CI: 1.4 to 11.8). Additionally, concomitant infections, including oral and dental infections ($P = 0.04$, OR 1.2, 95% CI: 1.0 to 1.4) and upper respiratory tract infections ($P = 0.02$, OR 1.2, 95% CI: 1.0 to 1.4), were identified as significant risk factors for the development of sepsis (Table 9). However, in multivariate logistic regression analysis, none of these risk factors remained significant.

Outcome

Table 10 summarizes the outcomes of patients who had a PJI of the knee in the nonsepsis and sepsis cohorts. Mortality was significantly higher in the sepsis group, with seven deaths (25.0%) compared to one death (3.1%) in the nonsepsis group ($P = 0.02$, OR 10.3, 95% CI: 1.2 to 90.3). The hospital stay was significantly longer for sepsis patients, with a median of 48.0 days compared to 29.5 days in the nonsepsis group ($P = 0.01$). In terms of ICU admission, 67.9% of sepsis patients required ICU care, compared to 34.4% in the

Table 6
Outcome of Patients With Periprosthetic Joint Infections of the Hip in the Nonsepsis Versus Sepsis Cohort.

Parameters	Nonsepsis (n = 31)	Sepsis (n = 17)	*P* Value	OR (95% CI)
Mortality, n (%)	1 (3.2)	4 (23.5)	**0.047**	9.2 (0.9 to 90.8)
Duration of hospital stay (days)	24.0 (0 to 219.0)	54.0 (3.0 to 278.0)	**0.002**	-
ICU n (%)	8 (25.8)	12 (70.6)	**0.005**	6.9 (1.8 to 25.8)
Duration of ICU stay (days)	0 (0 to 12.0)	3 (0 to 67.0)	**≤0.001**	-
Total number of surgeries	2.0 (0 to 7.0)	3.0 (0 to 8.0)	0.45	

P-value numbers marked in bold indicate significance ($P < 0.05$).
ICU, intensive care unit; CI, confidence interval; OR, odds ratio.

Table 7
Diagnostic Findings in Nonsepsis and Sepsis Patients With Periprosthetic Joint Infections of the Knee.

Diagnostic Findings	Nonsepsis (n = 32)	Sepsis (n = 28)	*P* Value
Systemic			
CRP at admission	115.0 (3.0 to 400.0) mg/L	157.0 (17.0 to 494.0) mg/L	**0.009**
PCT at admission[a]	0.14 (0.02 to 36.4) ng/mL	0.76 (0.05 to 24.88) ng/mL	**0.01**
Leukocyte count/µl at admission	11,500.0 (6,000.0 to 21,000.0)/µL	12,000.0 (5,000.0 to 35,000.0)/µL	**0.46**
Blood culture positive (%)	1 of 18 (5.6)	15 of 27 (55.6)	**≤0.001**
Identical pathogen in blood culture and intraoperative sample (%)	0 of 1	10 of 15 (66.7)	0.38
Local			
Culture positive aspiration fluid (%)	19 (59.4)	24 (85.7)	**0.02**
Positive culture of deep tissue samples (%)	22 (68.8)	26 (92.9)	**0.02**

P-value numbers marked in bold indicate significance ($P < 0.05$).
CRP, C-reactive protein; PCT, procalcitonin; PJI, Periprosthetic joint infection.
[a] Data available in 41 patients.

nonsepsis group ($P = 0.02$, OR 4.0, 95% CI: 1.4 to 11.8). The median duration of ICU stay was also significantly longer for sepsis patients, with 4.5 days versus zero days in the nonsepsis group ($P = 0.004$). Also, the total number of surgeries was higher in the sepsis cohort (median 2.5) compared to the nonsepsis cohort (median 2.0), with a significant difference observed ($P = 0.02$).

Discussion

A PJI is considered one of the most devastating complications in the orthopaedic field, associated with considerable morbidity and mortality. However, less is known about the systemic spread of infection and its association with sepsis and mortality. Therefore, the objective of the present study was to investigate the incidence of septic courses in PJI of the hip and knee, risk factors that could be used to identify patients at risk, and the outcome of septic patients. The present study revealed that over 40% of patients who had PJI met sepsis criteria. Risk factors include higher CCI, PJI due to MSSA, and comorbidities like kidney disease or cardiac diseases. Concurrent infections like pneumonia or upper respiratory tract infections increase sepsis risk up to tenfold. Also, septic patients experienced a doubled length of hospital stay, higher ICU treatment rates, and a tenfold higher risk of in-hospital mortality, emphasizing the critical impact of sepsis on patient outcomes in PJI.

Data on the incidence of septic courses in PJI are scarce in the literature. A recent study reported a similar incidence of 44% among patients who had an acute PJI treated with a DAIR procedure. In contrast, Tokarski et al. [18] found a lower SIRS incidence of 27% in PJI patients. The higher incidence of patients meeting the SIRS criteria in our presented cohort could be attributed to the study's conduct at a tertiary care center, which typically deals with a population characterized by severe morbidity.

In a patient cohort suffering from acute PJI, factors related to sepsis and the persistence or recurrence of infection have been investigated. Elevated serum CRP and men was associated with the development of sepsis and with higher persistence and recurrence of PJI [19]. Similarly, higher CRP and PCT levels were observed in the sepsis cohort in our study.

A higher prevalence of comorbidities was revealed as a significant risk factor for a septic course of hip PJI. This is consistent with the existing literature, which indicates that a higher CCI is more likely to lead to the development of sepsis, but also to a higher need for intensive care treatment and higher mortality rates in PJI [19–22]. More specifically, univariate analyses revealed significant associations between the onset of sepsis and known risk factors such as renal disease and concomitant cardiac disease (including myocardial infarction and atrial fibrillation), which are recognized risk factors for PJI-related treatment failure and increased mortality. In hip PJI, renal disease remained a stable predictor in the multivariate analysis, indicating that it continues to be important even after other variables are taken into account [22–25].

The systemic dissemination of infection was substantiated by a higher proportion of positive blood cultures in the septic cohort, which was also seen in the cohort study conducted by Ludwick et al. [19]. Although Kuo et al. [26] reported a poorer outcome in patients who had a hematogenous PJI, no significant differences

Table 8
Isolated Microorganisms in Tissue Samples and Blood Cultures in Patients With Periprosthetic Joint Infections of the Knee.

Pathogen	Pathogen in PJI			Pathogen in Blood Cultures		
	Nonsepsis	Sepsis	*P* Value	Nonsepsis	Sepsis	*P* Value
Staphylococcus aureus (%)	8 (25.0)	14 (50.0)	**0.04**	0	10 (35.7)	**≤0.001**
MSSA (%)	8 (25.0)	12 (42.9)	0.14	0	9 (32.1)	**≤0.001**
MRSA (%)	0	2 (7.1)	0.21	0	1 (3.6)	0.47
Coagulase-negative staphylococci (%)	18 (56.3)	5 (17.9)	**0.003**	1 (3.1)	6 (21.4)	**0.04**
Staphylococcus epidermidis (%)	12 (37.5)	4 (14.3)	0.08	1 (3.1)	4 (14.3)	0.18
Other Staphylococcus species (%)	6 (18.8)	1 (3.6)	0.11	0	2 (7.1)	0.21
Streptococci (%)	3 (9.4)	7 (25.0)	0.17	0	0	-
Enterococci (%)	3 (9.4)	1 (3.6)	0.62	0	0	-
Gram-negative bacteria (%)	4 (12.5)	6 (21.4)	0.49	0	1 (3.6)	0.47
Anaerobic bacteria (%)	2 (6.25)	0	0.50	0	0	-
Other (%)	5 (15.6)	3 (10.7)	0.71	0	0	-
Fungi (%)	0	2 (7.1)	0.21	0	3 (10.7)	0.10
Polymicrobial (%)	8 (25.0)	0 (32.1)	0.59	1 (3.1)	5 (17.9)	0.09

P-value numbers marked in bold indicate significance ($P < 0.05$).
PJI, periprosthetic joint infection; MSSA, Methicillin-sensitive *Staphylococcus aureus*; MRSA, Methicillin-resistant *Staphylococcus aureus*.

Table 9
Potential Risk Factors for the Onset of Concomitant Sepsis in Periprosthetic Joint Infections of the Knee.

Characteristics	Nonsepsis (n = 32)	Sepsis (n = 28)	*P* Value	OR (95% CI)
Men (%)	17 (53.1)	15 (53.6)	0.97	1.0 (0.4 to 2.8)
Age (years)	76.5 (41.0 to 91.0)	78.0 (53.0 to 91.0)	0.52	1.1 (0.96 to 1.1)
BMI (range)	29.7 (20.5 to 58.6)	28.3 (15.6 to 51.4)	0.54	1.0 (0.9 to 1.0)
Charlson Comorbidity Index	3.0 (0 to 9.0)	3.0 (0 to 7.0)	0.18	1.2 (0.9 to 1.1)
Coronary heart disease (%)	9 (28.1)	8 (28.6)	0.97	1.0 (0.3 to 3.1)
Myocardial infarction (%)	5 (15.6)	9 (32.1)	0.13	2.6 (0.7 to 8.9)
Congestive heart failure (%)	7 (18.3)	11 (34.1)	0.14	2.3 (0.8 to 7.2)
Atrial fibrillation (%)	6 (18.8)	12 (42.9)	**0.04**	3.3 (1.0 to 10.4)
Peripheral artery disease (%)	6 (18.8)	4 (14.3)	0.74	0.76 (0.2 to 2.9)
Apoplex (%)	2 (6.3)	4 (14.3)	0.40	2.5 (0.4 to 14.8)
Dementia (%)	0	1 (3.6)	0.47	0.46 (0.4 to 0.6)
COPD (%)	4 (12.5)	5 (17.9)	0.72	1.5 (0.4 to 6.3)
Liver disease (%)	3 (9.4)	6 (21.4)	0.28	2.6 (0.6 to 11.7)
Cancer (%)	8 (25.0)	3 (10.7)	0.19	0.4 (0.1 to 1.5)
Rheumatic disease (%)	5 (15.6)	6 (21.4)	0.40	1.7 (0.4 to 5.5)
Kidney disease (%)	11 (34.4)	19 (67.9)	**0.02**	4.0 (1.4 to 11.8)
Diabetes mellitus (%)	9 (28.1)	11 (39.3)	0.36	1.7 (0.6 to 4.9)
Urinary tract infection (%)	3 (9.4)	7 (25.0)	0.17	3.2 (0.8 to 13.9)
Oral and dental infection (%)	0	4 (14.3)	**0.04**	1.2 (1.0 to 1.4)
Upper respiratory tract infection (%)	0	5 (17.9)	**0.02**	1.2 (1.0 to 1.5)
Pneumonia (%)	2 (6.3)	6 (21.4)	0.13	4.0 (0.8 to 22.2)
Endocarditis (%)	0	3 (10.7)	0.10	**1.1** (1.0 to 1.3)

P-value numbers marked in bold indicate significance ($P < 0.05$).
BMI, body mass index; COPD, chronic obstructive pulmonary disease; CI, confidence interval; OR, odds ratio.

were observed regarding the hematogenous source in the presented study. This leaves an intriguing question unanswered: whether the PJI or the concomitant infection occurred first, necessitating further investigations.

Regarding microbiological findings, our results confirmed the high prevalence of *S. aureus* in the septic cohort while coagulase-negative staphylococci were the dominant causative pathogen in nonseptic patients, which aligns with the observations made by Ludwick et al. [19]. This implies that highly virulent pathogens play a major role in causing sepsis in patients suffering from PJI.

While sepsis is a well-known condition associated with high mortality in various infectious diseases, the specifics of mortality rates of sepsis associated with PJI are sparsely studied and often based on anecdotal experience of treating physicians [27]. In the presented sepsis cohort, the in-hospital mortality rate was reported as 23.5% for patients who had a hip PJI and 25.0% for patients who had a PJI of the knee, which was 10 times higher compared to the nonsepsis cohort. There were two studies reporting lower, but still high, mortality rates in septic patients of five and 13% [18,19]. Compared to a general in-hospital mortality of 0.77% in a large cohort of more than 20,000 patients suffering from PJI [28], this underscores the life-threatening effect of sepsis development in PJI.

This retrospective study has several potential limitations. The generalizability of the results may be constrained by the small number of patients in the study group. In addition, there is the inability to distinctly categorize patients based on their initial point of contact. Our cohort included patients from the outpatient clinic, emergency department, and planned transfers, with elective and nonemergency admissions organized via the emergency department. This overlap makes it impractical to distinguish between outpatient and emergency department recruitment, which may affect the interpretation and generalizability of our findings. Another drawback is the reliance on already-existing medical data and records, which may contain biased or insufficient information. The study's design does not allow to account for all potential confounders, which makes it difficult to establish a cause-and-effect connection between the factors under consideration. Additionally, sepsis criteria have undergone multiple revisions in the last decades. The current consensus definition ("sepsis-3") focuses on organ dysfunction as quantified by the Sequential Organ Failure Assessment to improve sensitivity and specificity compared to the SIRS criteria [6]. In our study, however, we used the older definition primarily due to data availability (e.g., missing bilirubin values) in the retrospective study design. The SIRS criteria may still be useful for screening, e.g., in the emergency department, and we actually discriminated patients who had a high mortality risk (> 20%) from those who had a low risk (< 5%) in our cohort. Also, retrospectively, it is not possible to determine whether the treated PJI was the initial cause of sepsis rather than the result of hematogenous infection in the course of sepsis with different infection origins. Given these limitations, caution should be exercised when interpreting the results of this study. Further prospective studies with larger patient cohorts are warranted to validate and expand on these findings.

Table 10
Outcome of Patients With Periprosthetic Joint Infections of the Knee in the Nonsepsis Versus Sepsis Cohort.

Parameters	Nonsepsis (n = 32)	Sepsis (n = 28)	*P* Value	OR (95% CI)
Mortality, n (%)	1 (3.1)	7 (25.0)	**0.02**	10.3 (1.2 to 90.3)
Duration of hospital stay (days)	29.5 (0 to 130.0)	48.0 (3.0 to 195.0)	**0.01**	-
ICU n (%)	11 (34.4)	19 (67.9)	**0.02**	4.0 (1.4 to 11.8)
Duration of ICU stay (days)	0 (0 to 40.0)	4.5 (0 to 54.0)	**0.004**	-
Total number of surgeries	2.0 (0 to 5.0)	2.5 (0 to 15.0)	**0.02**	-

P-value numbers marked in bold indicate significance ($P < 0.05$).
ICU, intensive care unit; CI, confidence interval; OR, odds ratio.

Conclusions

This study showed that a high proportion of patients who had PJI present with sepsis, which is predictive of higher resource utilization in terms of length of stay, ICU admission, and surgical procedures as well as mortality; the diagnostic work-up and therapeutic strategy should be chosen and hastened accordingly. Beyond the presence of SIRS criteria, elevated CRP levels and the presence of multiple comorbidities should serve as major indicators for healthcare providers.

CRediT authorship contribution statement

Susanne Baertl: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **David Lovasz:** Methodology, Investigation, Data curation. **Martin G. Kees:** Writing – original draft, Supervision, Methodology. **Nike Walter:** Writing – review & editing, Methodology, Investigation. **Melanie Schindler:** Writing – review & editing, Visualization, Data curation. **Jing Li:** Methodology, Investigation. **Jan Reinhard:** Writing – review & editing, Visualization, Methodology. **Volker Alt:** Writing – review & editing, Project administration, Conceptualization. **Markus Rupp:** Writing – original draft, Supervision, Investigation, Conceptualization.

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