Journal of Microbiology, Immunology and Infection 58 (2025) 318–324

Contents lists available at ScienceDirect

Journal of Microbiology, Immunology and Infection

journal homepage: www.e-jmii.com

Predictors of bloodstream infection and its impact on mortality in septic arthritis: A 15-year review

Yongseop Lee [1], Yong Chan Kim [1], Jaeeun Seong, Sangmin Ahn, Min Han, Jung Ah Lee, Jung Ho Kim, Jin Young Ahn, Nam Su Ku, Jun Yong Choi, Joon-Sup Yeom, Su Jin Jeong [*]

Division of Infectious Diseases, Department of Internal Medicine and AIDS Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Septic arthritis
Bloodstream infection
Lymphopenia
Sequential organ failure assessment score
Staphylococcus aureus

ABSTRACT

Background: Septic arthritis is frequently complicated by bloodstream infection (BSI), which can lead to metastatic infections and sepsis. In the current study, we aimed to identify risk factors for septic arthritis-related BSI and assess its impact on clinical outcomes.

Methods: A retrospective review spanning 15 years (January 2009 to May 2023) was conducted on patients diagnosed with septic arthritis. Data from patients with positive synovial fluid cultures were analyzed.

Results: Among 456 patients with septic arthritis, 16.8 % (n = 77) developed BSI. The 90-day mortality rate was significantly higher in patients with BSI than in those without BSI (14.3 % vs. 5.3 %, $p = 0.004$). *Staphylococcus aureus* was the most commonly identified organism in synovial fluid cultures, and the presence of *S. aureus* infection was associated with an increased risk of BSI (adjusted odds ratio [aOR], 2.20; 95 % confidence interval [CI], 1.15–4.34; $p = 0.019$). Independent risk factors for BSI included a higher Sequential Organ Failure Assessment (SOFA) score (aOR, 1.23; 95 % CI, 1.06–1.44; $p = 0.009$), lymphopenia (aOR, 2.84; 95 % CI, 1.38–6.15; $p = 0.006$), and elevated C-reactive protein (mg/dL) levels (aOR, 1.07; 95 % CI, 1.05–1.10; $p < 0.001$). Age ≥70 years (aOR, 3.96; 95 % CI, 1.49–11.85; $p = 0.009$) and a higher SOFA score (aOR, 1.36; 95 % CI, 1.12–1.67; $p = 0.002$) were significant predictors of 90-day mortality, although BSI itself was not.

Conclusion: Mortality in patients with septic arthritis was primarily associated with systemic sepsis due to BSI rather than BSI itself. Understanding the relationship between septic arthritis-related BSI and clinical outcomes could aid physicians in managing systemic infections and improving patient care.

1. Introduction

Septic arthritis poses a notable threat, capable of swiftly damaging articular cartilage and leading to permanent joint impairment or even death.[1] Up to 30 % of cases experience persistent joint dysfunction,[2] with a six-fold increase in subsequent arthroplasty rate compared with that in the general population.[3] Mortality rates can reach up to 11 %, escalating to 22.7 % among patients aged ≥79 years.[1,3] Accumulated evidence has highlighted age and comorbidities such as diabetes and chronic kidney disease as exacerbating factors for the clinical progression of septic arthritis.[2,4,5] The incidence rate of septic arthritis varies from 4 to 10 per 100,000 patient-years across different study populations,[4,6–8] with risk factors including rheumatoid arthritis, advanced age, diabetes mellitus, orthopedic prostheses, history of joint surgery, and skin infections.[9–11] The growing incidence of septic arthritis can be attributed to the aging population and the increasing prevalence of comorbidities.[12]

Bloodstream infection (BSI) frequently accompanies septic arthritis, affecting 24–35 % of patients and potentially leading to metastatic infections in distant organs. Critical complications of BSI, such as infective endocarditis and mycotic aneurysms, increase the risk of mortality and necessitate prolonged antimicrobial therapy and hospitalization, leading to elevated healthcare costs.[13–16] Moreover, incomplete clearance of bacterial reservoirs can lead to the relapse of infection.[14] Consequently, several physicians closely monitor patients with positive blood cultures for potential complications.

Understanding the predisposing factors for septic arthritis-related BSI and its impact on clinical outcomes is essential. However, current

* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine and AIDS Research Institute, Yonsei University College of Medicine, Yonsei University Health System, 50-1, Yonsei-ro, Seodaemun-gu, Seoul, 03722, Republic of Korea.
E-mail address: JSJ@yuhs.ac (S.J. Jeong).
[1] These two authors contributed to the study equally.

https://doi.org/10.1016/j.jmii.2025.02.006
Received 21 May 2024; Received in revised form 27 November 2024; Accepted 22 February 2025
Available online 26 February 2025

knowledge regarding these aspects remains limited. Here, we aimed to assess the risk factors and clinical consequences of BSI in patients with septic arthritis, as well as investigate the microbiological characteristics associated with this condition. These findings will provide valuable insights for clinicians, enhancing their understanding and management of septic arthritis.

2. Methods

2.1. Study design and study population

This retrospective cohort study spanned from January 2009 to May 2023 at Severance Hospital, a tertiary teaching facility in South Korea with 2400 beds. Patients diagnosed with septic arthritis and positive synovial fluid culture results were identified. Only the initial episode of septic arthritis per patient was considered. Patients with positive synovial fluid cultures obtained during routine joint replacement surgeries, who displayed no signs of infection, were excluded. Similarly, cases exhibiting mold in synovial cultures, likely due to contamination, were also omitted. The study was performed in compliance with relevant laws and institutional guidelines and was approved by the appropriate institutional committee (4-2023-0757), and the need for patient consent was waived owing to the retrospective nature of the study.

2.2. Variables and outcome measures

Demographic characteristics (age and sex), date of death, comorbidities, history of joint replacement, microbiological findings (synovial fluid and blood culture), laboratory results (platelet, neutrophil, and lymphocyte counts; C-reactive protein [CRP], creatinine, and total bilirubin levels; arterial oxygen pressure/fraction of inspired oxygen; and synovial fluid analysis), mean blood pressure, Glasgow Coma Scale, and use of inotropic and ventilator were extracted using the hospital's data extraction system. Comorbidities were classified using diagnostic codes up to 1 year before synovial culture, and the Charlson Comorbidity Index was calculated to assess underlying disease severity.[17] BSI was defined as the presence of identical organisms in both synovial and blood cultures within 3 days of each other. Sequential Organ Failure Assessment (SOFA) scores were calculated using the most abnormal values obtained within 48 h of synovial culture.[18] Similarly, the laboratory findings included in the analyses comprised the most abnormal values obtained within 48 h of synovial fluid culture. Neutropenia and lymphopenia were defined as counts below 1000 cells/μL, whereas shock was characterized by a blood pressure decrease requiring inotropic support. Infective endocarditis, vertebral osteomyelitis, and septic emboli diagnosed at the time of discharge were defined as distant infections. The primary outcome of this study was the 90-day mortality rate.

2.3. Microbiological tests

Identification testing was performed using the VITEK 2 automated analyzer system (bioMérieux, Marcy-l'Étoile, France) until 2013, which was subsequently transitioned to the Bruker Biotyper matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) system (Bruker Daltonics, Bremen, Germany). Susceptibility tests were conducted using the VITEK 2 automated analyzer system with a VITEK AST2 N212 card (bioMérieux), and the results were interpreted according to Clinical and Laboratory Standards Institute criteria.[19]

2.4. Statistical analysis

Continuous variables are expressed as mean ± standard deviation for normally distributed data or median (interquartile range [IQR]) for non-normally distributed data. Categorical variables are presented as count (percentage). Two-tailed independent t-tests or Mann–Whitney U tests were performed to compare continuous variables between the BSI and non-BSI groups. Data normality was determined using the Shapiro–Wilk test, and non-parametric tests were performed to analyze non-normally distributed data. Pearson's chi-square or Fisher's exact tests were performed to analyze categorical variables.

Variables with a p-value of <0.05 in univariable analysis were included in multivariable logistic regression and Cox regression models to identify independent risk factors for BSI and 90-day mortality, respectively. Stratified analyses were then conducted using statistically significant variables from the Cox regression model to further clarify the association between BSI and 90-day mortality. Multicollinearity was assessed using a variance inflation factor >10. The Hosmer-Lemeshow test was used to evaluate the goodness-of-fit for the multivariable logistic regression model, whereas the Grambsch-Therneau test was implemented to assess the proportional hazards assumption in the Cox regression model. Statistical significance was set at a p-value of <0.05. Statistical analysis was performed using R, V.4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

A total of 682 cases of septic arthritis with positive synovial fluid culture were identified, as depicted in Fig. 1. After excluding 166 cases that did not represent the initial episode of septic arthritis and 60 cases with positive results from routine joint replacement surgery cultures or mold identification in synovial cultures, 456 patients were included in the final analysis. Of these patients, 77 (16.8 %) had BSI and 379 (83.2 %) did not have BSI. Blood cultures were performed within 3 days in 167 patients (44.1 %) in the non-BSI group. The median age of patients with and without BSI was 70 years (IQR: 61–77 years) and 68 years (IQR: 57–77 years), respectively (Table 1). There were no significant differences in sex distribution or the proportion of prosthetic joint infections between the BSI and non-BSI groups (women: 44.2 % vs. 50.7 %, $p = 0.298$ and prosthetic joint infection: 10.8 % vs. 5.2 %, $p = 0.131$, respectively). Comorbidity profiles, including the Charlson Comorbidity Index, did not differ significantly between the two groups.

Patients with BSI exhibited greater disease severity and worse outcomes compared to those without BSI (Table 1). The proportion of patients who experienced shock was significantly higher in the BSI group than in the non-BSI group (15.6 % vs. 6.1 %, $p = 0.004$). Additionally, the BSI group had a higher SOFA score (2.0, IQR: 1.0–5.0) than did the non-BSI group (1.0, IQR: 0.0–2.0). The BSI group showed significantly higher rates of 90-day mortality (14.3 % vs. 5.3 %, $p = 0.004$) and distant infections (16.9 % vs. 0.5 %, $p < 0.001$) compared to the non-BSI group.

3.2. Laboratory findings

Significant differences were detected upon comparing laboratory findings between the groups (Table 2). The BSI group had significantly higher white blood cell counts, neutrophil counts, and CRP levels compared to the non-BSI group. In contrast, the BSI group had significantly lower lymphocyte counts, with a higher prevalence of lymphopenia compared to the non-BSI group (84.2 % vs. 49.3 %, $p < 0.001$). However, there was no significant difference with regard to neutropenia and synovial fluid analysis between the two groups.

3.3. Microbiologic characteristics

Microbiologic characteristics of patients with septic arthritis were further examined based on BSI status (Table 2). Gram-positive bacterial infections predominated in both BSI (88.8 %) and non-BSI (81.0 %) groups. The proportion of gram-negative bacterial infections in the BSI group was 10.4 %, which was not different from that in the non-BSI

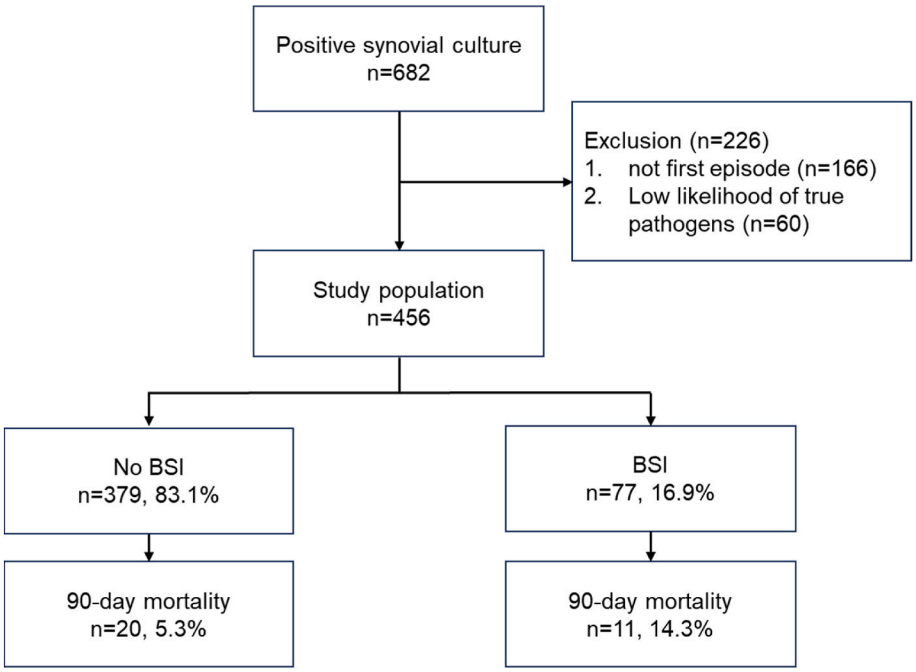

Fig. 1. Study flowchart.
BSI, bloodstream infection.

Table 1
Comparison of clinical characteristics of septic arthritis patients with and without bloodstream infection.

	Total (n = 456)	No BSI (n = 379)	BSI (n = 77)	*p*-value
Age (years)	69.0 (58.0–77.0)	68.0 (57.0–77.0)	70.0 (61.0–77.0)	0.772
Female sex	226 (49.6 %)	192 (50.7 %)	34 (44.2 %)	0.298
Prosthetic joint infection	45 (9.9 %)	41 (10.8 %)	4 (5.2 %)	0.131
Joint replacement within 1 year	6 (1.3 %)	4 (1.1 %)	2 (2.6 %)	0.279
Comorbidities				
Diabetes mellitus	175 (38.4 %)	145 (38.3 %)	30 (39.0 %)	0.908
Chronic renal disease	130 (28.5 %)	102 (26.9 %)	28 (36.4 %)	0.094
Chronic liver disease	81 (17.8 %)	62 (16.4 %)	19 (24.7 %)	0.082
CVD	66 (14.5 %)	60 (15.8 %)	6 (7.8 %)	0.068
CHF	46 (10.1 %)	37 (9.8 %)	9 (11.7 %)	0.609
COPD	44 (9.6 %)	35 (9.2 %)	9 (11.7 %)	0.506
CTD	30 (6.6 %)	25 (6.6 %)	5 (6.5 %)	0.974
Cancer	93 (20.4 %)	74 (19.5 %)	19 (24.7 %)	0.307
CCI	2.0 (0.0–4.0)	2.0 (0.0–4.0)	2.0 (1.0–4.0)	0.253
Ventilator use	10 (2.2 %)	4 (1.1 %)	6 (7.8 %)	<0.001
Shock	35 (7.7 %)	23 (6.1 %)	12 (15.6 %)	0.004
SOFA score	1.0 (0.0–2.0)	0.0 (0.0–2.0)	2.0 (1.0–5.0)	<0.001
Days of antibiotic use	17.0 (7.0–34.0)	15.0 (6.0–26.0)	34.0 (18.0–63.5)	<0.001
90-day mortality	31 (6.8 %)	20 (5.3 %)	11 (14.3 %)	0.004
Metastatic infection	15 (3.3 %)	2 (0.5 %)	13 (16.9 %)	<0.001
Infective endocarditis	7 (1.5 %)	1 (0.3 %)	6 (7.8 %)	<0.001
Vertebral osteomyelitis	8 (1.8 %)	1 (0.3 %)	7 (9.1 %)	<0.001

CVD, cerebrovascular disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; CCI, Charlson Comorbidity Index; SOFA, Sequential Organ Failure Assessment.

group. The BSI group had a higher proportion of *S. aureus* (61.0 % vs. 43.5 %, $p = 0.005$) and a lower proportion of coagulase-negative staphylococci (6.5 % vs. 16.9 %, $p = 0.020$) than did the non-BSI group. Additionally, streptococcal infections accounted for 18.2 % of BSI cases, with one case of Candida infection, neither of which differed significantly from that in the non-BSI group.

We analyzed how microbiological characteristics, which may influence the likelihood of BSI, varied in different subgroups. The distribution of causative organisms by age, sex, BSI, and type of joint is illustrated in Fig. 2, and the distribution of causative organisms of septic arthritis by year is depicted in Fig. 3. Gram-positive infections were more prevalent in men (87.4 % vs. 77.0 %, $p = 0.004$), primarily caused by *S. aureus* (52.2 % vs. 40.7 %, $p = 0.014$), whereas gram-negative infections were more common in women (19.5 % vs. 10.9 %, $p = 0.010$). The proportion of coagulase-negative staphylococcal infections was higher in patients aged ≥65 years (19.5 % vs. 8.7 % in younger patients, $p = 0.002$). The proportion of streptococcal infections decreased from 16.1 % before 2020 to 8.3 % after 2020 ($p = 0.036$).

3.4. Risk factors for BSI and 90-day mortality

Binary logistic regression and Cox regression were used to analyze risk factors for BSI and 90-day mortality, respectively (Table 3). Independent risk factors for BSI were elevated SOFA scores (adjusted odds ratio [aOR], 1.23; 95 % confidence interval [CI], 1.06–1.44; $p = 0.009$), lymphopenia (aOR, 2.84; 95 % CI, 1.38–6.15; $p = 0.006$), elevated CRP

Table 2
Laboratory and microbiologic findings of patients with septic arthritis according to bloodstream infections.

	Total (n = 456)	No BSI (n = 379)	BSI (n = 77)	*p*-value
Laboratory findings				
WBC (10^3/μL)	11.1 (8.3–15.9)	10.5 (7.9–14.2)	17.6 (11.8–21.7)	<0.001
Neutrophil (%)	83.5 (74.6–89.3)	81.3 (71.7–87.7)	90.1 (86.5–92.3)	<0.001
Neutrophil (10^3/μL)	8.9 (6.2–13.5)	8.1 (5.6–11.8)	15.0 (10.3–19.6)	<0.001
Lymphocyte (10^3/μL)	0.9 (0.6–1.4)	1.0 (0.7–1.5)	0.6 (0.4–0.9)	<0.001
CRP (mg/dL)	12.4 (5.1–21.5)	8.9 (3.9–18.8)	25.0 (17.6–31.1)	<0.001
Neutropenia	5 (1.1 %)	5 (1.4 %)	0 (0.0 %)	0.305
Lymphopenia	244 (55.3 %)	180 (49.3 %)	64 (84.2 %)	<0.001
Synovial WBC (10^3/μL)	50.0 (23.0–52.2)	50.0 (22.5–50.0)	50.0 (40.8–102.3)	0.055
Synovial protein (g/dL)	4.6 (3.7–5.4)	4.6 (3.7–5.4)	4.3 (3.5–5.1)	0.138
Synovial glucose (mg/dL)	33.0 (10.0–79.0)	36.0 (10.0–82.0)	25.0 (10.0–53.5)	0.194
Microbiologic findings				
Gram-positive bacteria	375 (82.2 %)	307 (81.0 %)	68 (88.3 %)	0.126
S. aureus	212 (46.5 %)	165 (43.5 %)	47 (61.0 %)	0.005
CoNS	69 (15.1 %)	64 (16.9 %)	5 (6.5 %)	0.020
Streptococcus ssp.	64 (14.0 %)	50 (13.2 %)	14 (18.2 %)	0.251
Other gram-positive[a]	37 (8.1 %)	34 (9.0 %)	3 (3.9 %)	0.137
Gram-negative bacteria	69 (15.1 %)	61 (16.1 %)	8 (10.4 %)	0.203
Escherichia ssp.	23 (5.0 %)	18 (4.7 %)	5 (6.5 %)	0.524
Pseudomonas ssp.	14 (3.1 %)	13 (3.4 %)	1 (1.3 %)	0.323
Klebsiella ssp.	8 (1.8 %)	7 (1.8 %)	1 (1.3 %)	0.738
Other gram-negative[b]	25 (5.5 %)	24 (6.3 %)	1 (1.3 %)	0.077
Candida ssp.	22 (4.8 %)	21 (5.5 %)	1 (1.3 %)	0.113

BSI, bloodstream infection; CRP, C-reactive protein; WBC, white blood cells; CoNS, coagulase-negative staphylococci.

[a] Other gram-positive organisms include *Enterococcus*, *Corynebacterium*, *Bacillus*, *Diphtheroids*, *Gemella*, *Micrococcus*, and *Nocardia* spp.

[b] Other gram-negative organisms include *Serratia*, *Proteus*, *Acinetobacter*, *Enterobacter*, *Achromobacter*, *Burkholderia*, *Citrobacter*, *Morganella*, and *Stenotrophomonas* spp.

levels (mg/dL) (aOR, 1.07; 95 % CI, 1.05–1.10; $p < 0.001$), and *S. aureus* infection (aOR, 2.20; 95 % CI, 1.15–4.34; $p = 0.019$).

Although BSI was associated with 90-day mortality in univariable analysis (hazard ratio, 2.77; 95 % CI, 1.32–5.77; $p = 0.007$), this association was not detected in multivariable analysis. In the multivariable analysis, age ≥70 years (adjusted hazard ratio [aHR], 2.70; 95 % CI, 1.11–6.52; $p = 0.028$) and increased SOFA score (aHR, 1.30; 95 % CI, 1.10–1.53; $p = 0.002$) were significant risk factors for 90-day mortality.

The association between BSI and 90-day mortality was analyzed in subgroups based on age and SOFA score. BSI was significantly associated with 90-day mortality in patients aged ≥70 years (HR, 3.10; 95 % CI, 1.34–7.17; $p = 0.008$). However, this association was no longer significant after adjusting for the SOFA score (aHR, 1.72; 95 % CI, 0.69–4.29; $p = 0.244$). No significant association between BSI and 90-day mortality was observed in the other subgroups.

4. Discussion

Our study provides a comprehensive analysis of the clinical characteristics of septic arthritis with BSI and identifies key risk factors associated with BSI. Notably, 16.9 % of patients with septic arthritis presented with concomitant BSI, and this subgroup exhibited higher disease severity and increased 90-day mortality compared to those without BSI. Independent risk factors for BSI included elevated CRP

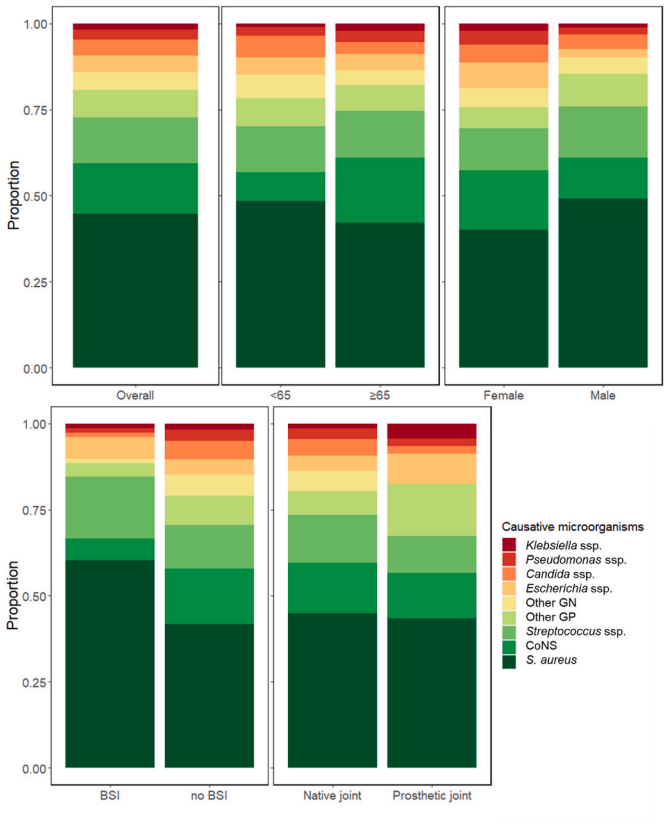

Fig. 2. Distribution of causative organisms of septic arthritis.
GN, gram-negative organisms; GP, gram-positive organisms; CoNS, coagulase-negative staphylococci; BSI, bloodstream infection.

levels, higher SOFA scores, lymphopenia, and *S. aureus* infection. Conversely, advanced age and elevated SOFA scores emerged as significant predictors of 90-day mortality.

We also examined the microbial profile of patients with septic arthritis with regard to BSI. Patients with BSI exhibited a higher proportion of *S. aureus* infection than did those without BSI, whereas the proportion of gram-negative bacteria was similar between the groups (10.4 %). These findings are consistent with those reported previously,[1,20–23] which have also noted a predominance of gram-positive bacteria in patients with septic arthritis. For instance, a study on hematogenous periprosthetic joint infections found that the majority of causative organisms were gram-positive, with gram-negative bacteria accounting for only 8 % of cases.[24] Although urinary tract infections caused by gram-negative bacteria are common sources of hematogenous osteoarticular infections,[1] our study did not find a significant association between gram-negative infections and BSI.

The clinical significance of lymphopenia in septic arthritis remains poorly understood. While one study has suggested that an elevated serum neutrophil-to-lymphocyte ratio is associated with treatment failure and mortality,[25] the direct impact of lymphopenia itself has not been extensively explored. Lymphocytes, including B cells, T cells, and natural killer cells and their subtypes, play crucial roles in the immune response to bacterial and fungal pathogens.[26] Lymphopenia is frequently observed in infectious diseases, with a reported prevalence of 52 % in patients hospitalized with community-acquired pneumonia.[27] The mechanisms underlying lymphopenia in sepsis may involve decreased production of lymphocytes and their precursors in the bone marrow and thymus, increased trafficking of lymphocytes to infected tissues, and enhanced destruction through activation-induced cell death or apoptosis.[26] Importantly, lymphopenia has been identified as a significant risk factor for both short- and long-term mortality in patients

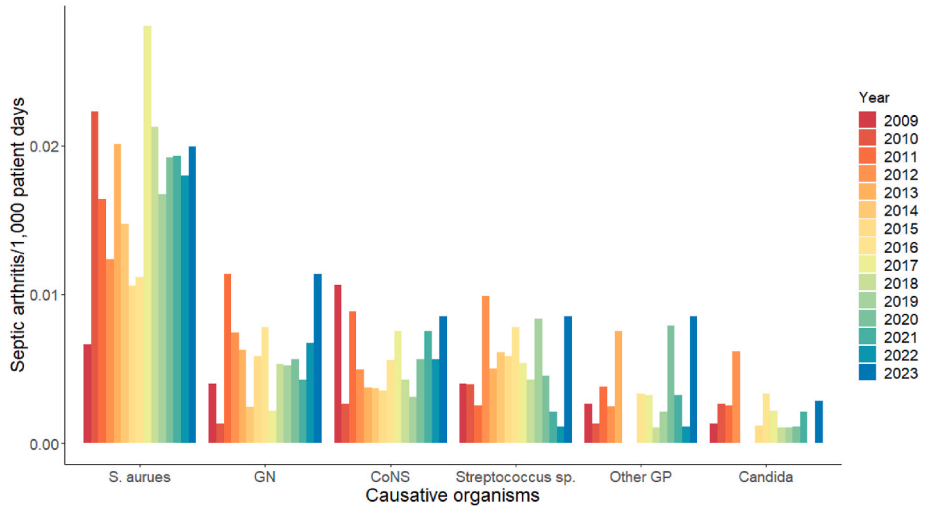

Fig. 3. Changes in the distribution of causative organisms of septic arthritis by year.
GN, gram-negative organisms; GP, gram-positive organisms; CoNS, coagulase-negative staphylococci.

Table 3
Multivariable analysis of risk factors for bloodstream infection and 90-day mortality in patients with septic arthritis.

	Bloodstream infection		90-day mortality	
	aOR (95 % CI)	p-value	aHR (95 % CI)	p-value
Age ≥70 years	1.01 (0.55–1.84)	0.972	2.70 (1.11–6.52)	0.028
Female sex	0.87 (0.47–1.58)	0.644	1.51 (0.70–3.29)	0.294
Charlson Comorbidity Index	1.00 (0.89–1.11)	0.962	1.10 (0.94–1.30)	0.223
Ventilator use	1.46 (0.31–7.33)	0.632	0.55 (0.11–2.68)	0.458
Shock	0.37 (0.11–1.19)	0.106	1.31 (0.44–3.90)	0.623
SOFA score	1.23 (1.06–1.44)	0.009	1.30 (1.10–1.53)	0.002
Lymphopenia	2.84 (1.38–6.15)	0.006	2.33 (0.64–8.56)	0.201
CRP (mg/dL)	1.07 (1.05–1.10)	<0.001	1.02 (0.99–1.05)	0.257
Bloodstream infection	N/A		1.14 (0.46–2.84)	0.778
Microorganism				
S. aureus	2.20 (1.15–4.34)	0.019	–	
CoNS	1.34 (0.40–3.83)	0.609	–	

Multivariable logistic regression and Cox regression models were used to identify independent risk factors for BSI and 90-day mortality, respectively. Variables with a *p*-value of <0.05 in univariable analysis were included in multivariable analysis. Variance inflation factor was found to be < 5 in both logistic regression and Cox regression models. Hosmer-Lemeshow test for goodness-of-fit showed no significant lack of fit for the logistic regression model ($p = 0.566$). The Grambsch-Therneau test showed proportionality for all variables in the Cox regression model.
aOR, adjusted odds ratio; CI, confidence interval; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment; CRP, C-reactive protein; CoNS, coagulase-negative staphylococci.

with sepsis.[27–29] Persistent lymphopenia, lasting for >3 days after the onset of sepsis, is particularly associated with a higher risk of death.[27,29]

To the best of our knowledge, our study is the first to highlight the clinical relevance of lymphopenia in septic arthritis, thus representing a substantial contribution. Our findings suggest that patients with lymphopenia may be at increased risk of developing severe disease, and lymphopenia has the potential to serve as a valuable biomarker for assessing the severity of septic arthritis.

CRP serves as a valuable diagnostic biomarker for distinguishing septic arthritis from other inflammatory arthritides.[30] Studies have consistently demonstrated higher serum CRP levels in patients with septic arthritis than in those with other forms of inflammatory arthritis.[31,32] Moreover, elevated CRP levels have been linked to adverse clinical outcomes in septic arthritis. For instance, Kim et al. observed that high CRP levels were associated with treatment failure in patients with native joint septic arthritis caused by *S. aureus*,[21] whereas Ferrand et al. reported a higher risk of death in patients with elevated CRP levels.[2] In our study, patients with BSI exhibited a median CRP level of 25.0 mg/dL, which was significantly higher than the 8.9 mg/dL observed in patients without BSI. Multivariable analysis further underscored the significant association between elevated CRP levels and BSI, suggesting that CRP may offer additional diagnostic value in identifying septic arthritis patients with BSIs.

S. aureus emerges as the predominant causative microorganism of septic arthritis, often contributing to poor prognoses.[5,33] Septic arthritis resulting from *S. aureus* infection frequently coincides with BSI, as evidenced by a previous study reporting BSI in 53 % of patients with *S. aureus* infection.[21] Our study corroborates these findings, revealing that 22.2 % of patients with *S. aureus* infection were also affected by BSI, albeit at a slightly lower rate than that previously reported. Notably, *S. aureus* is a major contributor to both community- and hospital-acquired BSI, posing a heightened risk of metastatic complications.[34] The secretion of staphylococcal α-hemolysin, a pore-forming cytotoxin secreted by most *S. aureus* strains, exacerbates tissue invasion by inducing vascular endothelial dysfunction and compromising vascular integrity.[35,36] Consequently, the incidence of endocarditis in patients with *S. aureus*-associated BSI is high (approximately 30 %), with septic arthritis associated with *S. aureus* posing a grim prognosis when accompanied by metastatic infections, particularly infective endocarditis.[5] Thus, our findings underscore the substantial risk of BSI and its associated metastatic complications in *S. aureus*-induced septic arthritis, emphasizing the need for heightened vigilance in these patients.

The findings of our study highlight that, in patients with septic arthritis, mortality is primarily attributable to sepsis resulting from BSI rather than BSI itself. Although few studies have directly linked BSI to increased mortality in septic arthritis, they are often constrained by small sample sizes and a lack of consideration of variables associated with disease severity.[2,5] Our study revealed that 15.6 % of patients with BSI experienced septic shock and exhibited higher SOFA scores, indicative of greater disease severity. Although patients with BSI had higher

90-day mortality rates than did those without, no significant association was observed between BSI and 90-day mortality after adjusting for other confounders. In cases of BSI, delays in achieving source control have been linked to persistent BSI, formation of metastatic foci, and worse clinical outcomes.[37] Nevertheless, the relatively straightforward detection of infection foci and prompt initiation of source control measures in patients with septic arthritis can help to distinguish it from other complex infections, such as prosthetic valve infective endocarditis and vertebral osteomyelitis. Consequently, differences in disease severity and underlying conditions appear to exert a more pronounced influence on mortality outcomes than the presence of BSI itself.

Several limitations need to be acknowledged when interpreting the results of this study. This was a retrospective cohort study conducted in a single large tertiary hospital in South Korea, potentially introducing selection bias and limiting its generalizability. Additionally, the inclusion of patients who did not undergo blood culture represents a notable limitation. However, the inclusion of these patients is relevant for reflecting real-world data because blood culture is often not performed in cases of septic arthritis when there are no signs of systemic infection. Moreover, the limited number of patients complicated the analysis of short-term mortality. Functional outcomes could not be considered owing to the limitations of a retrospective study. Furthermore, several important confounding factors, such as the site of involved joints, treatment-related factors, and use of immunosuppressants causing lymphocytopenia, were not accounted for in the analysis. Further multicenter prospective studies are needed to address these limitations and provide a more comprehensive understanding of septic arthritis.

In conclusion, our study sheds light on the relationship between BSI and mortality in patients with septic arthritis. Contrary to previous assumptions, our findings suggest that mortality in these patients is more closely linked to the sepsis resulting from BSI rather than from BSI itself. By delineating this distinction, our study provides valuable insights into the pathophysiology of septic arthritis and its associated clinical outcomes. These findings have important implications for clinical practice, highlighting the need for heightened awareness and early detection of BSI in patients with septic arthritis. Recognizing the systemic nature of infection in patients with septic arthritis, physicians can better tailor their treatment strategies to address the underlying septic process and mitigate the risk of adverse outcomes.

CRediT authorship contribution statement

Yongseop Lee: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Yong Chan Kim:** Writing – review & editing, Supervision, Conceptualization. **Jaeeun Seong:** Writing – review & editing. **Sangmin Ahn:** Writing – review & editing. **Min Han:** Writing – review & editing. **Jung Ah Lee:** Writing – review & editing. **Jung Ho Kim:** Writing – review & editing. **Jin Young Ahn:** Writing – review & editing. **Nam Su Ku:** Writing – review & editing. **Jun Yong Choi:** Writing – review & editing. **Joon-Sup Yeom:** Writing – review & editing. **Su Jin Jeong:** Writing – review & editing, Supervision, Conceptualization.

Data statement

The datasets used for the current study are available from the corresponding author upon reasonable request.

Funding

This study was supported by a faculty research grant from Yonsei University College of Medicine (6-2022-0172).

Declaration of competing interest

None.

References

1. Mathews CJ, Weston VC, Jones A, Field M, Coakley G. Bacterial septic arthritis in adults. *Lancet*. 2010;375:846–855.
2. Ferrand J, El Samad Y, Brunschweiler B, et al. Morbimortality in adult patients with septic arthritis: a three-year hospital-based study. *BMC Infect Dis*. 2016;16:239.
3. Abram SGF, Alvand A, Judge A, Beard DJ, Price AJ. Mortality and adverse joint outcomes following septic arthritis of the native knee: a longitudinal cohort study of patients receiving arthroscopic washout. *Lancet Infect Dis*. 2020;20:341–349.
4. Weston VC, Jones AC, Bradbury N, Fawthrop F, Doherty M. Clinical features and outcome of septic arthritis in a single UK Health District 1982-1991. *Ann Rheum Dis*. 1999;58:214–219.
5. Maneiro JR, Souto A, Cervantes EC, Mera A, Carmona L, Gomez-Reino JJ. Predictors of treatment failure and mortality in native septic arthritis. *Clin Rheumatol*. 2015;34:1961–1967.
6. Morgan DS, Fisher D, Merianos A, Currie BJ. An 18 year clinical review of septic arthritis from tropical Australia. *Epidemiol Infect*. 1996;117:423–428.
7. Kaandorp CJ, Dinant HJ, van de Laar MA, Moens HJ, Prins AP, Dijkmans BA. Incidence and sources of native and prosthetic joint infection: a community based prospective survey. *Ann Rheum Dis*. 1997;56:470–475.
8. Geirsson AJ, Statkevicius S, Víkingsson A. Septic arthritis in Iceland 1990-2002: increasing incidence due to iatrogenic infections. *Ann Rheum Dis*. 2008;67:638–643.
9. Edwards CJ, Cooper C, Fisher D, Field M, van Staa TP, Arden NK. The importance of the disease process and disease-modifying antirheumatic drug treatment in the development of septic arthritis in patients with rheumatoid arthritis. *Arthritis Rheum*. 2007;57:1151–1157.
10. Favero M, Schiavon F, Riato L, Carraro V, Punzi L. Rheumatoid arthritis is the major risk factor for septic arthritis in rheumatological settings. *Autoimmun Rev*. 2008;8:59–61.
11. Kaandorp CJ, Van Schaardenburg D, Krijnen P, Habbema JD, van de Laar MA. Risk factors for septic arthritis in patients with joint disease. A prospective study. *Arthritis Rheum*. 1995;38:1819–1825.
12. He M, Arthur Vithran DT, Pan L, et al. An update on recent progress of the epidemiology, etiology, diagnosis, and treatment of acute septic arthritis: a review. *Front Cell Infect Microbiol*. 2023;13, 1193645.
13. Horino T, Hori S. Metastatic infection during Staphylococcus aureus bacteremia. *J Infect Chemother*. 2020;26:162–169.
14. Hsu CC, Lin PC, Chen KT. The presence of bacteremia indicates higher inflammatory response and augments disease severity in adult patients with urinary tract infections. *J Clin Med*. 2022;11.
15. Kim TW, Lee SU, Park B, et al. Clinical effects of bacteremia in sepsis patients with community-acquired pneumonia. *BMC Infect Dis*. 2023;23:887.
16. Vos FJ, Kullberg BJ, Sturm PD, et al. Metastatic infectious disease and clinical outcome in Staphylococcus aureus and Streptococcus species bacteremia. *Medicine (Baltim)*. 2012;91:86–94.
17. Lee C, Sung NJ, Lim HS, Lee JH. Emergency department visits can Be reduced by having a regular doctor for adults with diabetes mellitus: secondary analysis of 2013 Korea health panel data. *J Kor Med Sci*. 2017;32:1921–1930.
18. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286:1754–1758.
19. P W. USA: Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: 26th informational supplement. *CLSI document M100S*. 2016. ISBN 1-56238-923-8.
20. Ryan MJ, Kavanagh R, Wall PG, Hazleman BL. Bacterial joint infections in England and Wales: analysis of bacterial isolates over a four year period. *Br J Rheumatol*. 1997;36:370–373.
21. Kim J, Park SY, Sohn KM, Kim B, Joo EJ. Methicillin resistance increased the risk of treatment failure in native joint septic arthritis caused by Staphylococcus aureus. *Antibiotics (Basel)*. 2023;12.
22. Le Dantec L, Maury F, Flipo RM, et al. Peripheral pyogenic arthritis. A study of one hundred seventy-nine cases. *Rev Rhum Engl*. 1996;63:103–110.
23. Gupta MN, Sturrock RD, Field M. A prospective 2-year study of 75 patients with adult-onset septic arthritis. *Rheumatology*. 2001;40:24–30.
24. Rakow A, Perka C, Trampuz A, Renz N. Origin and characteristics of haematogenous periprosthetic joint infection. *Clin Microbiol Infect*. 2019;25:845–850.
25. Varady NH, Schwab PE, Kheir MM, Dilley JE, Bedair H, Chen AF. Synovial fluid and serum neutrophil-to-lymphocyte ratio: novel biomarkers for the diagnosis and

prognosis of native septic arthritis in adults. *J Bone Joint Surg Am*. 2022;104:1516–1522.
26. Finfer S, Venkatesh B, Hotchkiss RS, Sasson SC. Lymphopenia in sepsis-an acquired immunodeficiency? *Immunol Cell Biol*. 2023;101:535–544.
27. Bermejo-Martin JF, Cilloniz C, Mendez R, et al. Lymphopenic community acquired pneumonia (L-CAP), an immunological phenotype associated with higher risk of mortality. *EBioMedicine*. 2017;24:231–236.
28. Drewry AM, Samra N, Skrupky LP, Fuller BM, Compton SM, Hotchkiss RS. Persistent lymphopenia after diagnosis of sepsis predicts mortality. *Shock*. 2014;42:383–391.
29. Jiang J, Du H, Su Y, et al. Nonviral infection-related lymphocytopenia for the prediction of adult sepsis and its persistence indicates a higher mortality. *Medicine (Baltim)*. 2019;98, e16535.
30. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis*. 2004;39:206–217.
31. Thornton L, Ormsby N, Allgar V, Thomas G. Can C-reactive protein Be used to predict acute septic arthritis in the adult population? *South Med J*. 2019;112:108–111.
32. Ernst AA, Weiss SJ, Tracy LA, Weiss NR. Usefulness of CRP and ESR in predicting septic joints. *South Med J*. 2010;103:522–526.
33. Dubost JJ, Soubrier M, De Champs C, Ristori JM, Bussiére JL, Sauvezie B. No changes in the distribution of organisms responsible for septic arthritis over a 20 year period. *Ann Rheum Dis*. 2002;61:267–269.
34. Keynan Y, Rubinstein E. Staphylococcus aureus bacteremia, risk factors, complications, and management. *Crit Care Clin*. 2013;29:547–562.
35. Menzies BE, Kourteva I. Staphylococcus aureus alpha-toxin induces apoptosis in endothelial cells. *FEMS Immunol Med Microbiol*. 2000;29:39–45.
36. Hocke AC, Temmesfeld-Wollbrueck B, Schmeck B, et al. Perturbation of endothelial junction proteins by Staphylococcus aureus alpha-toxin: inhibition of endothelial gap formation by adrenomedullin. *Histochem Cell Biol*. 2006;126:305–316.
37. Minter DJ, Appa A, Chambers HF, Doernberg SB. Contemporary management of Staphylococcus aureus bacteremia-controversies in clinical practice. *Clin Infect Dis*. 2023;77:e57–e68.