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ORIGINAL PAPER

# Clinical features of patients with septic arthritis and echocardiographic findings of infective endocarditis

Sarah B. Lieber[1,5] · Ori Tishler[2] · Kunwal Nasrullah[3] · Mary Louise Fowler[3] · Robert H. Shmerling[1] · Ziv Paz[1,2,4]

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## Abstract

**Purpose** Patients with septic arthritis (SA) often undergo echocardiographic evaluation to identify concomitant infective endocarditis (IE). The purpose of this study is to identify distinguishing features of patients with SA and IE by comparing them to patients with SA alone.

**Methods** We conducted a retrospective study of all patients 18 and older admitted to a single tertiary hospital between 1998 and 2015 with culture-positive SA. Patients were stratified by echocardiogram status and the presence of vegetations: those who had echocardiographic evaluation with no evidence of infective endocarditis (ECHO + IE−) or with a vegetation present (ECHO + IE+) and those who had no echocardiographic evaluation (ECHO−). Demographic data, clinical characteristics, microbiology data, treatment strategies, and patient outcomes were recorded and compared.

**Results** We identified 513 patients with SA. Transthoracic echocardiogram and/or transesophageal echocardiogram were performed in 263 patients (51.2%) and demonstrated evidence for IE in 19 patients (3.7%). While most demographic features, comorbidities, and clinical characteristics did not differ significantly between those with and without IE, those with IE had higher rates of sepsis and septic shock. In addition, patients with SA and IE had higher rates of positive blood cultures and *Methicillin-sensitive staphylococcus aureus* (MSSA) infection when compared to those with SA without IE. Patients with IE had higher rates of intensive care unit admission and increased 30-day mortality.

**Conclusions** IE is uncommon among patients with SA. Echocardiography may be overutilized and may be more useful among patients presenting with sepsis, shock, or positive blood cultures, especially when MSSA is isolated.

**Keywords** Septic arthritis · Infective endocarditis · Bacterial infection · Echocardiogram

## Introduction

There are an estimated 20,000–30,000 cases annually of septic arthritis (SA) in western Europe and the United States [1, 2]. Risk factors predisposing to the development of SA include older age, rheumatoid arthritis (RA), diabetes mellitus (DM), presence of a prosthetic joint, intravenous drug use (IVDU), and recent joint surgery [3, 4].

SA may be accompanied by infective endocarditis (IE), which necessitates early diagnosis and possible surgical intervention or an extended duration of antibiotic therapy. IE is associated with a broad array of systemic complications due to septic embolization and/or immune reactions [5–7]. The rate of arthritis in patients with IE varies by cohort, but is typically low, ranging from nearly 5–31% in prior studies, depending on whether observation alone or synovial culture is used to classify arthritis [8–12]. In one cohort of patients with IE and suspected SA, *Staphylococcus aureus*

Sarah B. Lieber and Ori Tishler contributed equally to this work.

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✉ Sarah B. Lieber
liebers@hss.edu

1 Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

2 Azrieli Faculty of Medicine, Bar-Ilan University, Ramat Gan, Israel

3 Boston University School of Medicine, Boston, MA, USA

4 Galilee Medical Center, Nahariya, Israel

5 Present Address: Hospital for Special Surgery, New York, NY, USA

was the most commonly isolated organism from the synovial fluid [8]. In the same cohort, when demographic and clinical features and complications in patients with and without rheumatic manifestations were compared, no significant differences were found, with the exception of more frequent rural origin, microhematuria, and septic embolism among those with rheumatic manifestations. However, those with and without culture-proven SA were not compared directly. In another cohort of patients with IE, women and those with Streptococcal infection more often experienced musculoskeletal symptoms [13]. In another series, concomitant bone or joint infection accompanied IE only among intravenous drug users [14].

The available literature describing the association between IE and SA is limited. Many prior studies have included broad definitions of musculoskeletal manifestations, without a specific focus on SA. In fact, in one widely cited review of SA, the association of IE with arthralgias, myalgias, and a sterile inflammatory arthritis is emphasized [15]. To our knowledge, there are few studies assessing the incidence or prevalence of IE among patients with SA. As a result, there are no clear guidelines regarding when to screen patients with SA with echocardiography, and there is the potential for over- or underutilization of cardiac imaging in this population.

The aim of our study is to identify clinical features of patients with SA and concomitant IE that distinguish them from patients who have SA alone. These findings could help clinicians decide which patients with SA would benefit most from echocardiogram.

## Methods

### Study design

We conducted a retrospective chart review of patients with septic arthritis admitted to a single tertiary care center between 1998 and 2015. Permission to conduct this study was obtained from the Beth Israel Deaconess Medical Center (BIDMC) Institutional Review Board. All authors attest to the accuracy of the reported data and analyses.

### Study population

Eligible patients were 18 years old or older and identified using an ICD-9 code for septic arthritis. We included only patients who experienced documented acute arthritis in one or more joints with confirmed positive synovial fluid or positive blood cultures. We excluded patients with septic bursitis or concurrent osteomyelitis. In contrast to a prior study from our group in which only cases of monoarticular arthritis with culture-proven synovial fluid or synovial tissue positivity were included [16], the current study also included cases of polyarticular SA and acute arthritis occurring in the context of positive blood or synovial fluid cultures as this allowed for a broader recognition of cases of SA.

### Data collection

The electronic medical records of eligible patients were reviewed to obtain demographic data and comorbidities at the time of index admission, presenting clinical and laboratory features, echocardiography findings, sites of joint involvement, synovial fluid data, and timing of antibiotic administration and operative intervention. Study data were collected and managed using REDCap electronic data capture tools hosted at BIDMC. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies [17].

### Patient groups

Patients with SA were stratified by whether echocardiography was performed (ECHO+/ECHO−) and by diagnosis of infective endocarditis (IE+/IE−). Echocardiography was obtained at the discretion of the treating clinicians over the course of the study period. The diagnosis of IE in our cohort was defined by the presence of a valvular vegetation observed on transthoracic (TTE) or transesophageal echocardiogram (TEE), as reported by the reviewing cardiologist.

### Outcomes

We determined length of stay (LOS), discharge to a rehabilitation facility, intensive care unit (ICU) admission rates, 60-day readmission rates, and 30-day mortality post-discharge.

### Statistical analysis

Quantitative variables were described by mean, standard deviation, median, and range while qualitative variables were described by frequencies and percentages. Differences between groups for quantitative variables were analysed using the Student's two-sample $t$ test or the Mann–Whitney $U$ test. Differences between groups for categorical variables were tested using the Chi-square test or Fisher's exact test. A two-sided $p$ value of $<0.05$ was considered to be significant. Analyses were conducted in IBM IPSS statistics, Release 19.

## Results

### Characteristics of the study population

513 patients with culture positive septic arthritis (SA) were identified. Among these, 263 (51%) patients

underwent TTE and/or TEE during the index admission. In 19 (3.7%) patients, valvular vegetations were detected, consistent with the diagnosis of infective endocarditis (IE) (ECHO + IE + group). The three groups (ECHO−, ECHO + IE− and ECHO + IE+) were similar with respect to age, gender, and prevalence of comorbidities (Table 1). In our cohort, echocardiography utilization among patients with SA varied over the period of study and reached a peak between the years of 2006–2008 with rates of up to 55.8% (Fig. 1).

**Table 1** Demographic features and comorbidities of patients with septic arthritis stratified by echocardiographic status and the presence of valvular vegetations

| | Echocardiography done ($N=263$) | | Echocardiography not done ($N=250$) | $p$ value |
|---|---|---|---|---|
| | Negative for infective endocarditis ($N=244$) | Positive for infective endocarditis ($N=19$) | | |
| Age, years, median (range) | 63.0 (21–95) | 58.0 (24–86) | 60.0 (19–82) | 0.33 |
| Gender, female, no. (%) | 100 (41.0) | 6 (31.6) | 117 (46.8) | 0.35 |
| Chronic kidney disease, no. (%) | 53 (21.7) | 3 (15.8) | 25 (10.0) | 0.65 |
| Current cancer, no. (%) | 9 (3.7) | 1 (5.3) | 12 (4.8) | 0.57 |
| Current immunosuppression, no. (%) | 31 (12.7) | 3 (15.8) | 27 (10.8) | 0.48 |
| Dementia, no. (%) | 6 (2.5) | 0 (0.0) | 5 (2.0) | 0.51 |
| Diabetes mellitus, no. (%) | 94 (38.5) | 6 (31.6) | 67 (26.8) | 0.93 |
| Dialysis, no. (%) | 18 (7.4) | 1 (5.3) | 11 (4.4) | 0.91 |
| Cirrhosis, no. (%) | 13 (5.3) | 0 (0) | 4 (1.6) | 0.41 |
| Gout, no. (%) | 10 (4.1) | 2 (10.5) | 13 (5.2) | 0.23 |
| Hepatitis B virus, no. (%) | 6 (2.5) | 0 (0) | 9 (3.6) | 0.44 |
| Current hepatitis C virus, no. (%) | 32 (13.1) | 1 (5.3) | 22 (8.8) | 0.71 |
| HIV, no. (%) | 6 (2.5) | 1 (5.3) | 8 (3.2) | 0.44 |
| IVDU, no. (%) | 18 (7.4) | 2 (10.5) | 11 (4.4) | 0.32 |
| Past endocarditis, no. (%) | 3 (1.2) | 1 (5.3) | 4 (1.6) | 0.26 |
| Past MRSA infection, no. (%) | 8 (3.3) | 1 (5.3) | 4 (1.6) | 0.39 |
| Previous kidney transplant, no. (%) | 9 (3.7) | 0 (0) | 1 (0.04) | 0.53 |
| SLE, no. (%) | 1 (0.4) | 1 (5.3) | 1 (0.4) | 0.11 |
| Rheumatoid arthritis, no. (%) | 20 (8.2) | 1 (5.3) | 15 (6.0) | 0.76 |

*HIV* human immunodeficiency virus, *MRSA* methicillin-resistant *Staphylococcus aureus, SD* standard deviation, *IVDU* intravenous drug use, *SLE* systemic lupus erythematosus

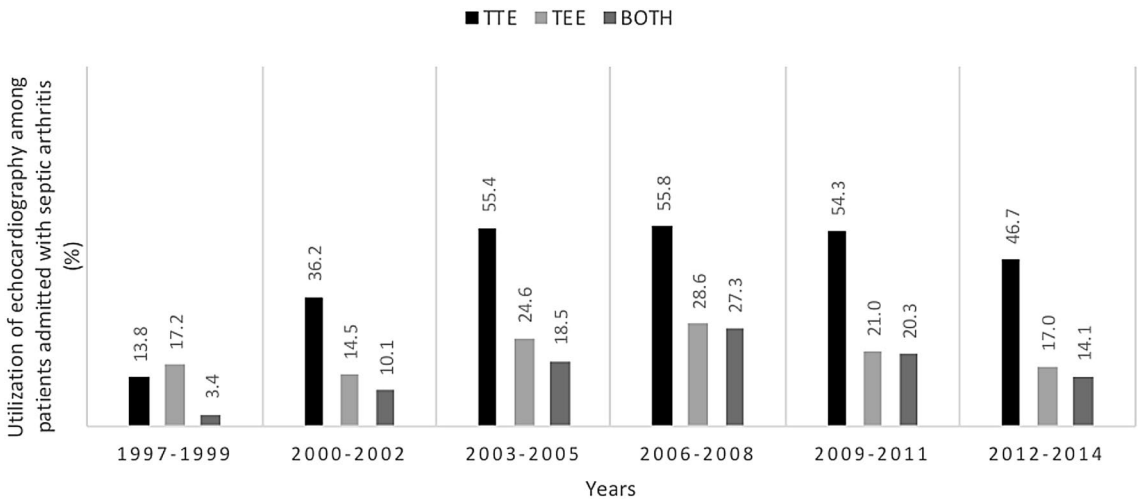


**Fig. 1** Utilization of echocardiography over time. *TTE* transthoracic echocardiography, *TEE* transesophageal echocardiography

## Characteristics of joint involvement

The knee was the most commonly involved joint in all groups (Fig. 2). Patients with prosthetic joint septic arthritis had lower rates of IE ($p = 0.01$) (Table 2).

## Characteristics of clinical presentation

Patients with IE had higher rates of sepsis (68.4% versus 46.9% versus 26.1%; $p = 0.01$) and septic shock (21.1% versus 9.3% versus 1.8%; $p = 0.03$) at presentation as compared to those with SA only in the ECHO + IE− and ECHO− groups (Table 3). Patients with IE had higher mean peripheral white blood cell (WBC) count and trends toward higher percentage of peripheral polymorphonuclear (PMN) cells and levels of C-reactive protein (CRP) than those without IE (Table 3). The aortic valve was involved in 11 out of 19 patients with IE; 4 patients had more than one valve involved (Fig. 3). Only one of these patients had a mechanical aortic valve.

## Microbiologic data

Bacteremia was significantly more common among patients with IE as compared to the ECHO + IE− and ECHO− groups (84.2% versus 58.3% versus 8%; $p < 0.001$) (Fig. 4). The most prevalent organism identified in all groups was *Methicillin-sensitive staphylococcus aureus* (MSSA). MSSA was significantly more prevalent among patients with IE (66.7% versus 39.8% versus 27.2%; $p < 0.001$) as compared to patients with SA only in the ECHO + IE− and ECHO− groups (Table S1). *Methicillin-resistant staphylococcus aureus* (MRSA) was the second most commonly isolated organism in the ECHO + IE + and ECHO− groups (11.1% and 21.3%, respectively) while *Coagulase-negative staphylococcus* (CoNS) was the second most frequent in the ECHO + IE− group (22.3%) (Fig. 5). A complete list of bacterial isolates is provided in Table S1.

## Antibiotic treatment

Vancomycin was prescribed empirically (prior to isolation of an organism) in the majority of patients (Table S2). In patients with IE, gentamicin ($p < 0.001$), oxacillin ($p = 0.02$), and clindamycin ($p = 0.05$) were used more commonly during the course of treatment (Table S3).

## Surgical management

Patients with IE had significantly fewer joint-related surgeries as compared to the ECHO + IE− and the ECHO− groups (68.4% versus 86.4% and 85.8%; $p = 0.04$) (Table S4). Six of the IE patients underwent valve-related operations. Five had aortic valve replacement and one had mitral valve repair.

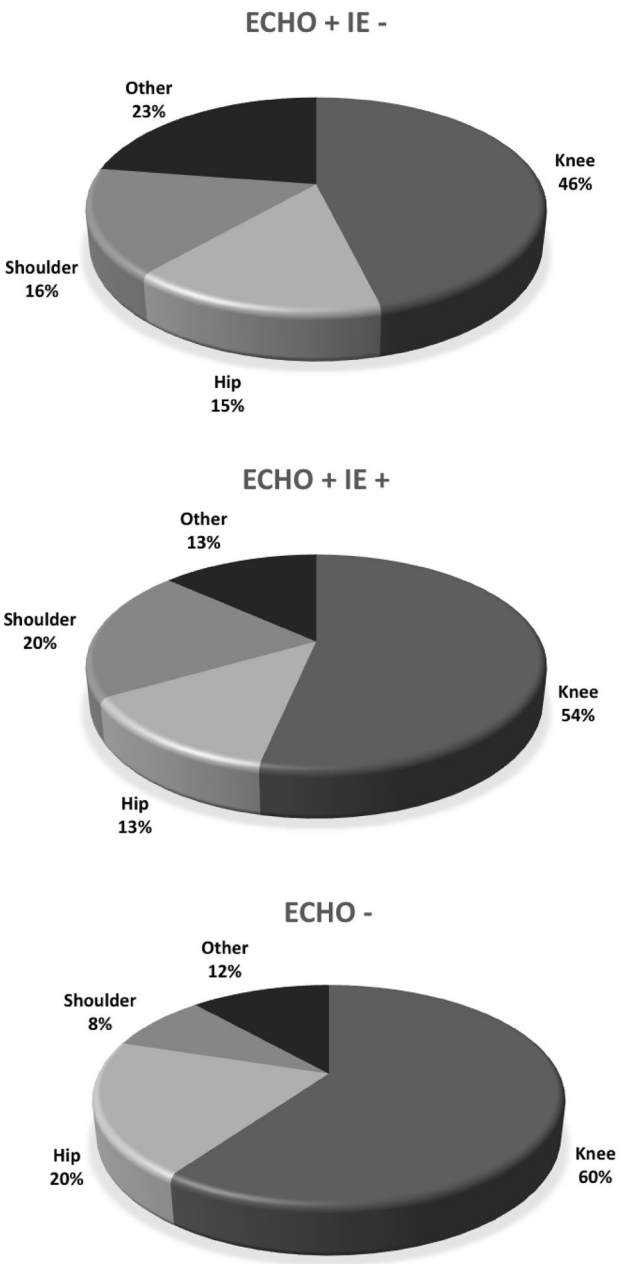


**Fig. 2** Distribution of joint involvement among patients with septic arthritis stratified by echocardiographic status and infective endocarditis diagnosis. *ECHO−* echocardiography was not performed; *ECHO + IE−* echocardiography was performed without findings of valvular vegetations, *ECHO + IE+* echocardiography was performed with findings of valvular vegetations, *TTE* transthoracic echocardiography, TEE transesophageal echocardiography, IE infective endocarditis

## Outcomes

The average length of stay (LOS) was 18.6 days (range 6–59 days) for the ECHO + IE + group, 13.9 days (range 3–77 days) for the ECHO + IE− group and 8 days (range 1–37

**Table 2** Joint characteristics of patients with septic arthritis stratified by echocardiographic status and presence of valvular vegetations

| | Echocardiography done ($N=263$) | | Echocardiography not done ($N=250$) | $p$ value |
|---|---|---|---|---|
| | Negative for infective endocarditis ($N=244$) | Positive for infective endocarditis ($N=19$) | | |
| Previous joint pathology, no. (%) | 140 (57.6) | 11 (57.9) | 187 (74.8) | 0.46 |
| Gout, no. (%) | 10 (4.1) | 2 (10.5) | 13 (5.2) | 0.23 |
| Rheumatoid arthritis, no. (%) | 20 (8.2) | 1 (5.3) | 15 (6.0) | 0.76 |
| OA, no. (%) | 63 (25.8) | 6 (31.6) | 83 (33.2) | 0.85 |
| Recent trauma[a], no. (%) | 37 (15.2) | 0 (0.0) | 35 (14.0) | 0.09 |
| Prosthetic joint, no. (%) | 69 (28.4) | 1 (5.3) | 116 (46.6) | 0.01 |
| Polymicrobial joint infection, no. (%) | 20 (8.3) | 1 (5.3) | 25 (10.8) | 0.71 |
| Polyarticular infection, no. (%) | 35 (14.4) | 4 (21.1) | 8 (3.2) | 0.08 |

*OA* osteoarthritis

[a]Occurring in the last 6 weeks

**Table 3** Clinical characteristics and laboratory values of patients with septic arthritis stratified by echocardiographic status and the presence of valvular vegetations

| | Echocardiography done ($N=263$) | | Echocardiography not done ($N=250$) | $p$ value |
|---|---|---|---|---|
| | Negative for infective endocarditis ($N=244$) | Positive for infective endocarditis ($N=19$) | | |
| Fever[a], no. (%) | 118 (49.6) | 11 (57.9) | 66 (29.3) | 0.15 |
| Sepsis[b], no. (%) | 112 (46.9) | 13 (68.4) | 57 (26.1) | 0.01 |
| Septic shock, no (%) | 22 (9.3) | 4 (21.1) | 4 (1.8) | 0.03 |
| Peripheral WBC count, thousands, mean (SD) | 12.47 (6.01) | 16.2 (9.1) | 10.9 (4.9) | 0.02 |
| Peripheral PMN percentage, mean (SD) | 79.9 (11.5) | 81.0 (13.3) | 75.8 (10.7) | 0.08 |
| ESR, mm/h, mean (SD) | 82.1 (37.4) | 74.6 (32.8) | 72.3 (38.8) | 0.85 |
| CRP mg/dL, mean (SD) | 173 (108.2) | 209 (106.1) | 118 (99.6) | 0.06 |
| Synovial WBC count, thousands, mean (SD) | 121.3 (209.6) | 57.8 (94.4) | 77.0 (105.2) | 0.09 |
| Synovial fluid PMN percentage, mean (SD) | 87.6 (16.2) | 83.7 (14.6) | 87.1 (18.3) | 0.06 |
| Synovial fluid crystals, no. (%) | 25 (15.3) | 0 (0) | 10 (7.8) | 0.23 |

*WBC* white blood cells, *SD* standard deviation, *PMN* polymorphonuclear granulocyte, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

[a]Fever is defined as temperature above 100 F

[b]As defined by SIRS criteria: Systemic inflammatory response syndrome is defined as 2 or more of the following variables- Fever of more than 38 °C (100.4 F) or less than 36 °C (96.8 F), heart rate of more than 90 beats/min, respiratory rate of more than 20 breaths/min or arterial carbon dioxide tension ($PaCO_2$) of less than 32 mmHg, abnormal white blood cell count (> 12,000/μL or < 4000/μL or > 10% immature [band] forms)

days) for the ECHO− group ($p<0.001$). Patients with SA and IE were more likely to be admitted to the intensive care unit (ICU) (57.9% versus 30.6% versus 5.7%; $p<0.001$) with higher rates of mortality within 30 days (21.1% versus 9.1% versus 1.6%; $p=0.02$) compared with those with SA without IE in the ECHO + IE− and ECHO− groups (Table 4).

## Discussion

In this study, we compared clinical characteristics, management, and outcomes of patients diagnosed with SA with or without IE. The majority of echocardiographic studies were negative for vegetation (92.7%). Of 513 patients with SA, 19 patients (3.7%) had findings of concurrent IE by echocardiographic evaluation. While patients with IE did not differ in their comorbidities or by joint involvement, they were sicker at presentation with higher rates of sepsis and septic shock, as well as higher mean peripheral WBC count and CRP levels when compared with the patients with SA only. Patients with IE tended to have more native joint involvement than those without IE. MSSA was significantly more prevalent among patients with IE, and patients with IE had significantly higher rates of concurrent bacteremia (84.1% versus 58.3%); only 3 of 513 patients with SA had IE in the absence of positive blood cultures. Perhaps not

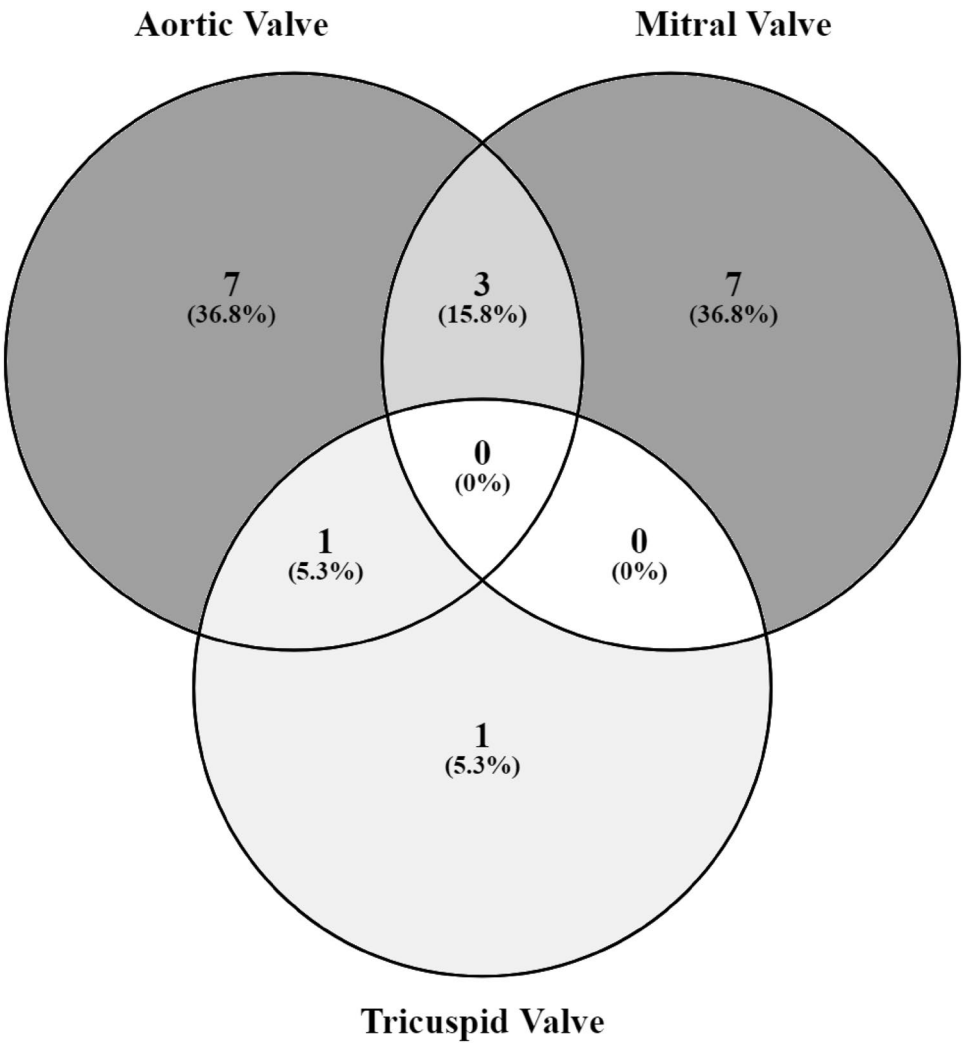


**Fig. 3** Distribution of valves affected with Infective endocarditis (IE). Each circle includes the absolute number of patients in bold and the percentage (%) of all patients with IE

unexpectedly, patients with concomitant SA and IE had worse outcomes with prolonged LOS and higher rates of ICU admission and mortality within 30 days of discharge. These differences likely reflected more severe systemic disease among those with IE as there were no significant differences in antibiotic management among groups.

The rate of SA with concomitant IE described here (3.7%) is similar to the rates described in patients with IE and concomitant SA in the limited literature available [8]. However, the rate of IE in SA in our study falls below that recently reported in association with native vertebral osteomyelitis (30.4%) [18]. To our knowledge, there is limited existing literature on differences between patients with SA with and without IE, as the emphasis of prior studies has been on the comparisons of patients with IE with and without SA. *Staphylococcus aureus* was the predominant organism involved in IE with SA in prior series [8, 14, 19], similar to what was observed in the current study. It is notable that patients with IE had fewer joint surgeries than those without IE; this may have been because those with IE were sicker and, therefore, suboptimal surgical candidates.

There are several limitations to this study. The IE group was small, and our study was limited to the population of

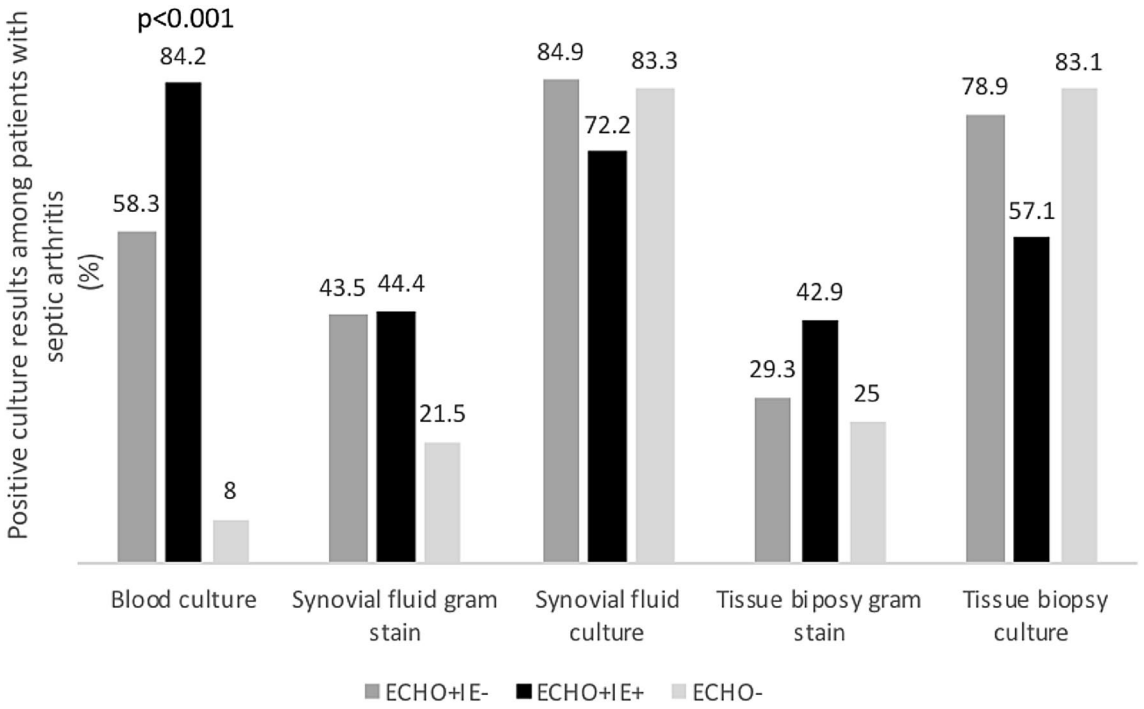


**Fig. 4** Culture positivity rates stratified by modality, echocardiography status, and presence of vegetation. *ECHO−* echocardiography was not performed, *ECHO + IE−* echocardiography was performed without findings of valvular vegetations, *ECHO + IE+* echocardiography was performed with findings of valvular vegetations, *IE* infective endocarditis

a single tertiary care center, potentially limiting statistical power, the diversity of the sample and the generalizability of the findings. In addition, it is possible that cases of IE were not captured among patients for whom an echocardiogram was not ordered, who had IE without vegetations or who underwent only a TTE, which is known to be less sensitive than TEE in detecting IE [7]. As patients were classified as having IE on the basis of echocardiography rather than modified Duke criteria, some patients could have been misclassified. As in any retrospective record-based study, data collection was limited by inconsistent documentation and incomplete access to follow-up data, including mortality rates, as some patients received follow-up in other healthcare settings. Further, while 30-day mortality and 60-day readmission rates were designated as clinically relevant endpoints that were likely to be available, these may represent insufficient observation periods.

To our knowledge, this study is among the first to examine the relationship between SA and IE among patients with SA. Although the rate of IE among patients with SA was low, this group is distinctive and requires specific attention. While it seems appropriate to obtain blood cultures from all patients with SA, universal echocardiographic assessment may not be necessary. Prompt echocardiographic screening for patients with SA who have known risk factors for IE, such as IV drug use, or a clinical presentation that includes sepsis or septic shock, positive blood cultures, or isolation of *S. aureus* from blood or synovial fluid may benefit most from echocardiographic evaluation.

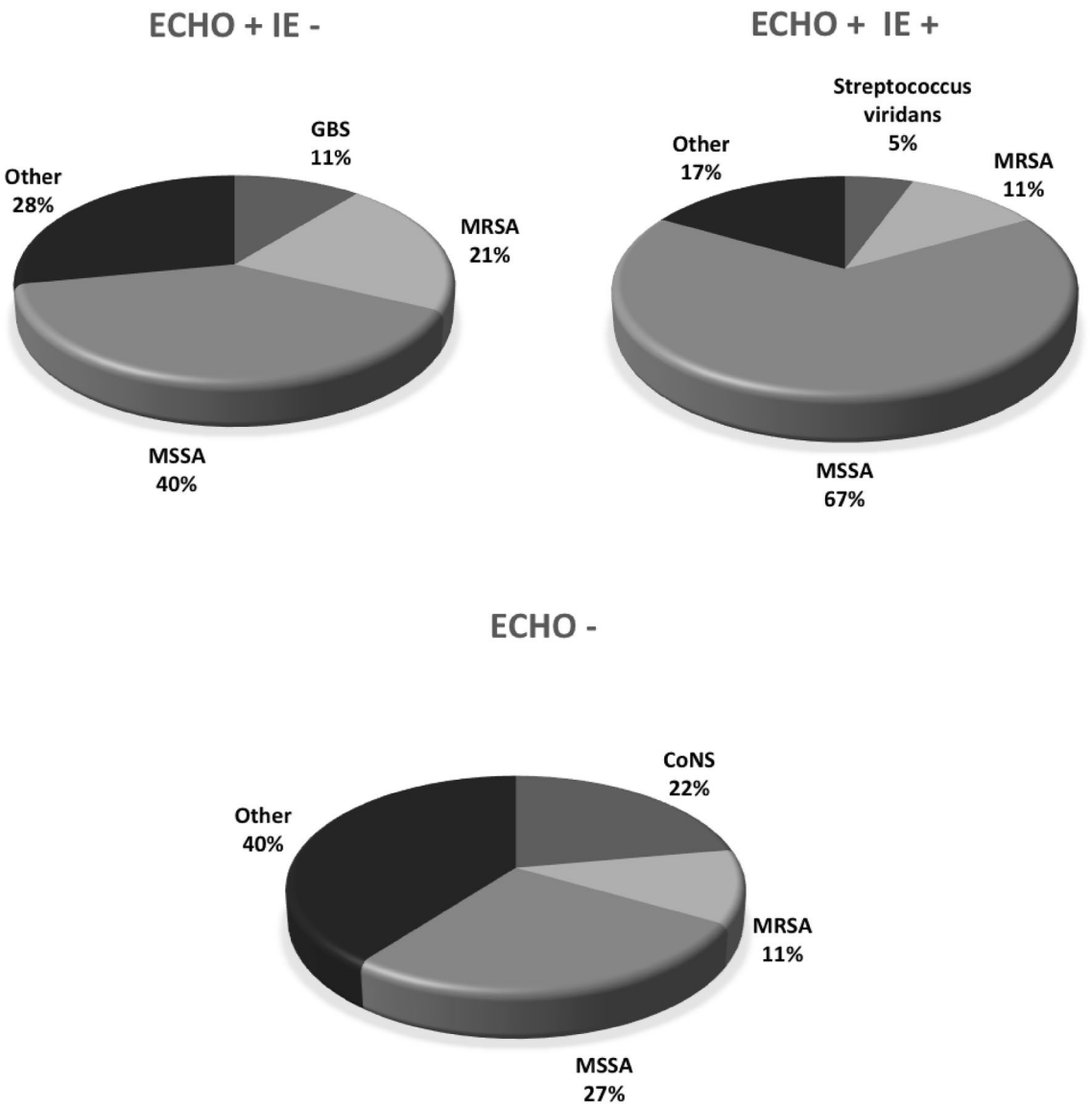


**Fig. 5** Distribution of bacterial isolation stratified by echocardiography status and presence of vegetation. *ECHO−* echocardiography was not performed, *ECHO+IE−* echocardiography was performed without findings of valvular vegetations; *ECHO+IE+* echocardiography was performed with findings of valvular vegetations, *IE* infective endocarditis, *MRSA* methicillin-resistant *Staphyloccocus aureus, MSSA* methicillin-sensitive *Staphyloccocus aureus, CoNS* coagulase-negative staphylococcus, *GBS* group-B streptococcus. "Other" represents the sum of all other isolated microorganisms

**Table 4** Outcomes of patients with septic arthritis stratified by echocardiographic status and by presence of valvular vegetations

| | Echocardiography done ($N=263$) | | Echocardiography not done ($N=250$) | $p$ value |
|---|---|---|---|---|
| | Negative for infective endocarditis ($N=244$) | Positive for infective endocarditis ($N=19$) | | |
| LOS, days, mean (SD) | 13.9 (9.9) | 18.6 (13.0) | 8.0 (5.9) | <0.001 |
| Discharge to a rehabilitation facility, no. (%) | 151 (68.0) | 10 (62.5) | 112 (46.9) | 0.80 |
| ICU admission, no. (%) | 74 (30.6) | 11 (57.9) | 14 (5.7) | <0.001 |
| Readmission within 60 days, no. (%) | 41 (18.6) | 2 (12.5) | 53 (22.0) | 0.75 |
| Death within 30 days of discharge, no. (%) | 22 (9.1) | 4 (21.1) | 4 (1.6) | 0.02 |

*LOS* length of hospital stay, *SD* standard deviation, *ICU* intensive care unit

## Compliance with ethical standards

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

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