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Detection of septic metastases in catheter-related *Staphylococcus aureus* bacteremia using 18^{F}FDG-PET/CT: a before-and-after study

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Abstract

Purpose To evaluate the detection rate of septic metastases in catheter-related *S. aureus* bacteremia (CR-SAB) episodes by using [18F]FDG-PET/CT.

Methods We conducted a retrospective, before-and-after, single-center study of a prospectively identified catheter-related SAB (CR-SAB) cohort at Hospital Clínic Barcelona. All adult patients hospitalized from January 2006 to December 2022 were included. Primary outcome was the detection of septic metastases before and after integrating [18F]FDG-PET/CT into the diagnostic workflow of CR-SAB in January 2020. Secondary outcomes included 30-day mortality, length of stay, and treatment duration.

Results A total of 598 episodes of CR-SAB were included, 100 in the post-intervention period (2020–2022) and 498 in the pre-intervention period (2006–2019). [18F]FDG-PET/CT scan was performed in 28/100 episodes (28.0%) in post-intervention period, versus 9/498 in pre-intervention period (1.8%). Septic metastases detection rate was higher after [18F]FDG-PET/CT implementation (22/100, 22% *vs.* 56/498, 11.2% *p* .004), mainly due to pulmonary septic emboli (13/100, 13.0% *vs*. 12/498, 2.4% $p < .001$) and osteoarticular seeding (7/100, 7.0% *vs*. 11/498, 2.2% *p* .019). Neither pulmonary septic emboli nor osteoarticular metastases increased 30-day mortality (3/25, 12.0% vs. 57/573, 10.0%, *p* .732; and 2/18, 11.1% vs. 58/580 10.0%, *p* .702, respectively). Patients with septic metastases had longer treatment [25.0 (16.0–37.0) *vs*. 15.0 (13.0–19.0) days, $p < .001$].

Conclusions [18F]FDG-PET/CT use in patients with CR-SAB was associated with a higher rate of septic metastases diagnosis, mainly pulmonary and osteoarticular, resulting in longer treatment, but no differences in clinical outcomes were observed.

Keywords *Staphylococcus aureus*, Catheter-related bacteremia, [18F]FDG-PET/CT, Septic metastases, Before-and-after study

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Introduction

Staphylococcus aureus bacteremia (SAB) is a serious infection with high morbidity and mortality, largely due to its ability to cause hematogenous complications [1]. Catheter-related infection is one of the most common sources of SAB and, although it is considered a 'low risk' focus within its spectrum, it is also a potential cause of metastatic infection [2, 3]. The risk of hematogenous complications is higher in those patients with community acquire infections, carriers of a foreign body or when persistent bacteremia occurs [4]. For these high-risk patients, current guidelines recommend prolonged intravenous treatment of 4 to 6 weeks [5]. Nonetheless, clinical guidelines tend to recommend prolonged antibiotic courses in both those who are at high risk of hematogenous complications and those with proven distant foci of infection. In this scenario, several authors have shown that 2-[18 F]fluoro-2-deoxy-D-glucose Positron Emission Tomography ([18 F]FDG-PET)/CT may help to identify septic metastases in patients with high-risk SAB [6, 7] with a positive impact on clinical outcomes (e.g., allowing to establish source control strategies or to shorten treatment if no metastases are found) [8]. However, the specific role of [18 F]FDG-PET/CT in catheter-related *S. aureus* bacteremia (CR-SAB) has not been studied. The aim of this study is to evaluate the impact of [18 F]FDG-PET/CT implementation on the detection of septic metastases and its clinical consequences, by comparing CR-SAB episodes before and after the introduction of [18 F]FDG-PET/CT as a widely available diagnostic imaging technique in SAB.

Methods

Study design

We conducted a retrospective, observational, before-and-after, single-center study in our prospectively identified cohort of *Staphylococcus aureus* bacteremia in Hospital Clínic Barcelona, Spain. All catheter-related *S. aureus* bacteremia (CR-SAB) episodes in adult patients (≥ 16 years old) who required hospital admission or were already hospitalized at the presentation of the bacteremia between January 1st, 2006, and December 31st, 2022, were included. Septic metastases detection rate was compared before and after the integration of [18 F]FDG-PET/CT into the diagnostic workflow of SAB, in January 2020.

Patients with early death (< 72 h), transfer to another center, incomplete follow-up information or polymicrobial infection were excluded.

Study definitions and clinical management

S. aureus bacteremia episodes were identified through a prospective, hospital-wide registry managed by the Infectious Diseases (ID) Nosocomial Team. All positive blood cultures for *S. aureus* were systematically reported to the ID team, who evaluated each case and prospectively recorded relevant epidemiological, microbiological, and clinical data using a standardized report form. CR-SAB was considered if one of the following criteria was met: i) *S. aureus* growth in a culture of the removed catheter tip; ii) 2 blood samples were drawn, 1 from a catheter hub and the other from a peripheral vein, with a differential time to positivity of > 2 h according to CR-BSI criteria [5]; iii) clinical signs of phlebitis or suppuration from catheter insertion site was present. All episodes of CR-SAB meeting these definitions were included, both peripheral and central line catheters, including arterial catheter, and short and long-term catheters.

Management of the episodes during the entire study period included ID specialist consultation, initiation of appropriate antibiotic treatment and removal of the catheter as soon as possible. Follow-up blood cultures were recommended every 24–48 h until negative [9]. Days of bacteremia were calculated by the difference between last and first positive blood cultures. Throughout the entire study, the diagnostic work-up for the detection of septic metastases (including echocardiography, conventional radiography, CT, magnetic resonance imaging, or, when available, [18 F]FDG-PET/CT) was guided by the attending physician based on individual risk factors and clinical suspicion. The performance of [18 F]FDG-PET/CT in the routine management of patients with SAB, when deemed indicated at the discretion of the attending physician, was established as part of a research project (PI19/01116) from January 2020, which established the acquisition of [18 F]FDG-PET/CT within the first 10 days of SAB detection.

High-risk CR-SAB was defined if one of the following features was present: 1) community onset (catheter-associated bacteremia acquired by patients living in their own residence); 2) endovascular prosthetic material (prosthetic heart valve, intracardiac device or endovascular grafts excluding coronary artery stents); or 3) positive blood cultures ≥ 48 h after initiation of active antibiotic regimen [4, 6, 9].

Outcomes measurement

The primary outcome was the diagnostic rate of metastatic infection in patients with CR-SAB before and after the implementation of [18 F]FDG-PET/CT in the routine workup of SAB, in January 2020. Septic metastases were defined as *S. aureus* infection foci distant from the catheter infection site, regardless the diagnostic method. Local complications, such as thrombophlebitis at the insertion site or surrounding cellulitis, were not considered as metastatic complications. Secondary outcomes were 30 and

90-day mortality, 90-day recurrence, length of stay after CR-SAB episode and total treatment duration.

Data collection and statistical analysis

Demographic data, clinical presentation, laboratory results, microbiology and imaging were manually retrieved by Infectious Diseases specialist from electronic medical records. [18 F]FDG-PET/CT findings were evaluated by a multidisciplinary team of Nuclear Medicine and Infectious Diseases specialists.

Continuous variables, presented as median and interquartile range (IQR), were compared using the Mann–Whitney U test after demonstrating the absence of normal distribution, whereas categorical variables, presented as absolute count and percentage, were compared using the Chi-square test or Fisher exact test. Differences were considered statistically significant at a 2-sides p value <0.05. The Youden index was used to identify the cut-off point from the ROC curves to convert continuous quantitative variables into binary variables when necessary. All statistical analysis was performed using SPSS IBM (Version 25, SPSS, IBM Corp., USA).

Results

Patient characteristics

We identified 635 episodes of CR-SAB. 37 episodes were excluded (14 polymicrobial bacteremia, 11 death prior evaluation, 6 referrals to other centers, 6 insufficient follow-up information). 598 episodes were finally included, 100 episodes after implementation of [18 F]FDG-PET/CT into the standard diagnostic workflow of SAB (post-intervention period, 2020—2022) and 498 episodes from the previous period as a comparison group (pre-intervention period, 2006—2019).

Both periods were comparable in terms of patient's age, sex and comorbidity, except for community onset origin of SAB episode and patients' renal replacement therapy, which were significantly more common in the post-intervention period, and thus the high-risk subgroup. Patients' characteristics are summarized in Table 1.

[18 F]FDG-PET/CT and detection of metastatic infection

A [18 F]FDG-PET/CT scan was performed in 37 patients (6.2%), 9/498 in the pre-intervention period (1.8%) and 28/100 (28.0%) in the post-intervention period (p <0.001). Time from SAB to [18 F]FDG-PET/CT was shortened from 10 (7.5–14) to 7 (4.25–10) days in the study period (p 0.014). In 28/37 episodes (75.7%), [18 F]FDG-PET/CT showed abnormal FDG uptake at the catheter site or due to septic metastases (Fig. 1) and led to a change in management in 17/37 episodes (46.0%).

Septic metastases detection rate was significantly higher after the introduction of [18 F]FDG-PET/CT into the diagnostic workflow of CR-SAB episodes (22/100, 22.0% vs. 56/498, 11.2%, p 0.004). This increment was mainly due to pulmonary septic emboli and, to a lesser extent, osteoarticular or muscular septic metastases (Fig. 2). The number of [18 F]FDG-PET/CT scans needed to diagnose a septic metastasis was 9.3 (IC95% 5.2–45.0).

No differences in mortality or recurrence rates were observed between periods, except for higher mortality among high-risk patients in the pre-intervention period, although this was not statistically significant (32/223, 14.3%; vs. 4/57, 7.0%, p 0.184).

There were no differences in length of treatment (LOT) between pre- and post-intervention periods [16 (12–21) vs. 16 (14–22) days, p 0.507]. This finding was consistent across both low-risk [15.5 (10–21) vs. 16 (14–21) days, p 0.375] and high-risk subgroups [16 (13–22.5) vs. 17 (14–24) days, p 0.872]. Regarding length of stay (LOS), the median was 15 (9–25) days in the pre-intervention period, compared to 16 (11–23) days in the post-intervention period (p 0.416).

Impact of metastatic infection on outcomes

Overall, the diagnosis of any type of septic metastases was associated with a higher 30-day (14/78, 17.9% vs. 46/520, 8.8%, p 0.014) and 90-day mortality (15/78, 19.2% vs. 52/520, 10.0%, p 0.017). In detail, pulmonary septic emboli and osteoarticular metastases were not associated with higher 30-day mortality (3/25, 12.0% vs. 57/573, 10.0%, p 0.732; and 2/18, 11.1% vs. 58/580 10.0%, p 0.702, respectively), but endovascular metastases were (7/26, 26.9% vs. 53/572, 9.3%, p 0.011). All patients with septic metastases received longer treatment [25.0 (16.0–37.0) vs. 15.0 (13.0–19.0) days, p <0.001], whatever the location of metastases [pulmonary 21.5 (16.3–29.8), osteoarticular 25.5 (18.3–49.8) or endovascular 27.0 (13.0–42.0) days]. Similarly, length of stay was prolonged in patients with detected septic metastases [22 (13.5–30) vs. 15 (9–24) days, $p<0.001$].

Discussion

In this observational, retrospective, before and after study, we found that the integration of [18 F]FDG-PET/CT scan in the diagnostic workflow of CR-SAB revealed an unexpectedly high rate of septic metastases, especially pulmonary septic embolisms. Although the presence of metastatic infection in the whole cohort was associated with a higher 30-day mortality rate, the increased detection by [18 F]FDG-PET/CT was not linked to substantial modifications in patients' outcomes (recurrence or mortality). This is attributable to the increase in pulmonary and osteoarticular sites with lower lethality than endovascular ones [10]. The identification of septic metastases

Table 1 Characteristics of 598 episodes of catheter-related *S. aureus* bacteremia

	Post-intervention period (2020–2022) (*n* = 100)	Pre-intervention period (2006–2019) (*n* = 498)	p
Age	58.5 (50.3–73.0)	65.0 (50.0–76.0)	.135
Female sex	30 (30.0)	183 (36.7)	.199
Methicillin-resistant *S. aureus*	18 (18.0)	96 (19.3)	.767
Persistent bacteremia (≥ 48 h)	16 (16.0)	108 (21.7)	.201
Community-onset	43 (43.0)	108 (21.8)	<.001
Endovascular foreign body	11 (11.0)	54 (10.9)	.969
Diabetes mellitus	27 (27.0)	126 (25.3)	.722
Delay in catheter removal ≥ 48 h	19/79 (24.1)	85/368 (23.1)	.884
High-risk episodes	57 (57.0)	223 (44.8)	.025
Renal replacement therapy	23 (23.0)	60 (12.0)	.003
Malignancy	36 (36.0)	137 (27.6)	.09
Immunosuppression[a]	50 (50.0)	202 (40.6)	.133
HIV	2 (2.0)	17 (3.4)	.754
McCabe prognostic scale			.082
- Non-fatal	43 (43.0)	274 (55.0)	
- Ultimately fatal	51 (51.0)	204 (41.0)	
- Rapidly fatal	6 (6.0)	20 (4.0)	
CRP baseline (mg/dL)	6.35 (3.14–13.22)	7.50 (3.74–14.94)	.198
CRP day 3–5 (mg/dL)	7.16 (3.41–15.14)	7.63 (3.84–14.03)	.892
Echocardiography	69/99 (69.9)	246/494 (49.8)	<.001
[18 F]FDG-PET/CT	28 (28.0)	9 (1.8)	<.001
[18 F]FDG-PET/CT in high-risk subpopulation	20/57 (35.1)	9/223 (4.0)	<.001
[18 F]FDG-PET/CT in low-risk subpopulation	8/43 (18.6)	0/275 (0.0)	<.001
Septic shock at presentation	5 (5.0)	27 (5.4)	.864
Intensive Care Unit admission	7 (7.0)	37 (7.5)	.861
Length of stay (days)	16.0 (11.0–23.0)	15.0 (9.0–25.0)	.416
Treatment duration (days)	16.0 (14.0–22.0) (96/100)	16.0 (12.0–21.0) (108/498)	.507
90-day recurrence	3 (3.0)	5 (1.0)	.135
30-day mortality	7 (7.0)	53 (10.6)	.259
90-day mortality	8 (8.0)	59 (11.8)	.256

HIV human immunodeficiency virus, *CRP* C-reactive protein

[a] Immunosuppression: Active cancer treatment, solid organ or bone marrow transplantation, corticosteroids therapy (> 0.5 mg/kg/day for > 4 weeks), or neutropenia (< 500 neutrophils/μl)

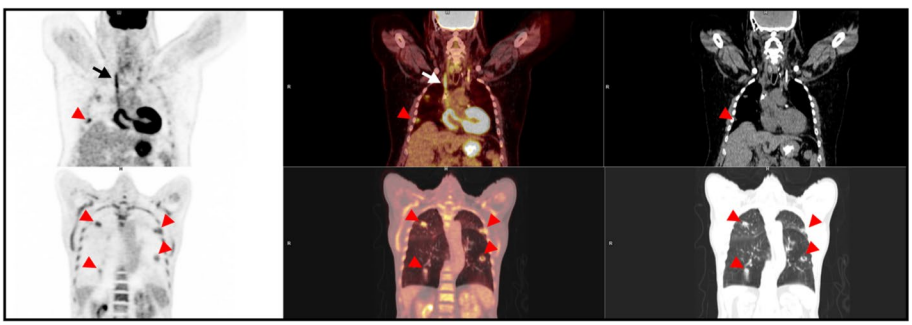

Fig. 1 Coronal view of [18 F]FDG-PET/CT where abnormal uptake was found in the tract of the already extracted central catheter (arrow) and in bilateral septic pulmonary embolism (arrowhead)

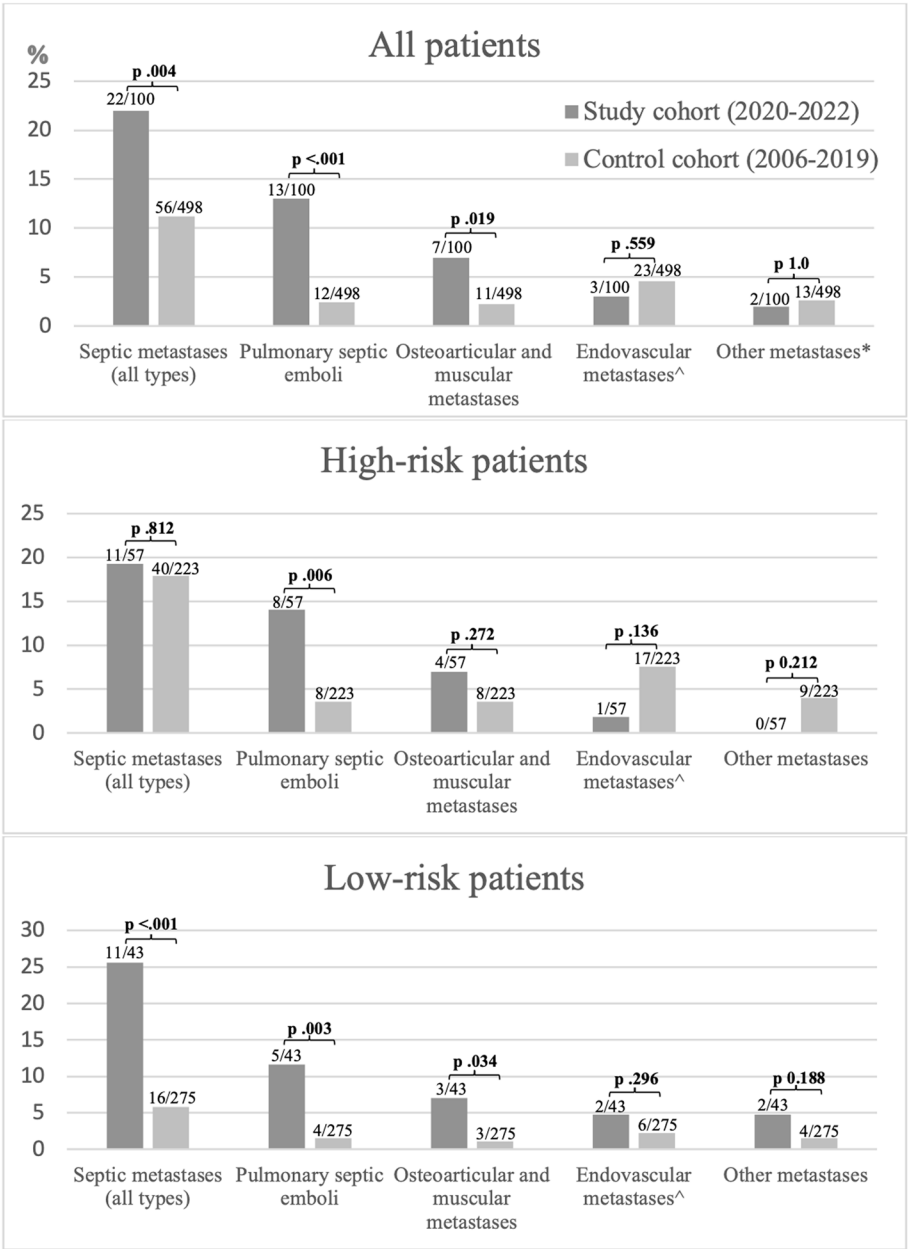

Fig. 2 Detection rates of septic metastases in CR-SAB cohorts before and after the introduction of [18 F]FDG-PET/CT in diagnostic workflow (an episode may include more than one type of metastasis). ^Native or prosthetic endocarditis, infection of intracardiac device, mycotic aneurism or endovascular graft infection. *Skin and soft tissue infection ($n=7$), intra-abdominal infection ($n=6$), endophthalmitis ($n=1$) and central nervous system ($n=1$)

had a significant effect on both the length of hospitalization and the subsequent treatment plan.

CR-SAB has generally been considered a lower-risk entity in the spectrum of SAB, especially if prompt removal of the catheter and initiation of therapy is achieved [10–12]. However, the largest cohort including 324 episodes of CR-SAB, before [18 F]FDG-PET/CT was available, described rates of septic metastases of 13% [3], similar to our rate before implementing [18 F]FDG-PET/CT (11.2%). Interestingly, no pulmonary embolism was reported in the study by Fowler et al., and we have found other series, not using [18 F]FDG-PET/CT, reporting pulmonary embolisms in 2.3–5.7% of patients with CR-SAB [2, 13–17], and up to 10% in patients with cancer [18], in line with our results in general population (2.4%). For osteoarticular metastases, Fowler et al. describe a

rate of 5.6%, while other groups vary between 2.4–5% [2, 13, 16, 17] and, again, higher in cancer patients (8%) [14]. In our series we found a 2.2% rate in the pre-intervention period. Together, these results confirm that our control period is valid and supports that [18 F]FDG-PET/CT significantly increases the detection of pulmonary and osteoarticular metastases.

Given the risk of septic metastases, strict criteria have been established to define uncomplicated CR-SAB (prompt resolution of fever after catheter removal, no intravascular hardware, no evidence of infective endocarditis or suppurative thrombophlebitis, absence of active malignancy or immunosuppression -including diabetes mellitus-) [5, 19], leading to prolonged antibiotic treatment in patients who do not meet any of these features. In this scenario, [18 F]FDG-PET/CT has grown substantially in recent years, demonstrating its ability to either detect or exclude metastatic foci of infection [20–22], leading to additional source control procedures [6] and ultimately to fewer infection relapses and lower mortality [6, 7, 23], although the impact on survival rates has been refuted as being secondary to the immortal time bias [24]. In addition, Ong et al. proved that a strategy of using [18 F]FDG-PET/CT in high-risk patients is more cost-effective than not using [18 F]FDG-PET/CT [25]. However, our data show that the clinical criteria for defining high- and low-risk groups among patients with CR-SAB is not accurate since using [18 F]FDG-PET/CT in selected patients with classical low-risk criteria had similar septic metastasis rate (25.6%) than those with high-risk (19.2%).

We did not find worse outcomes in patients with pulmonary or osteoarticular septic metastases, although we cannot exclude that these results are the consequence of a longer antibiotic treatment when septic metastases are detected, or on the contrary, that those with undetected metastases in these sites were already cured after 2 weeks of treatment. The second hypothesis would explain the recent results from Hendriks et al. showing that low-risk patients could be managed without routine imaging, with similar 90-days relapse-free survival rates [26]. Accordingly, [18 F]FDG-PET/CT would not be necessary if all patients were treated for two weeks, but another question arises: could we safely shorten treatment in patients with negative [18 F]FDG-PET/CT, no persistent bacteremia and normal echocardiography? And if so, in which patients should we perform [18 F]FDG-PET/CT, given the high cost and limited availability of [18 F]FDG-PET/CT? In this regard, we found that a persistently elevated CRP level (≥ 12 mg/dL) on days 3 to 5 after the first positive blood culture was associated with septic metastases found on[18 F]FDG-PET/CT (data not shown). This finding supports the biological impact of [18 F]FDG-PET/CT findings, and suggests that CRP may guide the need to perform a [18 F]FDG-PET/CT. Further studies are needed to determine whether other biomarkers are more accurate than CRP in assessing the burden of staphylococcal disease [27].

This study has several limitations. Firstly, its retrospective design inherently introduces biases, although the before-and-after approach helps to partially mitigate this limitation. However, significant differences remained between the periods, such as renal replacement therapy and community-onset of SAB episode. Secondly, there is probably a selection bias in the low-risk sub-cohort receiving [18 F]FDG-PET/CT, where medical characteristics (persistent fever or bad general status) not collected in the present study were the most likely drivers for [18 F]FDG-PET/CT performance and it could explain the high rate of metastases detection. Thirdly, [18 F]FDG-PET/CT was conducted in only 28% of the study cohort due to the significant logistical challenges involved in obtaining such an advanced diagnostic imaging technique within the first days of SAB. Finally, the study was conducted in a single center and this fact may limit the generalizability of the findings.

In conclusion, our study shows that the increased use of [18 F]FDG-PET/CT is associated with significant increase in the detection of septic metastases in CR-SAB. However, despite the higher diagnostic yield, our study found no significant differences in clinical outcomes between patients who underwent [18 F]FDG-PET/CT and those who did not. These findings highlight the need of randomized clinical trials to determine the clinical impact of [18 F]FDG-PET/CT-guided management in CR-SAB and to validate our results in larger, multi-center studies.

Abbreviations

CR-BSI	Catheter-Related Bloodstream Infection
CR-SAB	Catheter-Related *Staphylococcus aureus* Bacteremia
CRP	C-Reactive Protein
CT	Computed Tomography
FDG	Fluorodeoxyglucose
ID	Infectious Disease
IQR	Interquartile Range
LOT	Length of Treatment
LOS	Length of Stay
MRSA	Methicillin-Resistant *Staphylococcus aureus*
PET	Positron Emission Tomography
ROC	Receiver Operating Characteristic
SAB	*Staphylococcus aureus* Bacteremia

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Clinical trial number
Not applicable.

Authors' contributions
MÁV, LM and AS conceived the original idea and designed the study. AP and DF reviewed the nuclear imaging findings. The remaining authors (CP, GC, MHM, MB, SH, CGV, PPA, JAM, AR and ME) contributed to the prospective data collection and clinical assessment. MÁV and DMB revised the database. MÁV drafted the original manuscript. All authors reviewed and approved the final manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author, MÁV, upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB), "Comité de Ética de la Investigación con Medicamentos (CEIM) del Hospital Clínic de Barcelona" (approval reference HCB-2023–0507). Due to the retrospective and anonymized observational design of the study, the need for informed consent to participate was waived by the IRB (CEIM).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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