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MAJOR ARTICLE

Integration of FDG-PET/CT in the Diagnostic Workup for *Staphylococcus aureus* Bacteremia: A Prospective Interventional Matched-cohort Study

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Background. *Staphylococcus aureus* bacteremia (SAB) is uniquely characterized by focal pyogenic complications that might not be apparent clinically. We investigated the benefit of adding fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) in the workup of patients with SAB.

Methods. In a matched-cohort study patients with SAB (intervention group) were prospectively recruited to undergo FDG-PET/CT 7–14 days after diagnosis. Treatment was directed by FDG-PET/CT findings. Clinical outcomes were compared with a control group of patients with SAB who had not undergone FDG-PET/CT, matched by age, Charlson score, methicillin susceptibility, and survival duration to FDG-PET/CT. The primary outcome was 90-day mortality. Residual confounding was controlled through regression analyses.

Results. During the study period 149 patients with 151 separate episodes of SAB underwent FDG-PET/CT and were compared with 150 matched patients with 151 SAB episodes. Patients in the intervention group acquired infections more frequently in the community and had less frequently solid malignancies and more frequently high-risk SAB. Ninety-day mortality in the intervention group was significantly lower than in the control group (21/151 [13.9%] vs 43/151 [28.5%], $P = .002$). The difference remained significant in a subgroup analysis of patients with community-onset infections without malignancy and among patients with low-risk SAB. Controlling for other risk factors for mortality, FDG-PET/CT performance among all patients was independently associated with lower mortality (OR, .39; 95% CI, .18–.84). Patients in the intervention group had longer duration of treatment and more focus control procedures performed compared with the control group.

Conclusions. FDG-PET/CT in patients with SAB seems to improve survival through guidance of treatment duration and co-interventions.

Keywords. *Staphylococcus aureus* bacteremia; FDG-PET/CT; mortality; focal infection; complication.

Complications *of Staphylococcus aureus* bacteremia (SAB) are frequent and serious, including infective endocarditis, vascular infections, osteomyelitis, and other deep-seated infections. This is due to the tendency of *S. aureus* for localization in tissues and foreign bodies, creating a nidus of persistent infection. Accordingly, the management of SAB is unique among all bloodstream infections, with current guidelines recommending routine repeat blood cultures, the performance of echocardiography for all patients, and prolonged therapy of 4 to 6 weeks (compared with 7 days for gram-negative bacteremia [1]) unless, rarely, the patient fulfills criteria for low-risk SAB [2, 3]. Criteria for shortening treatment duration for SAB vary between different guidelines. Despite these practice recommendations, mortality following SAB remains between 20% and 40% in recent studies [4, 5]. A possibility exists that the current strategies are not sensitive enough to detect all foci of infection with SAB that necessitate surgical interventions or tailoring of antibiotic treatment.

Fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) has been proposed as an imaging modality to diagnose focal infections in SAB in recent observational studies [6–9]. Recommendations on use of FDG-PET/CT for diagnosis of complications seen in SAB are variable. The European guidelines for endocarditis published in 2015 endorse FDG-PET/CT (or radiolabeled white blood cell single-photon emission computed tomography [SPECT/CT]) in the diagnostic algorithm of prosthetic valve endocarditis [10], but the American guidelines published at the same time state that the evidence is insufficient to recommend on FDG-PET/CT for diagnosis of endocarditis [11]. FDG-PET/CT has been recommended as an alternative imaging modality in

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native vertebral osteomyelitis [12] and vascular graft infection [13]. All recommendations are weak given the lack of strong evidence for diagnostic accuracy or impact.

In the present interventional study, we assessed the role of integrating FDG-PET/CT in the diagnostic investigation of SAB and the effect of FDG-PET/CT on clinical outcomes.

METHODS

Study Design and Location

This was a prospective, interventional, matched-cohort study conducted at Rambam Health Care Campus, a primary and tertiary 960-bed university-affiliated hospital.

Participants

Adult patients (age >18 years old) with SAB, defined as at least 1 positive blood culture in monobacterial bacteremia and at least 2 blood culture bottles in polymicrobial bacteremia with clinical signs of infection, were enrolled. Patients were eligible for inclusion for every new episode of SAB. A new episode was defined if it happened more than 6 months after the end of treatment of the previous episode. Exclusion criteria included pregnancy and patients with survival expectation of less than 1 week.

Intervention Group

The intervention group included consenting patients recruited to undergo FDG-PET/CT in an interventional study (NCT02476487), 7–14 days after the diagnosis of SAB, and patients who underwent FDG-PET/CT as part of physicians' clinical decision (clinical indication) between 1 July 2015 and 15 February 2019. Results of the FDG-PET/CT were available to clinicians in real time to direct patient management. We encouraged direction of treatment by FDG-PET/CT results. Among patients considered for a short course of antibiotic treatment, treatment was prolonged if FDG-PET/CT demonstrated a focus of residual infection. Among patients planned for prolonged antibiotic treatment, antibiotics were stopped at 2 weeks if FDG-PET/CT was normal. However, the final treatment decision was left to the discretion of the treating physician.

Matched Control Group

Patients undergoing FDG-PET/CT (intervention group) were matched to patients with SAB who had not undergone FDG-PET/CT between 1 January 2015 and 31 December 2018. Matching was performed hierarchically according to the following criteria. Criteria 2 and 3 were skipped if no eligible match could be found.

1. Control survived at least for the same number of days as the number of days from the first positive blood culture and the day the FDG-PET/CT was performed among cases.
2. Methicillin susceptibility, ie, methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) concordance.
3. The ability to provide informed consent.
4. Charlson's comorbidity score based on a score computed in the hospital registry based on discharge diagnoses, ±3, choosing the best match.
5. Age in range of ±10 years, choosing the best match.

FDG-PET/CT Acquisition, Interpretation, and Analysis

PET/CT imaging (Discovery 690; GE Healthcare) was performed approximately 60 minutes after intravenous (IV) injection of 0.14 mCi/kg of F-18-FDG. Oral and IV contrast media were administered unless contraindicated. In order to suppress physiological FDG uptake in normal myocardium, patients were instructed to keep a low-carbohydrate and fat and protein-enriched diet for 12 hours followed by a prolonged fasting of 12–14 hours prior to the PET/CT scan. Blood glucose levels were measured before administration of the radiotracer. Patients underwent eye-to-midthigh PET/CT, with head and lower limb scanning added when clinically indicated. PET/CT images were reviewed in axial, coronal, and sagittal planes on a dedicated workstation (Xeleris; GE Healthcare).

All FDG-PET/CT studies were interpreted by a nuclear medicine physician with access to clinical information and previous imaging reports. Sites of nonphysiological increased radiotracer activity were recorded. The final diagnosis of infection was made in consultation with the referring clinical team.

Outcomes

We defined 90-day all-cause mortality as the primary outcome. Secondary outcomes included all-cause mortality at 30 days, 6 months, and relapse defined as a clinical relapse of infection with a phenotypically identical *S. aureus* isolated from any site (excluding colonization) within 6 months after end of treatment.

Data Collection and Variable Definitions

A dataset for this analysis was prospectively designed. Data were collected from patients' computerized health records. Mortality data postdischarge are updated in the hospital's health records from the national registry.

Place of acquisition was defined as nosocomial if bacteremia onset occurred more than 48 hours after admission, healthcare associated if patients were on chronic hemodialysis or home intravenous treatment, or hospitalized in 90 days preceding index admission; otherwise, it was defined as community acquired. Polymicrobial bacteremia was defined if any other clinically significant pathogen was isolated from blood cultures taken 7 days pre/post start of SAB. Prolonged bacteremia was defined as

positive blood culture after at least 72 hours after start of appropriate treatment. High-risk SAB was defined if community acquired, patient had prolonged bacteremia, or fever lasted more than 72 hours after start of appropriate treatment [14].

Statistical Analysis

We compared patients undergoing FDG-PET/CT with control patients and those who died with those who survived. Dichotomous and categorical data were compared using a chi-square test and continuous data using a *t* test for normal distribution (expressed by means and standard deviations) and Mann-Whitney *U* test for skewed data (expressed by medians and 25–75% percentiles). Post hoc subgroup analyses were performed excluding the 25 patients undergoing FDG-PET/CT as part of the clinical routine (and their 25 matched pairs), for patients with low- and high-risk SAB, and for patients with community-onset SAB without solid malignancies (due to imbalance in these variables despite matching). Variables significant on the univariate analysis and not clinically or statistically highly correlated were entered into a backward stepwise logistic regression (removal/entry probabilities, 0.1/0.05) to assess the adjusted association between FDG-PET/CT performance and 90-day mortality. We also performed Cox regression for 90-day survival. Analyses were conducted using SPSS version 24 (IBM Corporation).

The study was approved by the local hospital ethics committee. Patients provided written informed consent for the intervention study, and anonymized retrospective data collection was approved without informed consent for patients observed without intervening.

RESULTS

We included 149 patients with 151 separate episodes of SAB undergoing FDG-PET/CT, of whom 124 patients (126 episodes) were recruited in the interventional study and 25 patients (25 episodes) underwent FDG-PET/CT by clinical indication. The

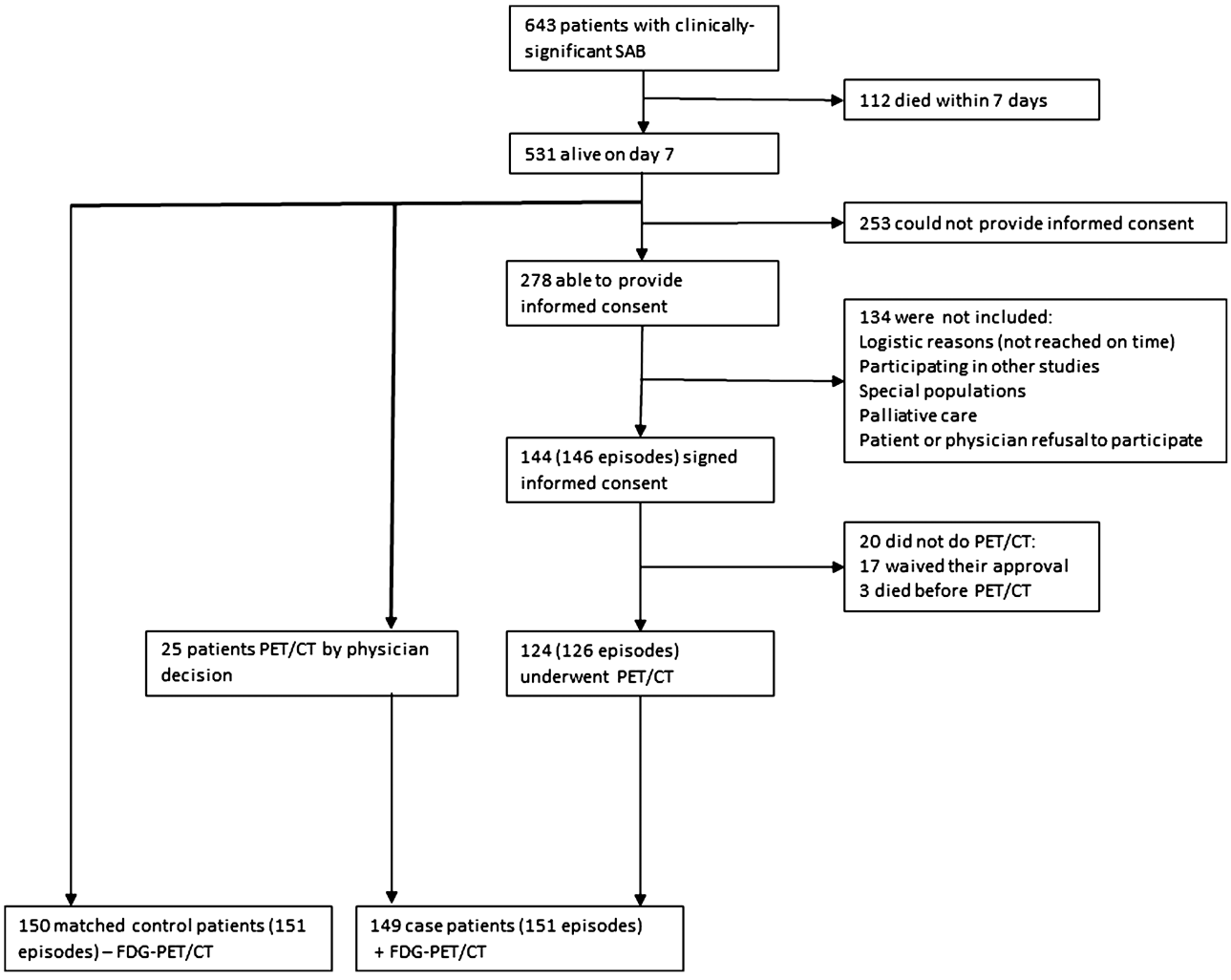

Figure 1. Study flow. Abbreviations: FDG-PET/CT, fluorodeoxyglucose–positron emission tomography/computed tomography; PET/CT, positron emission tomography/computed tomography; SAB, *Staphylococcus aureus* bacteremia.

control group included 150 matched patients with 151 separate episodes of SAB who had not undergone FDG-PET/CT (Figure 1). Compared with patients with SAB excluded from the case-control cohort, patients included in our cohort were younger, more frequently male, had lower Charlson scores, had more frequently community-acquired SAB and MSSA, and survived the first week (Supplementary Table 1). All differences except for patients' sex are explained by the requisite informed-consent ability in the case-control groups.

FDG-PET/CT was performed at a median of 11 (8–13) days after the first positive blood culture in the intervention group. Positive findings suggestive of at least 1 infectious focus were observed in 107 episodes (70.8%), with additional inconclusive results in 6 episodes (3.9%). Involvement of a single organ was observed in 66 cases (61.6% of positive cases), while in 41 cases (38.4%) more than 1 organ system was observed (Table 1). The most common focus was bone and joint including spinal and skeletal osteomyelitis, septic arthritis, and prosthetic joint infections. Other common foci involved skin/soft tissue and the lungs. New findings detected first by FDG-PET/CT were observed in 72 of 107 positive episodes (67.2%). Focus control interventions following FDG-PET/CT occurred in 27 of 151 episodes (17.9%).

Comparing between the study groups, the matching criteria (ie, age, methicillin susceptibility of *S. aureus*, ability to provide informed consent, and Charlson comorbidity score) were almost identical (Table 2). Most other background conditions were also well balanced, except for community- or healthcare-associated acquisition of bacteremia, which was more common in the FDG-PET/CT intervention group, and solid malignancies, which were less common among the intervention group. Infection characteristics were also overall balanced (Table 3), but patients in the intervention group had a significantly higher frequency of prolonged bacteremia (44/151 [29.1%] >3 days vs 25 [16.6%] among controls). Consequently, more patients in the intervention group were defined as high-risk bacteremia and more underwent echocardiography. There was no significant difference in the frequency of infective endocarditis between groups.

Ninety-day mortality in the intervention group was significantly lower compared with the control group (21 [13.9%] vs 43 [28.5%], respectively; $P = .002$). A significant difference in mortality was also observed after 30 days and 6 months (Table 3). Relapse rates were low in both groups. Patients who underwent FDG-PET/CT had undergone more interventions throughout the bacteremia course, received longer durations of antimicrobial treatment, and had longer hospitalizations after bacteremia onset (Table 3).

Factors associated with mortality on univariate analysis are shown in Supplementary Table 2. Adjusting for the significant noncorrelated variables entered into the multivariable analysis, FDG-PET/CT performance was significantly associated with lower 90-day mortality (odds ratio [OR], .39; 95% confidence interval [CI], .18–.84; $P = .016$) (Table 4). Other significant independent factors included age, Charlson score, Pitt score, prolonged bacteremia, and fever on appropriate treatment, which were associated with mortality, while transesophageal echocardiography performance and normal functional status were associated with survival. The model had good discrimination with an area under curve of .85 (95% CI, .79–.9) (Supplementary Figure 1). The adjusted hazard ratio (HR) for 90-day mortality with FDG-PET/CT was .42 (95% CI, .22–.73) (survival curve shown in Figure 2).

On subgroup analyses, the mortality difference between groups was maintained for patients with community-onset SAB without solid malignancies, low-risk and high-risk bacteremia, and excluding the 25 case patients who underwent FDG-PET/CT by clinical indication and their matched controls (Supplementary Table 3). In the latter subgroup, the adjusted HR for 90-day mortality for patients who underwent FDG-PET/CT was .45 (95% CI, .24–.85). Due to small numbers, we did not proceed to adjusted analyses for the other subgroups,

Table 1. Infectious Sites Detected by FDG-PET/CT in the Intervention Group According to Clinical Suspicion Before FDG-PET/CT

		Results According to FDG-PET/CT			
Site of Infection	Suspected Before FDG-PET/CT	Excluded by FDG-PET/CT	Confirmed by FDG-PET/CT	Newly Diagnosed by FDG-PET/CT	Number of Cases (% of Total Cases) as Detected by FDG-PET/CT
Bone and joint	37	10	27	31	58 (38.4)
Skin and soft tissue	42	22	20	15	35 (23.1)
Muscles	…	…	…	16	16 (10.6)
Vascular-extracardiac	4	1	3	17	20 (13.2)
Cardiac	17	10	7	2	9 (5.9)
Internal organs (abdomen, pelvis, thorax)	…	…	…	9	9 (5.9)
Lungs	9	5	4	28	32 (21.1)
No focus identified	27	16	11	27	38 (25.1)

N = 151. Sum of diagnoses is >100% due to multiple foci detected.

Abbreviation: FDG-PET/CT, fluorodeoxyglucose–positron emission tomography/computed tomography.

Table 2. Baseline Characteristics of Patients (Intervention and Control Groups)

Variable	Intervention Group (+ FDG-PET/CT) (N = 151)	Control Group (– FDG-PET/CT) (N = 151)	*P*
Male	108 (71.5)	104 (68.9)	.61
Age,[a] years	60.19 ± 16.07	60.30 ± 16.04	.954
Charlson comorbidity score[a]	6 [3, 8]	6 [3, 9]	.864
Unable to sign informed consent	6 (4)	10 (6.6)	.304
Admission from			.447
Home	90 (59.6)	82 (54.3)	
LTFC	49 (32.5)	51 (33.8)	
Other hospital	12 (7.9)	18 (11.9)	
Place of SAB acquisition			.001
Community	52 (34.4)	34 (22.5)	
Healthcare associated	59 (39.1)	51 (33.8)	
Nosocomial	40 (26.5)	66 (43.7)	
Normal basic functional status	123 (81.5)	124 (82.1)	.881
Basic mental status			.621
Normal	141 (93.4)	41 (93.4)	
Dementia	6 (4)	8 (5.3)	
Other	4 (2.6)	2 (1.3)	
Surgical department admission	30 (19.9)	40 (26.5)	.173
Congestive heart failure	24 (15.9)	27 (17.9)	.64
End-stage kidney disease	16 (10.6)	13 (8.6)	.558
Diabetes	74 (49)	59 (39.1)	.082
Chronic pulmonary disease	15 (9.9)	14 (9.3)	.845
Solid malignancy	14 (9.3)	29 (19.2)	.014
Leukemia	4 (2.6)	4 (2.6)	1
Lymphoma	6 (4)	8 (5.3)	.58
Intravenous drug user	5 (3.3)	6 (4)	.759
Any prosthetic device	37 (24.5)	24 (15.9)	.062
Cardiac prosthetic device (valve/CIED)	25 (16.6)	15 (9.9)	.09
Immunosuppressive treatment	38 (25.2)	40 (26.5)	.793
Any CVC existence during bacteremia onset	32 (21.2)	33 (21.9)	.889

Data are presented as means ± SDs, medians [Q1, Q3], or n (%).

Abbreviations: CIED, cardiac implanted electrical device; CVC, central vascular catheter; FDG-PET/CT, fluorodeoxyglucose–positron emission tomography/computed tomography; LTCF, long-term care facility; Q, quartile; SAB, *Staphylococcus aureus* bacteremia.

[a]Matching variable.

but there were no statistically significant baseline differences between patients who did or did not undergo FDG-PET/CT in all subgroup analyses. The difference in mortality was more marked among low-risk than among high-risk patients with SAB (unadjusted ORs [95% CI], .27 [.10–.72] and .44 [.20–.98], respectively). In the FDG-PET/CT group, 67 (44.4%) patients had low-risk SAB, of whom 41 (61.2%) had findings suggestive of infectious foci, and 84 (55.6%) had high-risk SAB, of whom 56 (66.7%) had infectious foci on FDG-PET/CT.

DISCUSSION

In the present study we evaluated the benefit of integrating FDG-PET/CT in the diagnostic workup of SAB and found it to be associated independently with lower mortality. FDG-PET/CT performance revealed new focal infections in more than two-thirds of patients in the intervention group, leading to significantly longer duration of antimicrobial treatment and more interventions including debridement and drainage of focal infections as well as extraction of foreign bodies. These findings highlight the benefit of earlier diagnosis and consequently appropriate treatment of focal infections in SAB.

Several previous studies reported the performance of FDG-PET/CT among patients with SAB (Supplementary Table 4) [6–9] . Only one was prospective; all 3 comparative studies showed an association between FDG-PET/CT performance and lower mortality adjusting for confounders. We observed lower mortality in patients who underwent FDG-PET/CT, similar to that observed in previous studies, with the same limitation of the observational design of all studies to date. Physicians may opt to perform FDG-PET/CT in patients with a better prognosis. To control for this, we used matching for important baseline prognostic factors and multivariable analysis for residual confounding. Through subgroup analyses we addressed residual differences between groups (solid malignancies and nosocomial SAB were more common among controls) and attempted to define subgroups benefitting more or less from FDG-PET/

Table 3. Clinical Presentation, Course, and Outcome of *Staphylococcus aureus* Bacteremia in the Intervention and Control Groups

Variable	Intervention Group (+ FDG-PET/CT) (N = 151)	Control Group (– FDG-PET/CT) (N = 151)	*P*
MRSA[a]	34 (22.5)	33 (21.9)	.89
Fever duration before start of treatment, days	1 [0, 2]	1 [0, 1]	.159
Pitt bacteremia score	2 [0, 3]	2 [0, 3]	.49
Suspected source of SAB at onset			.73
Primary	63 (41.7)	52 (34.4)	
CVC related	14 (9.3)	20 (13.2)	
Phlebitis	27 (17.9)	31 (20.5)	
Cellulitis or other SSTI	23 (15.2)	24 (15.9)	
Other focus	12 (7.9)	10 (6.6)	
Infective endocarditis without other focus	12 (7.9)	14 (9.3)	
C- reactive protein, mg/dL	21.95 [11.30, 30.72] (n = 109)	20.55 [9.73, 28.68] (n = 95)	.54
CVC extraction within 3 days			.823
No CVC	119 (78.8)	118 (78.1)	
CVC not extracted	14 (9.3)	12 (7.9)	
CVC extracted	18 (11.9)	21 (13.9)	
Appropriate treatment within 24 hours	80 (53)	91 (60.3)	.20
Positive blood cultures >3 days on appropriate treatment	44 (29.1)	25 (16.6)	.009
Negative follow-up blood cultures within 3 days of appropriate treatment	53 (35.8)	58 (40.6)	.404
Polymicrobial BSI (7 days pre/post SAB onset)	12 (7.9)	14 (9.3)	.682
Fever >3 days after start of appropriate treatment	14 (9.3)	11 (7.3)	.531
High-risk SAB	84 (55.6)	55 (36.4)	.001
TEE performed	133 (88.7)	90 (61.2)	.001
Infective endocarditis	31 (20.5)	29 (19.2)	.773
Any intervention after bacteremia	33 (21.9)	18 (11.9)	.021
Days between bacteremia to first intervention	9 [2, 16]	3 [1, 9]	.056
Duration of appropriate treatment, days	42 [19, 50]	19 [15, 38]	.0001
Duration of hospitalization after bacteremia, days	21 [16, 39]	17 [12, 29]	.002
90-Day mortality	21 (13.9)	43 (28.5)	.002
30-Day mortality	6 (4)	20 (13.2)	.004
6-Month mortality	35 (23.2)	53 (35.1)	.023
Relapse	5 (3.3)	4 (2.6)	.735

Data are presented as means ± SDs, medians [Q1, Q3], or n (%).

Abbreviations: BSI, bloodstream infection; CVC, central vascular catheter; FDG-PET/CT, fluorodeoxyglucose–positron emission tomography/computed tomography; MRSA, methicillin-resistant *Staphylococcus aureus*; SAB, *Staphylococcus aureus* bacteremia; SSTI, skin and soft tissue infection; TEE, transesophageal echocardiography.

[a]Matching variable.

CT. Mortality was lower with FDG-PET/CT in all analyses, and we could not define a certain subgroup that derives the benefit. Specifically, the association with lower mortality was larger in patients with low-risk SAB compared with those with high-risk bacteremia (defined by community acquisition, persistent SAB, or prolonged fever).

We found a high rate of infectious foci newly detected by FDG-PET/CT that otherwise would have been missed or, in the best-case scenario, diagnosed with delay, both in low-risk and high-risk SAB: skeletal (bone and joint) involvement was detected in 58 of 151 episodes (38.4%), of which they were not clinically suspected in 31 cases (53%); pulmonary involvement was observed in 32 cases (21.1%), of which it was suspected in only 4 episodes before FDG-PE/CT; and vascular infection was diagnosed for the first time by FDG-PET/CT in 17 out of 20 patients. Multiple foci were detected simultaneously in 41 (38.3%) patients. These findings are similar to those from the previous studies performing FDG-PET/CT in SAB or gram-positive bacteremia (Supplementary Table 4) [7–9]. The most frequent findings in these studies were bone and joint infections and, as in our study, a surprising rate of pulmonary involvement in SAB. In an earlier study 11 of 111 (9.9%) had spondylodiscitis [15]. Findings on FDG-PET/CT led to prolonged antimicrobial treatment and performance of interventions in our study. Detection of new infectious foci might be the explanation linking FDG-PET/CT to reduced mortality in SAB, through better management. This includes earlier interventions, better targeted antimicrobials, such as adding clindamycin in bone infections or anti-biofilm drugs in foreign body infections that cannot be extracted, and antibiotic treatment prolongation. Conversely, FDG-PET/CT had good performance in excluding infectious focus in high-risk SAB, allowing safe shortening of antibiotic treatment in a small cohort of 36 patients from 2 centers in the Netherlands [16].

Table 4. Multivariate Logistic Regression Analysis of 90-Day Mortality

Variable	OR [95% CI]	*P*
Age	1.03 [1.00–1.06]	.015
Charlson comorbidity score	1.11 [1.01–1.23]	.028
Normal functional status	.37 [.17–.80]	.011
Place of SAB acquisition		
Community	Reference	
Healthcare associated	1.87 [.68–5.14]	.22
Nosocomial	3.23 [1.23–8.46]	.017
Admission to surgical department	.52 [.19–1.41]	.20
Pitt bacteremia score	1.29 [1.10–1.51]	.002
TEE performance	.4 [.18–.85]	.018
Fever after 3 days on appropriate treatment	6.88 [2.11–22.39]	.001
Solid malignancy	1.34 [.54–3.33]	.52
Staphylococcus aureus susceptibility		
Penicillin susceptible	Reference	
Methicillin susceptible	1.41 [.56–3.57]	.45
Methicillin resistant	1.48 [.51–4.27]	.46
Concomitant polymicrobial BSI	2.22 [.81–6.08]	.12
Infective endocarditis	1.9 [.86–4.17]	.10
Bacteremia after 3 days on appropriate treatment	2.69 [1.22–5.92]	.014
Any intervention after bacteremia	.7 [.21–2.36]	.57
FDG-PET/CT performance	.39 [.18–.84]	.016

Abbreviations: BSI, bloodstream infection; CI, confidence interval; FDG-PET/CT, fluorodeoxyglucose–positron emission tomography/computed tomography; OR, odds ratio; SAB, *Staphylococcus aureus* bacteremia, TEE, transesophageal echocardiography.

FDG-PET/CT is a costly diagnostic modality, but perhaps not relative to the total costs of SAB, it was recently estimated to range between $32 347 and $36 134 in US hospitals between 2010 and 2014 [17]. Furthermore, while potentially reducing mortality, FDG-PET/CT increases the crude cost of patient management through required interventions, treatment, and possible hospitalization prolongation. A cost-effectiveness analysis based on the prospective clinical study conducted in the Netherlands between 2005 and 2008 concluded an incremental cost-effectiveness ratio of $72 487 (95% CI, $11 388–$323 379) to prevent 1 fatality by the addition of FDG-PET/CT [18]. This was considered as cost-beneficial in the Netherlands. However, further cost-effectiveness analyses considering contemporary costs are needed.

Limitations of our study include the baseline differences between the intervention and control groups, although most differences were in favor of better outcomes in the control group and yet the mortality was significantly lower in the intervention group. Other limitations include the retrospective data collection in the control group, a fact that might have affected our data quality. We observed an overall low relapse rate. In the intervention cohort, patients were followed up prospectively; the lack of difference in relapse rates between groups might be true or might hide a benefit for FDG-PET/CT masked by missed detection among controls. Echocardiography was not performed in all patients and was performed more frequently in patients undergoing FDG-PET/CT. However, this can be explained by the higher incidence of high-risk bacteremia among them, biasing results against the intervention. In contrast

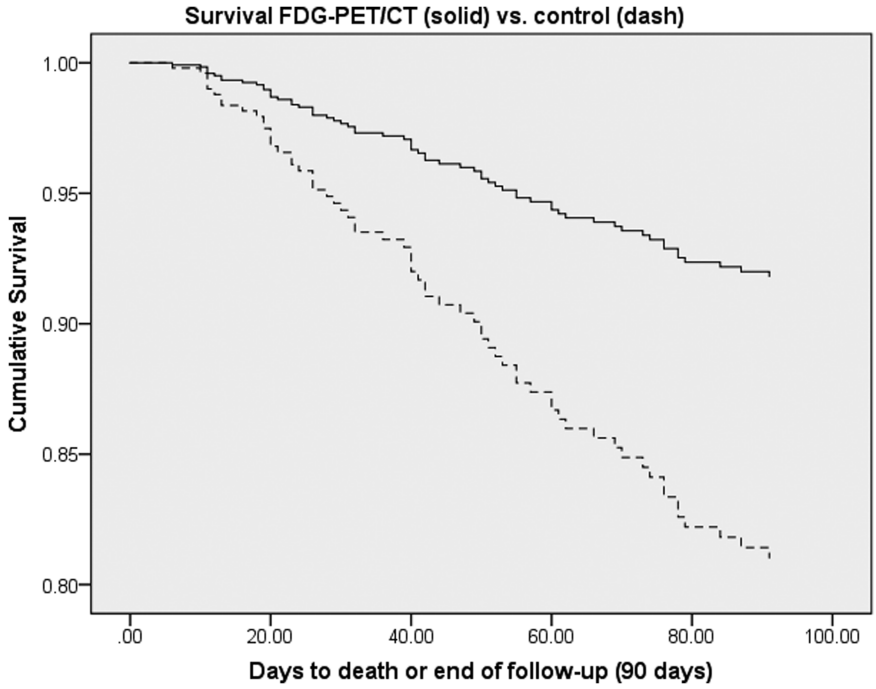

Figure 2. Ninety-day survival curves of the Cox regression model for the intervention (+ FDG-PET/CT) and control (– FDG-PET/CT) groups. Abbreviation: FDG-PET/CT, fluorodeoxyglucose–positron emission tomography/computed tomography.

to what is widely accepted as a risk factor for complications and mortality in SAB [14, 19], community acquisition in our study was associated with better survival. A similar finding was reported in a recent large multinational study [5]. Finally, this was a single-center study.

To summarize, integrating FDG-PET/CT in the diagnostic workup of SAB seems to improve survival. The benefit might be mediated by infective foci detection, earlier interventions to control infection, prolongation of antimicrobial treatment, and possibly optimized antimicrobial treatment for deep infections. Ultimately, only a randomized controlled trial (RCT) will provide proof of effects. A question arises whether an RCT is needed and ethical with the current knowledge. Better identification of patients who will benefit from FDG-PET/CT in SAB needs further evaluation.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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