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Positive Impact of [18F]FDG-PET/CT on Mortality in Patients With *Staphylococcus aureus* Bacteremia Explained by Immortal Time Bias

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(See the Editorial Commentary by Lee et al. on pages 16–8.)

Background. Several studies have suggested that in patients with *Staphylococcus aureus* bacteremia (SAB) [18F] fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG-PET/CT) improves outcome. However, these studies often ignored possible immortal time bias.

Methods. Prospective multicenter cohort study in 2 university and 5 non-university hospitals, including all patients with SAB. [18F]FDG-PET/CT was performed on clinical indication as part of usual care. Primary outcome was 90-day all-cause mortality. Effect of [18F]FDG-PET/CT was modeled with a Cox proportional hazards model using [18F]FDG-PET/CT as a time-varying variable and corrected for confounders for mortality (age, Charlson score, positive follow-up cultures, septic shock, and endocarditis). Secondary outcome was 90-day infection-related mortality (assessed by adjudication committee) using the same analysis. In a subgroup-analysis, we determined the effect of [18F]FDG-PET/CT in patients with high risk of metastatic infection.

Results. Of 476 patients, 178 (37%) underwent [18F]FDG-PET/CT. Day-90 all-cause mortality was 31% (147 patients), and infection-related mortality was 17% (83 patients). The confounder adjusted hazard ratio (aHR) for all-cause mortality was 0.50 (95% confidence interval [CI]: .34–.74) in patients that underwent [18F]FDG-PET/CT. Adjustment for immortal time bias changed the aHR to 1.00 (95% CI .68–1.48). Likewise, after correction for immortal time bias, [18F]FDG-PET/CT had no effect on infection-related mortality (cause specific aHR 1.30 [95% CI .77–2.21]), on all-cause mortality in patients with high-risk SAB (aHR 1.07 (95% CI .63–1.83) or on infection-related mortality in high-risk SAB (aHR for 1.24 [95% CI .67–2.28]).

Conclusions. After adjustment for immortal time bias [18F]FDG-PET/CT was not associated with day-90 all-cause or infection-related mortality in patients with SAB.

Keywords. *Staphylococcus aureus* bacteraemia; immortal time bias; [18F]FDG-PET/CT; mortality.

Staphylococcus aureus bacteraemia (SAB) is a common and frequently fatal disease [1–3]. SAB is often complicated by metastatic foci of infection such as endocarditis, vertebral osteomyelitis, and deep tissue abscesses, which may not be clinically apparent during initial evaluation. Presence of these metastatic foci warrants extended treatment with antimicrobial therapy and evaluation for potential source control interventions. [18F] fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG-PET/CT) is an imaging modality that can detect these metastatic foci, and several studies have indicated that therapeutic management guided by [18F]FDG-PET/CT imaging is associated with decreased mortality in patients with SAB [4–6]. However, the effect estimates were remarkably large, with adjusted odds-ratios (aOR) of 0.28 and 0.41 for 3 month all-cause mortality [4, 5], which raises questions about the validity of the results, as a diagnostic test alone is unlikely to greatly reduce mortality unless its findings result in a live saving intervention that would not have been performed otherwise. Indeed, a recent systematic review identified 5 studies examining the effect of [18F]FDG-PET/CT and concluded that all had either severe or moderate risk of bias, such as confounding by indication and immortal time

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bias, which may skew the results in favor of [18F]FDG-PET/CT [7, 8]. Immortal time bias might be especially important in studies examining the effect of [18F]FDG-PET/CT on mortality, as patients who did undergo [18F]FDG-PET/CT lived long enough to undergo the procedure. This immortal time bias may lead to false conclusions about efficacy of an intervention [9–11]. In this study, we examined the effects of [18F]FDG-PET/CT on mortality in a large cohort of patients with SAB while controlling for confounding and immortal time bias.

METHODS

Study Setting and Participants

We used data from the Improved Diagnostic Strategies in *Staphylococcus aureus* bacteremia (IDISA) cohort study, which has been described in detail elsewhere [12]. In short, IDISA was a prospective cohort study in 2 university and 5 non-university hospitals that recruited consecutive patients aged 18 years and older with ≥1 blood cultures positive for *Staphylococcus aureus*. The inclusion period was from August 2017 through September 2019. Written informed consent was obtained from all patients. Patients who died before informed consent could be obtained were also included as appropriate under Dutch law. The Medical Ethics Committee of the Academic Medical Centre Amsterdam approved this study (METC2017_094). This study is registered in the Netherlands Trial Register under trial code 6669. For the current analysis, patients who died within 48 hours of collection of the first positive blood culture were excluded, as [18F]FDG-PET/CT is highly unlikely to be feasible in these patients. This study is reported using the STROBE guidelines for reporting of observational studies [13].

Data Sources, Variables, and Procedures

Demographic and clinical data were collected from the electronic health records by the research physician and trained junior researchers. Place of acquisition was defined as proposed by Friedman, endocarditis was diagnosed according to the modified Duke criteria, and ranked focus of infection as defined by Kaasch [2, 14, 15]. We used the Sepsis-3 criteria for defining sepsis and septic shock [16]. All hospitals had an active antimicrobial stewardship team that performed bedside consultations in all patients with SAB.

[18F]FDG-PET/CT was available at all hospitals and was performed at the discretion of the treating physician but was not a mandatory procedure in the work-up of SAB. A low-carbohydrate diet was recommended in all hospitals as standard preparation before [18F]FDG-PET/CT. Follow-up duration was 90 days after the first day of bacteremia. Follow-up was conducted through telephone interview with the patient and, if they could not be reached, through contact with their primary care physician or by checking the electronic health records. In patients lost to follow-up, vital status was confirmed using municipal death records.

Outcome

Primary outcome was 90 day all-cause mortality. Secondary outcome was 90-day infection-related mortality. Mortality was considered infection-related if patients died from direct complications of infection (e.g., septic brain haemorrhage, death following infection control surgery) or in case of persistent signs of infection (ongoing fever, persistent positive blood cultures, leucocytosis, elevated c-reactive protein (CRP) at the time of death, as determined by an adjudication committee of 2 independent infectious disease specialists based on all available data [17]. The adjudication was done without prior knowledge of the research question for present study.

Statistical Analysis

We analysed the effect of [18F]FDG-PET/CT on 90-day all-cause mortality using a Cox proportional hazards model. To correct for immortal time bias, [18F]FDG-PET/CT was modelled as a time-varying covariate, which means that all patients were part of the no-[18F]FDG-PET/CT group until they underwent [18F]FDG-PET/CT. We did not use a lag-time after performance of [18F]FDG-PET/CT. To control for confounders, we corrected for factors with known influence on death: age, Charlson comorbidity index, positive follow-up blood cultures at 48 hours, septic shock at presentation, and presence of endocarditis [3, 18]. These variables were previously found to be associated with all-cause mortality in this cohort [17]. We did not perform a stepwise model selection method for the current analysis. All confounders were modelled as time-fixed covariates. To demonstrate the effect of not correcting for immortal time bias, we also provided a model where [18F]FDG-PET/CT is not a time-varying covariate.

The secondary outcome was infection-related mortality at 90 days. For this outcome, non-infection related mortality is a competing risk and as such a Fine and Gray model would be appropriate. However, Fine and Gray models with a time varying covariate result in sub-distribution hazard ratios (HR) that are difficult to interpret [19]. Therefore, we calculated the cause-specific HR as normal and estimated the subdistribution hazard ratio (sHR) by modeling all patients with a competing event as having reached the maximum follow-up time without having had the event of interest (infection-related mortality). Because there was no loss to follow-up, estimates from this model approximate the sHR. The proportional hazards assumptions of the models were checked by examining the scaled Schoenfeld residuals over time. For covariates that violated the proportional hazards assumption we added a time transformation function to see if this improved fit by comparing Akaike's information criterion (AIC) for each model.

In a subgroup analysis, we determined the effect of applying [18F]FDG-PET/CT only in SAB patients with high risk of complicated SAB, defined as community acquisition of the bacteremia, fever more than 72 hours after initiation of appropriate antibiotic treatment or positive blood cultures more than 48 hours after initiation of appropriate antibiotic treatment, as defined previously [5, 20].

Because usage of [18F]FDG-PET/CT potentially differed between hospitals, a random intercept per hospital (frailty term in the Cox regression models) was added to each regression model.

Due to the prospective nature of data collection, there were no missing data on outcomes, exposure. or variables that were used in the statistical models. As such, no imputation of missing data was required.

All data were analyzed in R version 4.1.2 (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was tested at a 2-sided alpha of 0.05, and 95% confidence intervals (95% CI) are reported for all inferential statistics.

RESULTS

Included Patients

Out of 490 patients included in IDISA, 14 patients died within 48 hours of the first positive blood culture and were excluded, leaving 476 patients eligible for this research question. Of these 476 patients, 178 (37.4%) underwent [18F]FDG-PET/CT. Median time from positive blood culture to [18F]FDG-PET/CT was 9 days (interquartile range [IQR]: 6–13 days). Patients who underwent [18F]FDG-PET/CT more often had implanted prosthetic material (46% vs 35%), community-acquired bacteremia (48% vs 26%) and endocarditis or osteoarticular infection as a focus. Infectious diseases consultation and performance of echocardiography were also more common in the [18F]FDG-PET/CT group, and total treatment duration was longer (median 42 vs 16 days). Full overview of demographic and clinical characteristics is shown in Table 1.

Visual Examination of the Kaplan-Meier Curves

Visual examination of the Kaplan-Meier curves with PET-CT as a time-fixed effect shows considerable risk of immortal time bias: in the [18F]FDG-PET/CT group there are no deaths in the first 7 days after bacteremia, whereas in the no-[18F]FDG-PET/CT group 24% of deaths (25/103) occur in the first week (Figure 1).

Effect of Performing [18F]FDG-PET/CT on Patient Outcome

In crude analysis [18F]FDG-PET/CT appeared to have a protective effect on all-cause mortality, with a univariate HR of 0.59 (95% CI: .41–.86) (Table 2). After correction for known risk factors and predictors of all-cause mortality, this association remained with an adjusted Hazard Ratio (aHR) of 0.50 (95% CI: .34–.74). A model with time-transformed functions for age and Charlson comorbidity index did not result in improved model fit.

When modelling [18F]FDG-PET/CT as a time-dependent variable to correct for immortal time bias, the crude HR for [18F]FDG-PET/CT was 1.07 (95% CI: .72–1.57) (Table 2). Adding covariates (age, Charlson comorbidity index, positive follow-up blood cultures at 48 hours, septic shock at presentation, and presence of endocarditis) to the model to correct for confounding, yielded an aHR for the effect of [18F]FDG-PET/CT on all-cause mortality of 1.00 (95% CI .68–1.48). Adding time-transformed functions for age and Charlson comorbidity index did not result in improved model fit. Adding additional relevant variables (malignancy, congestive heart failure, chronic lung disease, dementia, McCabe comorbidity score, admission to surgical service) to the immortal time bias and confounder-adjusted model did not result in a meaningful change in the adjusted HR: 1.10 (95% CI .74–1.64).

Regression coefficients and their 95% CIs are reported in Supplementary Table 1.

The cause-specific aHR of [18F]FDG-PET/CT on infection-related mortality, which is a measure of the hazard after censoring for competing events (unrelated mortality), was 1.30 (95% CI .77–2.21) after correction for immortal time and confounders. The subdistribution hazard ratio, which can be interpreted as the rate of occurrence of infection-related mortality without censoring for the competing events was 1.38 (95% CI .81–2.34).

In the subgroup analysis of patients with high risk SAB (236 of 476 patients), 120 (51%) underwent [18F]FDG-PET/CT. In this subgroup, the crude HR for all-cause mortality after correction for immortal time bias was 1.22 (95% CI .73–2.04) and the aHR 1.07 (95% CI .63–1.83).

DISCUSSION

In this prospective cohort study, no association was found between performing [18F]FDG-PET/CT imaging with improved all-cause 90-day survival in patients with SAB. However, an analysis without adjustment for immortal time bias would have falsely suggested that [18F]FDG-PET/CT was associated with lower day-90 mortality.

Without adjustment for immortal time bias, the aHR of [18F]FDG-PET/CT for all-cause mortality was 0.50 (95% CI: .34–.74), which was comparable to results from previous studies that also adjusted for possible confounders such as age, comorbidity and disease severity, but not for immortal time bias [4, 21]. Ghanem-Zoubi used another approach to control for immortal time bias, by matching exposed patients (who had [18F]FDG-PET/CT) to unexposed patients who had at least survived until the time of [18F]FDG-PET/CT [5].

Table 1. Demographic and Clinical Characteristics

	No [18F]FDG-PET/CT (n = 298)	[18F]FDG-PET/CT (n = 178)	*P* Value
Demographics and comorbidities			
Sex (male)	202 (67.8)	117 (65.7)	.72
Age (median, IQR)	68 [58–77]	66 [56–75]	.48
Diabetes mellitus	95 (31.9)	57 (32.0)	1
Immunosuppressive medication	48 (16.1)	38 (21.3)	.19
HIV – AIDS	3 (1.0)	0 (0.0)	.46
Chronic renal failure	80 (26.8)	51 (28.7)	.75
Hemodialysis	16 (5.4)	12 (6.7)	.68
Chronic pulmonary disease	53 (17.8)	31 (17.4)	1.00
Congestive heart failure	86 (28.9)	43 (24.2)	.31
Malignancy	86 (28.9)	42 (23.6)	.25
Dementia	15 (5.0)	4 (2.2)	.21
Intravenous drug use	4 (1.3)	1 (0.6)	.73
Charlson comorbidity index (median, IQR)	3 [2–5]	3 [1–4]	.07
McCabe-score: rapidly fatal disease	49 (16.4)	10 (5.6)	.001
Any implanted prosthetic material	103 (34.6)	81 (45.5)	.02
Prosthetic heart valve	22 (7.4)	16 (9.0)	.65
Cardiac implantable electronic device	27 (9.1)	23 (12.9)	.24
Non-vascular prosthetic materials	47 (15.8)	46 (25.8)	.01
Prosthetic joints	31 (10.4)	32 (18.0)	.03
Place of acquisition			<.001
Community-acquired	78 (26.2)	86 (48.3)	
Healthcare-associated	94 (31.5)	61 (34.3)	
Hospital-acquired	126 (42.3)	31 (17.4)	
Surgical discipline as admitting specialty	89 (29.9)	41 (23.0)	.13
Clinical characteristics			
Septic shock	28 (9.4)	15 (8.4)	.85
qSOFA score (median, IQR)	2 [1–3]	2 [1–3]	.91
MRSA	8 (2.7)	2 (1.1)	.41
Positive blood culture at 48 hours	61 (20.5)	79 (44.4)	<.001
High-risk bacteremia	116 (38.9)	120 (67.4)	<.001
Final diagnosis[a]			<.001
Unknown	23 (7.7)	18 (10.1)	
Periperal IV infection	61 (20.5)	9 (5.1)	
CVC infection	29 (9.7)	11 (6.2)	
SSTI	26 (8.7)	13 (7.3)	
Pneumonia	34 (11.4)	8 (4.5)	
Osteoarticulair infection	46 (15.4)	51 (28.7)	
Endocarditis	35 (11.7)	51 (28.7)	
Other	44 (14.8)	17 (9.6)	
Management			
Infectious diseases consultation	222 (74.5)	160 (89.9)	<.001
TTE performed	235 (78.9)	168 (94.4)	<.001
TEE performed	92 (30.9)	108 (60.7)	<.001
Days of antibiotic treatment (median, IQR)	16 (14–30)	42 (19–50)	<.001
Source control intervention performed	100 (33.6)	79 (44.3)	.02
Outcomes			
30-day all-cause mortality	76 (25.5)	26 (14.6)	.01
90-day all-cause mortality	103 (34.6)	44 (24.7)	.03
90-day infection-unrelated mortality	48 (16.1)	16 (9.0)	.04
90-day infection-related mortality	55 (18.5)	28 (15.7)	.53

All data are n (%) unless otherwise noted.

Abbreviations: CVC, central venous catheter; [18F]FDG-PET/CT, [18F] fluorodeoxyglucose positron emission tomography/computed tomography; IQR, interquartile range; IV, intravenous line; MRSA, methicillin-resistant *Staphylococcus aureus*; qSOFA, quick Sequential Organ Failure Assessment; SSTI, skin and soft tissue infection; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a]As classified by Kaasch [2].

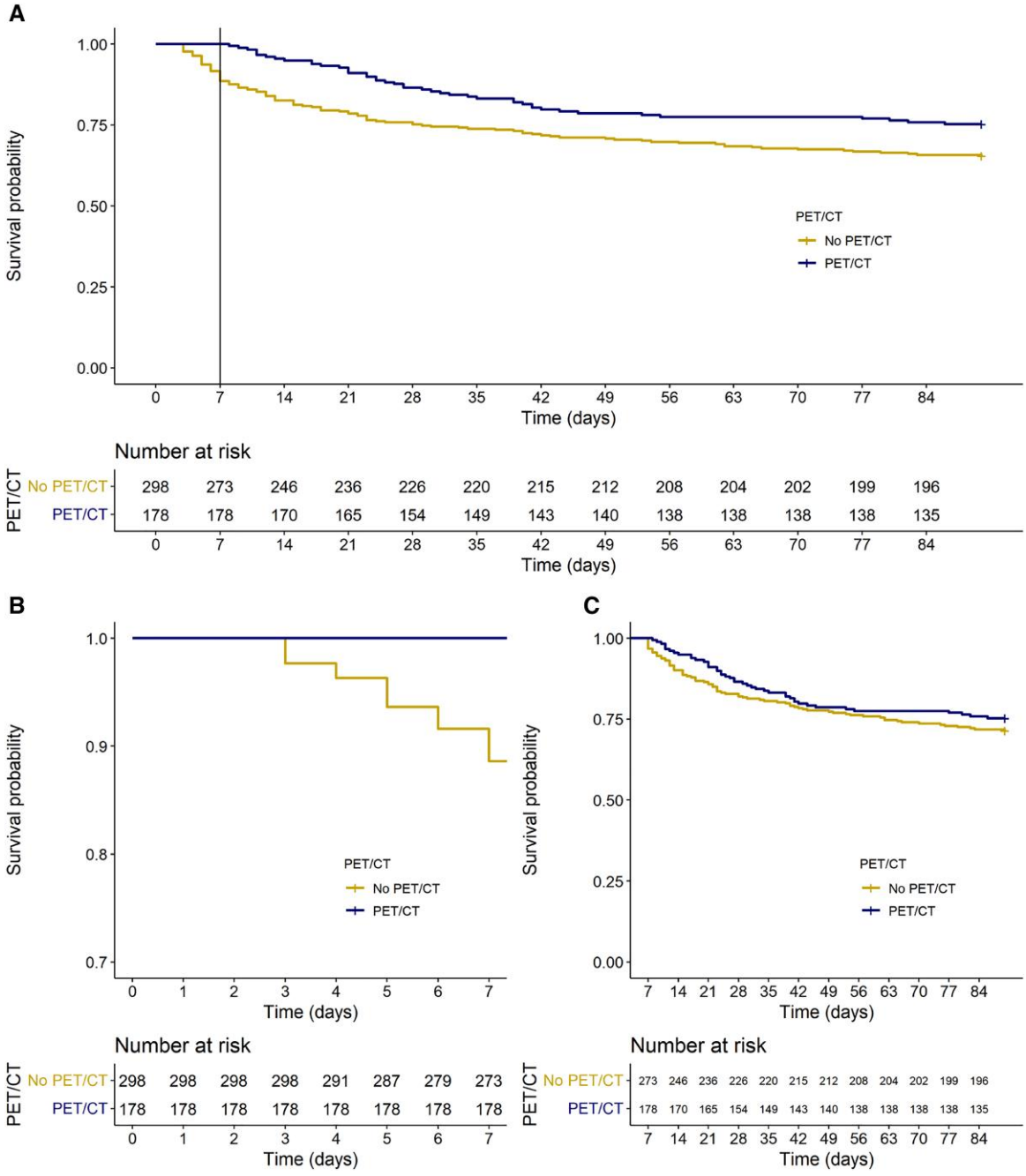

Figure 1. Kaplan-Meier survival curves with PET/CT as a time-fixed effect. *A*, The Kaplan-Meier curves with PET/CT as a time-fixed effect. *B*, Magnification of the first 7 days which clearly demonstrate risk of immortal time bias, as no deaths occur in the PET/CT group in the first 7 days, while in the no PET/CT group 24% of total deaths (n = 25) occur in the first 7 days. *C*, The effect of drawing the Kaplan-Meier curves after 7 days, demonstrating that after this time period the curves are nearly overlapping. Abbreviation: PET/CT, positron emission tomography/computed tomography.

In this study from Israel, a total of 149 patients underwent [18F]FDG-PET/CT, 25 requested by the clinical team because of a clinical indication and 124 who provided consent (with or without a clinical indication). Controls were recruited from a population that included patients unable to provide informed consent for the study-mandated [18F]FDG-PET/CT, which may have introduced selection bias. Matched controls more frequently had solid malignancies (19% vs 9%) and less frequently community-acquired infection (23% vs 34%) or high-risk SAB (36% vs 46%). [18F]FDG-PET/CT was associated with an adjusted odds ratio for day-90 mortality of 0.39 (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. Of note, most

Table 2. Effect of Correcting for Confounders (Age, Charlson Comorbidity Index, Positive Follow-up Blood Cultures, Septic Shock and Presence of Endocarditis) and Immortal Time on the Effect of [18F]FDG-PET/CT on 90-day Mortality Rates

	Crude Model HR (95% CI)	Model Corrected for Confounders aHR (95% CI)	Crude Model Corrected for Immortal Time Bias HR (95% CI)	Model Corrected for Confounders and Immortal Time Bias aHR (95% CI)
Primary outcome				
All-cause mortality	0.59 (.41–.86)	0.50 (.34–.74)	1.07 (.72–1.57)	1.00 (.68–1.48)
Secondary outcome				
Infection-related mortality: cause specific hazard ratio	0.69 (.43–1.11)	0.41 (.25–.68)	1.74 (1.05–2.90)	1.30 (.77–2.21)
Subgroup analyses—high-risk SAB (n = 236)				
High-risk SAB—all-cause mortality	0.62 (.38–.99)	0.47 (.28–.77)	1.22 (.73–2.04)	1.07 (.63–1.83)
High-risk SAB—infection-related mortality: cause specific hazard ratio	0.65 (.38–1.11)	0.42 (.24–.75)	1.51 (.84–2.71)	1.24 (.67–2.28)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; 18F]FDG-PET/CT, [18F] fluorodeoxyglucose positron emission tomography/computed tomography; HR, hazard ratio; SAB, *Staphylococcus aureus* bacteremia.

mortality took place after 30 days, when deaths are more likely to be non-infection related [22]. The contrasting results of this study and ours underline the need for a randomized evaluation of the costs and benefits of routinely performing [18F]FDG-PET/CT in patients with SAB.

Immortal time bias is an important source of bias in epidemiological research [9–11]. Attention has been drawn before to immortal time bias in *S. aureus* bacteremia studies [8, 23], but statistical methods to avoid this phenomenon are not widely used. Reexamining existing cohorts reported by previous studies while controlling for immortal time bias could be an efficient way of confirming or contradicting our results.

There is not an obvious biologically plausible explanation for decreased mortality after [18F]FDG-PET/CT in patients with SAB. Berrevoets reported that [18F]FDG-PET/CT resulted in longer treatment duration in 35% of patients with high-risk SAB who underwent [18F]FDG-PET/CT [4]. However, the vast majority of infection-related deaths occur in the first 4 weeks of infection, when antimicrobial treatment for complicated SAB is mostly ongoing irrespective of [18F]FDG-PET/CT [2, 22, 24]. Extension of antimicrobial therapy would affect mortality only after this time period. [18F]FDG-PET/CT based identification of abscesses or other undrained infectious foci could lead to better source-control intervention, which could influence mortality in this earlier stage. Indeed, 18.9% of patients in the study by Ghanem-Zoubi underwent a focus control intervention following 18[F]FDG-PET/CT and an undrained focus was reported in 19% of patients after [18F]FDG-PET/CT in the study by Berrevoets [4, 5]. But in order to explain the observed difference in mortality, the effect of these [18F]FDG-PET/CT guided source control interventions would have to be very large, which relies on the assumption that these interventions would not have taken place without [18F]FDG-PET/CT and that each of these interventions following [18F]FDG-PET/CT was indeed the 1 factor that decided whether or not the patient survived.

A recent narrative review argued that because of the reported beneficial effects of [18F]FDG-PET/CT on patient outcome, clinicians and scientific societies in the United States should advocate that this diagnostic intervention should be more widely accessible [25]. If, as evidenced by our study, [18F]FDG-PET/CT is not associated with decreased mortality, then the added value of [18F]FDG-PET/CT needs serious consideration before it is implemented as routine practice. Apart from exposure to ionizing radiation, [18F]FDG-PET/CT incurs significant costs and the possibility of finding non-infectious pathology that may not be relevant. On the other hand, [18F]FDG-PET/CT may identify patients without metastatic complications despite the presence of epidemiological or clinical risk factors, which could shorten treatment duration and decrease healthcare costs [26]. Therefore, we do not suggest that [18F]FDG-PET/CT is not useful in patients with SAB, but that further research, preferably a randomized controlled trial, will need to examine in which patients [18F]FDG-PET/CT alters treatment and whether [18F]FDG-PET/CT is a cost-effective intervention in these patients.

Strengths of our study include the sample size, completeness of data and rigorous statistical methods applied. We also examined infection-related mortality and mortality in high-risk SAB and found no effect of [18F]FDG-PET/CT in these analyses either, which supports the robustness of our findings. The main limitation of our study is that we did not examine whether [18F]FDG-PET/CT may have influenced patient management by either extending or shortening antimicrobial treatment or by leading to source control intervention. There is also the possibility of residual confounding: [18F]FDG-PET/CT may have been performed in the sickest patients only, which may have skewed the results against [18F]FDG-PET/CT. Some evidence

for confounding by indication can be seen in the median duration of treatment, which was 42 days in patients who underwent [18F]FDG-PET/CT and 16 days in patients who did not, indicating that patients in whom [18F]FDG-PET/CT was not done more often were judged to have uncomplicated bacteremia. Finally, observational studies are primarily able to demonstrate association and statements about causal inference should be interpreted cautiously.

In conclusion, after correction for immortal time bias, [18F]FDG-PET/CT does not influence all-cause or infection-related mortality in patients with SAB. Future studies need to examine in which patients [18F]FDG-PET/CT influences treatment and how such treatment impacts outcome, and should evaluate the cost-effectiveness of [18F]FDG-PET/CT. Careful attention to immortal time bias is essential in observational studies in patients with SAB—or other conditions with high mortality rates.

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

Data sharing statement. The statistical code and an anonymized data set are available from the corresponding author upon request.

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