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Original Article

Mortality in patients with high risk *Staphylococcus aureus* bacteremia undergoing or not PET-CT: A single center experience☆

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ABSTRACT

Background: *Staphylococcus aureus* bacteremia (SAB) is associated with significant morbidity and mortality. Previous studies had shown that PET/CT can be helpfull in the management of SAB, leading to reduction of mortality. Factors associated with increased or reduced mortality are not well known. Our objective was to analyze mortality in high risk SAB patients undergoing PET/CT and to identify factors associated with mortality rate.

Materials and methods: We performed a retrospective study and reviewed all cases of high risk adult SAB between 2014 and 2017. We analyzed medical records and mortality at 30 days and 90 days and 1 year.

Results: A total of 102 patients were included in whom 48 undergone PET/CT. Metastatic foci was identified in 45.8% of cases (22/48). The overall mortality rate was 31.4% (32/102). The mortality rate was 16.6% (8/48) and 44.4% (24/54) in patients undergoing or not PET/CT respectively ($P = 0.002$). There was a signicantly difference in mortality rate at 30 days ($P = 0.001$), 90 days ($P = 0.004$) and one at 1 year ($P = 0.002$) between patients undergoing or not PET/CT respectively.

In multivariate analysis only 18-FDGPET/CT, kidney failure and bacteremia of unknown origin were the 3 mains factors modifying mortality in patients with high risk SAB.

Conclusion: In our study mortality rate was reduced in high risk SAB patients undergoing PET/CT. kidney failure and bacteremia of unknown origin were other factors associtated with high mortality. Our study confirm that PET/CT is a usefull tool in the management of SAB.

1. Introduction

Staphylococcus aureus (*S. aureus*) is a leading cause of both community and healthcare -associated bacteremia [1]. *S. aureus* bacteremia (SAB) can seed to virtually any body site and result in complications that may further result in severe disease, significant morbidity and high mortality. Multiple independent risk-factors for a fatal outcome have been describe in the literature including ageing patient, immunosuppression, alcoholism,

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haemodialysis, kidney failure, septic shock, noneradicable or noneradicated foci (metastatic foci), underlying cirrhosis, cancer and methicillin resistant *Staphylococcus aureus* (MRSA) [2–6]. Known risk factors for development of metastatic infection in SAB patients are community acquisition of the bacteremia, signs of infection present for more than 48 h before initiation of appropriate antibiotic treatment, fever more than 72 h after initiation of appropriate antibiotic treatment, and positive blood cultures more than 48 h after initiation of appropriate antibiotic treatment [7,8]. Early detection of metastatic infection is crucial, because morbidity and mortality are higher in the presence of these foci, probably due to incomplete eradication during treatment [7,9]. However, metastatic infectious foci are often asymptomatic. Despite many progress made in terms of diagnosis and early initiation of appropriate antibiotherapy to reduced mortality during the last decades, there is still many challenges [10]. 18F-FDG PET/CT has been extensively used in diagnosing infectious diseases. Previous studies had shown that 18F-FDG PET/CT detected more metastatic foci and leaded to treatment modification and finally decrease relapses and mortality rate [7,11–13]. However, high risk patient are not well represented in studies and other factors affecting mortality are not well known. Our objective was to analyze mortality rate in high risk adults SAB patients undergoing or not 18F-FDG PET/CT and to identify other factors modifying mortality rate.

2. Materials and methods

2.1. Study design and patients

This was a retrospective study which was performed at a University hospital of 1000 beds in Belgium. All cases of adult SAB between January 2014 and June 2017 were reviewed. SAB was defined as 1 or more positive blood cultures for *S. aureus*. We included only high risk SAB. High risk SAB patient was defined as: signs of infection for more than 48 h before initiation of appropriate antibiotic treatment, community acquisition of the bacteremia, fever and positive blood cultures 72 h and 48 h after initiation of appropriate antibiotic treatment [8]. Exclusion criteria were the following: age <18 years old, patient with cancer, death within 48 h after the first positive blood culture, inappropriate antibiotic treatment (the inappropriateness of antibiotic was judge by infectious diseases physician). Patients were treated in collaboration with infectious diseases specialist consultant which follow the international, national and institutionnal guidelines for SAB [14,15]. All results of 18F-FDG PET/CT were reviewed by two nuclear medicine physician and one radiologist. The 18F-FDG PET/CT was performed within 1 week.

2.2. Ethical issues

Our institutional ethics committee stated that a written consent is not needed for analyses of anonymized data bases concerning data coming from routine practice, as permitted by country and European laws. Consequently, institutional ethical committee approval was granted for this study, and the committee approved this consent procedure. The institutional ethical committee give its authorization (N° CEHF 2015/17MAR/119).

2.3. Data collection

Using our institutionnal database Medical explorer v3r49b7 and the database of microbiology laboratory, we reviewed the medical records of all patients and collected the following data: age, sex, methicillin sensitive or resistant *S. aureus* (MRSA or MSSA), diagnostic investigation (echocardiography, 18-FDG PET/CT, thoraco-abdominal CT scan, cerebral CT Scan or Magnetic resonance imaging (MRI, spine MRI), past medical history, kidney function (estimated glomerular filtration (eGFr), type of infection, existence of prosthetic material or plate, presence and number of metastatic foci on 18F-FDG PET/CT, mortality at 30 days, 90 days, 1 year and overall mortality.

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 22 (SPSS Corp., Somers, New York). Chi square was used to compare the proportions and SAB patients with or without 18F-FDG PET/CT. Mortality rates were estimated by using Kaplan-Meier method. Univariate linear regression was used to evaluate the importance and significance of the relationships between the variables and survival (at 30 days, 90 days and 1 year). After univariate analysis, parameters with a $P < 0.05$ were proposed for inclusion in the multiple linear regression analysis with a forward selection procedure.

3. Results

In total 198 patients with *SAB* were analyzed and 96 patients were excluded (see flowchart Fig. 1). Finally 102 patients met our inclusion criteria. Clinical and demographic characteristics of the 102 patients are summarized in Table 1. Mean age of patients were 64.9 years old with 76.4% (N = 78) being male. In 94.1% (N = 96) SAB were due to MSSA. 18F-FDG PET/CT was performed in 47% (N = 48) of patients and a metastatic foci was identified in 45.8% of cases (N = 22/48). Clinical characteristics and the severity of bacteremia (PITT score) of the patient with or without 18-FDG PET/CT were comparable (Table 1). Localization and number of metastatic foci identified in patient with and without 18F-FDG PET/CT are shown in Table 2. The total number of metastatic foci identified in patient with and without PET/CT were 49 and 13 respectively (P = <0.00001). Most of the cases were multimetastatic site. The number of single metastatic site were 9 (4 spondilodiscitis, 1 arthritis, 3 endovascular infection, 1 mediastinitis) and 3 (1 spondilodiscitis, 2 arthritis) in patients undergoing or not 18F-FDGPET/CT respectively. In patient in whom PET/CT have not been performed, the following exams were performed: transthoracic and transesophageal echocardiography (N = 54 and 41 respectively), joint echography (N = 6), thoraco-abdominal CT scan (N = 27), spine MRI (N = 11), brain CT scan (N = 9) and brain MRI (N = 7).

3.1. 18-FDG PET/CT, age and mortality

We analyzed the relationship between mortality and 18-FDG PET/CT.The overall mortality rate was 31.4% (32/102). The mortality rate was 16.6% (8/48) and 44.4% (24/54) in patients undergoing or not 18F-FDG PET/CT respectively (P = 0.002). Using Kaplan Meier method, there was a signicantly difference in mortality rate at 30 days (P = 0.001), 90 days (P = 0.004) and 1 year (P = 0.002) between patients undergoing or not 18F-FDG PET/CT respectively (see Fig. 2).

We also analyzed mortality rate according to age (Table 3). The overall mortality rate according to age was at 15.3% (4/26), 26.9% (7/26), 27.6% (8/29) and 61.9% (13/21) in patients of age <60 years old,

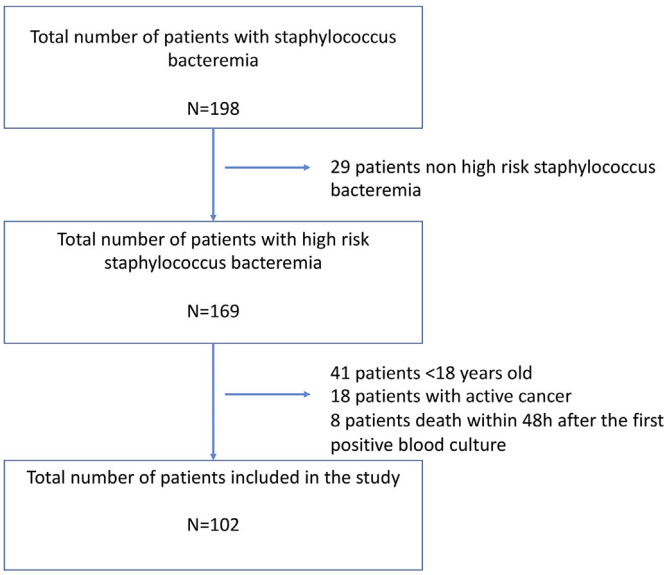

Fig. 1. Flowchart.

age 60 to <70 years old, age 70 to <80 years old and >80 years old respectively (p = 0.006). There was a significantly difference in mortality at 30 days (p = 0.009), at 90 days (p = 0.003) and at one year (p = 0.01) between these subgroup of analysis.

3.2. Univariate and multivariate analysis

Given that the overall mortality rate and the 30 days, 90 days and one year mortality rate were significantly reduced in patients undergoing 18F-FDG PET/CT, we performed an univariate analysis in order to identify which factors may contributed to difference of mortality.

Univariate analysis (Table 4) showed that kidney failure, diabetic foot infection, bacteremia of unknown origin, prosthetic or plate joint infection, septic arthritis, age and 18-FDG PET-CT were the main factors significantly modifying mortality. However when these factors were analyzed in multivariate analysis (Table 5), the 3 mains factors which remain significant were kidney failure, 18-FDG PET/CT and bacteremia of unknown origin.

4. Discussion

The main finding of our study was that in high risk SAB patients, the overall mortality rate, the 30 days, 90 days and one year mortality rate was significantly lower in the group of patient in whom 18F-FDG PET/CT was performed. However, the high mortality rate at 90 days and one year was probably due to the high mortality rate at 30 days. Therefore, PET/CT should be useful in reducing mortality within 30 days.

Previous studies had shown that 18F-FDG PET/CT had a positive impact on outcome and the management of gram positive bacteremia and it's cost effective [7,11–13,16,17]. The positive impact can been explain by the fact that 18F-FDG PET/CT detected more metastatic foci and can lead to treatment modification [7]. Metastatic foci have been associated with high mortality rate in high risk SAB [3,6]. Vos et al. [11] in a prospective study of 115 patients with high-risk Gram-positive bacteremia, showed that the addition of 18F-FDG PET/CT to standard care led to significantly more patients who were diagnosed with metastatic infection compared with a matched historical control group of 230 patients in whom no 18F-FDG PET/CT was performed (67.8% vs. 35.7% in the control group). Furthermore, 6-months mortality rate decreased from 32.2% to 19.1% when 18F-FDG PET/CT was performed. The same authors found in another study that in patients with Gram-positive bacteremia and a high risk of developing complicated infection, a structured protocol including echocardiography and FDG-PET/CT contributed to detected more metastatic infectious foci (73%, 84/115) and this can contribute to improved outcome [16]. More recently, a study in high risk SAB showed a higher detection rate of metastatic foci by 18F-FDG PET/CT (73.7%). This high rate of detection of metastatic foci lead in their study to the adaptation of treatment in patients at high risk of relapse [7]. The 3-months relapse rate was only 2.2%, which is low compared with the rates reported in the literature for complicated SAB (2.1%–23%). An important finding of their study is that patients with risk factors for metastatic infection who not undergo 18F-FDG PET/CT had a significantly higher mortality rate than those who underwent 18F-FDG PET/CT (32.7% vs. 12.1%, P < 0.003). In our study the detection

Table 1
Baseline demographics and clinical characteristics of patients.

Characteristic	No. of patients (%)	PET CT	No PET CT	P
Total (N)	102	48	54	/
Male	78 (76.4%)	35	43	0.42
Mean age	64.9	63.4 (±16.4)	66.5 (±19.2)	0.59
MSSA	96 (94.1%)	45	51	0.88
MRSA	6 (5.9%)	3	3	0.88
Diabetes mellitus	39 (38.2%)	18	21	0.88
Joint prosthesis	18 (17.6%)	7	11	0.44
Cirrhosis	5 (4.9%)	2	3	0.74
Heart device	15 (14.7%)	9	6	0.27
Kidney failure (eGFR <60 ml/min)	57 (55.8%)	29	29	0.49
Dialyse	6 (5.9%)	1	5	0.12
Immunodéprimé	15 (14.7%)	8	7	0.59
TTE	102 (100%)	48	54	NA
TEE	88 (86.3%)	47	41	0.001
18-FDG PET-CT	48 (47%)	/	/	/
PITT score* 0-1	95	44	51	0.560
2–3	7	4	3	

MSSA:Methicillin sensitive *staphylococcus aureus*, MRSA: Methicillin resistant *staphylococcus aureus*.
TTE transthoracic echocardiography, TEE: transesophageal echocardiography, NA: not applicable, eGFr:estimated glomerular filtration.
PITT score = Pitt bacteremia score graded within 48 h before or on the day of first positive blood culture. There was no patient with PITT score ⩾4.

Table 2
Localization and number of metastatic foci on 18-FDG PET-CT.

Metastatic foci identified	Patient with PET-CT (N = 48)	Patient without PET-CT (N = 54)
Spondilodiscitis	12/48 (25%)	3/54 (5.5%)
Arthritis, joint prosthesis infection and/or osteitis	16/48 (33.3%)	6/54 (11%)
Endovascular infection (excluding endocarditis)	3/48 (6.2%)	1/54 (1.8%)
Kidney	1/48 (2%)	0
Liver	1/48 (2%)	0
Lung	5/48 (10.4%)	0
Psoas Abscess	5/48 (10.4%)	2/54 (3.7%)
Sternocleidomastoid muscle	3/48 (6.2%)	0
Gluteal muscles	1/48 (2%)	1/54 (1.8%)
Endocarditis[a]	1/48 (2%)	0
Mediastinitis	1/48 (2%)	0

Note: Most of the cases were multimetastatic site. The number of single metastatic site were 9 (4 spondilodiscitis, 1 arthritis, 3 endovascular infection, 1 mediastinitis) and 3 (1 spondilodiscitis, 2 arthritis) in patients undergoing or not 18F-FDGPET/CT respectively.
[a] 18F-FDG-Pet/CT was performed without specific preparation for endocarditis.

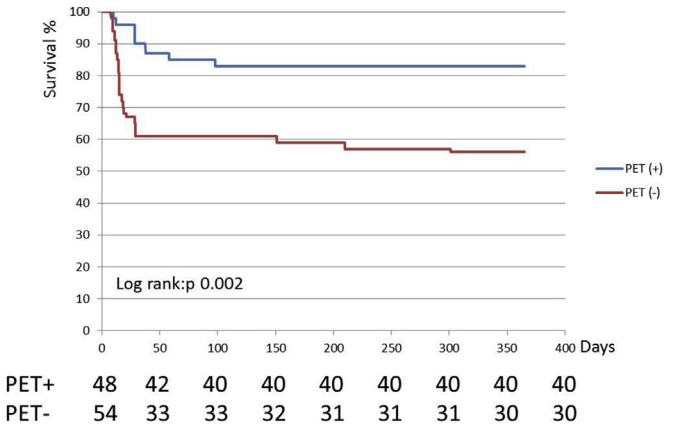

Fig. 2. This is a Kaplan-Meier curve showing mortality (at 1 year) in patient in whom PET CT was performed or not. We can see the significantly lower overall mortality rate in the group of patient in whom 18F-FDG PET/CT was performed. However, the high mortality rate at one year was probably due to the high mortality rate at 30 days (related to the infection by *staphylococcus aureus*).

of metastatic foci was 45.8% and the mortality rate was significantly reduced (16.6% vs 44.4%, P = 0.002) when the 18F-FDGPET/CT was performed. This reduction of mortality rate was due to metastatic foci detection (49 vs 13) who lead to treatment modification propably. Our results was then in the line with previous studies, [7,11–13,16,17].

Multiple independent risk-factors for a fatal outcome in high risk SAB patients have been extensively described in the literature [2–6]. However risk factors for increased or reduced mortality in patient in whom 18F-FDG PET/CT was performed is not well known and studies are scarces in the literature. The present study showed that kidney failure, diabetic foot infection, septic arthritis, prosthetic joint or plate infection, bacteremia of unknown origin and age were other factors that may contributed to change of mortality at 30 days, 90 days and 1 year in univariate analysis. However in multivariate, only kidney failure and bacteremia of unknown origine remain independent risk factor for mortality. Age >70 years old seems to be only related with higher mortality at 1 year of follow up.

Age has been confirmed as a strong independent predictor of mortality in many studies as we found [3,18–20]. A previous prospective study by Turnidge et al. suggests 30-day all-cause mortality of 20.6% which is significantly associated with older age and MRSA infection [18]. The mortality rate was found to be increased from 6% in young individuals (<15 years old) to 57% in adults older than 85 years of age by Lamagni et al. [19] In our study the mortality rate increased from 15.3% in patients with age < 60 years to 61.9% in patients age > 80 years old. To the best of our knowledge, there is no study comparing the mortality rate among patient with age <70 and >70 years old in whom 18F-FDGPET/CT was performed for SAB. Berrevoets et al. [7] in their study of high risk SAB in whom 18F-FDGPET/CT was performed found in the univariate analysis that, age (59 vs. 69 y, P < 0.05) was significantly different between survivors and nonsurvivors.

Kidney failure have been describe as risk factors for mortality in patients with SAB and endocarditis [2–6]. Quarles et al. found on 671 patients with end stage kidney failure under chronic haemodialysis with SAB that death occurred more often when bacteremia arose from an identifiable site other than the vascular access device. Patients who developed one or more metastatic foci of infection had a higher incidence of primary treatment failure and a higher mortality than did those with no metastatic infection. The use of 18F-FDG PET/CT identified those patients and lead probably to the reduction of mortality rate [21]. Bacteremia of unknown origin (BUO) and especially SAB of unknown origin [22] are associated with significant morbidity compared to bacteremic patients with an identified infectious focus [23]. Prosthetic joint or plate infection, diabetic foot infection are those where source control of the infection remain crucial (surgical debridement, removal of the material etc.) [4,16].

Table 3
Comparison of mortality according to age at 30 days, 90 days and 1 year.

	Overall mortality	P	Mortality at 30 days	P	Mortality at 90 days	P	Mortality at 1 year	P
Age <60 years old	4/26 (15.3%)	0.006	4/26 (15.3%)	0.009	4/26 (15.3%)	0.003	4/26 (15.3%)	0.01
Age 60-<70 years old	7/26 (26.9%)		7/26 (26.9%)		7/26 (26.9%)		7/26 (26.9%)	
Age 70- <80 years old	8/29 (27.6%)		4/29 (13.8%)		4/29 (13.8%)		8/29 (27.6%)	
Age >80 years old	13/21 (61.9%)		11/21 (52.4%)		12/21 (57.1%)		12/21 (57.1%)	
Age <70 years old	11/52 (21.1%)	0.023	11/52 (21.1%)	0.3	11/52 (21.1%)	0.21	11/52 (21.1%)	0.039
Age > 70 years old	21/50 (42%)		15/50 (30%)		16/50 (32%)		20/50 (40%)	

Table 4
Univariate analysis of factors associated with mortality at 30 days, 90 days and 1 year.

	Univariate analysis					
	30 days		90 days		1 year	
	Hazard ratio 95% CI	p value	Hazard ratio 95% CI	p value	Hazard ratio 95% CI	p value
Kidney failure (eGFR <60 ml/min) (N = 58)	0,135 [0.040; 0.446]	0.0001	0,169 [0.059; 0.489]	0.0001	0,183 [0.070; 0.476]	0.0001
MRSA (N = 6)	0.73 [0.185; 3.315]	0.74	0.84 [0.199; 3.539]	0.816	0.957 [0.229; 4.007]	0.953
Vascular graft infection (N = 5)	21 [0.013; 0.36709.84]	0.092	21 954 [0.018; 26815,323]	0.078	1.912 [0.261; 14.014]	0.479
Mycotic aneurysma (N = 1)	0.282 [0.038; 0.2.082]	0.3				
Endocarditis (N = 21)	0.415 [0.185; 0.932]	0.44	0.459 [0.207; 1.016]	0.69	0.550 [0.254; 1.190]	0.148
Neurostimulator infection (N = 1)	20.43 0.00; 2615618986]	0.456	20.43 [0.00; 130062958,889]	0.437	20.44 [0.00; 38885440,234]	0.399
Mediastinitis (N = 3)	21.153 [0.002; 286748,948	0.194	21.169 [0.002; 191338,791]	0.175	21.205 [0.002; 95133,807]	0.141
Diabetic foot infection (N = 16)	5.11 [0.693; 37739]	0.037	5.605 [0.761; 41.258]	0.024	6.641 [0.906; 448.666]	0.010
Bacteremia of unknown origin (N = 10)	0.217 [0.09; 0.520]	0.003	0.230 [0.097; 0.547]	0.004	0.211 [0.093; 0.475]	0.001
Arterio-venous fistula infection (N = 3)	21.153 [0.009; 286748,948]	0.194	21.169 [0.002; 191338,791]	0.175	21.205 [0.005; 95133,807]	0.141
18-FDG PET/CT	4.89 [1.690; 11.918]	0.001	3.248 [1,379; 7,651]	0.004	3.309 [1,484; 7,374]	0.002
Prosthetic or plate joint infection (N = 9)	23.631 [0.086; 65022203]	0.022	23.694 [0.109; 5141,982]	0.017	23.827 [0.165; 3432,277]	0.009
Septic arthritis (N = 7)	22.748 [0.041; 12646.05]	0.045	22.793 [0.054; 9693,745]	0.036	2.7303 [0.372; 20,003]	0.244
Osteitis (N = 6)	0.612 [0.145; 2.589]	0.53	0.428 [0.129; 1.417]	0.213	0.486 [0.148; 1.597]	0.28
Spondylodiscitis (N = 15)	1.015 [0.693; 2.945]	0.979	1.101 [0.382; 3.174]	0.857	1.280 [0.449; 3.651]	0.8633
Sex male/female (N = 78/24)	1.041 [0.418; 2.593]	0.93	0.937 [0.398; 2.205]	0.88	1.113 [0.481; 2.574]	0.8
Age <70 (N = 52)	1.495 [0.687; 3.255]	0.308	1.704 [0.798; 3.638]	0.163	1.150 [1.037; 4.462]	0.034
Immunosuppressive therapy (N = 15)	1.385 [0.416; 4.615]	0.58	1.088 [0.377; 3.185]	0.875	0.957 [0.375; 2.529]	0.957
Cirrhosis (N = 5)	0.550 [0.130; 2.331]	0.55	0.592 [0.140; 2.497]	0.507	0.679 [0.162; 2.842]	0.616

MRSA:methicillin resistant staphylococcus aureus, eGFR: estimated glomerular filtration.

Table 5
Multivariate analysis of factors associated with mortality at 30 days, 90 days and 1 year.

	Multivariate analysis					
	30 days		90 days		1 year	
	Hazard ratio 95% CI	p value	Hazard ratio 95% CI	p value	Hazard ratio 95% CI	p value
Kidney failure (eGFR <60 ml/min)	0,135 [0.040; 0.449]	0.0001	0,143 [0.049; 0.419]	0.0001	0,147 [0.056; 0.390]	0.0001
18-FDG PET/CT	6.144 [2.293; 16.492]	0.0001	3.942 [1.634; 9.508]	0.0001	4.117 [1.806; 9.387]	0.0001
Bacteremia of unknown origin	0.308 [0.222; 0.773]	0.021	0.301 [0.121; 0.746]	0.0001	0.256 [0.108; 0.607]	0.001

eGFr: estimated glomerular filtration.

18F-FDGPET/CT can be then a usefull tool for the diagnosis and management of these infections and therefore leading to reduction of mortality rate [24–26].

Our study has limitations: Firstly, this is a retrospective study and it's a single center experience. Secondly, due to the limited total number of patients, subgroups analysis included low number of patients and so we can't make a definitive conclusions (arterio-venous fistula infection, mediastinitis etc.).

5. Conclusion

Mortality rate was reduced in high risk SAB patients undergoing 18F-FDG PET/CT. Kidney failure and bacteremia of unknown origin were other factors associtated significantly with high mortality. Our study suggest that performing 18-FDG PET/CT in these patients can lead to a reduction of mortality by detecting metastatic foci. A larger multicentric and prospective study is needed to confirm our findings and to better understand how and in whom patients PET-CT lead to the reduction of mortality.

Conflicts of interest

All authors confirm that there is no conflict of interest.

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