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Detection of Synchronous Foci of Infection Using Positron Emission Tomography in Septic Patients Who Have a Periprosthetic Joint Infection

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ABSTRACT

Background: Periprosthetic joint infection (PJI) with sepsis is a life-threatening condition and identification of synchronous foci of infection is challenging. Positron emission tomography using ^{18}F-fluorodeoxyglucose combined with computed tomography (^{18}F-FDG-PET/CT) is useful to detect PJI in elective, nonseptic patients. We hypothesized that in patients who have PJI and concomitant sepsis requiring intensive care, ^{18}F-FDG-PET/CT could accurately identify synchronous foci of infection. We addressed the following questions: (1) How often were synchronous foci of infection detected?; (2) What were the confirmation rates of these infection foci by other complementary state-of-the-art methods?; (3) Did ^{18}F-FDG-PET/CT findings result in surgical treatment?; and (4) What is the risk of synchronous PJI in patients who have PJI and concomitant sepsis who have another indwelling arthroplasty?

Methods: We retrospectively analyzed mechanically ventilated septic PJI patients who underwent ^{18}F-FDG-PET/CT between January 1, 2017 and December 21, 2022. The identified synchronous foci of infection were categorized into musculoskeletal, cardiovascular, pulmonary, or other infections and compared to results from tissue culture, histopathology, magnetic resonance imaging, or transesophageal echocardiography.

Results: We identified 17 eligible patients. The ^{18}F-FDG-PET/CT revealed at least one additional infection focus in 15 patients with the following distribution: musculoskeletal (n = 12), cardiovascular (n = 3), pulmonary (n = 13), and other infections (n = 6). Synchronous foci of infection identified with ^{18}F-FDG-PET/CT were confirmed by another state-of-the-art method in 1 all 15 patients. Diagnoses with ^{18}F-FDG-PET/CT led to additional surgery in 11 patients. Of the patients, 10 of 17 had another arthroplasty with a risk in three of synchronous PJI.

Conclusions: We highlight the value of ^{18}F-FDG-PET/CT in patients who have PJI and sepsis, emphasizing its role in the comprehensive evaluation of these patients for subsequent therapeutic decision-making.

Periprosthetic joint infection (PJI) is a devastating complication following total joint arthroplasty (TJA). The infection rate is approximately 2% for primary hip and knee arthroplasty and even higher after revision procedures [1,2]. Patients suffering from PJI face a mortality rate more than three times higher than those without PJI [3]. A PJI can result in life-threatening sepsis [4–6], with mortality rates exceeding 50% despite the low risk of this complication [6–10]. During septic PJI, synchronous foci of infection, such as native joints, spondylodiscitis, endocarditis, or other indwelling

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implants, may be involved [11–13]. Intubation and mechanical ventilation often prevent patients from providing a medical history. Thus, a rapid and accurate diagnosis of all relevant infection foci is crucial for making therapeutic decisions that are essential to saving the patient's life [5,14]. However, identifying synchronous foci of infection remains difficult, relying on clinical examination, joint aspiration, ultrasound, and radiological tools (computer tomography and magnetic resonance imaging [MRI]), which may be limited by metallic implants [11,14].

Positron emission tomography using ^{18}F-fluorodeoxyglucose combined with computed tomography (^{18}F-FDG-PET/CT) enables the visualization of the glucose metabolism throughout the body [15]. Elevated glycolysis, as seen in neoplasms and inflammatory processes, results in increased ^{18}F-FDG uptake [15]. Over the last decades, this diagnostic tool has gained acceptance in almost all areas of oncology [16,17]. In terms of diagnosis, staging or restaging, extensive research has established the advantages of ^{18}F-FDG-PET/CT, including fast acquisition, high sensitivity, and major prognostic value [18,19]. The visualization of the entire body is also of interest in septic PJI. In systemic sepsis, ^{18}F-FDG-PET/CT has already been used to detect endocarditis and synchronous foci [20,21]. Recent literature highlights the efficacy of ^{18}F-FDG-PET/CT in diagnosing patients with fever of unknown origin, often resulting in therapeutic changes [15,20]. The evaluation of ^{18}F-FDG-PET/CT in 30 intensive care patients with systemic sepsis has shown high sensitivity and specificity in detecting the source of infection [20]. Similarly, ^{18}F-FDG-PET/CT exhibited high accuracy for diagnosing PJI in the elective nonseptic settings [22,23]. These promising findings suggest a crucial role for ^{18}F-FDG-PET/CT in evaluating intubated patients who have a septic PJI.

Aim of the Study

We hypothesized that ^{18}F-FDG-PET/CT could accurately identify synchronous foci of infection in patients who have PJI and concomitant sepsis undergoing intensive care therapy, who are unable to provide a medical history because of being intubated and on mechanical ventilation. We retrospectively evaluated the results of ^{18}F-FDG-PET/CT usage in patients who have septic PJI to address the following questions: (1) What was the detection frequency of synchronous foci of infection? (2) Could these infection foci be confirmed by other advanced diagnostic methods? (3) Did the findings from ^{18}F-FDG-PET/CT influence surgical treatment decisions? and (4) What is the risk of synchronous PJI in patients who have PJI and concomitant sepsis who also have another indwelling arthroplasty?

Patients and Methods

The present study was conducted in accordance with the ethical standards of the Declaration of Helsinki (1975) and was approved by the local ethics committee (University of Regensburg, Germany, file number 20-1,680-101).

Patients

We used a retrospective study design, including patients who had PJI and concomitant intensive care for sepsis who were unable to provide a medical history owing to being intubated and on mechanical ventilation, and who underwent ^{18}F-FDG-PET/CT diagnostics between January 1, 2017 and December 21, 2022 at our tertiary referral center. Data assessment was performed through a database search in SAP (hospital management software, widely used in Germany; SAP Healthcare version 769, SAP SE, Walldorf, Germany) using the International Statistical Classification of Diseases and Related Health Problems of the World Health Organization (https://www.bfarm.de/DE/Kodiersysteme/Klassifikationen/ICD/ICD-10-WHO/_node.html) and Official Operating and Procedure Classification in Germany (https://www.bfarm.de/DE/Kodiersysteme/Klassifikationen/OPS-ICHI/OPS/_node.html) codes. The SAP was searched for International Classification of Diseases, 10th Revision codes for sepsis (code A41) in combination with TJA complication code (code T84) and Official Operating and Procedure Classification in Germany codes for mechanical ventilation (code 8-71) and the use of ^{18}F-FDG-PET/CT (code 3-75). The accurate coding of diagnoses can be assumed given that Diagnosis-Related Groups' lump sum payment depends on it.

There were two groups of patients who were included: (1) patients who had septic PJI who underwent initial surgical treatment for PJI, but did not show marked improvement clinically or in laboratory examination during the first postoperative days; and (2) patients who had *Staphylococcus aureus* bacteremia and existing arthroplasty who underwent ^{18}F-FDG-PET/CT before surgical treatment. A PJI was diagnosed according to the definition by the *European Bone and Joint Infection Society* [24]. Sepsis has been defined as life-threatening organ dysfunction following a dysregulated host response to infection [25]. In this study, sepsis was diagnosed based on the "Sepsis-related Organ Failure Assessment" score [25]. Organ dysfunction was identified as an acute change in total Sepsis-related Organ Failure Assessment score $\geq$ two points [25] (Table 1). Moreover, secondary diagnoses were assessed, and the Charlson Comorbidity Index was calculated to evaluate the mortality risk of patients based on the patients' primary diseases [26].

In total, 17 patients (seven women and 10 men) who had confirmed PJI of total hip or knee arthroplasty and concomitant sepsis requiring intensive care therapy, who were unable to provide a medical history because of intubation and being on mechanical ventilation, and who received an ^{18}F-FDG-PET/CT at our tertiary referral center were included in this study (Table 2). Their mean age was 76 years (range, 59 to 90), their mean body mass index was 31.8 ± 6, and the mean Charlson Comorbidity Index was 4.2 ± 2.1. The main comorbidities included diabetes mellitus, coronary heart disease, atrial fibrillation, heart failure, and renal insufficiency. Their mean inpatient hospital duration was 77 ± 71 days, with a mean duration of intensive care therapy of 27 ± 38 days (Table 2). The primary infection of the foci included PJI of the knee in 10 patients and PJI of the hip in seven patients.

^{18}F-FDG-PET/CT

All ^{18}F-FDG-PET/CT scans were performed using European Association of Nuclear Medicine Research Ltd. accredited scanners: Siemens Biograph 16 Horizon, Siemens Biograph 40 mCT flow, and Siemens Biograph 16 [27]. Prior to the execution of ^{18}F-FDG-PET/CT, parental nutrition was halted for at least 6 hours. Blood glucose levels were measured before the tracer administration. The scan commenced approximately 60 minutes after injection of three MBq/kg body weight ^{18}F-FDG. Results were evaluated and interpreted by two board-certified nuclear medicine specialists.

Relevant ^{18}F-FDG-PET/CT diagnoses were compiled for each patient and categorized into four major groups (musculoskeletal, cardiovascular, pulmonary, and other infections). Musculoskeletal infections included synchronous PJI, native joint septic arthritis, spondylodiscitis, osteomyelitis, muscle abscess, and infection of indwelling fracture fixation devices. Cardiovascular infections were defined as infective endocarditis and infected aneurysms. Pulmonary infections included pneumonia and pulmonary abscesses. The fourth group, labeled "other infections", mainly included abdominal infections such as gall bladder empyema, pancreatitis, and

Table 1
Sepsis-Related Organ Failure Assessment (SOFA) Score.

System	0	1	2	3	4
Respiration					
PaO_2/FiO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine (any dose)	Dopamine 5.1-15 or epinephrine ≤ 0.1 or norepinephrine ≤0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Central nervous system					
Glasgow Coma Scale Score	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	< 1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

This table is in accordance with The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) 2016 (https://jamanetwork.com/journals/jama/fullarticle/2492881 - accessed 01.04.2024) [25]. Organ dysfunction can be identified as an acute change in total SOFA score ≥ 2 points.
MAP, mean arterial pressure.

ascites. For the calculation of the sensitivity and specificity of ^{18}F-FDG-PET/CT, the diagnoses made by ^{18}F-FDG-PET/CT were compared to those made by state-of-the-art diagnostic modalities for each infection group. For PJI and native joint septic arthritis, results were based on joint aspirations, microbiological cultures, and pathological findings from intraoperatively collected tissue samples. Spondylodiscitis diagnoses were compared with MRI findings, microbiological cultures, and pathological assessment of CT-guided vertebrae punctures and tissues collected intraoperatively. Endocarditis was evaluated through transesophageal echocardiography (TEE), microbiological cultures, and pathological examinations of valves removed intraoperatively.

Table 2
Demographic Data of the 17 Included Patients.

n = 17	Mean ± SD	Range
Age (years)	75 ± 7.3	59 to 90
Sex (men:women)	10:7	
Body mass index (BMI)	31.8 ± 6.1	22 to 51
Charlson comorbidity index (CCI) (%)	4.2 ± 2.1	0 to 9
Diabetes mellitus	6	
Coronary heart disease	5	
Heart attack	6	
Heart failure	7	
Atrial fibrillation	9	
Peripheral artery disease	4	
Stroke	2	
Dementia	0	
Chronic obstructive pulmonary disease	2	
Asthma	1	
Liver disease	5	
Malignancy	2	
Collagenosis	1	
Gastric ulcer	2	
Kidney disease	12	
Rheumatic disease	6	
Initial symptoms PJI (%)	16	
Redness	9	
Swelling	14	
Pain	16	
Fever	10	
Loss of function	16	
C-reactive protein (CRP)	236 ± 111 mg/L	
Leukocyte count	14.18 ± 9 × 10^9/L	
Duration of symptoms (days)	26.8 ± 38.1	1 to 162
Duration of hospitalization (days)	76.7 ± 71.6	3 to 300
Duration of intensive care therapy (days)	26.8 ± 38.1	3 to 85

SD, standard deviation; PJI, periprosthetic joint infection.

Data Analyses

All variables are reported as relative frequencies and as mean with standard deviation where appropriate. Statistical analyses were conducted using Statistical Package for Social Sciences (IBM SPSS Statistics 28, International Business Machines Corporation [IBM], Armonk, New York).

Results

On initial admission to our emergency room, 16 of the 17 patients reported loss of function and pain at the primary PJI site. Of these patients, nine showed redness, and 14 had swelling. The primary infection foci were PJI of the knee and hip in 10 and seven patients, respectively. Fever was observed in 10 patients. The mean C-reactive protein level was 236 ± 111 mg/L (normal value < 5 mg/L) with a mean serum leukocyte count of 14 ± 9 × 10^9 cells/L. In four patients, ^{18}F-FDG-PET/CT was performed prior to surgical treatment for PJI, and all four patients had *Staphylococcus aureus* bacteremia with a high suspicion of another synchronous focus of infection. The other 13patients underwent ^{18}F-FDG-PET/CT after their first surgical intervention for primary PJI owing to the absence of postoperative improvement in clinical symptoms and suspicion of another synchronous focus of infection.

^{18}F-FDG-PET/CT

^{18}F-FDG-PET/CT detected at least one additional infection focus in 15 patients (Table 3). Additional musculoskeletal infections were detected with ^{18}F-FDG-PET/CT in a substantial proportion of the patients (n = 12). Pulmonary infections were also frequently detected (n = 13). Cardiovascular and other infection sites were diagnosed in three and six patients, respectively.

In total, 48 synchronous infection foci, in addition to the primary PJI, were identified in the 17 patients, predominantly in the musculoskeletal and pulmonary systems, with 24 and 13 infections, respectively. The additional 24 musculoskeletal infections diagnosed with ^{18}F-FDG-PET/CT included seven synchronous PJIs of other indwelling TJA (six knees and one shoulder), two septic arthritis in other native joints (both native shoulders), two infections related to fracture fixation devices (one from a previously healed femur fracture and one from a sternal cerclage), four cases of spondylodiscitis, two infected postoperative hematomas, two cases of osteomyelitis, and five abscesses (including two psoas

Table 3
Further Relevant Findings in ^{18}F-FDG-PET/CT and Resulting Therapy (Diagnoses [DX]).

Included Patients	Further Relevant Infection in ^{18}F-FDG-PET/CT			Infection Confirmed by - Pathology/Microbiology - TEE - MRI			Surgical Intervention After ^{18}F-FDG-PET/CT		
Patients, n = 17	Patients, n = 15/17	Musculoskeletal	n = 12, 24 Dx	Patients, n = 15/15	Musculoskeletal	n = 11, 19/24 Dx	Patients, n = 11/17 (65)	Musculoskeletal	n = 10, 17/19 Dx
		Cardiovascular	n = 3, 4 Dx		Cardiovascular	n = 3/3 (100), 4/4 Dx		Cardiovascular	n = 3/3, 3/4 Dx
		Pulmonary	n = 13/15, 13 Dx		Pulmonary	n = 13/13, 13/13 Dx		Pulmonary	n = 0/13, 0/13 Dx
		Others	n = 6/15, 7 Dx		Others	n = 6/6, 7/7 Dx		Others	n = 2/6, 2/7 Dx

Seventeen patients with PJI were included. In 15 of these patients, ^{18}F-FDG-PET/CT detected 48 synchronous infections (24 times musculoskeletal, four times cardiovascular, 13 times pulmonary, and seven times others). These were confirmed in 43 cases by pathology, microbiology, transesophageal echocardiography (TEE), or/and magnetic resonance imaging (MRI). In 11 of 15 patients, ^{18}F-FDG-PET/CT diagnoses led to additional surgery.
^{18}F-FDG-PET/CT, ^{18}F-fluorodeoxyglucose combined with computed tomography; TEE, transesophageal echocardiography; MRI, magnetic resonance imaging; Dx, diagnosis.

abscesses). The 13 pulmonary infections included all cases of pneumonia, with one case also presenting a pulmonary abscess. Endocarditis affecting the mitral valve was identified with ^{18}F-FDG-PET/CT in two cases; in one of these cases, the aortic valve was also involved. Another case included an infected aneurysm of the superficial femoral artery. Gall bladder empyema was identified in one case, and a new abscess formation was found in a patient undergoing abdominal vacuum-assisted closure therapy. Pancreatitis detected in three patients, ascites in one, and gastritis in another patient.

Synchronous Foci of Infection

All diagnoses of at least one synchronous focus of infection with ^{18}F-FDG-PET/CT (15 of 15) were confirmed either by microbiological or pathohistological assessment, TEE, or MRI (Table 3). Confirmation rates were high for musculoskeletal (19 of 24) and pulmonary infections (13 of 13). Musculoskeletal infections with PJIs, native septic joints, infections of other indwelling implants (e.g., fixation devices), abscesses, and spondylodiscitis were diagnosed using microbiological cultures and/or pathohistological assessment of intraoperative tissue samples or CT-guided vertebrae punctures in case of a spondylodiscitis. Cardiovascular infections had all four confirmation rate using TEE, microbiological cultures, and pathological findings from intraoperatively removed valves. An infected aneurysm of the superficial femoral artery was confirmed by microbiological and pathological analysis of intraoperatively removed tissue. A gall bladder empyema and a new abscess formation in a patient with ongoing abdominal vacuum-assisted closure therapy were also confirmed by microbiological and pathological findings. A gastritis was confirmed through esophagogastroduodenoscopy, followed by microbiological and pathological assessment. Pancreatitis was confirmed by sonography.

Synchronous PJI

Of the 17 patients, 10 had other indwelling arthroplasties, totaling 16 different arthroplasties (10 knees, four hips, and two shoulders; Table 4). In five of these 10 patients, a synchronous PJI was diagnosed using ^{18}F-FDG-PET/CT, affecting a total of seven arthroplasties (six knees and one shoulder). All potentially infected arthroplasties were aspirated, and PJI was suspected in three of five patients and four of seven joints based on elevated leukocyte counts and microbiological culture growth from synovial fluid aspirates. Surgical intervention was performed in all of these patients, and microbiological culture growth along with pathological assessment of intraoperative tissue confirmed PJI in each case. Using ^{18}F-FDG-PET/CT, all synchronous PJIs were detected, ensuring no patient was treated for another synchronous PJI that was not found by ^{18}F-FDG-PET/CT during hospitalization. In summary, a majority 10 of 17, of patients who had septic PJI had another indwelling arthroplasty at the time of sepsis and these patients were at a high risk (three of 10 patients) of synchronous PJI.

Table 4
Illustration of Synchronous Musculoskeletal Infections (Periprosthetic Joint Infection [PJI], Native Joint Septic Arthritis [NJSA], and/or Infection of Fracture Fixation Devices) and Existing Total Joint Arthroplasty (TJA).

Included patients, n = 17 (100%)	Synchronous PJI			
	Further indwelling TJA	Further PJI in ^{18}F-FDG-PET/CT	PJI confirmed by pathology/ microbiology	Surgical intervention after ^{18}F-FDG-PET/CT
	n = 10/17 patients, 16 TJA	n = 5/10 patients, 7 PJI/16 TJA	n = 3/5 patients, 4/7 PJI	n = 3/3 patients, 4/4 PJI
	Synchronous NJSA			
		Further NJSA in ^{18}F-FDG-PET/CT	NJSA confirmed by pathology/ microbiology	Surgical intervention after ^{18}F-FDG-PET/CT
		n = 2/17 patients, 2 NJSA	n = 2/2 patients, 2/2 NJSA	n = 2/2 patients, 2/2 NJSA
	Synchronous infection of fracture fixation devices			
	Further indwelling fracture fixation devices	Infection of fracture fixation devices in ^{18}F FDG-PET/CT	Infection confirmed by pathology/microbiology	Surgical intervention after ^{18}F-FDG-PET/CT
	n = 6 patients, 6 fracture fixation devices	n = 2/6 patients, 2/6 fracture fixation devices	n = 2/2, 2/2 fracture fixation devices	n = 2/2, 2/2 fracture fixation devices

PJI, periprosthetic joint infection; TJA, total joint arthroplasty; ^{18}F-FDG-PET/CT, ^{18}F-fluorodeoxyglucose combined with computed tomography; NJSA, native joint septic arthritis.

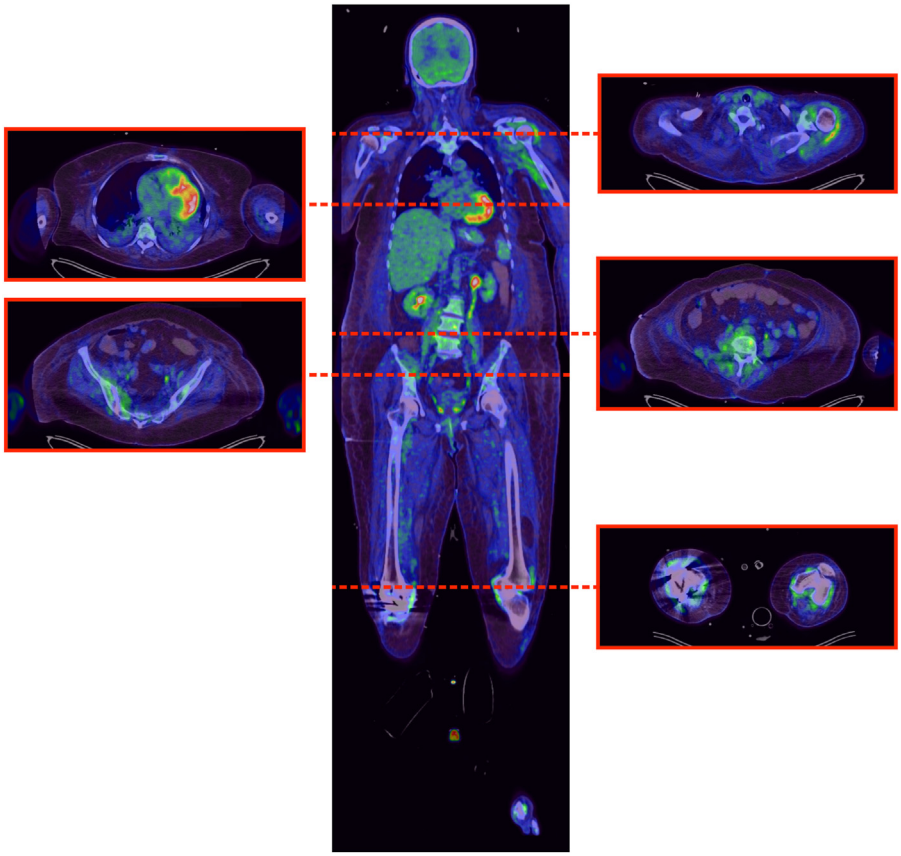

Figure 1. FDG-PET/CT in a woman who had septic shock syndrome. The FDG-PET/CT in a woman who had intensive care therapy due to a septic shock syndrome following periprosthetic joint infection. In the middle column frontal reconstruction of FDG -PET/CT is shown, on the left and right side each axial reconstructions of the shoulders, the heart and lung, the spine, the pelvis, and the knees are demonstrated. Higher glycolysis is illustrated by higher ^{18}F-FDG accumulation. A color gradient represents the accumulation, ranging from green (light) to red (strong ^{18}F-FDG uptake). Strong ^{18}F-FDG uptake can be seen in the left shoulder, the heart, both lungs, the vertebral disc (L4/L5), both M. iliopsoas, and both knees. The FDG-PET/CT diagnostics lead to operative removal of the prosthesis components of the right knee as well as arthroscopy of the left shoulder and left knee, drainage of psoas abscess, stabilization of the spine, and antibiotic therapy of endocarditis. → Figure 1 needs to be presented in color. FDG-PET/CT, F-fluorodeoxyglucose combined with computed tomography.

Need for Additional Surgery

In 11 of 17 patients, ^{18}F-FDG-PET/CT diagnoses led to additional surgery (Table 3). There was one patient who received supportive care because the condition was terminal. Surgery was mainly carried out in patients who had synchronous musculoskeletal infections through removal of the prosthesis in one patient, debridement and change of mobile parts in three patients, arthroscopic debridement and lavage in two patients, and removal of an infected fracture fixation device in one patient. Of the two patients who had spondylodiscitis, one needed internal dorsal stabilization of the spine, while the other was treated non-operatively. Regarding nonmusculoskeletal infections, surgical intervention was performed on one patient each who had an infected aneurysm of the superficial femoral artery, gall bladder empyema, and a new abscess formation following ongoing abdominal vacuum-assisted closure therapy. Surgery was also necessary for two patients who had endocarditis including one with valvular infection.

Discussion

This study highlights the value of ^{18}F-FDG-PET/CT in patients who had PJI and concomitant sepsis who are unable to provide a medical history due to intubation and mechanical ventilation. We identified synchronous foci of infection in 15 of 17 patients and determined the need for additional surgical therapy to resolve sepsis in 11 of 17 patients.

In septic patients who are unable to provide a history because of intubation and mechanical ventilation, the rapid diagnosis of additional foci of infection is of utmost importance for enabling targeted, often surgical, therapy. Literature on ^{18}F-FDG-PET/CT for intensive care patients is scarce. Pijl et al. evaluated the benefit of ^{18}F-FDG-PET/CT usage for focus search in 30 intensive care patients with bloodstream infections [20]. ^{18}F-FDG-PET/CT detected an infection focus in two-thirds of patients, leading to a change of therapy in almost half of them. The authors highlighted the high diagnostic benefit of ^{18}F-FDG-PET/CT and emphasized the importance of superior imaging quality. Our data confirmed these findings and supported the favorable use of ^{18}F-FDG-PET/CT for focus search in this vulnerable patient population. This diagnostic tool has been instrumental in finding foci of infection in patients suffering from fever of unknown origin. Kouijzer et al. recently performed a literature review on this topic and showed successful focus detection in at least 50% of patients who had fever of unknown origin [15]. Another recent study supported the usage of ^{18}F-FDG-PET/CT for re-evaluation of infection focus in patients who had bloodstream infections and ongoing antibiotic therapy for 6 weeks [28]. Furthermore, van Leerdam et al. evaluated the use of ^{18}F-FDG-PET/CT in patients with complicated *Staphylococcus aureus*

bacteremia and indicated that ^{18}F-FDG-PET/CT resulted in a change of antibiotic therapy in 22 of 132 patients with ongoing antibiotic therapy for 6 weeks [28].

As shown above, ^{18}F-FDG-PET/CT has proven its reliability in various studies, not only in oncology but also in suspected inflammation [29]. Regarding its specific use for detecting PJI, most studies focused on the diagnostic accuracy of ^{18}F-FDG-PET/CT in patients who had PJI or compared different radiotracers [30,31]. Xu et al. used ^{68}Gallium citrate radiotracer for PET/CT to differentiate between aseptic loosening and PJI [30]; they detected an improvement of sensitivity with its use in combination with ^{99m}Tc-MDP single photon emission CT in 23 patients. However, data were not compared with ^{18}F-FDG-PET/CT [30]. Leukocyte scintigraphy can also be considered for inpatients with suspected infections, but only a few studies have compared ^{18}F-FDG-PET/CT with leukocyte scintigraphy directly [32]. In a retrospective analysis, Dibble et al. evaluated both diagnostic tools and showed a higher sensitivity and comparable specificity for ^{18}F-FDG-PET/CT [32]. This diagnostic tool offers various advantages, such as shorter examination times, higher spatial resolution, and the possibility of performing quantitative analyses [33]. Furthermore, leukocyte scintigraphy requires the manipulation of blood products [34]. This may be the reason why the formerly used nuclear medicine procedures for infection imaging are being increasingly substituted by ^{18}F-FDG-PET/CT [35].

Our data show that the musculoskeletal system and the lungs are the most frequent synchronous foci of infection in patients who had septic PJI. Particularly, the high risk (three of 10) of synchronous PJI in PJI patients who had sepsis in our cohort is of high relevance. Nonseptic patients who had other indwelling arthroplasty are at risk of synchronous PJI with reported rates of 10 to 20% [12,13]. In septic patients, this elevated risk in our cohort showed the clinical relevance of synchronous PJI and stressed the need for them to be specifically addressed in these patients. A recent meta-analysis on the use of ^{18}F-FDG-PET/CT to detect PJI demonstrated a high sensitivity between 85 and 95% and variable specificity of 38 to 100% [23,30,31,36,37]. A multidisciplinary consensus conference in 2020 rated a negative result in ^{18}F-FDG-PET/CT diagnostics as a safe way to rule out PJI [38].

Regarding the use of ^{18}F-FDG-PET/CT in spinal infections, comparable diagnostic value in the diagnosis of spondylodiscitis was reported for the whole body ^{18}F-FDG PET/CT versus MRI [39]. A recent prospective multicenter study compared ^{18}F-FDG-PET/CT and MRI in terms of detection of postoperative spondylodiscitis and showed comparable diagnostic performance of both tools and recommended a combination of them [40]. Of the 17 patients, four were diagnosed with additional spondylodiscitis, which was confirmed in all of the cases, demonstrating both a high prevalence of spondylodiscitis in septic patients and reliability of ^{18}F-FDG-PET/CT for this type of spinal infections. Endocarditis is another relevant infection focus in septic patients, and it occurred in some of our patients (three of 17). A recent study proved a high sensitivity and specificity of ^{18}F-FDG-PET/CT in the detection of endocarditis [21,28]. However, it was also stated that a negative finding in ^{18}F-FDG-PET/CT was not sufficient enough to rule out a native valve infection, but it is highly recommended to search for a disseminated focus of infection [21]. Pancreatitis, ascites, and gastritis may also be found together in patients receiving intensive care therapy. In this study, we could not provide microbiological data for the pancreatitis case. Therefore, we cannot guarantee that this finding really demonstrates a synchronous bacterial infection.

The downsides of PET/CT include its relatively high cost and its limited availability outside specific centers compared to conventional diagnostics. In our clinical setting, the costs for a whole body ^{18}F-FDG-PET/CT examination are comparable to that in the catalog of the German statutory health insurance (German: Einheitlicher Bewertungsmaßstab, EBM) with about 930 Euro (€) as of January 2024. Kouijzer et al. conducted a cost-effectiveness analysis in patients who have unknown fever [15]. They concluded that the costs for ^{18}F-FDG-PET/CT itself were relatively low compared to prolonged hospital stays and unnecessary diagnostics prior to PET/CT [15]. Although we have not done a health-economic evaluation in our patient cohort, we strongly believe that the use of ^{18}F-FDG-PET/CT, particularly in intubated patients who have septic PJI, far outweighs its costs. The early detection of synchronous sources of infection is of utmost importance, guiding effective treatment and reducing overall healthcare costs.

There are several potential limitations to the present study, including the small sample size and its observational retrospective study design. Reasons for the small sample size are the low number of patients who have PJI and sepsis who consecutively require intensive care therapy and who are unable to provide a history because of intubation and mechanical ventilation. The retrospective study design does not allow for conclusions on potentially improved diagnostic and/or survival rates of these patients using ^{18}F-FDG-PET/CT compared to conventional diagnostics, such as aspiration and/or CT/MRI-based diagnostics; this should be the aim of future randomized controlled trials (Figure 1).

Conclusions

This study highlights the value of ^{18}F-FDG-PET/CT in intubated septic PJI patients, emphasizing its role in the comprehensive evaluation of patients with PJI for subsequent therapeutic decision-making.

Data Availability Statement

On request, data are available at the authors' institution.

Institutional Review Board Statement

The study was approved by the local ethics committee beforehand (file number 20-1,680-101).

Informed Consent Statement

The study was carried out in accordance with the ethical standards of the Declaration of Helsinki of 1975. The data were acquired pseudonymized.

CRediT authorship contribution statement

Jan Reinhard: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Stefanie Heidemanns:** Writing – review & editing, Validation. **Markus Rupp:** Writing – review & editing, Writing – original draft, Validation. **Nike Walter:** Writing – review & editing, Validation. **Derek F. Amanatullah:** Writing – review & editing, Formal analysis. **Hellwig Dirk:** Writing – review & editing, Validation, Supervision. **Volker Alt:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

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