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FDG-PET/CT for Detecting an Infection Focus in Patients With Bloodstream Infection

Factors Affecting Diagnostic Yield

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Purpose: To investigate the diagnostic performance of ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET/ CT for the detection of an infection focus in patients with a bloodstream infection (BSI) and to identify factors influencing the diagnostic yield of FDG-PET/CT.

Methods: This retrospective single-center study included 185 consecutive patients with a BSI who underwent an FDG-PET/CT scan for the detection of an infection focus between 2010 and 2017. The final diagnosis at hospital discharge was used as reference standard. Diagnostic performance of FDG-PET/CT for the detection of an infection focus was assessed, and logistic regression analyses were performed to identify factors associated with FDG-PET/CT yield.

Results: An infection focus was identified on FDG-PET/CT in 120 (64.8%) of 185 patients. FDG-PET/CT achieved a sensitivity of 80.2%, specificity of 79.6%, positive predictive value of 90.8%, and a negative predictive value of 61.4% for detecting an infection focus in patients with a BSI. Blood cultures positive for enterococci (odds ratio, 0.14; $P = 0.019$) and days of antibiotic treatment before FDG-PET/CT (odds ratio, 0.94 per day increase; $P = 0.014$) were statistically significant independent predictors of a lower odds of detecting an infection focus on FDG-PET/CT. In patients who received antibiotics for less than 7 days before FDG-PET/CT, an infection focus was found in 71% (56/79). In patients who received antibiotics for 8 to 14 days before FDG-PET/CT, an infection focus was found in 52% (22/42). After 15 to 21 days of antibiotic treatment, an infection focus was found in 61% (8/13), and for 22 days or more, this declined to 38% (5/13).

Conclusions: FDG-PET/CT is a useful method for detecting an infection focus in patients with BSI. However, longer duration of antibiotic treatment before FDG-PET/CT and bacteremia with enterococci reduce the diagnostic yield of FDG-PET/CT. These factors should be taken into account when considering an FDG-PET/CT scan for this indication.

Key Words: FDG-PET/CT, infection, focus, bacteremia, sepsis

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Conflicts of interest and sources of funding: none declared.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent: The local institutional review board approved this retrospective single-center study and waived the requirement for written informed consent (IRB number: 201700145).

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Bloodstream infection (BSI) is defined by the presence of viable pathogens in the blood and can be subdivided into bacteremia and fungemia.[1] The incidence of BSI has been reported to be between 100 and 200 per 100,000 people.[2–7] Most studies report an increasing trend in the incidence of BSI.[2–4] Possible explanations for this increase include aging of the population, more extensive use of invasive procedures including insertion of foreign body materials, increasing numbers of immunosuppressed patients, and rising antimicrobial resistance.[5,6]

Bloodstream infection is a major health problem. The 30-day-mortality is higher than 15%, and it ranks among the top 10 causes of death in Europe and North America.[2,8] The inability to identify the source of infection is strongly associated with increased mortality.[9,10] In up to one third of patients with a BSI, the source of infection cannot be identified.[10] These cases are eventually diagnosed as bacteremia or fungemia of unknown origin.

^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET/ CT can be used for evaluating infectious diseases, including BSI. In patients with BSI, it can be used to detect either the source of infection or whole body complications such as metastatic infectious foci.[11,12] Failure to detect an infection focus in a timely manner may potentially lead to an insufficient antibiotic treatment with risk of disease relapse.

Because FDG-PET/CT is a relatively expensive procedure,[13] a priori knowledge on when an FDG-PET/CT scan may be diagnostically helpful in a particular patient with a BSI is important. However, evidence on this topic is very limited.[14] We hypothesize that various factors, such as duration of antibiotic treatment before FDG-PET/CT, immunocompetence, laboratory infection parameters, and causative pathogen of the BSI, may influence the diagnostic yield of FDG-PET/CT.

Therefore, the aim of this study was to evaluate the diagnostic performance of FDG-PET/CT in a large cohort of patients with BSI and to determine which factors influence the diagnostic yield of FDG-PET/CT in patients with a BSI.

PATIENTS AND METHODS

Study Design and Patients

All patients with a BSI who underwent an FDG-PET/CT scan for the detection of an infection focus between 2010 and 2017 were potentially eligible for inclusion. We performed a search in our electronic hospital's patient database to identify patients who underwent an FDG-PET/CT scan for this indication by using the keywords *sepsis*, *bacteremia*, *infection focus*, and *blood culture*. Patients with a positive blood culture before and within 2 months of the FDG-PET/CT scan were included. Positive blood cultures that were considered as a contaminant by the medical microbiologist, and thus, not treated, were excluded. Patients without a reference standard to determine the presence or absence of an infection focus (which will be defined in a subsequent section), were also excluded. The local institutional review board approved this retrospective

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single-center study and waived the requirement for written informed consent.

Patient Record Review

The medical files of all patients were then further reviewed for relevant clinical and biochemical data (age, sex, medical history, current immunocompetence, current hemodialysis, C-reactive protein [CRP] level, leukocyte count, isolated pathogen(s), additional imaging performed during the same hospital stay, duration of antibiotic treatment, treatment outcome, and total duration of hospital stay). Only CRP levels and leukocyte counts determined within 24 hours of the FDG-PET/CT scan were included in the analyses. Patients were considered immunodeficient if they were immunocompromised because of acute leukemia or were treated with prednisolone, cyclosporine, mycophenolic acid, or other immunosuppressants.

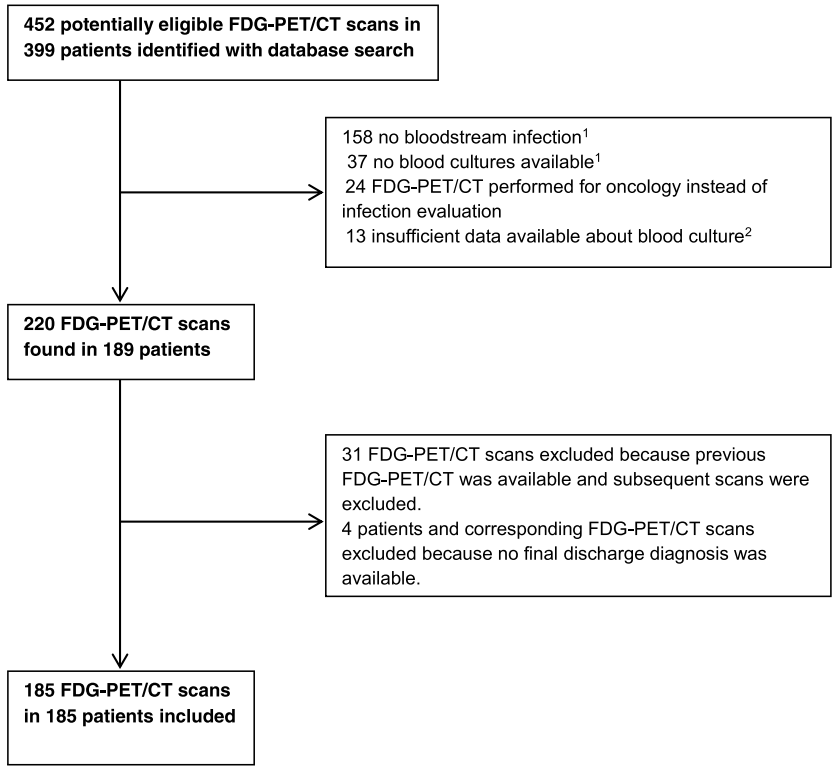
FDG-PET/CT Acquisition

Patients fasted for a minimum of 6 hours, and blood glucose concentrations were ensured to be less than 11 mmol/L before 3 MBq FDG/kg body weight was administered intravenously. When there was a clinical suspicion for infective endocarditis, patients were also prepared with a high–fat, low-carbohydrate diet for at least 24 hours. Approximately 60 minutes after FDG administration, PET scanning was performed using an integrated PET/CT system (Biograph mCT 64 slice PET/CT; Siemens, Knoxville, TN) with 3 minutes per bed position. Low-dose CT was performed for attenuation correction and anatomic mapping with 100 kV and 30 mAs. Data acquisition and reconstruction were in accordance with European Association of Nuclear Medicine/Research 4 Life guidelines.[15] In 37 patients, concomitant full-dose CT of the abdomen was performed with a constant tube potential of 100 or 120 kV and automatic adjustment of mAs in the z-direction.

FDG-PET Interpretation and Reference Standard

FDG-PET/CT scans were interpreted by nuclear medicine physicians as part of routine clinical care, using syngo.via software (Siemens Healthcare, Erlangen, Germany). All scans with inconclusive findings were reevaluated by another nuclear medicine physician (A.W.J.M.G.) who was blinded to original FDG-PET/CT interpretations, other imaging results, clinical, laboratory, and microbiologic tests. FDG-PET/CT scans showing at least 1 FDG-avid lesion localized to an area that did not correspond to physiologic biodistribution of FDG and did not suggest other pathology than infection were considered positive for an infection focus.

The final diagnosis made at hospital discharge with a definitive diagnosis of an infection focus was used as reference standard. This final diagnosis was, besides FDG-PET/CT results, also based on histology or microbiology reports (if available), other imaging results confirming the infection focus or foci found on FDG-PET/CT, such as CT, MRI, or ultrasonography, and/or clinical follow-up and treatment outcome for at least 6 months. The final diagnosis was never based on FDG-PET/CT results alone.



Notes:
[1] Within 60 days of the FDG-PET/CT scan.
[2] In these cases, blood cultures were taken in others hospitals and the date of the last positive blood culture was not mentioned in any of our documentation.

FIGURE 1. Flow diagram of FDG-PET/CT scan and patient selection.

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TABLE 1. Basic Demographics of Included Patients

Characteristic	n = 185
Age (yr)	63.0 (19.0)*
Men	116 (63%)
Time interval between hospital admission and FDG-PET/CT (d)	8.0 (12.0)*
Time interval between FDG-PET/CT and hospital discharge (d)	14.0 (19.8)*
Total hospital stay (d)	24.0 (28.0)*
CRP (mg/L)	87 (111)*
Leukocytes ($\times 10^9$/L)	9.4 (6.6)*
Immunocompromised	68 (37%)
Hemodialysis	22 (12%)
Duration of antibiotic treatment before FDG-PET/CT (d)	7.0 (9.0)*
Previous other imaging positive for infection focus	44 (24%)
Death within 30 days of admission	15 (8%)

*Median (IQR).

An FDG-PET/CT scan was considered true positive when the results from the scan matched the final diagnosis of the patient at hospital discharge. An FDG-PET/CT scan was considered false positive if it was positive for an infection focus, but the hospital discharge diagnosis stated that no infection focus was found. An FDG-PET/CT scan was considered true negative if no localized infectious process was identified on the scan or any other diagnostic test, and the final discharge diagnosis was BSI of unknown origin. An FDG-PET/CT scan was considered false negative if it did not identify an infection focus, whereas other diagnostic examinations were positive for an infection focus. An FDG-PET/CT scan was considered both false positive and false negative when an infection focus was identified on FDG-PET/CT, but the final discharge diagnosis stated a different infection focus. This reference standard was in line with previous large studies on the evaluation of FDG-PET/CT in patients with bacteremia.[12,14]

Statistical Analysis

Continuous variables were checked for normal distribution using Kolmogorov-Smirnov tests. Data were presented as mean ± standard deviation or median with interquartile range

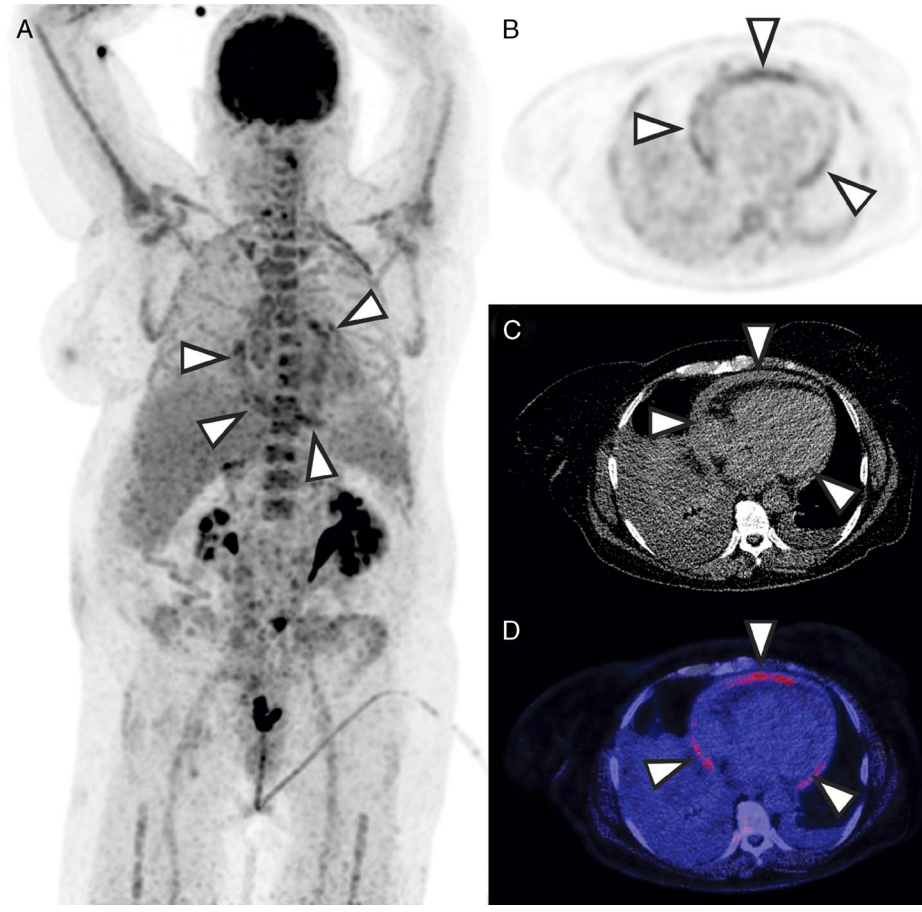

FIGURE 2. A 56-year-old woman underwent surgical debulking (ileocecal and sigmoid resection, with creation of a colostomy) because of recurrent cervical cancer. After surgery, she developed fever and de novo atrial fibrillation. Full-dose diagnostic CT (not shown) demonstrated pleural and pericardial fluid collections but no other acute pathology. Despite the use of intravenous meropenem, the fever persisted. Leukocyte and CRP levels were 14.7×10^9 and 156 mg/L, respectively. Blood cultures were positive for *Enterobacter aerogenes*. FDG-PET/CT was performed for depicting infectious foci. Coronal maximum intensity projection FDG-PET (**A**), axial FDG-PET (**B**), low-dose CT (**C**), and fused FDG-PET/CT (**D**) at the level of the heart showed foci of increased pericardial FDG uptake and diffuse pericardial fluid and thickening (arrowheads), indicating pericarditis. FDG-PET/CT detected no other infectious foci.

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(IQR) for normally distributed or non-normally distributed data, respectively. Sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET/CT for detecting an infection focus were calculated, along with 95% confidence intervals (CIs). Age, sex, medical history, current immunocompetence, current hemodialysis, CRP level, leukocyte count, cultured pathogen, previous imaging, treatment outcome, and duration of hospital stay were analyzed with univariate logistic regression as independent variables and FDG-PET/CT outcome as dependent variable. True-positive FDG-PET/CT outcomes were coded as '1', and FDG-PET/CT outcomes that were not true positive (false positives, true negatives, and false negatives) were coded as '0' for this purpose. Corresponding odds ratios (ORs) and 95% CIs were calculated, and $P < 0.05$ was considered significant. Variables with $P \leq 0.10$ on univariate analysis were included in the stepwise multivariate logistic regression model. Variables that cannot be used to predict FDG-PET/CT outcome because they can only be collected after the FDG-PET/CT scan (30-day mortality and days between FDG-PET/CT and hospital discharge) were separately analyzed using unpaired *t* tests for normally distributed data or Mann-Whitney *U* tests for non-normally distributed data.

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) version 25 (SPSS, Chicago, IL).

RESULTS

Patient Population

Approximately 452 FDG-PET/CT scans from 399 individual patients were potentially eligible for inclusion. Patients without a BSI or without a reference discharge diagnosis, FDG-PET/CT scans performed for another indication than to identify an infection focus, and follow-up FDG-PET/CT scans were excluded. Finally, 185 FDG-PET/CT scans from 185 unique patients were included (Fig. 1). These scans were performed in 116 men and 69 women, with a median age of 63.0 (IQR, 19.0) years (Table 1). Two exemplary patients are shown in Figures 2 and 3. In 92% of patients, CRP level and leukocyte count were determined within 24 hours of the FDG-PET/CT scan, which had a median of 87 (IQR, 111) mg/L and a median of 9.4×10^9/L (IQR, 6.6), respectively. The median total hospital stay was 24.0 (IQR, 28.0) days,

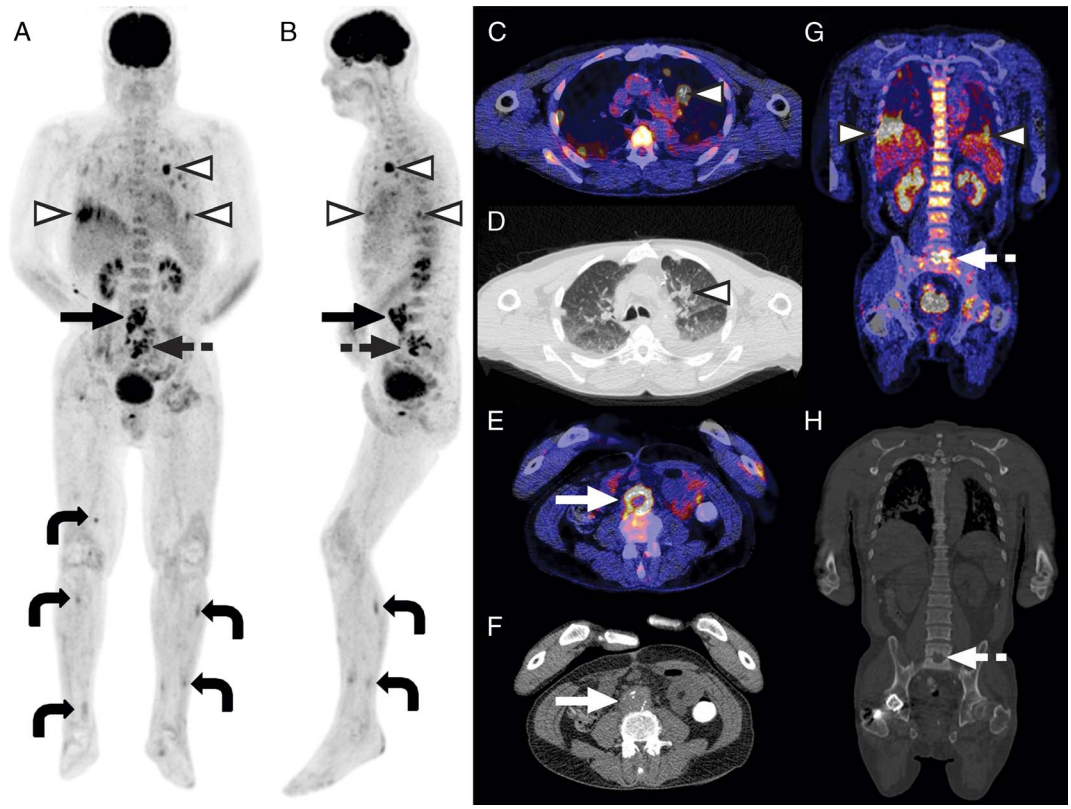

FIGURE 3. A 66-year-old man presented with fever, general malaise, and back pain 3 months after partial left nephrectomy because of renal cell carcinoma. MRI of the lumbar spine (not shown) suggested spondylodiscitis at the L5-S1 level. Biopsy at the L5-S1 level showed reactive changes but no signs of malignancy, whereas microbiological examination of the biopsy specimen was negative. The patient was given intravenous cefuroxime, but leukocyte and CRP levels remained high at 14.7×10^9 and 150 mg/L, respectively. In addition, blood cultures were positive for *Nocardia farcinica*. Transthoracic and transesophageal ultrasonography were negative for endocarditis. FDG-PET/CT was performed for depicting infectious foci. Coronal and sagittal maximum intensity projection FDG-PET (**A** and **B**), axial fused FDG-PET/CT (**C**) and low-dose CT (**D**) at the level of the chest, axial fused FDG-PET/CT (**E**) and low-dose CT (**F**) at the level of the lower abdominal aorta, and coronal fused FDG-PET/CT (**G**) and low-dose CT (**H**) showed multiple FDG-avid lesions, suggestive of an infected lower abdominal aorta (continuous arrows), spondylodiscitis at the L5-S1 level (dashed arrows), multiple septic lung emboli (arrowheads), and septic vasculitis in the lower extremities (bended arrows).

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TABLE 2. Diagnostic Power of FDG-PET/CT for Detecting an Infection Focus in Patients With BSI

Statistic	Value (%)	95% CI
Sensitivity	80.2	72.5–86.5
Specificity	79.6	66.5–89.4
Positive predictive value	90.8	85.3–94.4
Negative predictive value	61.4	52.5–69.6

with a median of 8.0 (IQR, 12.0) days between hospital admission and FDG-PET/CT and 14.0 (IQR 19.8) days between FDG-PET/CT and hospital discharge. The median duration of antibiotic treatment before FDG-PET/CT was 7.0 (IQR, 9.0) days. Of 185 included patients, 68 were immunocompromised, and 22 were on hemodialysis. Forty-eight patients had a BSI with *Staphylococcus aureus (*25%), 42 with Gram-negative rods (23%), 17 with enterococci (9%), 22 with coagulase-negative staphylococci (12%), 19 with streptococci (10%), 5 with yeast species (3%), and 5 other (3%). Twenty-seven patients (15%) had a polymicrobial BSI.

In 44 patients (24%), an infection focus was suggested on other imaging modalities (ultrasonography, X-ray, CT, or MRI) before FDG-PET/CT was performed. The 30-day all-cause mortality rate in our study population was 8% (n = 15).

Diagnostic Performance of FDG-PET/CT

FDG-PET/CT was positive for an infection focus in 120 (64.9%) of 185 scans. The most common infection foci identified on FDG-PET/CT were spondylodiscitis or sacroiliitis (15%), pulmonary infection (11%), vascular graft infection (6%), renal or hepatic cyst infection (8%), and endocarditis (9%). According to the reference standard, 109 FDG-PET/CT scans were true positive, 11 false positive, 43 true negative, and 27 false negative. Five FDG-PET/CT scans were both false positive and false negative. This translated into a sensitivity of 80.2%, specificity of 79.6%, positive predictive value of 90.8% and negative predictive value of 61.4% for diagnosing an infection focus with FDG-PET/CT (Table 2).

In 6 of 11 false-positive scans, the final diagnosis was BSI of unknown origin, although an infection focus was suggested on FDG-PET/CT. In the other 5 scans, an infection focus was identified on FDG-PET/CT, but the final discharge diagnosis mentioned another infection focus than the focus found on FDG-PET/CT.

In 8 of 27 false-negative scans, the final diagnosis was (possible) endocarditis based on the modified Duke criteria.[16] Seven of these 8 patients had an artificial heart valve, and in 3 patients, the myocardial FDG uptake was not fully suppressed, despite a high-fat, low-carbohydrate diet before FDG-PET/CT. There were 3 cases with probable cholangitis and 2 cases of urosepsis that were not identified on FDG-PET/CT.

The results of imaging performed before FDG-PET/CT and corresponding FDG-PET/CT results, subdivided by the most common discharge diagnoses, are shown in Table 3. The types of

TABLE 3. Alternative Imaging Results Before FDG-PET/CT and Subsequent FDG-PET/CT Results Subdivided by Discharge Diagnosis

Discharge Diagnosis	Imaging Performed Before FDG-PET/CT	Infection Found on Imaging Before FDG-PET/CT	Infection Found on FDG-PET/CT
Cyst infection (n = 11)	No relevant imaging: 5	—	5 (100%)
	Abdominal CT: 2	0 (0%)	2 (100%)
	Renal ultrasound: 3	0 (0%)	2 (67%)
	CT and ultrasound: 1	0 (0%)	1 (100%)
Endocarditis (n = 18)	No relevant imaging: 6	—	2 (33%)
	TTE: 3	1 (33%)	3 (100%)
	TEE: 3	0 (0%)	2 (67%)
	TTE and TEE: 4	0 (0%)	3 (75%)
	Thoracic CT: 1	0 (0%)	0 (0%)
	Thoracic CT and TEE: 1	1 (100%)	1 (100%)
Hepatobiliary infection (n = 9)	No relevant imaging: 2	—	1 (50%)
	Abdominal MRI: 2	1 (50%)	1 (50%)
	Abdominal ultrasound: 2	0 (0%)	2 (100%)
	Abdominal CT and ultrasound: 2	1 (50%)	2 (100%)
	Abdominal MRI and ultrasound: 1	0 (0%)	0 (0%)
Pulmonary infection (n = 11)	No relevant imaging: 1	—	1 (100%)
	Thoracic X-ray: 9	4 (44%)	8 (89%)
	Thoracic CT and X-ray: 1	0 (0%)	1 (100%)
Spondylodiscitis or sacroiliitis (n = 27)	No relevant imaging: 7	—	7 (100%)
	Vertebral column MRI: 11	10 (91%)	11 (100%)
	Vertebral column CT: 5	2 (40%)	5 (100%)
	Vertebral column CT and MRI: 4	4 (100%)	4 (100%)
Vascular graft infection (n = 8)	No relevant imaging:		
	TEE of graft: 2	0 (0%)	2 (100%)
	MRI of graft: 2	2 (100%)	2 (100%)
	MRI and TEE of graft: 1	0 (0%)	1 (100%)

TTE indicates transthoracic echocardiogram; TEE, transesophageal echocardiogram.

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pathogens and corresponding FDG-PET/CT results, subdivided by the most common diagnoses at discharge, are shown in Table 4.

Clinical Treatment After FDG-PET/CT

In 73 (39%) of 185 patients, the antibiotic regimen was changed shortly after FDG-PET/CT. These changes included starting antibiotic treatment, cessation of antibiotic treatment, or treatment with different antibiotics. In 24 (13%) of 185 patients, surgical procedures were performed shortly after FDG-PET/CT to cure infection. Infected endovascular grafts were removed in 8 patients, abcesses were drained in 4 patients, and an implantable cardioverter-defibrillator was removed in 2 patients. The other surgical procedures included removal of an infected gamma nail in 1 patient, removal of a subclavian central line in 1 patient, hepatobiliary stenting in 3 patients, resection of infected organs in 3 patients (1 sigmoidectomy, 1 pulmonary lobectomy, and 1 nephrectomy), drainage of pleural empyema in 1 patient, and retroperitoneal debridement in 1 patient with pancreatitis. The surgeries were related to infection findings on FDG-PET/CT in 18 (75%) of 24 patients. In 50 (27%) of 185 patients, imaging or gastrointestinal endoscopy was performed to confirm positive results of FDG-PET/CT. MRI was performed in 18 patients (10%), CT in 12 patients (6%), and ultrasound in 6 patients (3%). These results were congruent with FDG-PET/CT results in 49 (98%) of 50 patients. There was one false-positive FDG-PET/CT result, where a lesion was suspected to be an abscess on FDG-PET/CT, but diagnostic CT showed the lesion to more likely represent a hematoma.

TABLE 4. Causative Pathogen and FDG-PET/CT Result Subdivided by Discharge Diagnosis

Pathogen and Infection Focus	No. Cases	No. Cases Correctly Diagnosed on FDG-PET/CT
Coagulase-negative staphylococci	22	18 (81%)
Endocarditis	1 (4.5%)	1 (100%)
Spondylodiscitis	2 (9.1%)	2 (100%)
Pulmonary infection	1 (4.5%)	1 (100%)
Other	8 (36.4%)	6 (75%)
BSI of unknown origin	10 (45.5%)	8 (80%)
S. aureus	48	36 (75%)
Endocarditis	6 (12.5%)	1 (17%)
Spondylodiscitis	14 (29.2%)	14 (100%)
Vascular graft infection	2 (4.2%)	2 (100%)
Other	19 (39.6%)	13 (68%)
BSI of unknown origin	7 (14.6%)	6 (86%)
Streptococci	19	17 (89%)
Endocarditis	8 (42.1%)	6 (75%)
Spondylodiscitis	3 (15.8%)	3 (100%)
Vascular graft infection	3 (15.8%)	3 (100%)
Other	3 (15.8%)	3 (100%)
BSI of unknown origin	2 (10.5%)	2 (100%)
Enterococci	17	13 (76%)
Hepatic/renal cyst infection	1 (5.9%)	1 (100%)
Spondylodiscitis	2 (11.8%)	2 (100%)
Vascular graft infection	1 (5.9%)	1 (100%)
Other	3 (17.6%)	1 (33%)
BSI of unknown origin	10 (58.8%)	8 (80%)
Gram-negative rods	42	34 (81%)
Hepatic/renal cyst infection	9 (21.4%)	8 (89%)
Endocarditis	1 (2.4%)	0 (0%)
Hepatobiliary infection	6 (14.3%)	5 (83%)
Other	16 (38.1%)	12 (75%)
BSI of unknown origin	10 (23.8%)	9 (90%)
Yeast	5	4 (80%)
Systemic candidiasis	2 (40%)	2 (100%)
Pulmonary infection	1 (20%)	1 (100%)
Drain infection	1 (20%)	0 (0%)
rUrethral catheter	1 (20%)	1 (100%)
Polymicrobial	27	24 (88%)
Spondylodiscitis	3 (11.1%)	3 (100%)
Vascular graft infection	2 (7.4%)	2 (100%)
Pulmonary infection	3 (11.1%)	3 (100%)
Other	10 (37.0%)	8 (80%)
BSI of unknown origin	9 (33.3%)	8 (89%)

Factors Associated With FDG-PET/CT Outcome

On univariate logistic regression, a significant negative association was found between FDG-PET/CT yield and 3 parameters: blood cultures positive for enterococci (OR, 0.26; $P = 0.014$), days between hospital admission and the FDG-PET/CT scan (OR, 0.97 per day increase; $P = 0.030$), and days of antibiotic treatment before the FDG-PET/CT scan (OR, 0.95 per day increase; $P = 0.009$) (Table 5). Age, sex, days between admission and FDG-PET/CT, hemodialysis, CRP level, leukocyte count, blood cultures positive for coagulase-negative staphylococci, S. *aureus*, streptococci, Gram-negative rods, yeast species, or polymicrobial blood cultures were not significantly associated with FDG-PET/CT yield.

On subsequent multivariate logistic regression, blood cultures positive for enterococci (OR, 0.14; $P = 0.019$) and days of antibiotic treatment before FDG-PET/CT (OR, 0.94 per day increase; $P = 0.014$) remained as independently associated with FDG-PET/CT outcome (Table 5).

In patients who received antibiotics for less than 7 days before FDG-PET/CT, a true-positive infection focus was found in 71% (56/79). In patients who received antibiotics for 8 to 14 days before FDG-PET/CT, a true-positive infection focus was found in 52% (22/42). After 15 to 21 days of antibiotic treatment, a true-positive infection focus was found in 61% (8/13), and for 22 days or more, this declined to 38% (5/13).

Patients with a true-positive infection focus on FDG-PET/CT were discharged from the hospital after a median duration of 18.0 (IQR, 23.5) days after FDG-PET/CT. Patients with a negative FDG-PET/CT were discharged after a median duration of 12.0 (IQR, 12.0) days. The duration between FDG-PET/CT and hospital discharge was significantly associated with a true-positive FDG-PET/CT result ($P = 0.010$) (Table 6). The 30-day mortality rate was 8% (15/185), with no significant differences between the true-positive and negative population ($P = 0.12$).

DISCUSSION

The results of this study show that several clinical and biochemical factors significantly influence the diagnostic yield of FDG-PET/CT in detecting an infection focus in patients with a BSI.

The most important finding was that the duration of antimicrobial treatment before FDG-PET/CT negatively affected the diagnostic yield of FDG-PET/CT. On multivariate logistic regression analysis, the OR was calculated at 0.94 per day increase. This means that after 12 days of antibiotic treatment, the odds of identifying an infection focus on FDG-PET/CT are less than half the odds of identifying an infection focus in a patient who has not received any antibiotic treatment yet. This indicates that FDG-PET/CT should

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TABLE 5. Factors Associated With a True-Positive Result on FDG-PET/CT for Any Infection Focus

Parameter	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
Clinical				
Age	1.00* (0.98–1.02)	0.91		
Male sex	0.80 (0.43–1.47)	0.47		
Days between admission and FDG-PET/CT	0.97* (0.95–1.00)	0.030	-	-
Immunodeficient status	0.62 (0.34–1.13)	0.12		
Hemodialysis	1.25 (0.50–3.15)	0.63		
Days of antibiotic treatment before FDG-PET/CT†	0.95* (0.91–0.99)	0.009	0.94 (0.90–0.99)‡	0.014
Laboratory				
CRP	1.00* (1.00–1.01)	0.10	-	-
Leukocytes	1.00* (0.97–1.03)	0.91		
Microbiology				
Coagulase-negative staphylococci (n = 23)	0.44 (0.18–1.08)	0.073	-	-
S. aureus (n = 48)	1.38 (0.70–2.73)	0.36		
Streptococci (n = 19)	2.09 (0.72–6.08)	0.18		
Enterococci (n = 17)	0.26 (0.090–0.76)	0.014	0.14 (0.027–0.72)‡	0.019
Gram-negative rods (n = 42)	1.18 (0.58–2.38)	0.66		
Yeast (n = 5)	2.86 (0.31–26.01)	0.35		
Polymicrobial (n = 27)	1.02 (0.44–2.33)	0.97		

Notes: *Odds ratios for continuous variables are given per unit increase. †147 of 185 patients included. Nine patients received intermittent antibiotic treatment before FDG-PET/CT (because they were on hemodialysis) and were excluded, and for 30 patients, the start or end date of antibiotic treatment was not documented.

‡129 of 185 patients included because of 56 missing cases.

ideally be performed before or otherwise as soon as possible after antibiotic treatment is started. The duration between hospital admission and performing FDG-PET/CT was significantly associated with FDG-PET/CT outcome, where longer duration of admission led to a lower odds of finding an infection focus. However, this relation was only significant on univariate but not on multivariate logistic regression analysis.

A BSI based on enterococci was also found to be an independent predictive factor of FDG-PET/CT yield. When patients had a BSI with enterococci, the odds were less than 7 times the odds that a true-positive infection focus would be identified compared with other types of bacteria according to multivariate analysis. This is clinically relevant, given the fact that approximately 10% of all BSIs are caused by enterococci.[17] Most BSIs with enterococci have a genitourinary, endovascular, or intra-abdominal focus.[17–19] FDG-PET/CT has several pitfalls in diagnosing genitourinary and bowel infection because of physiologic FDG uptake in the endometrium and ovaries and renal excretion of FDG. Physiologic FDG uptake also occurs in the colon and small intestine, and use of the common antidiabetic drug metformin increases colonic FDG uptake further which can easily obscure infection.[20–22]

In this patient population, a sensitivity of 80.2% and a specificity of 79.6% of FDG-PET/CT were found for identifying an infection focus in patients with a BSI. These results are in line with previous studies on the diagnostic power of FDG-PET/CT for various infectious diseases.[23] The specificity of FDG-PET/CT in our population was slightly lower than could be expected from previous studies. This can probably be explained by the fact that a large number of infectious foci that were "missed" on FDG-PET/CT were eventually diagnosed based on clinical criteria, were "probable" diagnoses, or were diagnoses of exclusion. For example, almost one third of our false-negative population consisted of (possible) endocarditis patients based on modified Duke criteria. Also, FDG-PET/CT is known to have a low sensitivity for diagnosing native valve endocarditis.[24]

Although an infection focus had already been found on alternative imaging performed before FDG-PET/CT in some cases, the majority of infection foci were primarily detected using FDG-PET/CT. This was especially true for cyst infection and endocarditis. A diagnosis of spondylodiscitis or sacroiliitis was already established by other imaging modalities in the majority of cases, but FDG-PET/CT was still performed in those cases to not only confirm the results but also perform whole-body evaluation of possible metastatic foci.

Shortly or directly after FDG-PET/CT, changes in clinical management occurred in a large number of cases. These changes included antibiotic treatment modifications, surgical drainage or removal of infected material, and follow-up imaging to confirm or get a more detailed view of infection foci. Because of the retrospective design of the study, however, it is impossible to relate all changes directly to FDG-PET/CT outcome.

The results of this study show there are several clinical factors that can predict the outcome and, therefore, clinical utility of FDG-PET/CT in patients with BSI. Because FDG-PET/CT is a relatively expensive procedure,[13] clinicians should always consider whether it would be worthwhile to perform an FDG-PET/CT scan. Our results indicate that in a patient with a BSI based on enterococci who has already received antibiotics for a considerable amount of time, this may not be the case.

TABLE 6. Relation Between Parameters Collected After the FDG-PET/CT Scan and True-Positive Infection Focus or Negative Result on FDG-PET/CT

Parameter	FDG-PET/CT True Positive	FDG-PET/CT Negative	*P*
Duration between FDG-PET/CT scan and hospital discharge (d)	18.0 (23.5)*	12.0 (12.0)*	0.010
30-d mortality	6/109 (6%)	9/76 (12%)	0.12

*Median (IQR).

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In a previous study of Kagna et al that included 153 patients suspected of infection, the effects of antibiotic treatment on FDG-PET/CT outcome have been described.[14] They concluded that antibiotic treatment had no statistically significant effects on FDG-PET/CT outcome. However, only 31 of 153 patients had a microbiologically proven BSI. They compared maximum FDG standard uptake values of infection foci between patients that received appropriate and inappropriate antibiotic treatment and compared FDG uptake between patients who received appropriate antibiotic treatment for less or more than 1 week. Both analyses show no statistically significant differences. However, a difference in FDG uptake does not necessarily mean that an infection focus is more or less likely to be found. Also, they only included patients with true-positive infections in their analyses, and by excluding true-negative results, they did not take into account what effects antibiotic treatment had on not finding any infection focus.

Our study was accompanied by some limitations. First, because of the retrospective design of the study, there may have been selection bias. Some patients with BSI may have been too ill, or not ill enough, to be referred to FDG-PET/CT scanning. Other patients may not have undergone FDG-PET/CT because the focus of infection was already established by other diagnostic measures and the treating physician deemed FDG-PET/CT unnecessary. As a consequence, the results of this study may not reflect findings in the general patient with BSI. Second, the reference standard to distinguish between true-positive, false-positive, true–negative, and false-negative FDG-PET/CT results was suboptimal. Sometimes, follow-up imaging or histopathological confirmation of FDG-avid foci were not available, hence the final diagnosis was only based on the results of the FDG-PET/CT scan itself, together with treatment outcome and clinical follow-up. Also, several cases were considered as false negative because final diagnoses were diagnoses of probability such as endocarditis based on modified Duke criteria, for which no proof was found on FDG-PET/CT or the final diagnosis was a well-known reason for being false negative on FDG-PET/CT because of limited spatial resolution or high physiological background uptake in the liver or bladder.[25]

CONCLUSIONS

FDG-PET/CT is a useful method for detecting an infection focus in patients with BSI. Longer duration of antibiotic treatment before FDG-PET/CT and BSI based on enterococci were significantly and independently associated with a lower detection rate of an infection focus on FDG-PET/CT in patients with BSI. Clinicians should take this into account when considering FDG-PET/CT scan for this indication.

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