

Retrospective Study Comparing WBC scan and ¹⁸F-FDG PET/CT in Patients with Suspected Prosthetic Vascular Graft Infection

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WHAT THIS PAPER ADDS

This study is the second and the largest to compare ¹⁸F-fluoro-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) and white blood cell scan in the diagnosis of prosthetic vascular graft infections (PVGIs). The white blood cell scan was more accurate than ¹⁸F-FDG PET/CT. Moreover, there was only one false negative ¹⁸F-FDG PET/CT result under antibiotic therapy. Nuclear imaging results should be included in the diagnostic criteria for prosthetic vascular graft infections. Computed tomography angiography still remains the first radiological examination to perform when there is suspicion of PVGI. A white blood cell scan should be considered for patients with a suspicion of prosthetic vascular graft infection and negative or equivocal computed tomography angiography results. If a white blood cell scan is not readily available, ¹⁸F-FDG PET/CT can be performed. If the result is negative, prosthetic vascular graft infections can be ruled out thanks to a good negative predictive value. However, a positive result should be interpreted with caution, especially for thrombosed grafts.

Objectives: Prosthetic vascular graft infections (PVGIs) are associated with high mortality rates. To improve treatment outcome, an early and definite diagnosis is critical, and current diagnostic criteria are often insufficient. The accuracy of 2-deoxy-2-[fluorine-18]-fluoro-D-glucose positron emission tomography integrated with computed tomography (¹⁸F-FDG PET/CT) and white blood cell (WBC) scan for the diagnosis of PVGI were compared.

Methods: A retrospective single centre study was conducted on patients undergoing WBC scan and ¹⁸F-FDG PET/CT for a suspected PVGI between April 2013 and June 2016 at the Bordeaux University Hospital, France. The diagnostic value of both imaging tests was assessed for all grafts, using receiver operating characteristic (ROC) curve analysis. Images were independently interpreted by two nuclear medicine physicians blinded to the patients' clinical and other imaging data.

Results: Thirty-nine patients were included, of whom 15 had PVGI. Antibiotic treatment was started before nuclear imaging for 16 patients, including nine patients with a PVGI. The 96 grafts of these patients were analysed, and 19 were infected. The diagnostic value of the WBC scan was significantly higher than ¹⁸F-FDG PET/CT (ROC AUC = 0.902, 95% CI 0.824–0.980, and 0.759, CI 95% (0.659–0.858), respectively, $p = .0071$). Interobserver agreement was good for ¹⁸F-FDG PET/CT and excellent for WBC scan (kappa value of 0.76, 95% CI 0.62–0.9, and 0.97, 95% CI 0.92–1, respectively). Only one patient had a false negative ¹⁸F-FDG PET/CT result under antibiotic therapy.

Conclusion: The WBC scan has a better diagnostic value than ¹⁸F-FDG PET/CT for PVGI diagnosis.

Keywords: Prosthetic vascular graft infection, ¹⁸F-FDG PET/CT, WBC scan

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INTRODUCTION

Prosthetic vascular graft infections (PVGIs) are associated with high morbidity and mortality rates.^{1,2} Surgical treatment is burdened with high morbidity and mortality and

cannot be performed without a definitive diagnosis of infection. There are still no agreed diagnostic criteria; however the definition proposed by Fitzgerald et al.³ has been used in recent studies.^{4,5} These criteria may often be insufficient, especially in late onset and latent infections. Even when graft excision is possible, graft culture remains negative in 4–45%¹ because of the frequent use of antimicrobial therapy before graft removal and due to the presence of biofilm associated micro-organisms. Laboratory tests for inflammation are not specific to PVGI. Radiological criteria may also be difficult to fulfil since computed tomography (CT) angiography has a low sensitivity in low grade infections (around 55%) despite a high specificity.⁶

Therefore, the diagnostic performance of nuclear imaging has been evaluated in many studies. Unfortunately, the use of different diagnostic and nuclear imaging interpretation criteria explains the great variations in the results.⁶ Performance of the white blood cell (WBC) scan and ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has been compared in only one prospective study of 11 patients with no significant difference.⁷ The primary objective was to compare the accuracy of the WBC scan vs. ¹⁸F-FDG PET/CT in diagnosing PVGI.

METHODS

Patient population

This study was a retrospective analysis of consecutive adult patients with a suspected PVGI from four hospitals in the Aquitaine region, France, between April 2013 and June 2016 at the Bordeaux University Hospital. The patients were recruited by infectious diseases specialists or vascular surgeons at Bordeaux University Hospital during consultation or hospitalisation. Moreover, as a tertiary referring centre, many patients were referred to the institution by vascular surgeons or infectious disease specialists from secondary centres.

Patients with a confirmed diagnosis of PVGI were not eligible for recruitment, based on at least one major clinical criterion (clinical graft-cutaneous or graft-enteric fistulae, exposed grafts in open wounds) and at least one major CT angiogram criterion (perigraft air or fluid persisting for more than 8 weeks post-operatively). Every patient had CT angiography analysed by specialised radiologists before ¹⁸F-FDG PET/CT and the WBC scan. Patients who needed emergency surgery before undergoing the two tests were not eligible for recruitment either.

The inclusion criteria were adults over 18, with a suspected PVGI. PVGI was suspected in patients with one or several vascular grafts and at least one Fitzgerald's criteria [3]. The exclusion criteria were children, patients who did not undergo the two nuclear imaging tests and patients for whom the delay between two tests was longer than 45 days or if there had been clinical or therapeutic modification between the two examinations.

During the study period, all the eligible patients had requested both ¹⁸F-FDG PET/CT and WBC scan. Clinical signs and demographic, biological, and imaging data were

recorded for each patient by an infectious disease specialist (M.P.). Follow up occurred during consultation or hospitalisation by infectious diseases specialists and vascular surgeons. Follow up data were recorded in September 2017. The study protocol was approved by the local ethics committee (Comité de Protection des Personnes Sud-Ouest et Outre-Mer, reference DC 2016/106). Written informed consent was obtained from all participants included in this study.

Case definition of PVGI

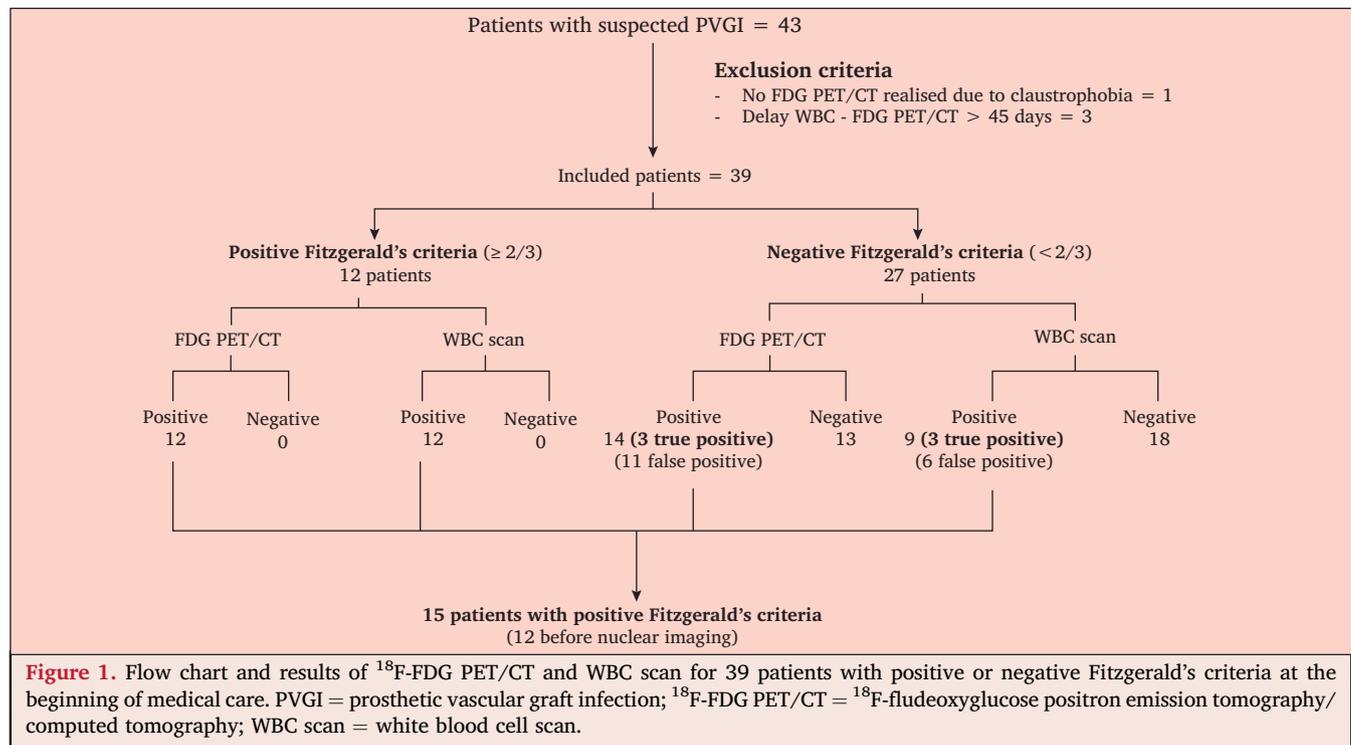
PVGI was diagnosed according to the Fitzgerald's criteria,³ already used in several studies.^{4,5} They were applied to all grafts at the end of follow up by an infectious diseases physician, blinded to nuclear imaging results, who made the final diagnosis (M.P.). The diagnosis of PVGI was retained if at least two of the three criteria (microbiological, clinical, and paraclinical) were present. The microbiological criterion was a positive culture of blood sample or intra-operative specimen (after vortexing and sonication). For less virulent micro-organisms which might be contaminants, i.e. coagulase negative *Staphylococcus* (CoNS), *Propionibacterium* spp., and *Corynebacterium* spp., at least two positive samples were required. The clinical criterion was the presence of general or local signs of sepsis. Paraclinical criteria were the presence of biological or radiological signs of infection. Finally, as usually done in the centre, all cases were discussed during a multidisciplinary group meeting, with nuclear imaging, clinical, and microbiological data. However, these conclusions did not change the patient's status as previously defined by infectious disease physicians.

Analysis of the impact of nuclear medicine examinations on medical care

Fitzgerald's criteria³ were applied before nuclear imaging and at the end of follow up, to determine patients who could have been diagnosed sooner thanks to ¹⁸F-FDG PET/CT and/or WBC scan (Fig. 1).

WBC scan protocol

Autologous radiolabeled WBCs were prepared and separated according to the European Association of Nuclear Medicine (EANM) guidelines and according to the characteristics of Ceretec® for labelling of neutrophils with ^{99m}Tc-HMPAO (technetium-99m hexamethylpropyleneamine oxime).⁸ Radiolabelling efficiency was always in the range of 70–85%. Whole body and spot planar images were obtained after 4–6 h (early images; 10 min acquisition) and 20–24 h (delayed images; 15 min acquisition) after re-infusion of 148–555 MBq (megabequerel) of Tc-99m HMPAO WBC. Resolution of the CT scans was 2.2 mm and images were localised with a pixel size of 4.5 mm, similar to nuclear medicine emission images. Matching pairs of X-ray transmission and radionuclide emission images were fused using Xeleris™ software (GE Healthcare, Milwaukee, WI, USA).



^{18}F -FDG PET/CT protocol

^{18}F -FDG PET was performed according to EANM guidelines.⁹ After intravenous injection of body weight adapted ^{18}F -FDG, patients rested for a standardised uptake time of 60 min. All scans were performed with an integrated ^{18}F -FDG PET/CT system (Discovery VCT; GE Healthcare). Low dose CT for attenuation correction was acquired from the mid-thigh to the vertex of the skull. Directly after CT data acquisition, ^{18}F -FDG PET data were acquired using the three dimensional mode (3D). The 3D volume of interest was used for quantification (size 1.7 cm³). Images were analysed on an AW Workstation Version 4.4 (GE Healthcare Biosciences, Pittsburgh, PA, USA).

Image analysis and interpretation

WBC scan and ^{18}F -FDG PET/CT images were independently and retrospectively interpreted by two nuclear medicine physicians (J.B.P, hospital practitioner specializing in PVGI, and J.B.R., senior resident) blinded to the clinical and radiological data of the patients. In case of disagreement between the two examiners, a consensus reading was performed. The ^{18}F -FDG PET/CT scale for PVGI diagnosis described by Sah et al. was used.¹⁰ This five point visual grading score takes into account the FDG uptake patterns and CT information as follows: Grade 1, normal background activity; Grade 2, mildly increased, but diffuse FDG uptake along the graft (mild uptake, less than twice the blood pool activity in the ascending aorta; strong uptake, more than twice the blood pool activity in the ascending aorta); Grade 3, focal, but only mild FDG uptake or strong diffuse FDG uptake along the graft; Grade 4, focal and intense FDG uptake (diffuse FDG uptake along the graft); Grade 5, focal

and intense FDG uptake plus fluid collections/abscess formation.

The WBC scan was classified as negative when no sites of increased uptake were observed. The WBC scan was considered positive when there was at least one focal increased accumulation along the graft on delayed images and/or by an increase in radioactivity from early to delayed images. Images in which activity decreased from early to late were considered negative.

CT was considered positive if there was perigraft air or fluid persisting for more than 8 weeks post-operatively, a false aneurysm, or a graft-cutaneous, graft-enteric, or graft-ureteral fistula.

Statistical analysis

Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy were estimated along with the 95% exact binomial confidence interval (CI) for the diagnosis of PVGI for CT angiography, the WBC scan and ^{18}F -FDG PET/CT, and calculated in comparison to Fitzgerald's criteria. Characteristics of patients and grafts were estimated as medians along with interquartile range (IQR) or means with range. Missing data were recorded and descriptive statistics calculated on the patient population with the available data.

The diagnostic value of WBC scan and ^{18}F -FDG PET/CT, defined by the sum of true positive and true negative results divided by all results, were compared using ROC curve analysis. ROC areas under the curve (AUC) were compared with the method of DeLong et al.¹¹ A p value < 0.05 was considered statistically significant. Statistical analyses were performed with Stata version 13.1 software (StataCorp,

Cary, NC, USA). Inter-examiner agreement was evaluated with Cohen's kappa statistics and classified according to the scale of Landis and Koch¹² as follows: kappa values of 0.2 or less, poor; 0.21–0.4, fair; 0.41–0.6, moderate; 0.61–0.8 as good; and 0.81–1.0, excellent agreement.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Comité de Protection des Personnes Sud-Ouest et Outre-Mer, reference DC 2016/106) and with the 1964 Helsinki declaration and its later amendments.

RESULTS

Patient population

Forty-three patients were evaluated for inclusion; 39 were finally included and received both ¹⁸F-FDG PET/CT and the WBC scan (Fig. 1). At inclusion, before nuclear imaging and a possible operation, 12 patients had at least two of three Fitzgerald criteria. At the end of follow up, after medical and surgical treatment, 15 patients had at least two of three Fitzgerald criteria and were considered infected. The main characteristics of the 39 patients are presented in Table 1. Antibiotic treatment was started before nuclear imaging in 16 patients (41%), seven with oral and nine with intravenous therapy, with a median duration before nuclear imaging examinations of 21 days (IQR 13–30). These antibiotic therapies were empirical in seven patients; the remaining nine patients had positive microbiological samples before antibiotic therapy (eight bacteremia, one local swab). Antibiotic therapy was started because of bacteremia in eight patients, isolated fever in two patients, and local signs of infection in six patients.

The median interval between CT angiography and ¹⁸F-FDG PET/CT or WBC was 16.6 days (IQR 11.5–21.7). The median time between ¹⁸F-FDG PET/CT and WBC scan was 13 days (IQR 4–28). Thirty patients underwent ¹⁸F-FDG PET/CT first and nine patients WBC scan first. The median follow up was 13 months (IQR 5–25). The median number of grafts per patient was two (IQR 1–4), the maximum number of grafts per patient was eight. Ninety-six grafts were analysed and 19 were infected (Table 2). Four patients had two different infected grafts. Thirty-three grafts (34.4%) were thrombosed. Age of thrombosis was available in 16 of 33 grafts, with a median of 10.5 months (IQR 5.75–15). Fourteen patients (12 with confirmed PVGI) underwent surgery. Microbiological culture was positive for only three grafts, one with *Staphylococcus aureus*, one with *Enterobacter cloacae*, and one with two potential contaminants (*P. acnes* and *Staphylococcus epidermidis*).

CT angiography results

CT angiography yielded good accuracy (ROC AUC = 0.697, 95% CI 0.581–0.813, accuracy 86.5%), and specificity (97%) but a low sensitivity (42%) (Table 3). There were two false

positive results, one because of a haematoma around a thoracic graft and the other because of a pseudo-aneurysm.

¹⁸F-FDG PET/CT results

¹⁸F-FDG PET/CT yielded good diagnostic performance (sensitivity 85%, specificity 68.4%, accuracy 71.9%, ROC AUC = 0.759, 95% CI 0.659–0.858) (Table 3). Inter-observer agreement was good (kappa value = 0.76, CI 95% 0.62–0.9). There were 10 discrepancies on the 96 grafts analysed, resolved by consensus. ¹⁸F-FDG PET/CT accuracy was not significantly different from CT angiography, either for PVGI diagnosis ($p = .467$) or for thrombosed graft infection ($p = .130$).

WBC scan results

WBC scans yielded good diagnostic performance, with 89.5% sensitivity, 90.9% specificity, and 90.6% accuracy. ROC AUC was 0.902 (95% CI 0.824–0.980) (Table 3). NPV was very good, 97.2% (95% CI 90.4–99.2) (Table 3). Inter-observer agreement was excellent (kappa value = 0.97, 95% CI 0.92–1). There was only one discrepancy on the 96 grafts analysed, resolved by consensus. The WBC scan was significantly more accurate than CT angiography for PVGI diagnosis ($p = .005$) and thrombosed graft infection ($p = .0004$).

Comparison of ¹⁸F-FDG PET/CT and WBC scan results

Using ROC curve analysis, the WBC scan was significantly better than ¹⁸F-FDG PET/CT for the diagnosis of PVGI ($p = .0071$), and also for the diagnosis of thrombosed grafts infection ($p < .0001$). The sensitivity of both techniques was not altered in the subset of patients on antibiotic therapy, and the WBC scan was significantly more accurate in this subgroup ($p = .0096$).

When Fitzgerald's criteria were applied at the beginning of medical care, there were 12 patients with at least two out of three criteria and all had both positive ¹⁸F-FDG PET/CT and WBC scan results (Fig. 1). Of the 27 patients with fewer than two criteria at inclusion, three had at least two criteria at the end of follow up and were considered infected. For the first one, CT images worsened with the accumulation of fluid, and the two others were operated on and signs of infection were observed during surgery. For these three patients, ¹⁸F-FDG PET/CT and WBC scan were both positive (Fig. 1).

The first patient had an aorto-bi-iliac bypass with no clinical or radiological signs of infection. He only suffered from lower back pain and had positive laboratory tests for inflammation. He was not initially considered infected, despite positive ¹⁸F-FDG PET/CT and the WBC scan results. Fluid appeared around the graft on CT angiography 10 months after nuclear imaging, and the diagnosis of PVGI was finally confirmed. The second one presented with an isolated fever but had no radiological signs of PVGI. ¹⁸F-FDG PET/CT and the WBC scan showed a positive result on his aorto-bi-femoral bypass. Suspecting PVGI, the graft was removed 16 days later, and gross purulence was found

Table 1. Baseline characteristics of 39 patients with suspected PVGI

Characteristics	Patients (n = 39)	Infected (n = 15)	Non-infected (n = 24)
Sex, n, Female/Male	3/36	0/15	3/21
Age, median (IQR)	68.5 (56.5–75)	69 (58.8–77.5)	68.5 (58–75)
Comorbidities, n (%)			
Cardiac disease ^a	20 (51.3)	9 (60)	11 (45.8)
Current tobacco use ^b /former smoker	8 (20.5)/9 (23.1)	1 (6.7)/4 (26.7)	7 (29.2)/5 (20.8)
Diabetes mellitus	7 (17.9)	2 (13.3)	5 (20.8)
Immunodeficiency ^c	9 (23.1)	4 (26.7)	5 (20.8)
Neutropenia	0	0	0
Kidney failure/haemodialysis	7 (17.9)/1 (2.6)	3 (20)/0	4 (20.8)/1 (4.2)
Vasculitis ^d	1 (2.6)	0	1 (4.2)
Marfan syndrome	1 (2.6)	0	1 (4.2)
Number of graft per patient, median (IQR)	2 (1–4)	3 (1–4.75)	2 (1–3)
Clinical symptoms, n (%)			
Fever	17 (43.6)	10 (66.7)	7 (29.2)
Local signs ^e	11 (28.2)	9 (60)	2 (8.3) [§]
Sinus tract infection	5 (12.8)	3 (20)	2 (8.3) [§]
Gastrointestinal bleeding	1 (2.6)	0	1 (4.2)
Abdominal pain	1 (2.6)	1 (6.7)	0
None	8 (20.5)	0	8 (33.3)
Pre-operative laboratory findings, n/total tested (%)			
Positive blood cultures	8/17 (47.1)	5/9 (55.6)	3/6 (50)
Serum C-reactive protein >10 mg/L	24/36 (66.7)	12/15 (80)	12/21 (57.1)
C-reactive protein, mean (range)	75.3 (3–350)	123 (6–300)	49.2 (3–350)
Blood granulocyte count > 7.5 G/L	12/36 (33.3)	6/15 (40)	6/21 (28.6)
Blood granulocyte count, mean (range)	6.6 (1.6–20)	8 (1.6–20)	5.9 (2.1–11.3)
Pre-operative CT angiography findings, n (%)			
False aneurysm	2 (5.1)	1 (6.7)	1 (4.2)
Graft thrombosis	16 (41)	5 (33.3)	11 (45.8)
Perigraft fluid/air/abscess	6 (15.4)	5 (33.3)	1 (4.2) ^h
Subcutaneous abscess with skin fistula	3 (7.8)	1 (6.7)	2 (8.3) [§]
Sternal fistula	1 (2.6)	1 (6.7)	0
Increasing aneurysm size	1 (2.6)	0	1 (4.2)
Normal CT	16 (41)	4 (26.7)	12 (50)
Antibiotic treatment before nuclear imaging, n (%)	16 (41)	9 (60)	7 (29.2)
Antibiotic treatment duration before nuclear imaging in days, median (IQR)	21 (13–30)	24 (19.8–36)	20 (7–30)
Surgical treatment, n (%)			
Intra-operative findings, n/total described (%)			
Peri-prosthetic purulence	14 (35.9)	12 (80)	2 (8.3)
Inflammatory tissue	5 (12.8)	5 (33.3)	0
Inflammatory tissue	2 (5)	2 (13.3)	0
Failure of graft consolidation	3 (7.7)	3 (20)	0
Anastomotic disunion	2 (5.1)	0	2 (8.3)
Aorto-enteric fistula ^f	1 (2.6)	1 (6.7)	0
Capillary glycaemia before FDG PET/CT in g/L [median (IQR)]	0.9 (0.8–1)	0.84 (0.8–1)	0.9 (0.8–1.1)
Time between FDG PET/CT and WBC scan [median (IQR)]	13 (4–28)	5 (2.5–12.5)	18.5 (7–36)

PVGI = prosthetic vascular graft infection; IQR = interquartile range; CT = computed tomography; ¹⁸F-FDG PET/CT = ¹⁸F fludeoxyglucose positron emission tomography/computed tomography; WBC scan = white blood cell scan.

^a Cardiac disease: heart failure, coronary heart disease.

^b Current tobacco use: actual or stopped within two months.

^c Immunodepression: neoplasia, chemotherapy for neoplasia, immunosuppressive therapy.

^d Vasculitis: one patient with immunoglobulin A vasculitis.

^e Local clinical signs: local inflammation, local pain, sinus tract infection, purulent discharge.

^f Aorto-enteric fistula with the duodenum, small intestine and/or colon.

[§] Local abscesses with fistula close to the graft but no infection of the graft on the CT and during the follow up.

^h Collection corresponding to a haematoma with no infection.

intra-operatively, but the intra-operative specimen culture was negative. The third one also had an isolated fever; CT angiography images showed no signs of infection. ¹⁸F-FDG PET/CT and the WBC scan showed infection of the

femoropopliteal graft which was surgically removed five months later and gross purulence was found. Graft culture was positive for *S. aureus*. Finally, for these three patients, nuclear imaging could have allowed an earlier diagnosis.

Table 2. Baseline characteristics of 96 grafts from 39 patients with suspected PVGI

Characteristics	Grafts (n = 96)	Infected grafts (n = 19)	Non-infected grafts (n = 77)
<i>Type of graft, n(%)</i>			
Polyester	31 (32.3)	4 (21)	27 (35.1)
PTFE	14 (14.6)	7 (36.8)	7 (9.1)
Polyester + PTFE	2 (2.1)	1 (5.3)	1 (1.3)
Stent	8 (8.3)	0	8 (10.4)
Synthetic with unknown material	37 (38.5)	6 (31.6)	31 (40.2)
Biological graft (arterial allograft/venous homograft/bovine pericardium graft)	4 (4.2) (1/2/1)	1 (5.3) (0/1/0)	3 (3.9) (1/1/1)
<i>Type of implantation</i>			
Endovascular	25 (26)	5 (26.3)	20 (30)
Open surgery	71 (74)	14 (73.7)	57 (70)
<i>Location, n (%)</i>			
Aortic ^a	39 (40.6)	10 (52.6)	29 (37.7)
Peripheral ^b	56 (58.4)	9 (47.4)	47 (61)
Prosthetic dialysis grafts	1 (1)	0	1 (1.3)
<i>Age of the graft, n (%)</i>			
<4 months	11 (11.5)	5 (26.3)	6 (7.8)
>4 months	85 (88.5)	14 (73.7)	71 (92.2)
Median in years (IQR)	3 (0.9–6)	3 (0.5–9.5)	3 (1–6)
Graft thrombosis, n (%)	33 (34.4)	5 (26.3)	28 (62.7)
<i>Indication for primary implantation, n (%)</i>			
Aortic aneurysm (AA)/ruptured AA/thrombosed AA	17 (17.7)/1/1	4 (21)/0/0	16 (21)/1/1
Lower limb arteriopathy/arterial thrombosis	67 (69.8)/2 (2)	12 (63.2)/1(0.5)	55 (71.4)/1
Dialysis vascular access	1 (1)	0	1 (1.3)
Peripheral aneurysm	2 (2)	2 (10.5)	0 (0)
PVGI	3 (3.1)	0	3 (3.9)
Chronic mesenteric ischaemia	1 (1)	0	1 (1.3)
Aortic dissection	2 (2)	0	2 (2.6)
Congenital heart disease	1 (1)	1	0
Grafts removed by surgery, n (%)	16 (16.7)	10 (52.6)	6 (7.8)
Grafts positive in microbiological culture, n	3	3	0

PVGI = prosthetic vascular graft infection; PTFE = polytetrafluoroethylene; IQR = Interquartile range.

^a Aortic grafts: thoracic aorta, Bentall, aorto-bifemoral, aorto-bi-iliac, aorto-aortic.

^b Peripheral grafts: ilio-femoral, iliac, femorofemoral, femoropopliteal, popliteal, axillofemoral, mesenteric.

Table 3. ¹⁸F-FDG PET/CT and WBC scan performances for PVGI diagnosis

	ROC AUC, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, % (95% CI)
¹⁸ F-FDG PET/CT	0.759 (0.659–0.858)	85 (64–94.8)	68.4 (57.3–77.8)	41.5 (27.8–56.6)	94.5 (85.1–98.1)	71.9 (62.2–79.9)
WBC scan	0.902 (0.824–0.980)	89.5 (68.6–97.1)	90.9 (82.4–95.5)	70.8 (50.8–85.1)	97.2 (90.4–99.2)	90.6 (83.1–94.5)
CT	0.697 (0.581–0.813)	42.1 (23.1–63.7)	97.4 (91–99.3)	80 (49–94.3)	87.2 (78.5–92.7)	86.5 (78.2–91.9)

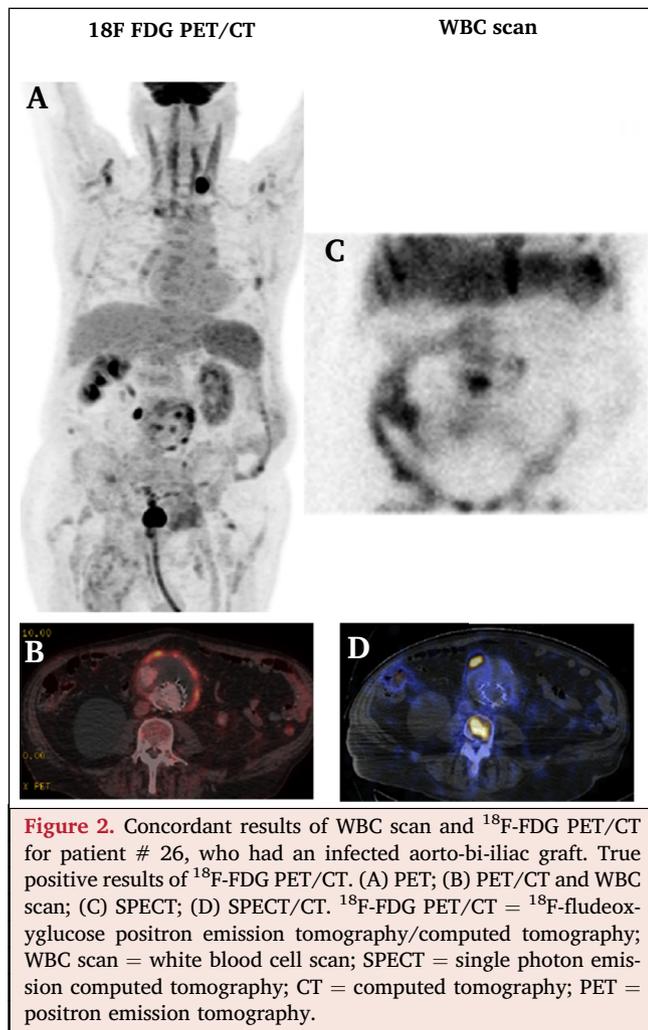
¹⁸F-FDG PET/CT = ¹⁸F fludeoxyglucose positron emission tomography/computed tomography; WBC scan = white blood cell scan; ROC AUC = receiver operating characteristic areas under the curve; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; PVGI = prosthetic vascular graft infection; CT = computed tomography.

In three cases, diagnosis of an extra-vascular infection was reached with both the WBC scan and ¹⁸F-FDG PET/CT. Knee arthritis next to an infected femoropopliteal graft was found in one patient. A subcutaneous abscess resulting in a skin fistula without any graft infection was found in two patients. No additional infectious site was identified by ¹⁸F-FDG PET/CT or WBC scan alone.

Discordant ¹⁸F-FDG PET/CT and WBC scan results

Selected images of discordant and concordant results are presented in Figs. 2–4.

False positive results. Nineteen patients (25 grafts) had false positive results. Thirteen patients (18 grafts) had false positive ¹⁸F-FDG PET/CT results. Besides one stent, all grafts had been implanted by open surgery. Graft composition was available only for 10 grafts, which were made of polyester, including two silver impregnated and one bovine gelatin sealed polyester. Several risk factors for false positive ¹⁸F-FDG PET/CT results were identified. Nine grafts were thrombosed. Two patients had type 2 diabetes mellitus, but capillary glycaemia before image acquisition was low. One patient had kidney failure. One graft had been

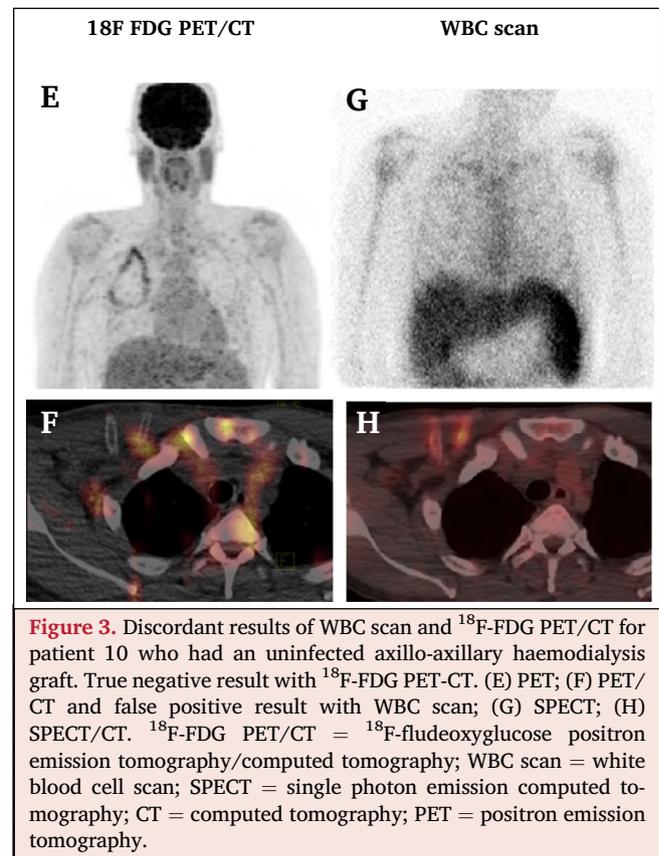


implanted two and a half months before ^{18}F -FDG PET/CT; all other grafts had been implanted more than three months before. One patient had a haematoma around his Bentall graft. Another patient had ongoing aortic endocarditis next to a thoracic aortic graft which was sealed with BioGlue® Surgical Adhesive made of bovine albumin and glutaraldehyde.

Only one patient had false positive WBC scan results. He had an axillo-axillary dialysis graft made of polytetrafluoroethylene which had been implanted by open surgery four months before, with no obvious reason for a false positive WBC scan result.

Five patients (6 grafts) had false positive ^{18}F -FDG PET/CT and WBC scan results. Two patients had been treated six and eight months before for a PVGI. Except for one endovascular thoracic aortic graft, all grafts had been implanted by open surgery. Risk factors for false positive results were identified in three cases: two grafts were thrombosed and one graft had been implanted only one month before.

False negative results. Four patients (four grafts) had false negative results. Two patients (two grafts) had false negative ^{18}F -FDG PET/CT results and only one patient had ongoing antibiotic therapy with amoxicillin-clavulanic acid for 60 days. There was no explanation for the other false



negative WBC scan result. There was no explanation for the patient with the false negative ^{18}F -FDG PET/CT and WBC scan result.

DISCUSSION

In the study, the WBC scan had a higher accuracy than ^{18}F -FDG PET/CT, because of the higher specificity. Moreover, inter-observer agreement was excellent. NPV was above 97% for the WBC scan. The WBC scan was also more accurate for thrombosed graft infection diagnosis. These data are concordant with the results of the recently published meta-analysis which concluded that the WBC scan had the best performance for PVGI diagnosis.¹³

Moreover, ^{18}F -FDG PET/CT had other drawbacks compared with the WBC scan: a higher radiation dose (7.6 mSv vs. 4–6 mSv, respectively), and its interpretation is more difficult than the WBC scan. Indeed, in the study, there were fewer cases of discrepancies and a better inter-observer agreement in the WBC scan interpretation than ^{18}F -FDG PET/CT. However, the WBC scan is more expensive, less available, and the procedure takes much longer than ^{18}F -FDG PET/CT. As a result, the WBC scan is more difficult to achieve than ^{18}F -FDG PET/CT and this is clearly the main drawback of this examination, despite better performance, as was discussed in a recent meta-analysis.¹³

In the study, nuclear imaging could have allowed an early diagnosis for three patients. These patients had negative Fitzgerald's criteria at the beginning of medical care but positive ^{18}F -FDG PET/CT and WBC scan and a confirmed PVGI diagnosis at the end of follow up. Nuclear imaging could help

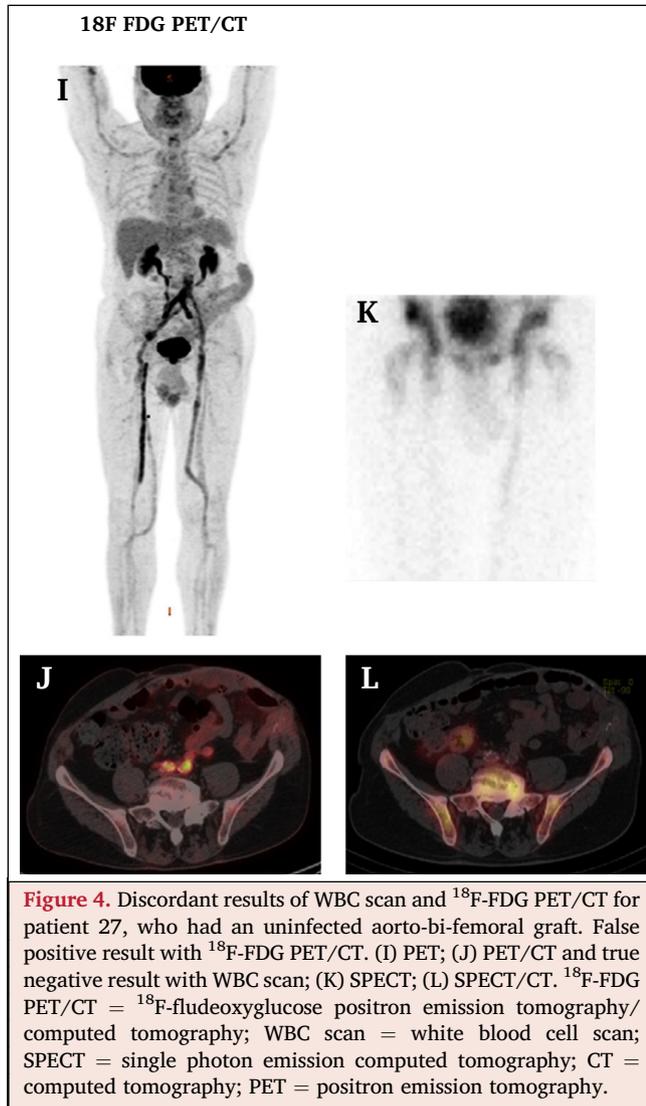


Figure 4. Discordant results of WBC scan and ^{18}F -FDG PET/CT for patient 27, who had an uninfected aorto-bi-femoral graft. False positive result with ^{18}F -FDG PET/CT. (I) PET; (J) PET/CT and true negative result with WBC scan; (K) SPECT; (L) SPECT/CT. ^{18}F -FDG PET/CT = ^{18}F -fludeoxyglucose positron emission tomography/computed tomography; WBC scan = white blood cell scan; SPECT = single photon emission computed tomography; CT = computed tomography; PET = positron emission tomography.

physicians make an earlier diagnosis than using clinical, biological, and radiological criteria. A British expert group recently published a new PVGI definition including ^{18}F -FDG PET/CT and the WBC scan as minor criteria,¹⁴ as was already done for endocarditis diagnosis by modified Duke criteria in which a positive ^{18}F -FDG PET/CT and/or WBC scan is considered to be a major criterion.¹⁵ Nuclear imaging results should be added to Fitzgerald's criteria as was recently done for infective endocarditis, especially the WBC scan.

However, CT angiography remains the first radiological examination to be performed when there is suspicion of PVGI. In this study, its accuracy was not statistically different from ^{18}F -FDG PET/CT, maybe because of a lack of statistical power and the small number of patients. The accuracy of the WBC scan was significantly higher than CT angiography. These data must be interpreted with caution because of the recruitment bias inherent in the study. Indeed, patients with a confirmed clinical and radiological diagnosis of PVGI were not eligible for inclusion. Therefore, the patients included were difficult to diagnose cases, with negative or equivocal CT angiography. CT angiography should be performed in the first place in patients with PVGI suspicion. If

CT angiography is negative or equivocal, the WBC scan should then be performed.

This study is the largest cohort and the second study that compares the diagnostic performance of ^{18}F -FDG PET/CT and the WBC scan in PVGI. The previous work published in 2011 included 11 patients (22 grafts) and found no statistical difference between the two tests. Evaluating ^{18}F -FDG PET/CT and the WBC scan performance separately, the results were similar to the most recently published studies. Erba et al.'s⁵ study published in 2014 on WBC scan performance in PVGI diagnosis showed 100% accuracy vs. 90.6% in this study. However, Sah's scale accuracy was inferior in this study compared with the original study published in 2015: 71.9% and 94%, respectively. This raises the question of the reproducibility of this particular scale.

In this study, diagnosis of PVGI was assessed according to Fitzgerald's criteria. Many studies use microbiological diagnosis with positive graft culture to confirm the diagnosis, alone or combined with other criteria (clinical, histopathological, surgical, and/or follow up). The microbiological criterion alone is not a good gold standard for the diagnosis of PVGI. Indeed, culture is often negative (4–45% in the literature),¹ especially when antibiotics are started before surgery, which was the case in 41.2% of the patients in this study. Moreover, patients who were unfit for surgery were excluded from these studies. The data show that 20% of infected patients did not undergo surgery. Diagnosis of PVGI needs several criteria, including microbiological data, as the Fitzgerald criteria propose.

The study has several limitations. First, the sample size is small due to the rarity of the disease and the single centre nature of the study, even though the institution is a regional referral centre for PVGI.

Moreover, all patients undergoing ^{18}F -FDG PET/CT and the WBC scan for suspected PVGI were included, excluding patients requiring urgent surgery and patients with an obvious diagnosis. Therefore, only patients with a low suspicion of PVGI, for whom physicians had difficulties establishing a diagnosis were included. This constitutes a major selection bias which could lead to underestimating the sensitivity of the two studied tests. Furthermore, all suspicions of PVGI, extra- and intracavity, were included. However, intracavity PVGIs are often less symptomatic¹⁶ and therefore more difficult to diagnose. Nuclear medicine examinations could be more useful in suspected intracavity PVGI than in peripheral ones.

There were a lot of false positive ^{18}F -FDG PET/CT results in the study, but they could be explained readily (graft thrombosis mainly, severe kidney failure, and recent implantation). False positive ^{18}F -FDG PET/CT and WBC scan results could be due to former PVGI, recent implantation, and graft thrombosis. Thrombosed grafts were focused on because thrombosis is a frequent complication in vascular surgery, mainly related to intimal hyperplasia or progression of arteriosclerosis. Nevertheless, unexpected thrombosis can reveal a graft infection. These frequent false positive results because of graft thrombosis, especially with ^{18}F -FDG PET/CT, may prompt evaluation of a new visual scale for ^{18}F -

FDG PET/CT interpretation, which will take into account graft thrombosis. Moreover, there is a physiological FDG uptake by vascular grafts which must be differentiated from the uptake of infected grafts. This physiological FDG uptake could impact ^{18}F -FDG PET/CT accuracy, particularly outside large centres with experienced nuclear medicine physicians. Nonetheless, physiological uptake was well studied by Keidar et al.¹⁷ In this study, ^{18}F -FDG uptake on polyester grafts seemed to be higher than PTFE grafts. However, this uptake is diffuse, not focal, and should easily be differentiated from pathological uptake. The WBC scan seems to be more specific for infection but there can still be false positive results since neutrophils are involved not only in antibacterial defence but also in inflammation and reaction to foreign bodies like grafts, as they belong to innate immunity.

Finally, PVGI from soft tissue infection surrounding the graft could not be differentiated, either with ^{18}F -FDG PET/CT or with the WBC scan. This is a major limitation since this differentiation has therapeutic implications (surgical intervention is much more invasive for PVGI).

To conclude, the WBC scan was more accurate than ^{18}F -FDG PET/CT in PVGI diagnosis. Moreover, thanks to a good NPV, a negative ^{18}F -FDG PET/CT and/or WBC scan result could rule out PVGI diagnosis. The WBC scan should be considered for patients with PVGI suspicion and negative or equivocal CT angiography results. If the WBC scan is not readily available, ^{18}F -FDG PET/CT can be performed. If the result is negative, PVGI can be ruled out thanks to a good NPV. However, a positive result should be interpreted with caution, especially for thrombosed grafts.

CONFLICTS OF INTEREST

None.

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