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Improving Infective Endocarditis Diagnosis by Combining Semi-Quantitative and Visual Findings Obtained from Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Imaging

Flor-18 Florodeoksiglukoz Pozitron Emisyon Tomografi / Bilgisayarlı Tomografiden Elde Edilen Yarı Kantitatif ve Görsel Bulguların İnfektif Endokardit Tanısına Katkısı

ABSTRACT

Objective: The aim of this study was to assess visual and semi-quantitative outputs of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) for diagnostic purposes in infective endocarditis (IE) and determine whether increased spleen or bone marrow FDG uptake secondary to infection can aid in the diagnosis of IE.

Method: Patients who underwent F-18 FDG PET/CT examinations for a preliminary diagnosis of IE between July 2020 and January 2024 were analyzed. IE diagnostic criteria were used to confirm diagnoses, categorizing patients into an IE-positive group and a control group (IE excluded). Demographics and imaging-related data, including mean standardized uptake value (SUV_{mean}) and/or SUV_{max} for lesions, liver, spleen, and lumbar vertebrae, were recorded. Spleen hypermetabolism and bone marrow hypermetabolism (BMH) were defined as spleen-to-liver or bone marrow-to-liver ratios exceeding 1, respectively. Visually assessed FDG uptake was scored from 0 to 3, forming the uptake score, which was dichotomized into low and high uptake groups.

Results: The study included 48 IE patients and 21 control patients. Lesion SUV, uptake score, spleen hypermetabolism, and BMH demonstrated significant differences between the groups. For distinguishing IE, a high uptake score showed a sensitivity of 85.42% and an overall accuracy of 84.06%, while lesion SUV_{max} (> 3.5) achieved the highest specificity (95.24%) and positive predictive value (96.77%).

Conclusion: Visual detection of uptake exceeding blood pool values on F-18 FDG PET/CT images, coupled with an SUV greater than 3.5, appears to distinguish IE patients with high accuracy. Additionally, increased bone marrow FDG uptake was strongly associated with IE.

Keywords: F-18 fluorodeoxyglucose positron emission tomography, infective endocarditis, standardized uptake value

ÖZET

Amaç: F-18 FDG PET/BT'de infektif endokardit (İE) şüpheli alanların görsel ve yarı-kantitatif değerlendirmelerinin tanıdaki rolünün belirlenmesi ve enfeksiyona ikincil dalak/kemik iliğindeki artmış FDG tutulumlarının tanıda kullanılıp kullanılamayacağının belirlenmesi amaçlandı.

Yöntem: Temmuz 2020–Ocak 2024 tarihlerinde İE ön tanısıyla F-18 FDG PET/BT uygulanan hastalar retrospektif olarak incelendi. IE pozitif grubu ve kontrol grubunu (KG) (IE hariç) oluşturmak için IE tanı kriterleri kullanıldı. Demografik ve görüntülemeyle ilgili veriler (lezyon, karaciğer, dalak ve lomber vertebra-kemik iliğinin standartlaştırılmış alım değeri (SUV) kaydedildi. Dalak/karaciğer veya kemik iliği/karaciğer oranları >1 olan hastalarda sırasıyla dalak hipermetabolizması ve kemik iliği hipermetabolizması (KİH) tanımlandı. Görsel değerlendirmede şüpheli alan FDG tutulum derecesine göre 0–3 arasında skorlanıp, düşük ve yüksek tutulum skorlu olmak üzere 2 grup oluşturuldu.

Bulgular: 48 İE ve 21 kontrol hastası dahil edildi. İki grup arasında lezyon SUV'ları, tutulum skorları, dalak hipermetabolizmaları ve KİH'leri yönünden anlamlı farklılık vardı. Hastalığın ayırt edilmesinde yüksek tutulum skoru %85,42 duyarlılık ve %84,06 doğruluk gösterirken, lezyon SUV_{max} (>3,5) en yüksek özgüllüğe (%95,24) ve en yüksek pozitif öngörü değerine sahipti (%96,77).

Sonuç: F-18 FDG PET/BT görüntülerinde lezyon bölgesinde görsel olarak kan havuzundan daha fazla tutulumun saptanması ve SUV değerinin >3,5 olması İE hastalarını yüksek doğrulukla ayırt edebilmektedir. Ek olarak, bu hasta grubunda kemik iliğindeki artmış FDG tutulumlarının İE ile bağımsız olarak ilişkisi vardır.

Anahtar Kelimeler: 18F-florodeoksiglukoz pozitron emisyon tomografisi, infektif endokardit, standartlaştırılmış alım değeri

ORIGINAL ARTICLE
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Infective endocarditis (IE) affects the endocardial surfaces of the heart, prosthetic valves, and intracardiac devices.[1] It is a highly significant condition due to the challenges associated with its diagnosis and treatment, as well as its high rates of mortality and morbidity. None of the diagnostic methods, whether clinical, laboratory, blood culture, or echocardiography, are sufficient on their own to establish a definitive diagnosis. Prompt diagnosis of IE facilitates the initiation of effective treatment and helps prevent complications.[2] Echocardiography is the primary imaging modality used to evaluate cardiac lesions in patients with IE. However, in 15% of cases, neither transthoracic nor transesophageal echocardiography is successful. This is most commonly due to the presence of intracardiac foreign bodies, severe valve lesions predating IE, small or embolized vegetations, or the complete absence of vegetations.[3]

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (18F FDG PET/CT), commonly used in oncology, is also effectively utilized in diagnosing certain infections and inflammatory diseases due to the high FDG uptake of immune cells.[4] The updated 2023 version of the European Society of Cardiology's guidelines for managing endocarditis includes increased FDG uptake around prosthetic valves as a major diagnostic criterion for IE. Similarly, the 2023 Duke-International Society for Cardiovascular Infectious Diseases (Duke-ISCVID) diagnostic criteria list increased FDG uptake in native or prosthetic valves, intracardiac device electrodes, and other prosthetic materials as a major criterion for IE, highlighting the growing significance of this modality.[5,6]

Unlike in oncological applications, the contribution of semi-quantitative assessment using standardized uptake values (SUV) in infections and inflammation has only been partially validated and remains controversial.[7] Some studies in the literature suggest SUV cutoff values to minimize false-positive results; however, there is no consensus, and caution is advised when using SUV measurements in clinical practice.[8] Additionally, some researchers have investigated increased FDG uptake in suspicious IE lesions by comparing it to liver and blood FDG uptake.[9,10] With whole-body imaging, F-18 FDG PET/CT can reveal indirect findings related to immune activation, such as increased FDG uptake in the spleen or bone marrow, which might support IE diagnosis.[11]

Although PET/CT has been established as one of the major diagnostic criteria for IE, the performance of 18F FDG PET/CT-derived visual and quantitative analyses in infection settings, particularly in IE, requires further confirmation. This study aimed to evaluate whether IE diagnosis could be achieved through visual and semi-quantitative assessments of the primary lesion on F-18 FDG PET/CT, given that IE remains challenging to diagnose early. Additionally, the study sought to determine whether spleen or bone marrow FDG uptake could contribute to IE diagnosis, as these parameters could serve as indirect indicators of systemic inflammation.

Materials and Methods

Patient Selection and Preparation

The study population consisted of patients who underwent F-18 FDG PET/CT at our nuclear medicine unit between July 2020 and January 2024 due to suspicion of IE. These patients were retrospectively evaluated. Inclusion criteria were as follows: no prior treatment for IE, no diagnosis of malignancy, history of prosthetic valve or intracardiac device surgery performed at least three months prior, absence of hematological diseases affecting splenic or bone marrow FDG uptake, attendance at follow-up appointments (≥ 6 months), and either a confirmed diagnosis of IE or definitive exclusion of IE based on diagnostic criteria.[12]

The indication for F-18 FDG PET/CT in cases of native valve disease included newly developed cardiac valve disease accompanied by symptoms such as high fever, elevated acute-phase reactants in laboratory tests, skin lesions, and cardiac vegetations identified through transesophageal echocardiography. Criteria for ruling out native valve endocarditis included two consecutive negative blood cultures, negative histopathology results, and the absence of endocarditis during subsequent follow-up evaluations.

Patients with a confirmed diagnosis were assigned to the IE-positive group, while those in whom IE was definitively excluded were assigned to the control group.

Subjects were excluded if they did not adhere to the required dietary regimen prior to imaging, had suspicious lesion areas that could not be optimally assessed due to physiological myocardial FDG uptake, had received antibiotic or steroid treatment, had a concurrent malignancy diagnosis, or had an inconclusive diagnosis based on the IE diagnostic criteria.

The Başakşehir Çam and Sakura Hospital Ethics Committee approved the study (Approval Number: E-96317027-514.10-241604048, Date: 22.04.2024), and informed consent was obtained throughout the diagnostic and therapeutic processes. The study was conducted in accordance with the Declaration of Helsinki.

F-18 FDG PET Imaging

Physiological myocardial FDG uptake was minimized during patient preparation by reducing basal glucose metabolism of the myocardium. Patients were instructed to follow a high-fat, low-carbohydrate (< 1 g) diet for at least 24 hours prior to the scan and to fast for 12-18 hours before imaging.[13] Patients with blood glucose levels below 150 mg/dL were intravenously administered 10-15 μCi/kg of F-18 FDG. Imaging was performed using a Philips Ingenuity TF 64 scanner (Philips Medical Systems, OH, USA) in accordance with the European Association of Nuclear Medicine (EANM) standards.[14] Following the injection, patients were placed in a private room to rest for 50 minutes before imaging. After the resting period, patients were brought in for imaging, which began with a whole-body computed tomography (CT) scan performed at 113 mAs (low-

ABBREVIATIONS

Duke-ISCVID	Duke-International Society for Cardiovascular Infectious Diseases
EANM	European Association of Nuclear Medicine
F-18 FDG PET/CT	Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography
IE	Infective endocarditis
ROC	Receiver operating characteristic
ROI	Region of interest
SUV	Standardized uptake values
VOI	Volume of interest

Table 1. Summary of Patient Characteristics and F-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F FDG PET/CT) Findings Related to Infective Endocarditis

	Infective endocarditis		P
	No (n = 21)	**Yes (n = 48)**	
Age, years	63 (49 - 71)	53.5 (41 - 63.5)	0.135‡
Sex			0.602#
Male	11 (52.38%)	30 (62.50%)	
Female	10 (47.62%)	18 (37.50%)	
Diagnosis			0.072§
Prosthetic valve	4 (19.05%)	13 (27.08%)	
Native valve endocarditis	9 (42.86%)	18 (37.50%)	
Intracardiac device	7 (33.33%)	6 (12.50%)	
Left ventricle assist device	0 (0.00%)	9 (18.75%)	
Vascular graft	1 (4.76%)	2 (4.17%)	
Uptake score			**<0.001**§
Score 0	11 (52.38%)	6 (12.50%)	
Score 1	6 (28.57%)	1 (2.08%)	
Score 2	1 (4.76%)	8 (16.67%)	
Score 3	3 (14.29%)	33 (68.75%)	
Liver			
SUV_{mean}	2.10 ± 0.58	1.87 ± 0.56	0.127†
SUV_{max}	3.1 (2.5 - 3.6)	2.75 (2.25 - 3.4)	0.220‡
Lesion			
SUV_{mean}	1.8 (1.6 - 1.9)	2.3 (1.6 - 3.15)	**0.009**‡
SUV_{max}	2.8 (2.4 - 3.0)	3.95 (2.4 - 5.65)	**0.002**‡
Normalized SUV	0.82 (0.77 - 0.89)	1.16 (0.96 - 1.62)	**<0.001**‡
Spleen			
SUV_{mean}	1.8 (1.7 - 2.5)	1.9 (1.5 - 2.3)	0.484‡
SUV_{max}	2.4 (2.3 - 3.1)	2.35 (2.05 - 3.2)	0.518‡
Bone marrow			
SUV_{mean}	1.7 (1.6 - 2.0)	2.0 (1.6 - 2.4)	0.143‡
SUV_{max}	2.46 ± 0.67	2.75 ± 0.85	0.162†
Spleen hypermetabolism	4 (19.05%)	26 (54.17%)	**0.015**#
BM hypermetabolism	3 (14.29%)	28 (58.33%)	**0.002**#

Continuous variables are reported as mean ± standard deviation (SD) (normally distributed) or median and 25^{th} - 75^{th} percentile for non-normally distributed data. Categorical variables are presented as frequency (percentage). †Student's t-test; ‡Mann-Whitney U test; #Chi-square test; §Fisher-Freeman Halton test.

dose) using 120 kV and 4-mm slices. This data was used for attenuation correction. PET imaging followed immediately, starting at the caudal end and moving cranially, covering the same field of view (3 minutes per bed position). Finally, maximum intensity projections and cross-sectional views (transaxial, coronal, sagittal) were utilized to review both attenuation-corrected and uncorrected PET and CT images.

Image Interpretation

The images were evaluated by two nuclear medicine specialists experienced in cardiac imaging. In cases of discrepancies between the specialists' visual assessments, a consensus reading was performed, and any disagreements were resolved through discussion. Artificial intelligence-assisted technologies were not used in this study.

A 4-point scale was applied during the visual evaluation to assess FDG uptake in suspicious lesion areas (uptake score). Patients without FDG uptake were scored as 0, those with FDG uptake lower than the blood pool were scored as 1, those with FDG uptake higher than the blood pool but lower than the liver were scored as 2, and those with FDG uptake equal to or higher than the liver were scored as 3. Nine patients with uptake scores of 0 and 1 were pooled into the 0 & 1 (low uptake) group, while those with uptake scores of 2 and 3 were pooled into the 2 & 3 (high uptake) group.

Table 2. Performance Metrics for Predicting Infective Endocarditis

	Cut-off	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC (95% CI)	P
Uptake score	Score 2 & 3 (high)	85.42%	80.95%	84.06%	91.11%	70.83%	0.824 (0.710 - 0.937)	<**0.001**
Lesion SUV_{mean}	>2.2	54.17%	95.24%	66.67%	96.30%	47.62%	0.698 (0.578 - 0.819)	**0.009**
Lesion SUV_{max}	>3.5	62.50%	95.24%	72.46%	96.77%	52.63%	0.732 (0.616 - 0.848)	**0.002**
Lesion normalized SUV	>0.85	83.33%	71.43%	79.71%	86.96%	65.22%	0.792 (0.680 - 0.904)	<**0.001**
Spleen hypermetabolism	Yes	54.17%	80.95%	62.32%	86.67%	43.59%	0.676 (0.542 - 0.809)	**0.021**
BM hypermetabolism	Yes	58.33%	85.71%	66.67%	90.32%	47.37%	0.720 (0.594 - 0.846)	**0.004**

AUC, Area Under the ROC Curve; CI, Confidence Interval; NPV, Negative Predictive Value; PPV, Positive Predictive Value; ROC, Receiver Operating Characteristic.

Semi-quantitative evaluation was performed using the maximum standardized uptake value (SUV_{max}), determined by a volume of interest (VOI) automatically defined as an isocontour encompassing regions with 40% intensity of the maximal signal in the suspected lesion. The average SUV within the VOI was recorded as the mean SUV (SUV_{mean}). SUV_{mean} and SUV_{max} values for the suspected lesion areas were documented. Spleen SUV_{mean} was calculated using a region of interest (ROI) near the spleen core, while liver SUV_{mean} was determined using a spherical ROI in the right lobe of the liver. To measure blood pool activity, a spherical ROI with maximum diameter was placed in the lumen of the ascending aorta, excluding vessel walls. Bone marrow SUV_{mean} (BM SUV_{mean}) was calculated as the mean of five SUV_{mean} values obtained from ROIs circled on the corpora of the lumbar vertebrae, excluding any pathological lesions in these areas. The SUV_{max} values of the lesions were normalized by dividing them by the liver SUV_{mean} to calculate the normalized lesion SUV. Similarly, spleen and bone marrow SUV_{mean} values were normalized by dividing them by the liver SUV_{mean}. Patients with a spleen SUV_{mean}/liver SUV_{mean} ratio > 1 were classified as having spleen hypermetabolism, while those with a BM SUV_{mean}/liver SUV_{mean} > 1 were classified as having bone marrow hypermetabolism.

Statistical Analysis

The threshold for statistical significance was set at $P < 0.05$, and analyses were conducted using SPSS for Windows (IBM, NY, USA). The Shapiro-Wilk test was used to assess the normality of variable distributions. Descriptive statistics were reported as mean ± standard deviation for continuous variables with a normal distribution, median (25^{th} – 75^{th} percentiles) for variables with a skewed distribution, and frequency (percentage) for categorical data. Group comparisons were performed using the Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Analyses of categorical variables were conducted using the Chi-square test or Fisher-Freeman-Halton test. To evaluate the predictive potential of variables, a receiver operating characteristic (ROC) curve analysis was performed, with Youden's index used to determine the optimal cutoff values. A multivariable logistic regression analysis was then conducted to identify independent predictors of IE, incorporating variables that showed significance in the univariate analysis.

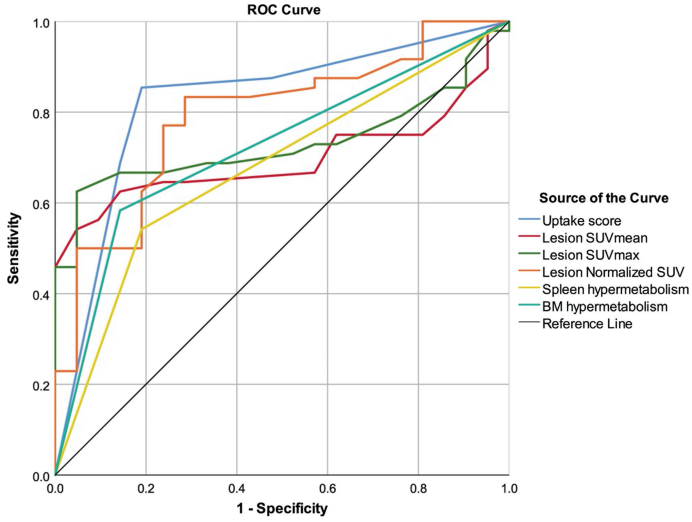

Figure 1. Receiver operating characteristic (ROC) curves for predicting infective endocarditis.

Results

We included 48 patients with IE and 21 controls in our study. The median age was 56 years (interquartile range: 42-68). Seventeen patients (24.64%) had a prosthetic valve, 27 (39.13%) had native valve endocarditis, 13 (18.84%) had an implantable cardioverter-defibrillator (ICD), nine (13.04%) had a left ventricular assist device (LVAD), and three (4.35%) had a vascular graft. The groups were similar in terms of age, sex, and diagnosis (Table 1). The clinical features observed in IE patients included fever, weight loss, elevated acute-phase reactants in laboratory tests, heart murmur, petechial skin lesions, Osler's nodes, splenomegaly, evidence of peripheral septic embolization, and cardiac vegetations identified via transesophageal echocardiography. The interval between the onset of symptoms and F-18 FDG PET/CT imaging ranged from 7 to 10 days. The most frequently isolated microorganisms were Staphylococcus aureus, followed by Viridans streptococci.

Compared to the control group, IE patients had significantly higher uptake scores ($P < 0.001$), lesion SUV_{mean} ($P = 0.009$), lesion SUV_{max} ($P = 0.002$), and normalized lesion SUV ($P < 0.001$). Additionally, spleen hypermetabolism ($P = 0.015$) and bone marrow hypermetabolism (BMH) ($P = 0.002$) were significantly more common in the IE group. Other SUV_{mean} and SUV_{max} values for the liver, spleen, and bone marrow were similar between the two groups (Table 1).

Table 3. True/False Positive and Negative Cases Based on 18F FDG PET/CT Findings

	Cut-off	True positive	True negative	False positive	False negative
Uptake score	Score 2 & 3	41 (59.42%)	17 (24.64%)	4 (5.80%)	7 (10.14%)
Lesion SUV_{mean}	>2.2	26 (37.68%)	20 (28.99%)	1 (1.45%)	22 (31.88%)
Lesion SUV_{max}	>3.5	30 (43.48%)	20 (28.99%)	1 (1.45%)	18 (26.09%)
Lesion normalized SUV	>0.85	40 (57.97%)	15 (21.74%)	6 (8.70%)	8 (11.59%)
Spleen hypermetabolism	Yes	26 (37.68%)	17 (24.64%)	4 (5.80%)	22 (31.88%)
BM hypermetabolism	Yes	28 (40.58%)	18 (26.09%)	3 (4.35%)	20 (28.99%)

Descriptive statistics are presented as frequency (row percentage) for categorical variables.

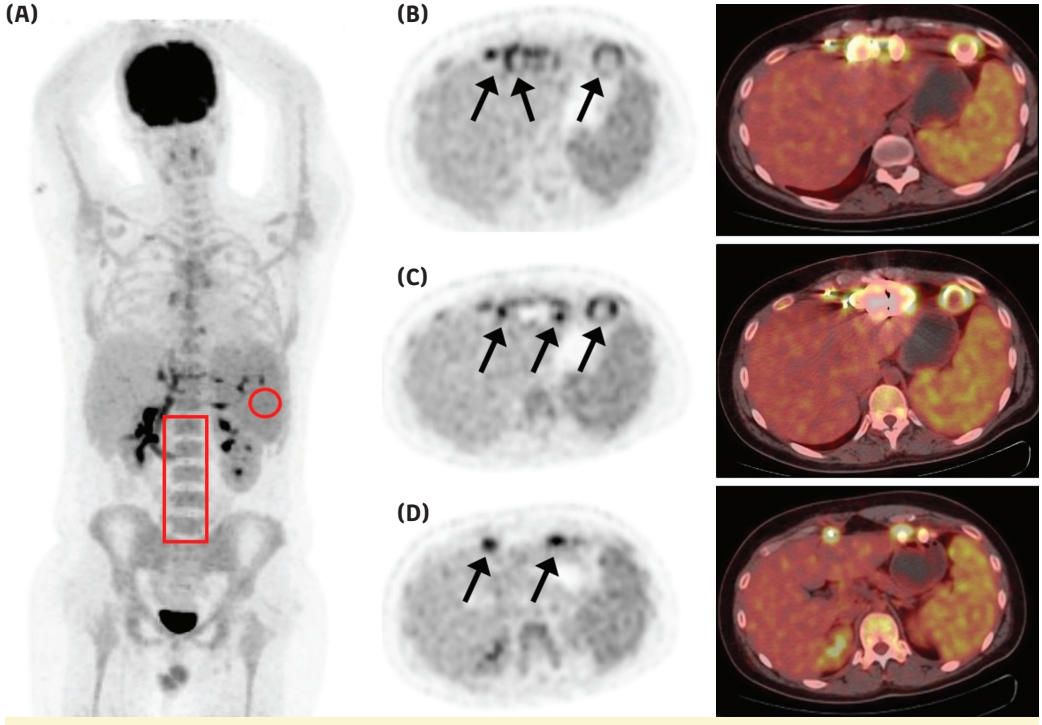

Figure 2. A patient with left ventricular assist device-related infective endocarditis with spleen and bone marrow hypermetabolism. (A) Increased fluorine-18 fluorodeoxyglucose (FDG) uptake in the spleen (red circle) and bone marrow (red rectangle) is observed on the maximum intensity projection (MIP) image (spleen mean standardized uptake value [SUV_{mean}]/Liver SUV_{mean} > 1 and bone marrow [BM] SUV_{mean}/Liver SUV_{mean} > 1). (B–D) Axial positron emission tomography (PET) and fusion PET/CT (computed tomography) images show widespread increased FDG uptake around the left ventricular assist device components (SUV_{max}: 7.6) (black arrows).

In terms of diagnostic performance, SUV_{mean} (P = 0.009), lesion SUV_{max} (P = 0.002), lesion normalized SUV (P < 0.001), spleen hypermetabolism (P = 0.021), and BMH (P = 0.004) were found to significantly differentiate between the IE and control groups. A high uptake score (scores 2 & 3) achieved the highest area under the ROC curve (area under the curve [AUC]: 0.824, 95% confidence interval [CI]: 0.710-0.937, P < 0.001) for detecting IE. It also demonstrated the highest sensitivity (85.42%), negative predictive value (70.83%), and accuracy (84.06%). Lesion SUV_{mean} (> 2.2) and lesion SUV_{max} (> 3.5) exhibited the highest specificity (95.24%), with lesion SUV_{max} (> 3.5) also achieving the highest positive predictive value (96.77%) for discriminating IE (Table 2, Figure 1). These results are summarized with absolute and relative frequencies (n, %) in Table 3. An illustrative F-18 FDG PET/CT image of an IE patient showing elevated FDG uptake in the spleen, bone marrow, and the vicinity of a left ventricular support device is provided (Figure 2).

According to the results of multivariable logistic regression analysis, a high uptake score (scores 2 & 3) (odds ratio [OR]: 19.037, 95% CI: 4.664-77.707; P < 0.001) and BMH (OR: 5.194, 95% CI: 1.073-25.140; P = 0.041) were independently associated with IE (Table 4). However, lesion SUV_{mean} (P = 0.185), lesion SUV_{max} (P = 0.075), lesion normalized SUV (P = 0.203), and spleen hypermetabolism (P = 0.171) were not found to be statistically significant.

Table 4. Independent Predictors of Infective Endocarditis: Logistic Regression

	β Coefficient	Standard error	P	Exp(β)	95% CI for Exp(β)	
Uptake score (score 2 & 3)	2.946	0.718	<**0.001**	19.037	4.664	77.707
BM hypermetabolism (yes)	1.647	0.805	**0.041**	5.194	1.073	25.140
Constant	-1.300	0.525	0.013	0.273		

CI, Confidence Interval; Nagelkerke R^2=0.543.

Discussion

The F-18 FDG PET/CT imaging modality has recently gained increased utility in the diagnosis of IE, particularly in challenging cases, likely due to its incorporation into diagnostic guidelines.[5-6] In our study, we visually scored the intensity of FDG uptake in suspicious lesion areas on F-18 FDG PET/CT, assessed semi-quantitative SUV measurements, and evaluated spleen and bone marrow FDG uptake values as potential indirect indicators of infection. We found that certain parameters exhibited significant alterations in patients with IE. A dichotomized uptake score (cut-off: 2 & 3) and a lesion SUV_{max} value (> 3.5) performed exceptionally well in distinguishing IE patients, achieving accuracies exceeding 84% and 72%, respectively. Despite their lower overall accuracy, lesion SUV_{max} and SUV_{mean} values demonstrated near-perfect specificity (> 95%) and positive predictive values, making them particularly valuable for ruling out IE and ensuring high accuracy in positive results.

To categorize lesions based on FDG uptake levels, we assessed FDG uptake relative to standard reference regions, such as the blood pool and liver. This approach employed a classification system similar to the Deauville criteria, which is used to evaluate treatment response in lymphoma via interim PET.[15] A few other studies in the literature have evaluated FDG uptake in IE patients using similar comparisons to the blood pool and liver.[9,10] The subsequent classification of patients into low and high uptake categories based on initial uptake scores proved to be the most effective method for differentiating IE. This approach achieved the highest sensitivity (85.42%) and accuracy (84.06%) (AUC: 0.824, 95% CI: 0.710-0.937; P < 0.001). Gazzilli et al.[10] reported high sensitivity (93%) and accuracy (87%) using a similar visual scoring system for distinguishing IE patients, which were slightly higher than the results in our study. This discrepancy is likely due to differences in patient distribution and heterogenous characteristics.

Although the use of semi-quantitative SUV measurements for diagnosing infection and inflammation has been partially validated, no clinically established SUV threshold for diagnosing IE currently exists.[7] Furthermore, several publications in the literature have suggested that there is no relationship between SUV measurements in lesion areas and IE diagnosis.[16,17] However, many studies have reported significantly higher SUV values in IE patients compared to controls groups.[18,19] In our study, we found that lesion SUV values were effective parameters for diagnosing IE. Notably, lesion SUV_{max} exhibited very high specificity (95.24%) and positive predictive value (96.77%) for differentiating IE based on a threshold of > 3.5. Similarly, Pizzi et al.,[19] in a study of 92 patients investigating F-18 FDG PET/CT for IE diagnosis in those with prosthetic valves and intracardiac devices, reported a threshold SUV_{max} value of ≥ 3.7, which yielded 90.74% sensitivity and 78.95% specificity (AUC: 0.89). Likewise, Swart et al.[8] examined patients with prosthetic heart valves and identified a threshold SUV_{max} value of 3.3, achieving 97% sensitivity and 79% specificity (AUC: 0.95). The SUV_{max} threshold value identified in our study aligns with findings in the literature and suggests that future studies with larger sample sizes could help establish a clinically useful threshold SUV_{max} value for routine use in diagnosing suspicious lesion areas in IE patients.

It is well established that elevated spleen and bone marrow FDG uptake can occur as a secondary effect of infection and inflammation.[20,21] We found that splenic elevation in FDG uptake was the most effective diagnostic parameter for IE in our study, and increased uptake in the bone marrow was associated with a higher likelihood of IE. Similar to our findings, other studies in the literature have reported elevated spleen and bone marrow FDG uptake in IE patients, which is linked to immune system activation.[10,11] The sensitivity of F-18 FDG PET/CT in diagnosing native valve endocarditis is known to be low (31%), and the absence of pathological FDG uptake in the native valve area does not definitively exclude IE in some cases.[5,22,23] Given the diagnostic challenges associated with this patient group, further studies are needed to explore the potential contributions of these characteristics to the diagnosis of IE.

A meta-analysis of 26 studies involving 1,358 patients reported that F-18 FDG PET achieved sensitivity and specificity values of 74% and 88%, respectively, for diagnosing IE.[24] In another meta-analysis of 13 studies involving 537 patients, sensitivity and specificity were reported as 76% and 78.5%, respectively.[25] In our study, visual scoring produced a sensitivity of 85%, while semi-quantitative assessment demonstrated a specificity of 95%. These findings suggest that visual comparison of FDG uptake in suspicious lesion areas relative to the blood pool is superior for identifying IE, whereas evaluation of lesion SUV values is more effective for ruling out IE. A combinatory approach to these imaging results may significantly enhance the overall diagnostic accuracy of IE. We believe that new multi-center collaborations involving larger patient groups are necessary to confirm the varying utility of these parameters.

This study is limited by its single-center, retrospective design. Another limitation is the relatively small patient count and the heterogeneous distribution of patients, which necessitated the combined assessment of groups with natural valve prostheses and intracardiac devices. Additionally, it is well known that factors such as the use of surgical adhesives during prosthetic heart valve implantation, low inflammatory activity due to isolated vegetation, or inadequate suppression of myocardial FDG-uptake may alter FDG uptake patterns. These factors can act as potential confounders and pose challenges in using F-18 FDG PET/CT imaging for infection diagnosis.[8]

Conclusion

F-18 FDG PET/CT increasingly being utilized in the diagnosis of IE. Visual assessment of FDG uptake in suspicious lesions, along with its dichotomization into low and high uptake categories, demonstrates high sensitivity and accuracy. In semi-quantitative evaluations, a lesion SUV_{max} value exceeding 3.5 effectively distinguished IE patients with exceptionally high accuracy. Furthermore, increased bone marrow FDG uptake, secondary to infection or inflammation, was found to be independently associated with IE.

Ethics Committee Approval: The Başakşehir Çam and Sakura Hospital Ethics Committee approved the study (Approval Number: E-96317027-514.10-241604048, Date: 22.04.2024.

Informed Consent: Informed consent was obtained throughout the diagnostic and therapeutic processes.

Peer-review: Externally peer-reviewed.

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References

1. Erba PA, Sollini M, Lazzeri E, Mariani G. FDG-PET in cardiac infections. *Semin Nucl Med*. 2013;43(5):377-395. [CrossRef]
2. Şimşek-Yavuz S, Akar AR, Aydoğdu S, et al. Diagnosis, treatment and prevention of infective endocarditis: Turkish consensus report-2019. *Turk Kardiyol Dern Ars*. 2020;48(2):187-226. Turkish. [CrossRef]
3. Feuchtner GM, Stolzmann P, Dichtl W, et al. Multislice computed tomography in infective endocarditis: Comparison with transesophageal echocardiography and intraoperative findings. *J Am Coll Cardiol*. 2009;53(5):436-444. [CrossRef]
4. Çakır T, Atasever T. F-18 flourodeoxy glucose positron emission tomography/ computed tomography imaging in infection and inflammation. *Nucl Med Semin*. 2016;2(2):79-89. Turkish. [CrossRef]
5. Delgado V, Ajmone Marsan N, de Waha S, et al; ESC Scientific Document Group. 2023 ESC Guidelines for the management of endocarditis. *Eur Heart J*. 2023;44(39):3948-4042. Erratum in: *Eur Heart J*. 2023;44(45):4780. Erratum in: *Eur Heart J*. 2024;45(1):56. [CrossRef]
6. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases criteria for infective endocarditis: Updating the modified duke criteria. *Clin Infect Dis*. 2023;77(4):518-526. Erratum in: *Clin Infect Dis*. 2023;77(8):1222. [CrossRef]
7. Slart RHJA, Glaudemans AWJM, Gheysens O, et al. Procedural recommendations of cardiac PET/CT imaging: Standardization in inflammatory-, infective-, infiltrative-, and innervation (4Is)-related cardiovascular diseases: A joint collaboration of the EACVI and the EANM. *Eur J Nucl Med Mol Imaging*. 2021;48(4):1016-1039. [CrossRef]
8. Swart LE, Gomes A, Scholtens AM, et al. Improving the diagnostic performance of 18f-fluorodeoxyglucose positron-emission tomography/computed tomography in prosthetic heart valve endocarditis. *Circulation*. 2018;138(14):1412-1427. [CrossRef]
9. Jiménez-Ballvé A, Pérez-Castejón MJ, Delgado-Bolton RC, et al. Assessment of the diagnostic accuracy of F-FDG PET/CT in prosthetic infective endocarditis and cardiac implantable electronic device infection: Comparison of different interpretation criteria. *Eur J Nucl Med Mol Imaging*. 2016;43(13):2401-2412. [CrossRef]
10. Gazzilli M, Albano D, Lucchini S, et al. New criteria for the diagnosis of infective endocarditis using 18F-FDG PET/CT imaging. *J Nucl Cardiol*. 2022;29(5):2188-2194. Erratum in: *J Nucl Cardiol*. 2022;29(2):890. [CrossRef]
11. Boursier C, Duval X, Mahida B, et al. Hypermetabolism of the spleen or bone marrow is an additional albeit indirect sign of infective endocarditis at FDG-PET. *J Nucl Cardiol*. 2021;28(6):2533-2542. [CrossRef]
12. Osborne MT, Hulten EA, Murthy VL, et al. Patient preparation for cardiac fluorine-18 fluorodeoxyglucose positron emission tomography imaging of inflammation. *J Nucl Cardiol*. 2017;24(1):86-99. [CrossRef]
13. Erba PA, Lancellotti P, Vilacosta I, et al. Recommendations on nuclear and multimodality imaging in IE and CIED infections. *Eur J Nucl Med Mol Imaging*. 2018;45(10):1795-1815. [CrossRef]
14. Boellaard R, Delgado-Bolton R, Oyen WJ, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: Version 2.0. *Eur J Nucl Med Mol Imaging*. 2015;42(2):328-354. [CrossRef]
15. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the first international workshop on interim-PET-scan in lymphoma. *Leuk Lymphoma*. 2009;50(8):1257-1260. [CrossRef]
16. Juneau D, Golfam M, Hazra S, et al. Molecular imaging for the diagnosis of infective endocarditis: A systematic literature review and meta-analysis. *Int J Cardiol*. 2018;253:183-188. [CrossRef]
17. Calais J, Touati A, Grall N, et al. Diagnostic impact of f-fluorodeoxyglucose positron emission tomography/computed tomography and white blood cell spect/computed tomography in patients with suspected cardiac implantable electronic device chronic infection. *Circ Cardiovasc Imaging*. 2019;12(7):e007188. [CrossRef]
18. Pretet V, Blondet C, Ruch Y, et al. Advantages of 18F-FDG PET/CT imaging over modified duke criteria and clinical presumption in patients with challenging suspicion of infective endocarditis. *Diagnostics (Basel)*. 2021;11(4):720. [CrossRef]
19. Pizzi MN, Roque A, Fernández-Hidalgo N, et al. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with 18f-fluordeoxyglucose positron emission tomography/computed tomography angiography: Initial results at an infective endocarditis referral center. *Circulation*. 2015;132(12):1113-1126. [CrossRef]
20. Inoue K, Goto R, Okada K, Kinomura S, Fukuda H. A bone marrow F-18 FDG uptake exceeding the liver uptake may indicate bone marrow hyperactivity. *Ann Nucl Med*. 2009;23(7):643-649. [CrossRef]
21. Ahn SS, Hwang SH, Jung SM, et al. Evaluation of spleen glucose metabolism using 18F-FDG PET/CT in patients with febrile autoimmune disease. *J Nucl Med*. 2017;58(3):507-513. [CrossRef]
22. Duval X, Le Moing V, Tubiana S, et al. Impact of systematic whole-body 18F-Fluorodeoxyglucose PET/CT on the management of patients suspected of infective endocarditis: The prospective multicenter TEPvENDO study. *Clin Infect Dis*. 2021;73(3):393-403. [CrossRef]
23. Albano D, Dondi F, Gazzilli M, Giubbini R, Bertagna F. Meta-analysis of the diagnostic performance of 18F-FDG-PET/CT imaging in native valve endocarditis. *JACC Cardiovasc Imaging*. 2021;14(5):1063-1065. [CrossRef]
24. Wang TKM, Sánchez-Nadales A, Igbinomwanhia E, Cremer P, Griffin B, Xu B. Diagnosis of infective endocarditis by subtype using 18f-fluorodeoxyglucose positron emission tomography/computed tomography: A contemporary meta-analysis. *Circ Cardiovasc Imaging*. 2020;13(6):e010600. [CrossRef]
25. Mahmood M, Kendi AT, Ajmal S, et al. Meta-analysis of 18F-FDG PET/CT in the diagnosis of infective endocarditis. *J Nucl Cardiol*. 2019;26(3):922-935. [CrossRef]