EJMI

DOI: 10.14744/ejmi.269392
EJMI 2026;10(3):392–398

Research Article

Diagnostic Value of 18F-FDG PET/CT in Patients with Suspected Paraneoplastic Syndrome

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Abstract

Objectives: To evaluate the diagnostic value of 18F-FDG PET/CT in patients with suspected paraneoplastic syndrome who present with unexplained elevation of acute-phase reactants (APR) and constitutional symptoms.

Methods: In this retrospective, single-center study, 102 adult patients who underwent 18F-FDG PET/CT from June 2018 to April 2025 for suspected paraneoplastic syndrome were included. All had unexplained elevated APR with or without constitutional symptoms after initial evaluation. PET/CT findings were categorized as suggestive of malignancy, infection, inflammatory/rheumatic disease, or negative. Final diagnoses were based on histopathology, microbiology, clinical criteria, or ≥6 months of follow-up.

Results: Malignancy was the most common final diagnosis (n=48, 47.1%), followed by inflammatory/rheumatic diseases (n=33, 32.4%). 18F-FDG PET/CT had 100% sensitivity and negative predictive value for detecting malignancy, with no false negatives. Specificity was 29.6%, and positive predictive value was 55.8%. Of 38 PET-positive, malignancy-negative cases, 28 (73.7%) were rheumatologic or inflammatory diseases, mostly polymyalgia rheumatica and vasculitis. Patients with both elevated APR and constitutional symptoms had a significantly higher risk of malignancy than those with isolated APR elevation (OR =12.33; 95% CI: 3.3–45.8; p=0.001).

Conclusion: 18F-FDG PET/CT is highly sensitive for detecting cancer in patients with suspected paraneoplastic syndrome and unexplained inflammation.

Keywords: Constitutional symptoms, Paraneoplastic syndrome, Positron emission tomography computed tomography

Cite This Article: *Çiftçi E. Diagnostic Value of 18F-FDG PET/CT in Patients with Suspected Paraneoplastic Syndrome. EJMI 2026;10(3):392–398.*

Paraneoplastic syndromes (PNS) are immune-mediated or humoral disorders associated with malignancy but not directly caused by tumor invasion or metastasis. They often precede the clinical detection of cancer and may serve as early indicators of occult malignancy (1). The clinical presentation is heterogeneous and may include neurologic and non-neurologic manifestations, often accompanied by constitutional symptoms such as fever, weight loss, and night sweats, as well as elevated inflammatory markers. Because these findings are typically nonspecific, establishing the underlying cause remains diagnostically challenging.[1,2]

Patients presenting with unexplained fever, elevated acute-phase reactants (APRs), and systemic symptoms are commonly evaluated for fever or inflammation of unknown origin (FUO/IUO). The differential diagnosis is broad and

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Submitted Date: May 11, 2026 **Revised Date:** July 18, 2026 **Accepted Date:** August 18, 2026

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includes infections, autoimmune disorders, and malignancies.[3] Conventional imaging modalities such as CT and MRI may fail to detect small, early-stage, or metabolically active tumors that lack clear structural abnormalities, thereby limiting their diagnostic sensitivity in this setting.[2,3]

18F-FDG PET/CT enables whole-body metabolic imaging and has emerged as a valuable tool for detecting occult malignancies associated with paraneoplastic processes. A meta-analysis of 1,293 patients with suspected PNS reported pooled sensitivity and specificity of 81% and 88%, respectively, highlighting its high diagnostic accuracy.[4] In addition, cohort studies have emphasized the particularly high negative predictive value of 18F-FDG PET/CT for excluding underlying malignancy in patients with suspected PNS.[1,5]

Beyond classical neurologic PNS, FDG PET/CT has demonstrated substantial diagnostic value in patients presenting primarily with constitutional symptoms and systemic inflammation. Studies of patients with constitutional symptoms and FUO have shown that PET/CT frequently identifies malignant, infectious, or inflammatory etiologies and may also provide clinically meaningful reassurance when findings are negative.[3,6,7]

However, most published data focus either on neurologic PNS or on heterogeneous FUO cohorts, and limited evidence addresses patients with unexplained elevated APR levels and constitutional symptoms who are being evaluated for suspected paraneoplastic syndrome. Therefore, this study aims to retrospectively evaluate the etiologic distribution and the diagnostic contribution of 18F-FDG PET/CT in patients undergoing imaging for suspected paraneoplastic syndrome in the setting of unexplained systemic inflammation.

Methods

Study Design and Patient Population

This retrospective, single-center observational study was conducted in accordance with the Declaration of Helsinki and approved by the Non-Interventional Scientific Research Ethics Committee of Sakarya University (Approval No: 16.03.2026-E.572647). Because of the retrospective design, informed consent was waived.

A total of 102 adult patients underwent 18F-FDG PET/CT imaging between June 2018 and April 2025 for suspected paraneoplastic syndrome in the setting of unexplained elevated acute-phase reactants (APR) and constitutional symptoms. All patients in the study underwent PET/CT imaging as part of the etiologic investigation. Before undergoing 18F-FDG PET/CT, all patients had undergone a routine diagnostic work-up directed by the referring physician, including laboratory investigations and conventional imaging modalities such as contrast-enhanced CT, ultrasonography, and/or MRI, as clinically indicated. Despite these evaluations, the underlying etiology remained unexplained, or the presence of an occult malignancy could not be confidently excluded. Therefore, 18F-FDG PET/CT was requested to identify the underlying cause, detect occult malignancy, evaluate alternative inflammatory or infectious etiologies, and, when appropriate, localize the most suitable site for tissue biopsy. Patients were identified from the institutional PET/CT database using indication-based keyword screening (e.g., "paraneoplastic," "constitutional symptoms," "elevated CRP/ESR," "anemia"). Electronic medical records were reviewed for clinical, laboratory, imaging, and follow-up data. Constitutional symptoms were defined as the presence of at least one of the following: unexplained fever (>38°C), unintentional weight loss (>5% within 6 months), night sweats, or persistent fatigue. Elevated APR was defined as CRP and/or ESR above institutional reference limits without an identified cause after standard first-line evaluation. Patients were excluded if they had a previously diagnosed active malignancy at the time of PET/CT, a known infectious or inflammatory disease that adequately explained the presenting symptoms before imaging, insufficient clinical follow-up (defined as less than 6 months unless a definitive diagnosis was established earlier), or incomplete imaging or laboratory data.

According to the clinical indication, patients were classified into seven indication groups: I. isolated APR elevation, II. APR elevation with constitutional symptoms, III. hypercalcemia with ESR elevation, IV. hyponatremia, V. polyneuropathy, VI. unexplained elevation of Ca markers, and VII. others. During multi-category analysis, most cells had expected counts below 5, violating chi-square assumptions. Therefore, indication categories were combined into three groups: (i) isolated APR elevation, (ii) APR elevation with constitutional symptoms, and (iii) other indications.

18F-FDG PET/CT Protocol

PET imaging was performed prior to any treatment, and images were acquired using a combined PET/CT scanner (Biograph mCT, Siemens Healthineers, Knoxville, USA). PET image acquisition was performed according to EANM guidelines for tumor imaging.[8] Each patient fasted for at least six hours before imaging. 18F-FDG [260–480 MBq (7–13 mCi)] was administered to patients with blood glucose levels lower than 150 mg/dL. The CT acquisition was performed without intravenous contrast and was intended for attenuation correction and anatomical localization rather than comprehensive diagnostic evaluation. CT data were

acquired with automated dose modulation (50–250 mA), tube voltage of 80–120 kV, a collimation of 16 × 1.2 mm, a measured field of view (FOV) of 78 mm, a spiral pitch factor of 0.8, and were reconstructed into images with a 0.625-mm transverse pixel size and a 5-mm slice thickness. PET data were acquired in 3D mode with a scan duration of 1.5 min per bed position. Acquired images were reconstructed using True X+TOF (ultra HD-PET) with two iterations, 21 subsets, and a Gaussian filter of 5 mm, with an image matrix size of 256 × 256. The data were transferred via the Digital Imaging and Communications in Medicine (DICOM) protocol to a processing workstation (Syngovia, Siemens).

Image Analysis and Definitive Diagnosis

All PET/CT images were independently reviewed by an experienced nuclear medicine physician who was blinded to the final diagnosis but aware of the clinical indication. PET/CT findings were categorized as suggestive of malignancy, infection, inflammatory/rheumatologic disease, or negative (no abnormal FDG uptake beyond physiological distribution). In cases where PET/CT demonstrated abnormal findings that were not suggestive of malignancy, infection, or inflammatory disease, the examination was classified as non-specific positive and interpreted in conjunction with the patient's clinical history, laboratory findings, and previous imaging studies. Focal FDG uptake exceeding background activity and not corresponding to the known physiological distribution was considered pathological.

The final diagnosis was established using histopathological confirmation when available, microbiological findings, established clinical diagnostic criteria for inflammatory or rheumatologic diseases, and/or clinical and imaging follow-up of at least six months. Based on the reference standard, patients were classified into one of the following diagnostic categories: malignancy, infectious disease, inflammatory and rheumatic diseases, or other diseases.

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics 24.0 (IBM SPSS Statistics for Windows, Version 24.0; Armonk, NY). Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on distribution. Normality was assessed with the Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages. In contingency table analyses involving multiple-category variables, several cells had low expected frequencies (<5), violating the chi-square test assumptions and limiting the reliability of asymptotic p-values. To ensure statistical validity and stability of the results, categories with sparse cell counts were combined into clinically meaningful groups before reanalysis. Subsequent analyses used the regrouped variables to provide more robust and interpretable statistical estimates. Comparisons between groups (malignancy vs. non-malignancy) were performed using Student's t-test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Diagnostic performance metrics of PET/CT (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy) were calculated using the final diagnosis as the reference standard. A univariate logistic regression analysis was performed to estimate odds ratios for malignancy across indication groups. A p-value <0.05 was considered statistically significant.

Results

A total of 102 patients were included in the analysis, of whom 47 (46.1%) were female and 55 (53.9%) were male. The most frequent indication for PET/CT was elevated APR and constitutional symptoms (n=60, 58.8%), followed by unexplained elevated APR alone (n=26, 25.5%), hyponatremia (n=5, 4.9%), hypercalcemia and elevated ESR (n=3, 2.9%), polyneuropathy (n=3, 2.9%), unexplained elevated cancer markers (including CA 19-9 and CA 125) (n=2, 2%), and other reasons (including 1 optic demyelination neuropathy, 1 rash on the body, and 1 encephalopathy) (n=3, 2.9%) (Table 1).

Although the initial multi-category analysis was statistically significant (p=0.001), a chi-square analysis was also performed because most cells had expected counts of less than 5, using three indication categories: (i) isolated APR elevation, (ii) APR elevation with concomitant constitutional symptoms, and (iii) other indications. For the diagnostic performance analysis, PET/CT was considered positive when any abnormal FDG uptake beyond the physiological distribution was detected, including findings suggestive of malignancy, infection, inflammatory/rheumatologic disease, or another pathological process. Of the 86 PET/CT-positive patients, 48 (47.1%) had a final diagnosis of malignancy, and 38 had non-malignant diagnoses. Of these, 33 (32.4%) had inflammatory/rheumatologic diseases, 9 (8.8%) had infections, 8 (7.8%) had other systemic diseases, and 4 (3.9%) had an undetermined diagnosis (Table 1, Figure 1). All 16 PET/CT-negative patients were free of malignancy, and no false-negative examinations were observed. The distribution of etiologies is shown in Table 2. To ensure statistical robustness, PET/CT outcomes and final diagnoses were dichotomized as malignancy versus non-malignancy (p=0.001). Accordingly, the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of PET/CT for detecting malignancy were 100%, 29.6%, 55.8%, 100%, and 62.7%, respectively.

Table 1. Demographics and clinical characteristics of the patients based on the definitive diagnosis

	Definitive Diagnosis					p
	Malignancy (n=48)	Inflam.& rheumatic diseases (n=33)	Infec. diseases (n=9)	Other diseases (n=8)	Undetermined (n=4)	
Gender, n						
Female (n=47)	18	19	4	2	4	**0.054**
Male (n=55)	30	14	5	6	0	
Indications						
↑APR & constitutional symptoms (n=60)	37	18	5	0	0	
Isolated ↑APR (n=26)	3	13	4	2	4	
Other Indications	8	2	0	6	0	
Hyponatremia (n=5)	1	1	-	3	-	**0.001**
Hypercalcemia & ↑ ESR (n=3)	3	-	-	-	-	
Polineuropathy (n=3)	1	-	-	2	-	
↑ Ca markers (n=2)	1	-	-	1	-	
Optic neuropathy	1	-	-	-	-	
Rash on the body	-	1	-	-	-	
Encephalopathy	1	-	-	-	-	

APR: acute-phase reactants; Ca: Cancer; ESR: erythrocyte sedimentation rate; Inflam: inflammation; Infec: Infectious

Among female patients, inflammatory/rheumatic diseases were the most common diagnosis (40.4%), followed by malignancy (38.3%). In contrast, malignancy was the predominant diagnosis in male patients (54.5%), whereas inflammatory/rheumatic diseases accounted for 25.5%. Notably, all patients with normal PET/CT findings were female (8.5% among females, 0% among males). Infections and other causes were relatively evenly distributed between the sexes, although a slight male predominance was observed in these categories. The association between gender and final diagnostic category did not reach statistical significance (p =0.054).

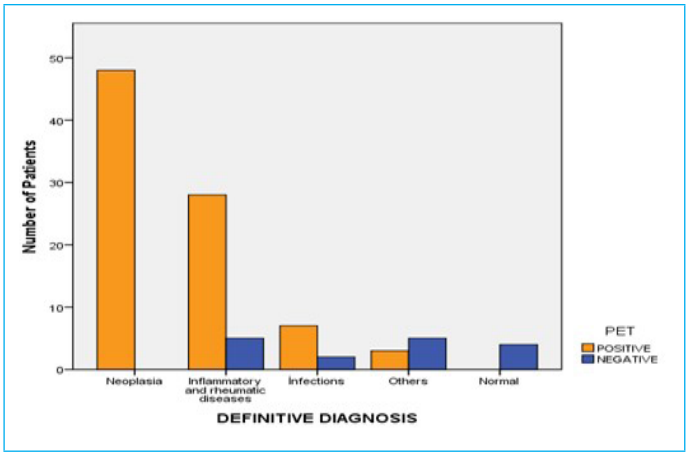

Figure 1. Distribution of definitive diagnoses and corresponding PET/CT results

The majority of patients with neoplasia showed positive PET findings, whereas patients with inflammatory/rheumatologic diseases showed a mixed distribution. Infectious and other causes were less frequently associated with PET positivity, while normal findings were observed only in PET-negative cases.

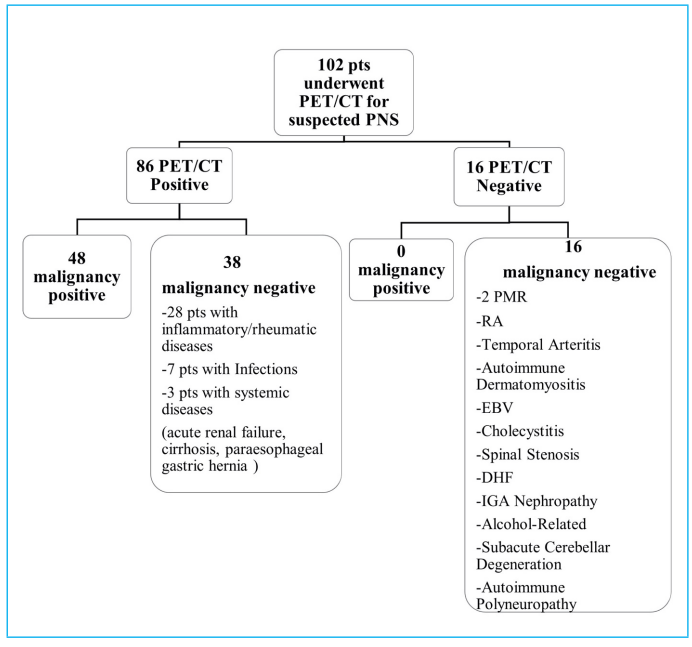

Figure 2. Flowchart of patient distribution and final diagnoses

EBV, Epstein-Barr virüs; DHF, decompensated heart failure; PNS, paraneoplastic syndromes; PMR, polymyalgia rheumatica; pts, patients; RA, rheumatoid arthritis. Of 102 patients undergoing 18F-FDG PET/CT for suspected paraneoplastic syndrome, 86 were PET-positive (48 malignancies, 38 non-malignant—mainly inflammatory/rheumatologic diseases, infections, and systemic conditions). Sixteen patients were PET-negative, and none had malignancy; all were diagnosed with.

Table 2. Distribution of etiologies

Malignancy (n=48)	Inflammatory & Rheumatic Diseases (n=33)	Infectious diseases (n=9)	Other diseases (n=8)
9 Multiple Myeloma	15 Polimyalgia Romatica	2 EBV w/ LN involvement	1 Cirrhosis
5 Lung Ca	6 Vasculitis	2 Cholesistitis	1 Acute renal failure
5 Klatskin Tm	1 Vasculitis + PMR	1 Lung Tuberculosis	1 Paraesophageal gastric hernia
4 Lymphoma	2 Rheumatoid Arthritis	1 Pericarditis	1 Spinal stenosis
2 DLNHL	4 Sarcoidosis	1 Osteomyelitis	1 Decompensated heart failure
1 T-cell NHL	1 w/ PAN	1 Retropharyngeal abscess	1 IGA nephropathy
1 HL	1 w/ Cutenous involvement	1 Generalized Tonsilits	1 Alcohol-related subacute cerebellar degeneration
3 Pancreas Ca	1 w/ peritonitis		1 Polyneuropathy
2 Gastric Ca	1 w/ classic form		
2 Duedenum Ca	1 PAN + Myositis		
2 Colorektal Ca	1 Ankylosing spondylitis		
2 Ovarian Ca	1 Dermatomyositis		
2 Mesothelioma	1 Lober otoimmune hepatitis		
1 Gallbaldder Ca	1 mesenteric panniculitis		
1 Cholangiocellullar Ca			
1 Renal Cell Ca			
1 Servix Ca			
1 Endometrium Ca			
1 Paraganglioma			
1 GIST			
1 NET			
1 Tongue Ca			
1 Erdheim-Chester Disease			
1 Kaposi Sarcoma			
1 Brain Glioblastoma			

Ca: Cancer; DLNHL: Diffuse large cell non-hodgkin lymphoma; EBV: Epstein-Barr virüs; GIST: Gastrointestinal stromal tumor; HL: Hodgkin Lymphoma; NHL: Non-Hodgkin Lymphoma; LN: Lymph node; NET. Neuroendocrine Tumor; PAN: Poliarthritis Nodosa; PMR, polymyalgia rheumatica

Compared with isolated APR elevation, the presence of concomitant constitutional symptoms was associated with a markedly increased risk of malignancy (OR =12.33; 95% CI: 3.3–45.8), and the "other indications" group also showed an elevated risk (OR =7.67; 95% CI: 1.62–36.2). A significant association was observed between PET classification and the final diagnostic category (p=0.001). PET findings were fully concordant with the final malignancy status, with no false-positive or false-negative cases. Among non-malignant cases, PET differentiated patients with active inflammatory findings from those with completely negative scans (Figures 1 and 2).

For malignancy detection, 18F-FDG PET/CT demonstrated 100% sensitivity and 100% negative predictive value, with no false-negative cases. However, specificity was 29.6% because of FDG uptake in inflammatory and infectious conditions, yielding a PPV of 55.8%. Among the 38 patients with PET-positive findings in whom malignancy was excluded, 28 (73.7%) were diagnosed with rheumatologic or inflammatory diseases, including polymyalgia rheumatica and vasculitis. The remaining cases were diagnosed with infectious or other systemic conditions.

Discussion

In this study, 18F-FDG PET/CT demonstrated a high diagnostic yield among patients suspected of paraneoplastic syndrome with unexplained elevated acute-phase reactants and constitutional symptoms. Nearly half of the cohort was ultimately diagnosed with cancer (47.1%), underscoring the high pretest probability in this carefully selected population and enabling earlier diagnosis. Consistent with our findings, Opalinska et al.[9] reported that FDG PET/CT identified malignancies in 53% of patients evaluated for PNSs who had normal structural imaging. Importantly, the presence of elevated APR combined with constitutional symptoms was strongly associated with malignancy, with more than 12 times the odds compared with isolated APR elevation. This supports the idea that systemic symptom burden significantly enhances the assessment of malignancy risk in patients undergoing whole-body metabolic imaging.

A multicenter cohort analysis across 21 countries found that the causes of FUO and their rates were 51.6% for infections, 11.4% for malignancies, 9.3% for inflammatory (collagen and vascular) disorders, and 7.7% for miscellaneous causes, with 20.1% remaining undiagnosed.[10] A separate meta-analysis of more than 1,600 FUO/IUO patients found that rheumatic diseases accounted for 22.2% of cases, led by Still's disease (22.8%), giant cell arteritis (11.4%), and systemic lupus erythematosus (11.1%).[11]

Wright et al.[12] noted that geographical differences exist, with infections more common in low- and middle-income

countries (43–63%), whereas in upper-middle- and high-income countries, infection prevalence decreases to 15–49%, and collagen-vessel inflammatory causes increase to 19–47%. FUO/IUO more frequently affects middle-aged and older adults and is often confused with comorbidities such as cancer or immunosuppression. However, undiagnosed cases persist in up to 10–20% of series, even in advanced healthcare settings.[10,12] In our study, only 4 patients (4%) had an undetermined diagnosis.

A key finding of this study was the 100% sensitivity and negative predictive value of PET/CT in detecting malignancy. No false-negative cases of malignancy were observed, indicating that a negative PET/CT significantly reduces the likelihood of hidden cancer in this clinical setting. Similar high sensitivity and strong rule-out performance have been reported in groups with suspected paraneoplastic and occult malignancy, where FDG PET/CT has proven especially useful in ruling out cancer when clinical suspicion is high but traditional imaging results are inconclusive.[4,5,13] This underscores the role of PET/CT as an essential triage tool for patients with diagnostic challenges.

Although specificity was limited (29.6%) due to FDG uptake in inflammatory and infectious conditions, the majority of PET-positive but malignancy-negative cases (73.7%) were ultimately diagnosed with rheumatologic or inflammatory diseases, particularly polymyalgia rheumatica and vasculitic syndromes. Similar to our study, Altınkaynak et al.[6] found that patients with constitutional symptoms underwent diagnostic PET/CT scans. PET showed a sensitivity of 97.5%, a specificity of 31.8%, and helped diagnose rheumatic diseases in 86.4% of cases, including 100% of vasculitis patients. This distribution aligns with the known nonspecific properties of FDG as a glucose analog and is consistent with the current literature, which shows that FDG PET/CT can identify systemic inflammatory diseases in patients with constitutional symptoms or inflammation of unknown cause.[3,13,14] In this context, PET/CT did not merely generate false-positive findings but instead redirected the diagnostic pathway toward clinically significant non-malignant causes.

In a study by Bleeker-Rovers et al.[15], high FDG uptake was observed in periaortitis associated with conditions such as Takayasu's arteritis, Wegener's granulomatosis, polymyalgia rheumatica, giant cell arteritis, and infectious vasculitis. The study also reported that 18F-FDG-PET/CT has a specificity of 89% and a sensitivity ranging from 77% to 100% for detecting vasculitis. Conversely, when giant cell arteritis is limited to the temporal arteries, the sensitivity of 18F-FDG-PET/CT may remain low because of the small size of the arteries and the high background FDG uptake in the brain.[15] Consistent with this, in our study, one patient with negative PET/CT imaging was diagnosed with temporal arteritis. The prominence of PMR and vasculitis among PET-positive non-malignant cases aligns with recent rheumatologic imaging studies emphasizing the role of FDG PET/CT in the diagnosis of large-vessel vasculitis and polymyalgia rheumatica. Current imaging guidelines and updated consensus documents increasingly recognize whole-body PET/CT as a valuable tool for patients with unexplained systemic inflammation and elevated APR, particularly when traditional diagnostic methods are inconclusive.[3,11,13,14,16] Our findings support this growing role in real-world clinical practice.

This study has several limitations that should be acknowledged. First, its retrospective single-center design carries an inherent risk of selection bias, and the relatively small sample size may have limited the power of subgroup analyses. Second, the study population was enriched with patients who had unexplained inflammatory syndromes and suspected paraneoplastic disease, likely increasing the observed prevalence of both malignancy and systemic inflammatory disorders compared with unselected referral groups. Nevertheless, the present study emphasizes the dual diagnostic value of 18F-FDG PET/CT in this population: reliable exclusion of malignancy and frequent identification of systemic inflammatory disease in patients presenting with unexplained constitutional symptoms. Future prospective studies with standardized referral criteria and predefined reference standards would help determine which clinical subgroups benefit most from early PET/CT.

Conclusion

In patients with suspected paraneoplastic syndrome who present with unexplained increases in acute-phase reactants and constitutional symptoms, 18F-FDG PET/CT has high sensitivity and excellent negative predictive value for detecting malignancy. Although specificity is limited by FDG uptake in inflammatory conditions, PET/CT often identifies clinically significant rheumatologic and inflammatory disorders. The presence of elevated APR and constitutional symptoms substantially increases the risk of malignancy, supporting a risk-based imaging approach. Overall, 18F-FDG PET/CT is a valuable whole-body diagnostic tool for evaluating unexplained systemic inflammatory conditions.

Disclosure

Ethics Committee Approval: The study protocol received approval from the Non-Interventional Scientific Research Ethics Committee of Sakarya University (committee (Approval No: 16.03.2026-E.572647).

Informed Consent: Because of the retrospective design, informed consent was waived.

Conflicts of Interest: No conflict of interest was declared by the authors.

Funding: The authors declare that they have no financial or personal relationships that could influence the work reported in this paper.

Use of AI for Writing Assistance: No generative artificial intelligence or automated tools were used to generate the text, analyze the data, or prepare any part of this manuscript.

Peer-review: Externally peer-reviewed.

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