DOI: 10.24938/kutfd.1539744 Kırıkkale Üniversitesi Tıp Fakültesi Dergisi 2025;27(1):22-28
Original Article *Özgün Araştırma*

THE SIGNIFICANCE OF QUANTITATIVE DATA FROM PET/CT IN THE COURSE OF SARCOIDOSIS AND THEIR ASSOCIATION WITH CLINICAL PARAMETERS

Sarkoidoz Seyrinde PET/BT'den Elde Edilen Kantitatif Verilerin Önemi ve Bunun Klinik Parametrelerle İlişkisi

İnci USLU BİNER[1] Özlem ÖZMEN[2] Berna AKINCI ÖZYÜREK[3] Ebru TATCI[2] Yurdanur ERDOĞAN[3] Atila GÖKCEK[4]

[1] *Department of Nuclear Medicine, Faculty of Medicine, Eskişehir Osmangazi University, ESKİŞEHİR, TÜRKİYE*
[2] *Department of Nuclear Medicine, Etlik City Hospital, ANKARA, TÜRKİYE*
[3] *Department of Chest Diseases, Atatürk Sanatorium Education and Research Hospital, ANKARA, TÜRKİYE*
[4] *Department of Radiology, Atatürk Sanatorium Education and Research Hospital, ANKARA, TÜRKİYE*

ABSTRACT

Objectives: To examine the potential correlation between the presence of a disease outside the chest and the likelihood of recurrence or need for therapy, as well as to assess the relationship between quantitative measurements obtained from 18F-FDG PET/CT scans and clinical and laboratory markers associated with sarcoidosis.

Material and Methods: 18F-FDG PET/CT images of 78 patients diagnosed with sarcoidosis were retrospectively examined. The SUV max value of the lesions with the highest uptake in the thoracic and extrathoracic regions of the disease was determined. Clinical and laboratory parameters, and SUV max values of the lesions were compared. The relationship between the detection of an extrathoracic disease and the need for treatment, and the development of recurrence was also investigated.

Results: No significant correlation was found between patients with thoracic and extrathoracic disease regarding SUVmax and clinical and laboratory results ($p>0.05$). A significant correlation was detected between the SUVmax value of mediastinal lymph nodes and the presence of extrathoracic disease ($p<0.05$). The need for treatment was found to be higher in patients with high 18F-FDG uptakes of the thoracic lesions. No relationship was found between the presence of extrathoracic disease and disease stage ($p=0.821$) and treatment requirement ($p=0.793$). A correlation was found between any organ involvement and the presence of recurrent disease at follow-up ($p=0.018$).

Conclusion: 18F-FDG uptake in lung lesions and mediastinal lymph nodes may be a guide to identify patients requiring treatment by confirming the association between disease activity and clinical stage. Additionally, detection of any organ involvement on 18F-FDG PET/CT may be a predictor of the recurrent disease at follow-up.

Keywords: *18F-FDG PET/CT, sarcoidosis, maximum standardized uptake value, extrathoracic disease*

ÖZ

Amaç: Toraks dışında bir hastalık varlığı ile nüksetme olasılığı veya tedavi ihtiyacı arasındaki potansiyel korelasyonun yanı sıra 18F-FDG PET/BT taramalarından elde edilen kantitatif ölçümler ile sarkoidozla ilişkili klinik ve laboratuvar belirteçleri arasındaki ilişkiyi değerlendirmek.

Gereç ve Yöntemler: Sarkoidoz tanısı alan 78 hastanın 18F-FDG PET/BT görüntüleri retrospektif olarak incelendi. Hastalığın torakal ve ekstratorasik bölgelerde tutulumu en yüksek olan lezyonların SUVmax değeri belirlendi. Lezyonların klinik ve laboratuvar parametreleri ile SUVmax değerleri karşılaştırıldı. Ayrıca toraks dışında bir hastalığın saptanması ile tedavi ihtiyacı ve nüks gelişimi arasındaki ilişki de araştırıldı.

Bulgular: Torasik ve ekstratorasik hastalığı olan hastalar arasında SUVmax ile klinik ve laboratuvar sonuçları arasında anlamlı bir korelasyon bulunamadı ($p>0,05$). Mediastinal lenf nodlarının SUVmax değeri ile ekstratorasik hastalık varlığı arasında anlamlı korelasyon tespit edildi ($p<0,05$). Torasik lezyonlarda 18F-FDG tutulumu yüksek olan hastalarda tedavi ihtiyacının daha fazla olduğu görüldü. Toraks dışı hastalık varlığı ile hastalığın evresi ($p=0,821$) ve tedavi gereksinimi ($p=0,793$) arasında ilişki bulunamadı. Herhangi bir organ tutulumu ile takipte hastalığın tekrarlaması arasında korelasyon bulundu ($p=0,018$).

Sonuç: Akciğer lezyonlarında ve mediastinal lenf düğümlerinde 18F-FDG tutulumu, hastalık aktivitesi ile klinik evre arasındaki ilişkiyi doğrulayarak tedavi gerektiren hastaların belirlenmesinde yol gösterici olabilir. Ayrıca 18F-FDG PET/BT'de herhangi bir organ tutulumunun saptanması, takipte tekrarlayan hastalığın habercisi olabilir.

Anahtar Kelimeler: *18F-FDG PET/BT, sarkoidoz, maksimum standardize edilmiş alım değeri, ekstratorasik hastalık*

Correspondence / Yazışma Adresi: **Dr. İnci USLU BİNER**
Department Of Nuclear Medicine, Faculty of Medicine, Eskişehir Osmangazi University, ESKİŞEHİR, TÜRKİYE
Phone / Tel: +902222392979/ 3453 **E-mail** / E-posta: inciuslu@yahoo.com
Received / Geliş Tarihi: 29.08.2024 **Accepted** / Kabul Tarihi: 18.12.2024

KÜ Tıp Fak Derg 2025;27(1):22-28
Doi: 10.24938/kutfd.1539744

INTRODUCTION

Sarcoidosis is an autoimmune illness defined by the presence of granulomas, which are small clusters of immune cells, and its exact cause is yet unknown. The lungs are the organs that are most frequently impacted. Lesions outside the chest are uncommon.[1] The progression of the disease differs on an individual basis. Conventional approaches may not be enough to evaluate ongoing inflammation and the severity of the disease. Various serum markers have been utilized, but, none definitively identify the presence of the condition. Therefore, accurately assessing the extent of systemic sarcoidosis is crucial. Fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (18F-FDG PET/CT) is being used more and more to assess different kinds of inflammatory lesions. The utilization of 18F-FDG PET/CT has garnered significant interest in assessing disease activity in persons with sarcoidosis. The objective of this investigation was to examine the utilization of 18F-FDG PET/CT in determining the extent of sarcoidosis and to ascertain the correlation between the clinical and laboratory parameters of sarcoidosis and the quantitative data from 18F-FDG PET/CT. The study also examined the potential correlation between the presence of extrathoracic disease and recurrence. There are research in the literature that demonstrate its impact on modifications in treatment. Furthermore, the significance of the extent of lung parenchymal involvement was predominantly highlighted. No study has been discovered that assesses the correlation between the existence of extrathoracic disease and the occurrence of recurrence. Additionally, we evaluated whether the identification of extrathoracic disease correlated with the likelihood of recurrence.

MATERIALS AND METHODS

We retrospectively checked the medical documentation of 78 individuals with histopathologically confirmed diagnosis of sarcoidosis Prior to diagnosis, all patients had 18F-FDG PET/CT to assess suspected malignant lesions in the lung or mediastinum. The study received approval from the Ethics Committee of the University of Health Sciences, Ataturk Sanatorium Training and Research Hospital on April 4, 2018, with decision number 590. A PET/CT scan was conducted using the Siemens Biograph 6 HI-REZ integrated PET/CT scanner from Siemens Medical Solutions in Knoxville, TN, USA Every patient abstained from eating for a minimum of 6 hours prior to the test. Only individuals with blood glucose levels below 180 mg/dL were subjected to scanning. An intravenous injection of 0.15 mCi/kg of 18F-FDG was given to the patient, who then rested for roughly 45 minutes. Following the delivery of a PET scan and low-dose CT scan, imaging was conducted from the cranial region to the upper thigh, without the use of intravenous contrast. Results are categorized as positive or negative based on whether there is an elevation in activity beyond the typical biological distribution of the radiotracer in the organ and lymph node region. The positive 18F-FDG PET/CT data were categorized into two groups: thoracic disease and extrathoracic disease. Thoracic disease has been reported to impact not just the lymph nodes in the mediastinum and axilla, but also the lung tissue and pleural membrane. Extrathoracic disease refers to the presence of abnormal tissue in other parts of the body such as the abdomen and cervical lymph nodes, visceral organs (including the liver and spleen), parotid glands, and bones. To measure the uptake of the radiopharmaceutical inside each abnormal tissue, the maximum standardized uptake value (SUVmax) was utilized. The study compared the clinical and laboratory parameters, including respiratory function tests (such as forced expiratory volume at 1 second (FEV1)/% predicted values for forced vital capacity (FVC)), serum angiotensin-converting enzyme (ACE) and calcium (Ca) levels, and radiographic disease stage, with the SUVmax values of the lesions. The study also examined the association between the extrathoracic disease and development of disease recurrence during follow-up.

Quantitative analysis

The statistical analysis was performed using version 21.0 of the Statistical Package for the Social Sciences (SPSS). Numerical values and frequencies were used to represent categorical variables. The Kolmogorov-Smirnov test and histograms were employed to ascertain if the continuous variables exhibited a normal or skewed distribution. Parameters that exhibited a normal distribution were compared by the t test, whereas the Mann-Whitney U test was utilized to assess other variables. The choice between the chi-square test and Fisher's exact test was based on the specific circumstances in order to compare categorical variables. The Spearman or Pearson correlation coefficients were employed to evaluate the extent of association between two variables. The sensitivity and specificity ratios were evaluated and quantified using receiver operating curve (ROC) analysis. This study examined the link between the class, which was divided by a predetermined cutoff value, and the variables and classifiers type of actuality. Quantitative variables are represented in the tables using the mean (standard deviation) and median (minimum-maximum) values. On the other hand, categorical variables are represented as the number of occurrences (percentage). The variables underwent testing with a confidence level of 95%, and any p-values below 0.05 were deemed statistically significant.

KÜ Tıp Fak Derg 2025;27(1):22-28
Doi: 10.24938/kutfd.1539744

RESULTS

We analysed 18F-FDG PET/CT results of the 78 people referred for the evaluation of lesions suspicious for malignancy in the mediastinum or lung between January 2008 and August 2015. The average age of 78 cases, 51 female and 27 male, included in the study was 49.32±14.14 (23-86) years**.** The patients were mostly suffered from fatigue, weight loss, cough, and shortness of breath. Four patients had uveitis and one had dermal lesions. There were no patients with cardiac or neurological findings. Histopathological specimens were acquired using mediastinoscopy (n=12) and bronchoscopy (n=16), transthoracic fine-needle aspiration biopsy (n=12), endobronchial ultrasonography (EBUS) (n=45), lung wedge resection (n=2) and cervical lymph node biopsy (n=1). All cases were diagnosed with granulomatosis inflammation. The SUVmax value of the lesions exhibiting the most significant uptake in both the thoracic and extrathoracic regions of the disease was calculated. The most frequently pathologic increased metabolic foci were the mediastinal lymph nodes. SUVmax in the mediastinal lymph nodes was 13.61±6.31. All patients exhibited thoracic abnormalities that were positive on 18F-FDG PET/CT scans, specifically in the mediastinum and/or the lung parenchyma. Out of the total of 78 patients, 41 individuals, which accounts for 70% of the sample, were diagnosed with an extrathoracic illness. The extrathoracic organs involved in the study were peripheral lymph nodes (n=41), spleen (n=7), parotid gland (N=7), liver (n=4), bone (n=1), and sinus area (n=1) as shown in Figure 1. Several patients exhibited more than two distinct extrathoracic locations. The SUVmax of the 18F-FDG PET/CT positive extrathoracic localisations had a median value of 7.38, with a range of 3.35 to 25.3. The patient groups were characterized by clinical and laboratory criteria, including pulmonary function tests (FEV1, FEV1/FVC), blood levels of angiotensin-converting enzyme (ACE) and calcium (Ca), and illness stage. No association was observed between serological inflammatory markers and the presence of any extrathoracic involvement (p=0.890). Serum ACE concentrations were elevated in 60% of patients (25 out of 41) with extrathoracic illness. However, 19% of patients with positive 18F-FDG PET/CT results had ACE levels within the normal range. All patients with extrathoracic disease had serum calcium values that fell within the normal range. Out of the total number of patients, eight exhibited obstructive disease based on the FEV1/FVC ratio, whereas the rest of the patients had normal results. There was no statistically significant link observed between individuals with thoracic and extrathoracic disease in terms of SUVmax and clinical and laboratory data (p>0.05). An association was seen between the SUVmax value of mediastinal lymph nodes and the presence of extrathoracic illness (p=0.035). The patient's laboratory and metabolic findings of the thoracic and extrathoracic groups are displayed in Table 1. Nevertheless, we discovered a moderate negative association (r=-0.369) between the SUVmax of the lung parenchyma and the assessed respiratory performance. The relationship between the results of pulmonary function tests and inflammatory markers is presented in Table 2.

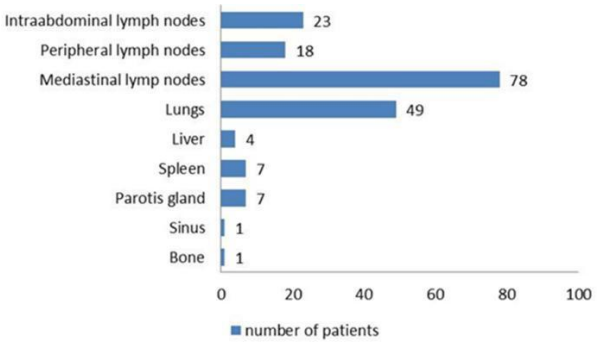

Figure 1: The numerical distribution of the organs' uptake of Fluorine-18-fluorodeoxyglucose- (18F-FDG) in 78 cases

When the cut-off value of 11.22 was determined in the ROC analysis, we can use the mediastinal SUVmax level to detect the presence of an extrathoracic disease with a sensitivity of 73% and specificity of 55% (Figure 2). Out of the total of 78 patients, 18 (23%) received corticosteroid treatment, while the remaining 59 patients were monitored. A single patient received post-diagnosis follow-up at a different hospital, and the details of their treatment are currently unknown. Patients with higher SUVmax of chest involvement (p=0.029) and pulmonary parenchyme (p=0.016) had a greater requirement for treatment. A significant association between the FEV1/FVC ratio and the need for therapy was seen (p =0.001).

In thirty-eight individuals, chest radiography revealed stage 1 disease, and in the remaining patients, stage 2 disease. No correlation was observed between the presence of extrathoracic disease and illness stage (p=0.821) and treatment requirement (p=0.793). During the clinical follow-up, recurrence was observed in 8 patients, out of which 6 patients exhibited extrathoracic illness (Table 1). The presence of any peripheral lymph node was not correlated with the recurrence of the disease (p=0.097). However, a correlation was found between any organ involvement and the presence of recurrent disease during follow-up (p=0.018). However, there was no correlation between the SUVmax value of the organs and recurrence (p=0.543). The Table 3 displays the correlation between patients with thoracic and extrathoracic

KÜ Tıp Fak Derg 2025;27(1):22-28
Doi: 10.24938/kutfd.1539744

disease in terms of treatment, SUVmax, and clinical and laboratory outcomes.

Table 1: Clinical, laboratory, and metabolic comparisons between groups with and without extrathoracic disease

	Extrathoracic disease		
	No (n=37) Mean±SD.	**Yes (n=41) Mean±SD.**	**p**
SUVmax mediastinal	12.07±5.64	15.00±6.63	**0.040** [t]
SUVmax thoracic (mediasten/lung)	12.50±5.72	15.00±6.63	0.079 [t]
SUVmax organ	5.26±0.85	5.60±2.24	0.0725[t]
	Median (Min-Max)	**Median (Min-Max)**	
SUVmax lung	5.60 (1.42-18.23)	6.09 (1.47-25.34)	0.645 [u]
SUVmax extrathoracic disease	-	7.38 (3.35-25.39)	**0.028** [u]
ACE	55 (10-147)	52 (18-380)	0.890 [u]
	Mean±SD.	**Mean±SD.**	
Ca	9.43±0.48	9.45±0.49	0.879[t]
FEV1/FVC	79.55±9.76	78.91±7.20	0.783 [t]
FEV1	89.68±19.96	90.25±18.85	0.916 [t]
	n (%)	**n (%)**	
Organ involvement			0.118 [f]
no	31 (83.8) [B]	27 (65.9)	
yes	6 (16.2)	14 (34.1) [A]	
Lung parenchyme lesion			0.999 [c]
no	14 (37.8)	15 (36.6)	
yes	23 (62.2)	26 (63.4)	
Stage			0.821 [c]
I	19 (51.4)	19 (46.3)	
II	18 (48.6)	22 (53.7)	
Relapse			0.268 [f]
no	35 (94.6)	35 (85.4)	
yes	2 (5.4)	6 (14.6)	
Treatment			0.793 [c]
None	27 (75.0)	32 (78.0)	
Steroid	9 (25.0)	9 (22.0)	
Comment			0.999 [f]
Normal	19 (86.4)	27 (84.4)	
Obstructive	3 (13.6)	5 (15.6)	

[t] t test, [u] Mann-Whitney U test, [c] Pearson's Chi-Squared Test, [f] Fisher's Exact Test, [or] The Odds Ratio (95% Confidence interval), A significance compared to the group without extrathoracic disease, B significance compared to the group with extrathoracic disease
SD: Standard Deviation, Min: Minimum, Max: Maximum
SUVmax: Maximum Standardised Uptake Value
FEV1/FVC: Forced Expiratory Volume/Forced Vital Capacity, ACE: Angiotensin convertign enzyme, Ca: Calcium

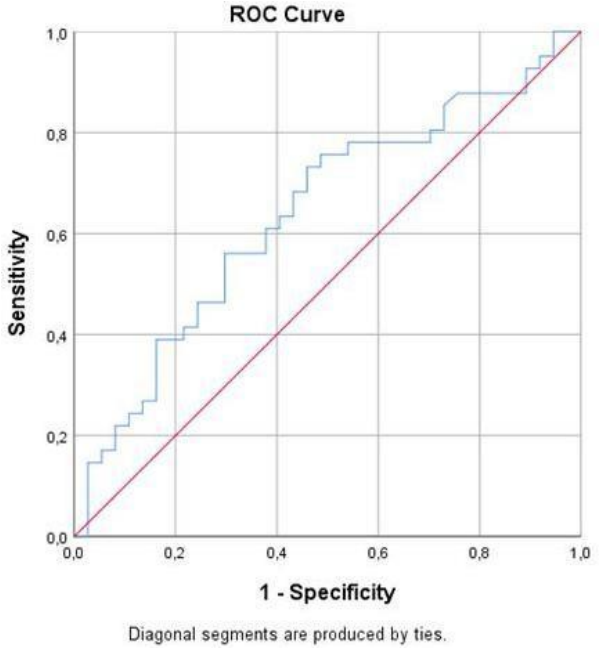

Figure 2: Receiver operating characteristic curve (ROC) for mediastinal SUVmax levels determined by 18F-FDG PET/CT in order to predict the disease's extent. The AUC (area under the curve) is 0.639 (SE:0.063)

Table 2: Correlation of study participants' metabolic data with clinical data

	ACE	Ca	FEV1/FVC	FEV1
SUVmax extrathoracic disease				
r	0,176	-0,272	0,165	-0,169
SUVmax mediastinal				
r	-197	-0,021	0,086	0,03
SUVmax thoracic (mediasten/lung)				
r	-0,207	-0,017	0,018	0,037
SUVmax organ				
r	0,379	-0,103	0,045	-0,239
SUVmax lung				
r	-0,03	0,117	-0.369*	0,021

SUVmax: Maximum standardised uptake value, r: The Pearson's correlation coefficient, ACE: Angiotensin convertign enzyme, Ca: Calcium
*: At the 0.05 level, the correlation is significant

DISCUSSION

18F-FDG PET/CT is utilized for identifying increased glucose metabolism and has demonstrated utility in assessing inflammatory activity.[2-5] It enables comprehensive visualization of the locations in the body where inflammation is occurring in sarcoidosis. The capacity to capture images of the entire body in a single examination is valuable in the diagnosis and monitoring of systemic disorders like sarcoidosis.[6] We examined whether the quantitative 18F-FDG PET/CT data are related to the clinical and laboratory measurements of sarcoidosis. The primary topics of discussion included the use of this tool to analyze the severity the and activity of the disease and to acquire

KÜ Tıp Fak Derg 2025;27(1):22-28
Doi: 10.24938/kutfd.1539744

crucial data for clinical outcome using a single imaging modality.

Table 3: Comparison of the need for treatment with clinical, laboratory and metabolic data

	Treatment		p- value
	None (n=59) Median (Min-Max)	Steroid (n=18) Median (Min-Max)	
SUVmax mediastinal	12.39 (3.50-28.87)	14.94 (5.19-27.70)	0.073 [u]
SUVmax thoracic (mediasten/lung)	12.39 (3.50-28.87)	15.45 (5.19-27.70)	**0.029** [u]
SUVmax organ	4.88 (3.35-9.67)	6.59 (3.20-6.77)	0.958 [u]
SUVmax lung	5.08 (1.42-18.23)	9.18 (4.79-25.34)	**0.016** [u]
SUVmax extrathoracic disease	7.19 (3.35-25.39)	8.83 (3.92-14.82)	0.810 [u]
ACE	55 (14-380)	45 (10-147)	0.193 [u]
	Mean±SD.	**Mean±SD.**	
Ca	9.43±0.52	9.47±0.35	0.754 [t]
FEV1/FVC	81.86±7.81	73.29±5.92	**0.001** [t]
FEV1	92.54±18.66	84.53±19.53	0.155 [t]
	n (%)	**n (%)**	
Organ involvement			
No	31 (83.8)	27 (65.8)	0.118 [f]
Yes	6 (16.2)	14 (34.2)	
Lung parenchme lesion			
No	22 (37.3)	7 (38.9)	0.999 [c]
Yes	37 (62.7)	11 (61.1)	
Stage			
I	33 (55.9) [B]	4 (22.2)	**0.016** [c]
II	26 (44.1)	14 (82.4) [A]	
Relapse			
No	53 (89.8)	16 (88.9)	0.999 [f]
Yes	6 (10.2)	2 (11.1)	
Comment			
Normal	35 (94.6)	11 (64.7)	0.009 [f]
Obstructive	2 (5.4)	6 (35.3)	

[t] t test, [u] Mann-Whitney U test, [c] Pearson's, chi squared test, [f] Fisher's exact test, [or] The odds ratio (95% Confidence interval),
A significance compared to the group without extrathoracic disease, B significance compared to the group with extrathoracic disease
SD: Standard deviation, Min: Minimum, Max: Maximum, SUVmax: Maximum standardised uptake value, Ca: Calcium, FEV1/FVC: Forced expiratory volume/Forced vital capacity

18F-FDG PET/CT is widely recognized as a sign of the activity of sarcoidosis.[7] In their initial report, Lewis et al. Observed 18F-FDG uptake in both intra and extrathoracic sarcoidosis in two patients.[8] In our study, we verified that active inflammation was present in the thorax of every patient (100%), which is consistent with previous research. Keijsers et al. and Soussan et al. also highlighted in their review that 18F-FDG PET/CT is advantageus for identifying extrathoracic inflammation in sarcoidosis.[9,10] Braun et al reported extrathoracic involvement in 7 out of 20 sarcoidosis patients.[11] Cremers JP et colleagues discovered a significant proportion of extrathoracic activity, specifically 75%.[12] Ambrosini et al documented the systemic manifestation of sarcoidosis by emphasizing the involvement of bones in a 37-year-old male.[13] Teirstein et al discovered hidden locations lesser (20 out of 137).[14] In our study, 18F-FDG PET/CT identified active inflammatory extrathoracic lesions that were not previously recognized in 52% (41/78) of patients. Oksuz et al. documented a case of sarcoidosis in a 43-year-old man, where both parotid glands were affected by inflammation.[15] Our analysis found that 7 patients exhibited bilateral involvement of the parotid glands, which is consistent with the findings reported in this case study.

SUVmax is a semi-quantitative method used to assess the level of disease activity.[16] Recent studies have utilized SUVmax as a biomarker to measure sarcoidosis activity in patients using 18F-FDG PET/CT imaging.[17] Metabolically active enlarged mediastinal lymph nodes is present in nearly all patients with active sarcoidosis. Elevated 18F-FDG uptake of the mediastinal lymph nodes is greatly reduced after effective treatment or spontaneous recovery without targeted intervention. Hence, 18F-FDG PET/CT can be utilized to assess the level of sarcoidosis activity.[17,18] Based on our findings, SUVmax in the mediastinum could potentially be a valuable factor in determining the presence of extrathoracic illness. However, it is important to note that other factors should also be taken into account in order to reach a conclusive determination (Figure 2).

Due to the high prevalence of sarcoidosis in the lungs, pulmonary function test results may exhibit abnormalities. Keijers et al. determined that the

KÜ Tıp Fak Derg 2025;27(1):22-28
Doi: 10.24938/kutfd.1539744

metabolic activity in the lung tissue might be used as an indicator of future decline in pulmonary function.[19] A retrospective study was conducted on 43 recently diagnosed sarcoidosis patients who had both a baseline and a 1-year follow-up 18F-FDG PET scan. The study found no correlation between the SUVmax value and functional indices. However, there was a significant difference in the thoracic SUVmax value between patients who required therapy and those who were treatment-naïve. Furthermore, the research conducted by Ambrosimi et al and Sobic Saranovic et al. showed that 18F-FDG PET/CT strongly effect disease management and is essential for clinical decision-making, especially when deciding whether to start treatment.[17,20] The choice of whether to start sarcoidosis treatment is difficult because many people with the disease have little to no organ impairment from the disease. Extrathoracic disease is not evaluated in the current staging system. It should be noted that additional data obtained with 18F-FDG PET/CT has the potential to influence clinical decision making. However, our investigation did not find any significant link between the existence of extrathoracic disease and radiologic disease stage, as well as treatment requirement.

Several published case reports and brief case series provide evidence of the effectiveness of 18F-FDG PET and 18F-FDG PET/CT in detecting metabolic response to treatment in sarcoidosis.[10,13] In our study, we did not evaluate the tretment response with 18F-FDG PET/CT. Serum ACE level testing is commonly used as an indication of inflammation in sarcoidosis.[21] Almost 50% of our patients who showed positive extrathoracic 18F-FDG PET/CT results had ACE levels that were considered normal. The results provided here corroborate the results of the study conducted by Mostard et al., which indicate that the negative predictive value of ACE is moderately low (65%) and that normal ACE levels do not always rule out the presence of active inflammatory areas.[22] Thus, the 18F-FDG PET/CT examination appears to be particularly beneficial. Therefore, the 18F-FDG PET/CT examination is especially advantageous for patients who have gotten negative ACE results, since it is expected that detecting inflammatory activity in these patients may impact clinical decision-making.

Mostard et al. discovered that individuals with positive 18F-FDG PET results in the pulmonary parenchyma had considerably lower FVC values.[22] Conversely, we observed a negative connection between lung activity and FEV1/FVC. Teinstein et al discovered that there is no connection between positive findings on a 18F-FDG PET scan and lung diffusion capacity for carbon monoxide (dlco) or serum ACE levels.[15] In a retrospective study, Mostard et al examined the correlation between 18F-FDG PET/CT findings and ACE levels. They found that 65 out of 73% of patients had a positive 18F-FDG PET/CT scan, and 52 of them showed signs of inflammatory activity in their blood, suggesting that 18F-FDG PET/CT can be useful in identifying disease in patients with persistent symptoms even when serum markers are not elevated, as well as in detecting lesions outside of the thoracic area.[22] The SUVmax of extrathoracic involvements did not exhibit any correlation with ACE and Ca levels in our investigation. A prior study on 18F-FDG in sarcoidosis yielded comparable findings, indicating that the SUVmax did not exhibit a correlation with angiotensin-converting enzyme (ACE) levels.[23]

The utility of 18F-FDG PET/CT imaging in predicting outcomes for patients with sarcoidosis is uncertain. There is a possibility that a widespread form of sarcoidosis may be linked to a more aggressive disease progression, including a higher likelihood of relapse after completing standard therapy. Several studies in the literature suggest that 18F-FDG PET/CT has an impact on therapy modifications.[19,24,25] The primary focus of the study conducted by Vorselears et al was on the prognostic significance of lung parenchymal activity.[26] The researchers discovered that a mediastinal SUVmax>6, as determined by 18F-FDG PET/CT at the initiation of infliximab therapy, was a strong indicator of relapse.[26] However, no study in the literature has examined the correlation between the presence of extrathoracic disease in initial 18F-FDG PET/CT and the occurrence of recurrence. Our subsequent data analysis indicated that 10% (8 out of 78) of the patients experienced a recurrence. In our study we discovered a relationship between the presence of any organ involvement outside the chest and the occurrence of relapse. Considering that extrathoracic disease is not evaluated in the current staging system, It is possible to argue that the existence of organ involvement may have a clinically meaningful impact on course of the disease and that is why 18F-FDG PET/CT is crucial.

There were certain constraints in this investigation. Our patient group included only stage 1 and 2 patients. The biopsy did not confirm the presence of aberrant uptake in the extrathoracic lesions. Cardiac involvement was assessed by routine clinical practice without any specific preparation prior to the imaging.

Ultimately, when there are no symptoms of inflammation detected through serologic means, 18F-FDG PET/CT proves to be an additional and valuable tool for evaluating the level of inflammatory activity in patients with sarcoidosis. 18F-FDG PET/CT is a valuable technique for assessing hidden disease locations in patients with sarcoidosis. 18F-FDG avidity of parenchymal lesions and metabolically active

mediastinal lymph nodes can serve as a diagnostic tool to determine whether patients need treatment by validating the correlation between disease activity and clinical stage. Moreover, the identification of any organ involvement on 18F-FDG PET/CT could potentially serve as an indicator of recurrent disease during follow-up. However, further research with large patient population with recurrence is required to validate the reliability of this indication in clinical assessment.

Conflict of Interest: The authors declared no conflicts of interest

Researchers' Contribution Rate Statement: Concept/Design: IUB, BAO; Analysis/Interpretation: IUB; Data Collection: OO, ET; Writer: IUB; Critical Review: YE, AG; Approver: IUB, BAO, OO, ET

Support and aknowledgement: No financial support was received from any institution or person.

Acknowledgment: I sincerely thank to Prof. Dr. Özlem Alpu (Department of Statistics, Eskişehir Osmangazi University) for her support to our statistical analysis.

Ethics Committee Approval: The study received approval from the Ethics Committee of the University of Health Sciences, Ataturk Sanatorium Training and Research Hospital on April 4, 2018, with Decision No. 590.

REFERENCES

1. Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. *Eur Respir J*. 1999;14(4):735-737.
2. Harsini S, Werner T, Revheim ME, Abass Alavi A, Saboury B. 18F-FDG PET/CT Imaging of infection and inflammation. *J Nucl Med*. 2022;63(2):2669.
3. Kung BT, Seraj SM, Zadeh MZ et al. An update on the role of 18F-FDG-PET/CT in major infectious and inflammatory diseases. *Am J Nucl Med Mol Imaging*. 2019;9(6):255-273.
4. Jamar F, Buscombe J, Chiti A, et al. EANM/SNMMI guideline for 18F-FDG use in inflammation and infection. *J Nucl Med.* 2013;54:647-658.
5. Zhuang H, Alavi A. 18-fluorodeoxyglucose positron emission tomographic imaging in the detection and monitoring of infection and inflammation. *Semin Nucl Med.* 2002;32:47-59.
6. Akaike G, Itani M, Shah H et al. PET/CT in the diagnosis and workup of sarcoidosis: Focus on atypical manifestations. *Radiographics.* 2018;38(5):1536-1549.
7. Keijers RG, Van den Heuvel DAF, Grutters JC. Imaging the inflammatory activity of sarcoidosis. *Eur Respir J*. 2013;41(3):743-751.
8. Lewis PJ, Salama A. Uptake of fluorine 18 fluorodeoxyglucose in sarcoidosis. J *Nuck Med.* 1994;35(10):1647-1649.
9. Keijsers RG, Verzijlbergen FJ, Oyen WJ et al. 18F-FDG PET, genotype-corrected ACE and sIL-2R in newly diagnosed sarcoidosis. *Eur J Nucl Med Mol Imaging.* 2009;36(7):1131-1137.
10. Soussan M, Augier A, Brillet PY, Weinmann P, Valeyre D. Functional imaging in extrapulmonary sarcoidosis: FDG-PET/CT and MR features. *Clin Nucl Med*. 2014;39(2):e146-e159.
11. Braun JJ, Kessler R, Constantinesco A, Imperiale A. 18F FDG PET/CT in sarcoidosis management: Review and report of 20 cases. Eur J Nucl Med Mol Imaging. 2008;35(8):537-543.
12. Cremers JP, Van Kroonenburgh MJ, Mostard RL, et al. Extent of disease activity assessed by 18F-FDG PET/CT in a Dutch sarcoidosis population. *Sarcoidosis Vasc Diffuse Lung Dis.* 2014;31(1):37-45.
13. Ambrosini V, Fasano L, Zumpattori M et al. 18F FDG PET/CT detects systemic involvement in sarcoidosis. *Eur J Nucl Med Mol Imaging.* 2011;38(11):2102.
14. Teirstein AS, Machac J, Almeida O, Lu P, Padilla ML, Lanuzzi MC. Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. *Chest.* 2007;132(6):1949-1953.
15. Oksüz MO, Werner MK, Aschoff P, Pfannenberg C. 18F-FDG PET/CT for the diagnosis of sarcoidosis in a patient with bilateral inflammatory involvement of the parotid and lacrimal glands (panda sign) and bilateral hilar and mediastinal lymphadenopathy (lambda sign). *Eur J Nucl Med Mol Imaging*. 2011;38(3):603.
16. Thie JA. Understanding the standardized uptake value, its methods, and implications for usage. *J Nucl Med*. 2004;45(9):1431-1434.
17. Sobic-Saranovic D, Grozdic I, Videnovic-Ivanov J et al. The utility of 18F-FDG PET/CT for diagnosis and adjustment of therapy in patients with active chronic sarcoidosis. *J Nucl Med*. 2012;53(10):1543-1549.
18. Brudin LH, Valind SO, Khudes CGet al. Fluorine-18 deoxyglucose uptake in sarcoidosis measured with positron emission tomography. *Eur J Nucl Med.* 1994;21(4):297-305.
19. Keijsers RG, Verzijlbergen EJ, van den Bosch JM et al. 18F-FDG PET as a predictor of pulmonary function in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2011;28(2):123-129.
20. Ambrosini V, Zompatori M, Fasano L et al. (18)F-FDG PET/CT for the assessment of disease extension and activity in patients with sarcoidosis: Results of a preliminary prospective study. *Clin Nucl Med*. 2013;38(4):e171-177.
21. Lieberman J. Elevation of serum angiotensin-converting-enzyme (ACE) level in sarcoidosis. *Am. J. Med.* 1975;59(3):365-372.
22. Mostard RL, Voo S, van Kroonenburgh MJ et al. Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis. *Respir Med.* 2011;105(12):1917-1924.
23. Keijsers RG, Verzijlbergen JF, van Diepen DM, van den Bosch JM, Grutters JC. 18F-FDG PET in sarcoidosis: An observational study in 12 patients treated with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis*. 2008;25(2):143-149.
24. Mostard RLM, Verschakelen JA, van Kroonenburgh MJPG et al. Severity of pulmonary involvement and (18)F-FDG PET activity in sarcoidosis. *Respir Med.* 2013;107(3):439-447.
25. Mostard RLM, Van Kuijk S, Verschakelen JA, et al. A predictive tool for an effective use of (18)F-FDG PET in assessing activity of sarcoidosis. *BMC Pulm Med*. 2012;12:57.
26. Vorselaars AD, Verwoerd A, van Moorsel CH, Keijsers RG, Rijkers GT, Grutters JC. Prediction of relapse after discontinuation of infliximab therapy in severe sarcoidosis. *Eur Respir J*. 2014;43(2):602-609.