F-18 FDG PET/CT in Relapsing Polychondritis Patients with Initial Respirotory Symptoms: Imaging Features and Association with Pulmonary Function and Disease Activity

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Research Article

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Abstract

Background: To summarize F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) imaging features of relapsing polychondritis (RP) and to evaluate the feasibility of imaging parameters in the estimation of pulmonary function and disease activity in a cohort of RP patients with airway involvement.

Methods: Thirty RP patients with respiratory symptoms who underwent PET/CT scans before corticosteroid treatment were included. Six patients underwent another post-therapeutic PET/CT scan. Imaging features were described by consensus, and FDG uptake values (SUV_{max}, PET FDG Burden Score (PETFBS) and PETCTindex) either for global cartilages or for the airway were calculated to correlate with clinical symptoms, pulmonary functional parameters and serological inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Results: Laryngo-tracheo-bronchial involvement was detected by PET/CT for all patients with increased FDG uptake in 28/30 patients. The incidence of positive PET was higher in segments with wall thickening (52.68% vs. 15.48%) but was not associated with calcification or stenosis. A total of 46.7% (14/30) of patients presented with sole respiratory symptoms, while PET/CT revealed additional abnormalities in addition to laryngo-tracheo-bronchia. FDG uptake values negatively correlated with disease duration but not with fever. All FDG uptake values showed a positive correlation with FEV1/FVC, with the highest coefficient for SUV_{max} in the airway (rs =0.628). CRP and ESR were negatively correlated with PETFBS and PETCTindex but not with SUV_{max}. The largest Spearman correlation coefficient resulted in PETFBS in the airway (rs =0.67). Re-examination PET/CT in 6 patients revealed partial therapeutic response (n = 4), stable disease (n = 1) and progressive disease (n = 1).

Conclusion: PET/CT is a valuable tool for assessing RP with airway involvement, especially for patients who present with sole respiratory symptoms. SUV_{max} and PETFBS have distinct advantages in the clinical evaluation of RP with respect to pulmonary function and disease activity.

Background

Relapsing polychondritis (RP) is a rare immune-mediated condition characterized by repeated inflammation of the affected cartilages and proteoglycan-rich tissues throughout the body[1,2]. Laryngotracheal involvement is the second most frequent initial feature and may cause life-threatening comorbidities[2-4]. However, the majority of RP patients with airway involvement were misdiagnosed at their first visit with a median time of delay to diagnosis of up to more than 10 years[1,4,5]. Our early studies[6-8], along with other previous case reports or sporadic cases have shown that 18F-fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT, hereafter termed PET/CT) with its semiquantitative parameter SUV_{max} may be a helpful tool in aiding in the diagnosis and for therapeutic response monitoring[9-15], with typical imaging characteristics of FDG uptake in the laryngo-tracheo-bronchial tree, often symmetrically.

On the other hand, we have encountered several cases with relatively low FDG uptake in the airway in our clinical practice, in keeping with the previous studies summarized by Lei et al.[13], where SUV_{max} showed a considerably wide range from 1.93 to 13.03, even in treatment-naïve patients, making the initial diagnosis ambiguous for low uptake patients. Moreover, patients who felt improved symptoms and inflammation may presented with increased SUV_{max} of some particular sites on PET[16]; and no correlation was demonstrated between SUV_{max} and the serological inflammatory markers ESR and CRP[11]. The above-mentioned situation partly limits the utility of the current widely used parameter SUV_{max} in the diagnosis, evaluation of disease activity and treatment response of this rare systemic disease. In recent years, a new PET-based parameter developed by adding the visual score of each targeted site has been assessed in patients with Takaysu's arteritis to reflect the global inflammatory burden of the aterials, showing superior performance in the assessment of disease activity compared with regional SUV_{max}[17-20]. However, whether it is valuable in RP patients is still unknown.

Accordingly, we conducted this retrospective study in a cohort of 30 treatment-naive patients in a respiratory center, which comprised the largest sample size to date, to investigate the feasibility and utility of PET/CT in evaluating RP patients with airway involvement in the scenario of imaging characteristics. Moreover, we aimed to explore the association of various PET parameters with clinical characteristics, serological inflammatory biomarkers and pulmonary function parameters.

Materials And Methods

Study design and subject selection

The study gained the approval of our institutional review board, and informed consent was waived for this retrospective study analysis. From January 2010 to April 2021, patients diagnosed with RP either histologically confirmed by biopsy or in accordance with either the criteria by McAdam's, Damiani and Levine's or Michet's criteria referred to our PET/CT center (n=45) were included for this study. The exclusion criteria were: 1) patients treated with corticosteroid therapy before PET/CT scan (n=13, 11 were previous diagnosed with RP, 2 was first diagnosed as RP clinically but was finally confirmed as tracheobronchial amyloidosis or rhinoscleroderma); 2) loss of Digital Imaging and Communications in Medicine (DICOM) information (n=2). Finally, 30 patients were included in this study.

Protocol of PET/CT scans

Patients need to fast for at least 6 hours and blood glucose levels should be controlled less than 11.1 mmol/L. 18F-FDG of 3.70-5.55 MBq/kg was administered intravenously. Approximately 60 min (range: 45 to 105 min) after 18F-FDG injection, a whole-body CT scan from the base of the skull to mid-thigh was performed, followed by a whole-body PET with the same range. The acquisition parameters were as follows: 140 kV, 150 mAs, pitch 1.675, 512 ×

512 image matrix, slice thickness of 3.75 mm, and a total of six or seven cradle positions with 3.5 min/ cradle position. All PET/CT studies were performed on an 8-section PET/CT scanner (Discovery ST 8, GE Healthcare, WI, USA). PET data were reconstructed with image matrix 128×128, and a two-dimensional ordered-subset expectation maximization (OSEM) algorithm.

Image Analysis

PET, CT, and fused PET/CT images were reviewed on the dedicated manufacturer's review workstation (Xeleris, Version No. 2.1753). Two board-certified nuclear medicine physicians (P. H. and J-W Y, with 9 and 6 years of PET/CT experience, respectively) independently analyzed the initial PET/CT images. Clinical information is available to readers. Discordant opinions were resolved by consensus.

PET imaging analysis included qualitative and quantitative analysis in the region of the nose, ears, larynx, tracheo-bronchia, ribs and peripheral joints. The degree of FDG uptake was visually assessed as visual score (VS) relative to mediastinum blood pool and liver uptake as: 0 = no uptake; 1 = slight uptake, but below the mediastinal blood pool; 2 = equal to or greater than the mediastinal blood pool, but below the liver; 3 = equal to or greater than liver. Generally, VS ≥ 1 was applied for all the sites, as mentioned above. Furthermore, the distribution of FDG uptake should be in accordance with the shape of tracheo-bronchia and ribs. For nasal cartilage in which physiologic tracer uptake was commonly detected, VS combined with morphological changes was determined to be positive (see **Supplementary Table 1, Additional file 1**). For quantitative assessment, three PET parameters were calculated, namely, SUV_{max}, PET FDG Burden Score (PETFBS) and PETCTindex. SUV_{max} was defined as the highest SUV_{max} in the chosen region. PETFBS reflecting the whole burden of FDG uptake was the summation of VS of the targeted sites. PETCTindex, aiming to display the heterogeneity of metabolism and structure, was defined as the number of PET-positive lesions/(number of PET-positive lesions + number of CT-positive lesions). Each parameter was measured both in the laryngo-tracheo-bronchia (hereafter termed $SUV_{maxairway}$, $PETFBS_{airway}$ and $PETCTindex_{airway}$) and around the region of the nose, ears, larynx, tracheo-bronchia, ribs and peripheral joints (hereafter termed SUV_{maxall}, $PETFBS_{all}$ and $PETCTindex_{all}$). Tracheo-bronchia was divided into 9 segments, including 2 segments of the trachea (cervical and thoracic) and 7 main branch segments (bilateral main-stem bronchi; 3 right lobar bronchi and 2 left lobar bronchi). Illustration of the segmentation of the tracheo-bronchia is shown in **Supplementary Fig.1 (Additional file 2)**, and a detailed definition and example of how to measure these parameters is shown in **Supplementary Fig.2 (Additional file 3)**.

The CT component was used to evaluate the morphology of the cartilage, mainly for the assessment of soft-tissue swelling, prevalence of calcification and structural destruction. Airway wall thickening was defined as thickness of the involved segments of the trachea or main bronchi greater than 2 mm[21].

Statistical analysis

Descriptive statistics are shown as the mean ± standard deviation or the median (interquartile range [IQR]). The chi-square test was applied to evaluate the relationship between PET and CT imaging characteristics of the airway. Nonparametric Mann–Whitney U tests were used to compare airway wall thickness and SUV_{max} between patients with or without posterior wall thickening of the trachea. Spearman's rank correlation coefficient (rs) was calculated to examine the correlations between PET/CT parameters and clinical data (disease duration, fever), pulmonary function parameters (FEV1%predicted, FVC%predicted and FEV1/FVC), and nonspecific inflammatory markers (CRP and ESR). All tests were two-sided, and p values of 0.05 or less denoted statistical significance. Analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

Thirty patients (19 males and 11 females, mean age 47±10) were enrolled in the study. Nineteen patients were diagnosed through biopsy (flexible bronchoscopy (FBO), n=4; auricular cartilage biopsy, n=13; nasal cartilage biopsy, n=1; one patient had positive bronchoscopy and auricular biopsy results), and the other 11 patients were diagnosed with clinical presentations assessed by clinicians. The duration between symptom onset and diagnosis ranged from 1 to 84 months (median, 6 months). All patients visited doctors due to respiratory symptoms, which were the only symptoms in 16 patients. The three most common signs were chronic cough (93.3%) and shortness of breath (73.3%), followed by expectoration (60.0%). Other symptomatic sites included the ears (30.0%), joints (20.6%), nose (20.0%), eyes (10.0%) and skin (3.3%) in 14 patients (46.7%) during subsequent careful physical examinations. Seven (23.3%) patients presented with fever. Pulmonary functional tests (PFTs) were successfully performed in 24 patients. Most patients (75%) demonstrated severe/extreme severe pulmonary function abnormalities, with obstructive and mixed ventilation dysfunction in 9 and 9 patients, respectively. The erythrocyte sedimentation rate (ESR) and C reaction protein (CRP) increased significantly in 16/23 and 18/24 patients, respectively. The clinical characteristics of all 30 patients are listed in **Table 1**.

Table 1 Clinical Characteristics of all 30 RP patients

Characteristic	Number of patients	Value
Mean age (yr),mean±SD	30	46.87±10.45
Sex	30	
Male		19 (63.3%)
Female		11 (36.7%)
Chief complain(n,%)	30	
Cough		28 (93.3%)
Fever		7 (23.3%)
Pain of chest/Chest tightness		5 (16.7%)
Shortness of the breath		22 (73.3%)
Hoarseness		12 (40.0%)
Expectoration		18 (60.0%)
Other symptomatic sites(n,%)	30	
Ears		9 (30.0%)
Joints		7 (20.6%)
Nose		6 (20.0%)
Skin		1 (3.3%)
Eyes		3 (10%)
Duration of symptoms(m) (median[IQR])	30	6[3,15]
Laboratory parameters		
WBC (*10^9/L)(median[IQR])	27	9.4 [7.7,12.27]
NEU (%)	27	71.11±12.50
HB (g/L)	25	120.3±17.58
PLT (*10^9/L) (median[IQR])	25	312.0 [238,416]
ESR (mm/L) (median[IQR])	24	61.0 [21.75,118.3]
CRP (mg/dL) (median[IQR])	23	2.11 [0.52,12.72]
RF (IU/ml) (median[IQR])	24	7 [2.32,10.85]
Lung function test	24	
Normal		1 (4.16%)
Mild OVD		3 (12.5%)
Medium OVD		2 (8.33%)
Severe/extremely severe		18 (75.0%)

OVD		9 (37.5%)
MVD		9 (37.5%)
Biopsy		
Bronchoscopic biopsy	24	5
Biopsy of auricular cartilage	20	14
Biopsy of nasal cartilage	2	1

WBC white blood cell count, NEU neutrophil, HB hemoglobin, PLT platelet count, ESR erythrocyte sedimentation rate, CRP C reaction protein, RF rheumatoid factors, FEV1, forced expiratory volume in 1 second, FVC, forced vital capacity, CTX, Cyclophosphamide.OVD obstructive ventilation dysfunction,MVD mixed ventilation dysfunction

Normal range: WBC (*109/L) 4.0 to 10.0, NEU (%) 40.0 to 70.0, HB (g/L) 110 to 150 (female) or 120-160 (male), PLT (*109/L) 100 to 400, ESR (mm/L) 0 to 20, CRP (mg/dL) 0 to 0.6, RF (IU/ml) <20.

PET/CT imaging features

The PET/CT presentations of each patient are outlined in **Table 2**. As demonstrated, laryngo-tracheo-bronchial involvement was shown on PET in 93.3% (28/30) of patients and 100% (30/30) on CT. Overall, PET/CT was positive in all 30 patients for at least one site, ≥2 or 3 sites of abnormalities in 29 (96.7%) and 23 (76.7%) of 30 patients, respectively. The representative figures are shown in **Fig. 1**. The frequency and mean SUV_{max} of each site of abnormalities are shown in **Fig. 2**. As shown, the SUV_{max} of each involved site was 4.04 [2.62, 5.11], 4.50 [3.40, 5.20], 2.90 [2.40,3.60], 3.55 [3.10, 4.25], 4.00 [3.02,4.98], and 2.90 [2.60, 4.95] for the tracheobronchial tree, laryngeal, auricular, costal, nasal cartilages and peripheral joints, respectively. In 14 patients who presented with sole respiratory symptoms, PET/CT revealed multiple lesions in the auricles (71.4%, 10/14), ribs (50%, 7/14), peripheral joints (21.4%, 3/14) and nasal cartilage (14.3%, 2/14) apart from laryngo-tracheo-bronchia (100%, 14/14).

Table 2 PET/CT Findings and Biopsy Results of 30 Patients with RP

Patient No./Sex/Age	Other symptomatic sites besides airway	PET			CT			Biopsy	
		Predominant Sites	SUV_{max}	Other sites and SUV_{max}	Sites	Abn.	Other sites and abn.	FOB	Ear
1/M/68	/	1-4	4.2, 2.8, 4.5, 3.1		1/3	22~24/21		+	/
2/M/55	/	1,2-4	3.0, 4.2, 4.9, 4.8		1/2/3	23/21/21,23		-	+ (L)
3/M/61	Fever	1-3, 6	4.7, 3.5, 4.4, 6.4	7:5.0	1/6	22~24, 21	7:0.8cm	/	/
4/M/58	Fever	1-3	5.3,4,4,6.4		1/2/3	22~24/21/21,24	7:1.1cm	-	+ (L)
5/M/35	Eyes, fever	1,2,4	10.4,7.0,2.6	Muscle: 4.3	1/2	22~24/21,24		/	+
6/M/52	/	2,4	4.5, 3.2	Nasopharynx□ 5.7	1	22~24		/	+ (L)
7/M/49	Ribs, rash, fever	1-4	5.2, 5.2, 4.9, 3.9	BM:3.9	1/2/3	22~24/21/21		-	-
8/F/50	/	1,2,4,5	5.1,3.4,2.3,3.0		1/5	22~24/21		-	+ (R)
9/F/44	/	1-4	6.1,2.8,5.7,1.9	7:3.2	1/2/3	22~24/21/21,23	7:0.9cm	-	+ (L)
10/M/36	Right ear, eyes, fever,	1,2,4,5	3.5,5.0,3.4,3.1		1/2/4/5	22,23/21,24,25/21/23		+	/
11/F/43	Joints	2,4	2.9,2.2		1/2	22~24/21,24,25		/	- (L)
12/M/41	Chest wall	1-3	5.2,3.6,4.7	7:4.5 BM:8.4 PI: 10.4	1/2	22~24/25	7:1.0cm	-	+ (L)
13/M/37	/	1,2,4,5	5.6,3.5,5.4,5.0	7:3.4	1/2/4/5	22,23,24/21/21,22/21	7:1.0cm	-	-
14/F/50	Ears, nose, eyes	/	/		1/4/5	22~24/21,22/26		+	/
15/F/50	Fever	1-4	4.9,3.8,3.4,1.7		1/3	22~24/21		-	+
16/F/42	/	1-4	3.7,3.4,4.3,3.2	7:3.5	1/2	22~24/21,24	7:0.7	-	/
17/M/45	Ears, ribs, nose, fever	1-4	5.0,3.9,5.5,2.5	7:3.6	1/2/3	22~24/21/21	7:0.7cm	-	+ (L)
18/M/60	/	2	2.8	7:2.5	1	22~24	7:0.7cm	-	+ (L)
19/M/51	Fever	1,3	1.8,3.2	7:4.3	1	22~24	7:0.8cm	-	/
20/M/55	/	1,4	4.5,2.4	7:4.3	1	23,24	7:0.8cm	-	/
21/M/27	/	1,2,4	4.0,4.5,2.7		1/2	23,24/21,24		/	- (L)
22/M/46	Left ear, nose, fever	1, 4, 6	4.1,2.8, 2.4	7:6.4	1	22~24	7:1.2cm	-	- (L)
23/M/49	/	3	5.5	Sacroiliac joint□2.8 Musles□4.6	1/3	22~24/23		+	- (R)
24/F/52	/	2-4, 6	3.3,3.3,4.1,3.5	BM: 4.1	1/4	22,23/21		/	/
25/F/32	Fever	1	3.1		1	22~24	7:0.7cm	+	/
26/F/52	/	1-3	3.2,2.3,5.2		1/2	22~24/25		-	+ (R)
27/F/29	Ears, nose	1,2,4	2.2,3.7,3.6	Muscle2.7	1/2/4	23/21,24/21		-	+ (L)
28/F/56	/	1, 6	2.3, 3.0		1/6	22,23,24/21		-	+

									(R)
29/M/26	Ears, left ribs, nose, fever	1,2,4,5	4.1,3.2,2.9,4.9	Sublingual and salivary gland□22.8	1/4/5	23/21/21		-	/
30/F/55	Ears	1,2	5.6, 7.2	7:2.5	1/2	22/23, 21/22/24	7:0.8	-	+ (R)

1.tracheobronchial tree; 2.larynx; 3.costicartilage; 4.auricular cartilage; 5.nasal cartilage; 6.joint; 7.mediastinal lymph nodes

21.swelling; 22.calcification; 23.thickening; 24.stenosis; 25.destruction; 26.collapse; BM:bone marrow; PI:pulmonary inflammation; Y=yes; N=No; +: positive, -: negative; /: undone; FOB: Fiberoptic bronchoscope

Association of 18F-FDG activity and morphological characteristics of the airway

A total of 111 tracheo-bronchial segments (34 in the trachea, 28 in the main bronchi, and 49 lobar bronchi) were positive among all 270 analyzed segments. The majority of FDG-avid segments showed wall thickening (98/111, 88.3%), followed by calcification (51/111, 45.9%), stenosis (42/111, 37.8%) and normal structure (12/111, 10.8%). Increased FDG uptake was associated with thickened wall (p=0.000) but not with calcification (p=0.076) or stenosis (p=0.230) **(Fig. 3a)**.

In addition, twenty-nine patients with 58 segments of the trachea were analyzed except for one patient whose airway was normal on CT. Overall, 22 segments of the trachea demonstrated circumferential thickening, whereas sparing of the posterior membranes was found in the remaining 36 segments. The FDG activity and wall thickness were significantly increased in the posterior wall involved group than in segments with spared posterior wall (SUV_{max}: 4.14 [3.16, 5.00] vs. 1.98 [1.49, 3.43], p<0.001; wall thickness: 0.50 [0.47, 0.67] vs. 0.43 [0.32, 0.55], p=0.014) (**Fig. 3b,c**). Representative cases are shown in **Fig. 4**.

For the larynx, soft-tissue swelling (13/24, 54.2%), subglottic stenosis (11/24, 45.8%) and destroyed/calcified laryngeal cartilage (4/24, 16.7%) were the main findings on CT of the affected larynx.

General symptoms and PET/CT

General symptoms, including disease duration and fever, were compared with PET/CT imaging. As shown in **Fig. 5**, all PET parameters showed a statistically significant negative correlation with disease duration. Among them, the correlation coefficient was highest for PETFBS either in the airway (rs = 0.657) or in the whole body (rs = 0.517). In contrast, there was no correlation between patients with fever and PET parameters (see **Supplementary Table 2, Additional file 4**).

Correlation of chest PET images with pulmonary function test

Table 3 demonstrates that there were statistically significant positive correlations between FEV1/FVC and PET parameters of the airway and a weak positive correlation between FEV1% predicted values and SUV_{max} (rs = 0.413). However, no correlation was found between PET parameters and FVC% predicted values. The coefficient was highest in SUV_{max} (rs = 0.628) compared with PETCTindex (rs = 0.519) or PETFBS (rs = 0.477).

Table 3 correlation between PET paramters and pulmonary function test

	FEV1/FVC		FEV1% predicted		FVC% predicted	
	rs	p	rs	p	rs	p
$SUV_{maxairway}$	0.628	**0.001****	0.413	**0.045***	0.120	0.576
$PETFBS_{airway}$	0.477	**0.018***	0.246	0.247	0.059	0.783
$PETCTindex_{airway}$	0.611	**0.002****	0.404	0.050	0.150	0.458

Disease activity and PET imaging

A correlation matrix (**Fig. 6a**) was drawn to compare serological inflammatory activity indicators and PET parameters. As demonstrated, $PETFBS_{airway}$, having a moderate Spearman correlation coefficient with both ESR and CRP, was superior in correlating with serological inflammatory markers, suggesting that the latter indicators may work better in the assessment of airway inflammation rather than whole-body evaluation. On the other hand, SUV_{max}, either in the airway or in the whole body, correlated with neither ESR nor CRP.

Six patients underwent a second PET/CT scan during follow-up (medium period: 5 months, range: 3-15 months). Five patients showed decreased SUV_{maxall} and $PETFBS_{all}$, 4 of whom had consistently improved symptoms, and the other patient was stable in clinical evaluation. The other patient evaluated as having progressive disease clinically had increased SUV_{maxall} and $PETFBS_{all}$ (**Fig. 6b**). In contrast to SUV_{max} and PETFBS, PETCTindex did not perform well in line with clinical disease evaluation.

Discussion

In the present study, we evaluated F-18 FDG PET/CT imaging characteristics and correlated imaging data with clinical information, pulmonary function and nonspecific inflammatory markers in a cohort of RP patients with symptomatic airway involvement. There were three major findings. First, isolated respiratory symptoms could be the only manifestation in nearly half of all RP-related symptomatic airway-involved cases. PET/CT established the diagnosis of airway involvement in all patients and revealed additional sites of abnormalities in more than 70% of the cases. Second, FDG uptake of the tracheo-bronchia was associated with wall thickness and disease duration. The posterior wall of the trachea can be affected in as many as 40% of segments. Third, the SUV_{max} of the airway was superior in correlation with pulmonary function parameters compared with other PET parameters but not with ESR and CRP. On the other hand, serological inflammatory markers moderately correlated with the inflammatory burden parameter PETFBS, especially PETFBS in the airway. These findings not only support the promising role of F-18 FDG PET/CT in identifying disease extent and describing the disease with respect to pathophysiology but also highlight the potential of utilizing PETFBS to assess disease activity.

The diagnosis of RP remains a challenge attributable to insidious and variable symptoms[4]. Growing research effort of PET/CT has displayed potential for this non-invasive modality for diagnosing and evaluating the extent of the disease, especially for evaluating tracheobronchial involvement[15]. In our series, approximately half of the patients showed only respiratory symptoms that were easily misdiagnosed as respiratory disease, and PET/CT helped establish the diagnosis by demonstrating multiple organs involvement in more than 70% of the cases. The three most commonly affected sites were the tracheobronchia, followed by the larynx and auricular cartilages, which are different from the results of previous studies[11,15]. This discrepancy may be due to the difference in patients' origin compared to all our patients from a respiratory center.

Further assessment of the airway demonstrated positive PET results of PET in all but two patients with diffuse calcification in the tracheobronchial wall. As is known, RP involves the inflammatory edema of the airway during the active phase, followed by malacia, which is secondary to cartilage destruction, and finally stenosis due to fibrous replacement of the impaired cartilage[2]. Therefore, typical pulmonary CT findings of RP include airway wall thickening, tracheal malacia, calcification and airway stenosis[21,22]. Thickening of the airway wall is commonly used as an index for activity. Our study showed that the incidence of positive FDG uptake was higher in segments with wall thickness, which partially supported wall thickness as an inflammatory indicator in clinical practice. Nevertheless, there is significant disparity in the extent of thickened airway walls between our study and previous results. Sparing of the posterior wall due to a lack of cartilage in the posterior part of the trachea was considered highly typical for the diagnosis of RP in previous studies[21-25]. However, in our current study, 22/58 segments of the trachea showed circumferential thickening, including the posterior membranous part, along with higher FDG uptake. In fact, the posterior side of the trachea was also observed in 2 of seven patients with airway wall thickening in Lin's research[26]. These impressive findings suggest that the extent of tracheal involvement is not a credible sign for differential diagnosis and may vary due to different degrees of inflammation.

Pulmonary function tests are essential for assessing respiratory involvement and evaluating the severity of RP in patients; however, spirometry is an effort-dependent maneuver, and sometimes it is difficult and dangerous to perform for patients with severe airway obstruction. To the best of our knowledge, there is no report evaluating the correlation between F-18 FDG PET/CT and pulmonary function tests in patients with RP. Our results showed a moderate positive correlation between FEV1/FVC and all PET parameters, including $SUV_{maxairway}$, $PETFBS_{airway}$ and $PETCTindex_{airway}$, while FEV1% predicted value was weakly associated with $SUV_{maxairway}$ and $PETCTindex_{airway}$, indicating that FDG PET parameters, especially SUV_{max} of the airway, may be a surrogate for assessing the severity of obstruction for patients who cannot tolerate pulmonary function tests. One explanation for the positive correlation may be that a lower SUV_{max} suggests a longer disease course, as demonstrated in our cohort, and more fibrotic lesions; thus, pulmonary function is worse.

In terms of assessing disease activity, our study showed that both SUV_{max} and PETFBS changed in parallel to the clinical assessment, which was consistent with previous results[11,13,15]. Apart from imaging markers, the nonspecific serological markers ESR and CRP are routinely used in clinical practice. Our current study revealed consistent results with a previously described study that these two markers did not show any correlation with SUV_{max}[11] , either for the whole body or for the airway. In contrast, both PETFBS and PETCTindex were positively correlated with both ESR and CRP, with a higher coefficient for the former. Furthermore, interestingly, we found that $PETFBS_{airway}$, rather than the whole-body FDG burden indicator $PETFBS_{all}$, showed the largest correlation coefficient with nonspecific serological markers, suggesting that the ESR and CRP may be more appropriate for reflecting disease activity of the airway. Despite the fact that adding PET visual scores of the whole body to assess inflammatory activity has been adopted in Takaysu's arteritis patients in many studies[17-20], this is the first study to adopt such method in RP patients. Further advanced investigations with larger sample sizes are required to verify the performance of this method for the assessment of disease activity.

There are some limitations of the study. First, histopathology was not available for all lesions, which may misjudge the pathological foci; thus, the calculation of PETFBS may be influenced. However, this condition can be found in many other multisystemetic diseases, such as Langerhans cell histiocytosis and IgG-4-related disease. PET/CT does improve confidence in the diagnosis clinically. Second, as a retrospective study, clinical data, such as past glucocorticoid therapy long ago, may not be traced for all patients and may have influenced the results. However, at least three days off of glucocorticoids was recommended according to recent procedural recommendations of several European and American societies[27]. To our knowledge, no patients in our cohort underwent glucocorticoid treatment during the last month. Third, expiratory CT was not performed because it is not a standard procedure for routine PET/CT acquisition; thus, some signs, such as air trapping and tracheal malacia, could not be analysed.

Conclusions

In conclusion, PET/CT is a powerful tool in aiding in the assessment of RP with airway involvement, especially for patients who present with sole respiratory symptoms. Among the three PET parameters, PETFBS and PETindex, particularly PETFBS of the airway, reflect disease duration and activity in patients with

RP more appropriately than SUV_{max}. Nevertheless, the SUV_{max} of the airway showed a moderate positive correlation with the FEV1/FVC ratio, suggesting that it is a good surrogate for evaluating the severity of obstruction. Further studies are warranted to clarify the role of PET/CT in monitoring this rare disease.

Abbreviations

RP: Relapsing polychondritis

F-18 FDG PET/CT: F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography

CRP: C-reactive protein

ESR: Erythrocyte sedimentation rate

SUV：Standard uptake value

PETFBS: PET FDG Burden Score

FEV1: Forced expiratory volume in the first second

FVC: Forced vital capacity

Declarations

Availability of data and materials

The data that supported the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Author's contributions

Y.J-W designed the study and wrote the paper. H.P, L.S-Y and W.M performed the data collection. W.X-L revised the design. W.J-L and Q.J evaluated the data and revised the paper. The authors read and approved the final manuscript.

Availability of data and materials

The datasets supporting the conclusions of this article are available from the corresponding author on reasonable request.

Ethics declarations

The study gained the approval of our institutional review board(2020-k-17) and the informed consent was waived for this retrospective study analysis.

Consent for publication

All patients have approved the manuscript and agree with the publication.

Competing interests

The authors declare that there are no financial or non-financial competing interests.

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Figures

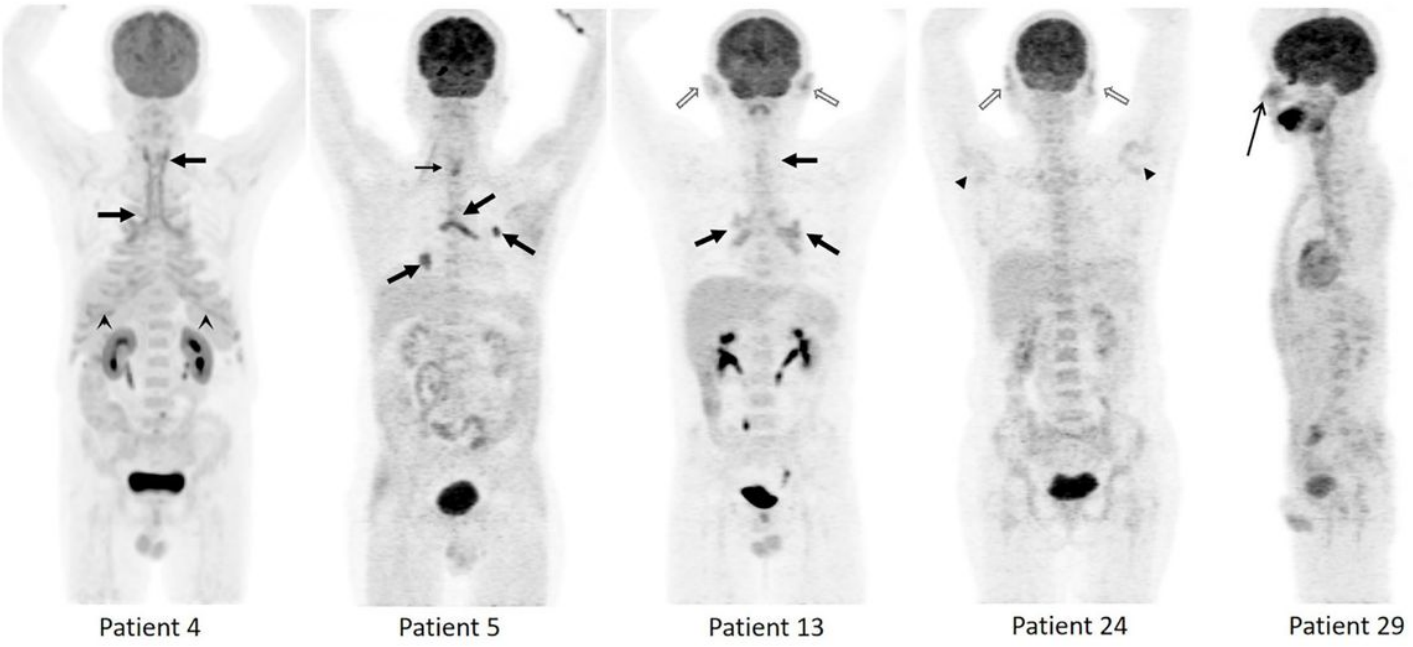

Figure 1

Representative cases of RP patients with airway involvement. FDG-avid laryngo-tracheo-bronchial tree involvement was shown in patients 13, 24, and 29 (black arrows). Other involved sites include auricles (Patient 4, 29; hollow arrows), costicartilages (Patient 24; open arrowheads), bilateral shoulder joints (Patient 4; closed arrowheads) and nasal cartilage (Patient 5; long thin arrow).

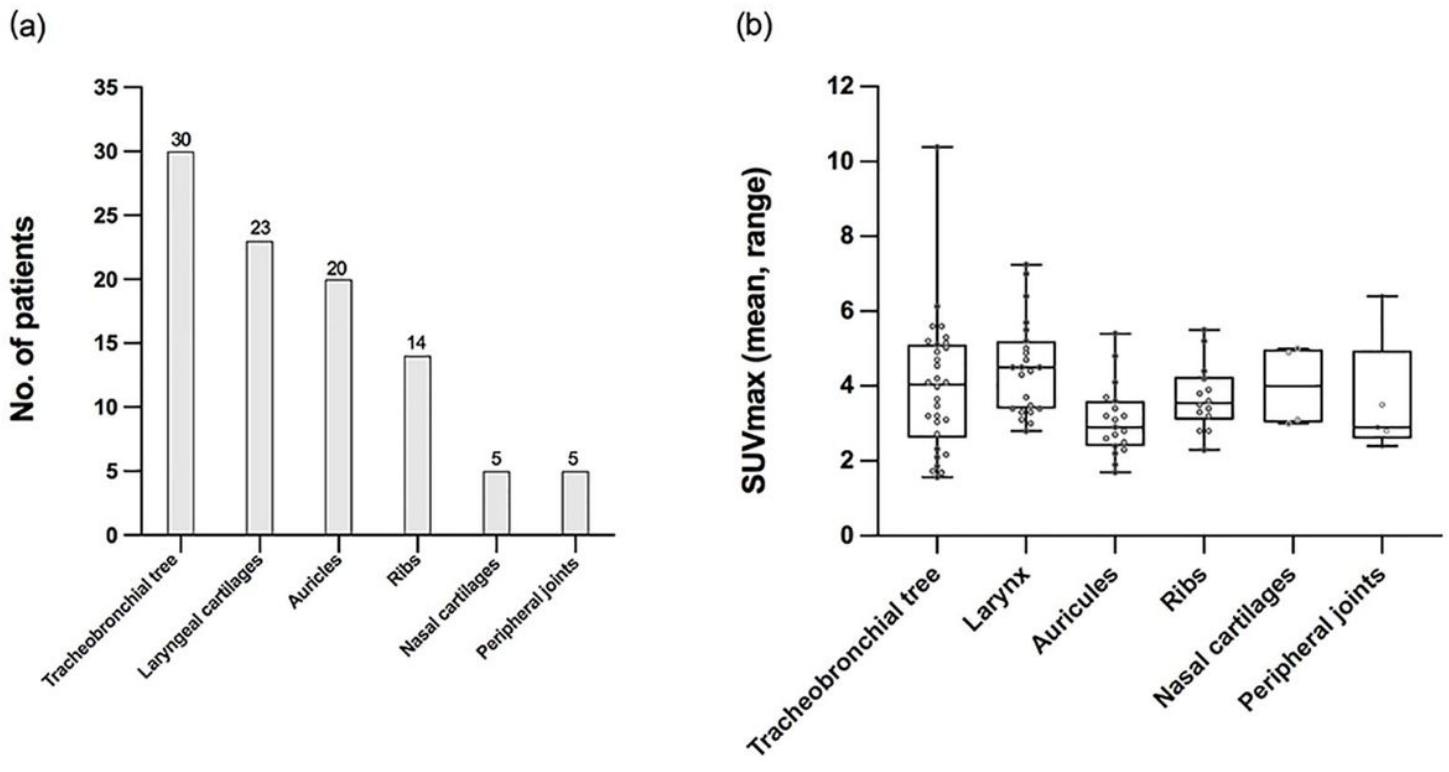

Figure 2

The frequency (a) and mean SUV_{max} (b) of each involved site. As is shown, the most commonly affected site was trcheobronchia, followed by the larynx and auricules. The SUV_{max} was lowest in the auricules and highest in the laryngeal cartilage. The SUV_{max} of the tracheobronchial tree showed the widest SUV_{max} range.

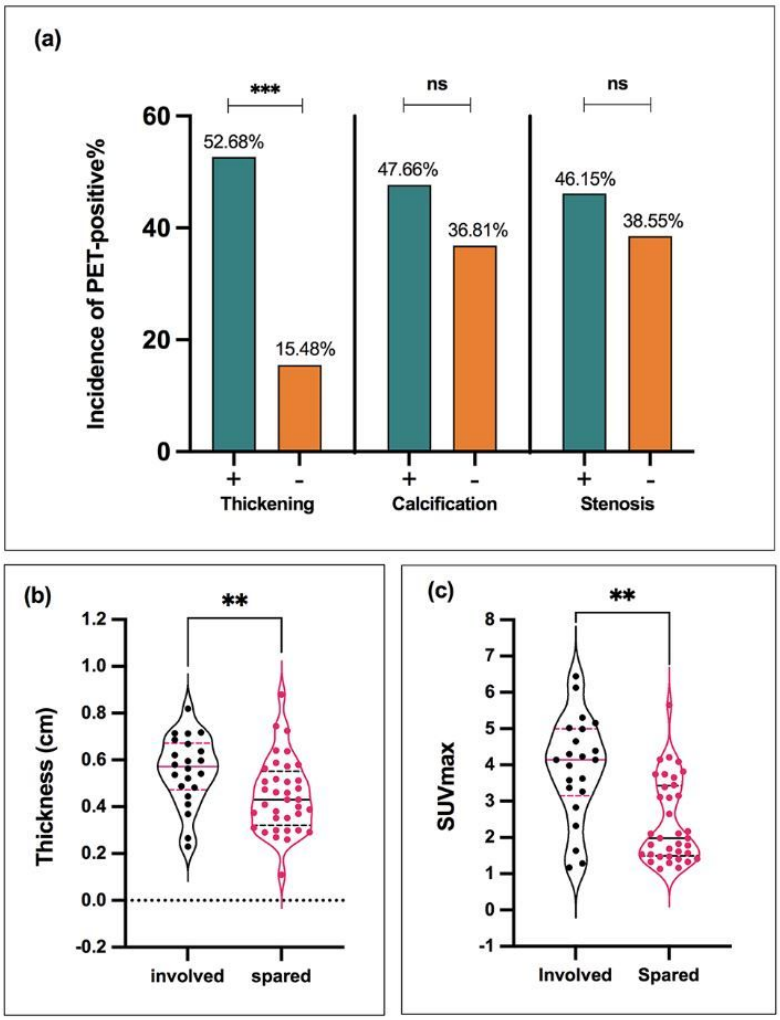

Figure 3

(a) Comparison of the incidence of PET positive rate among variable morphological abnormalities of the tracheobronchial tree. The graph shows a higher positive rate in patients with thickened walls but not with calcification or stenosis. Comparison of tracheal wall thickness (b) and SUV_{max} (c) with and without posterior wall involvement. Increased thickness and SUV_{max} were revealed in patients with circumferential thickening, as demonstrated in the figure.

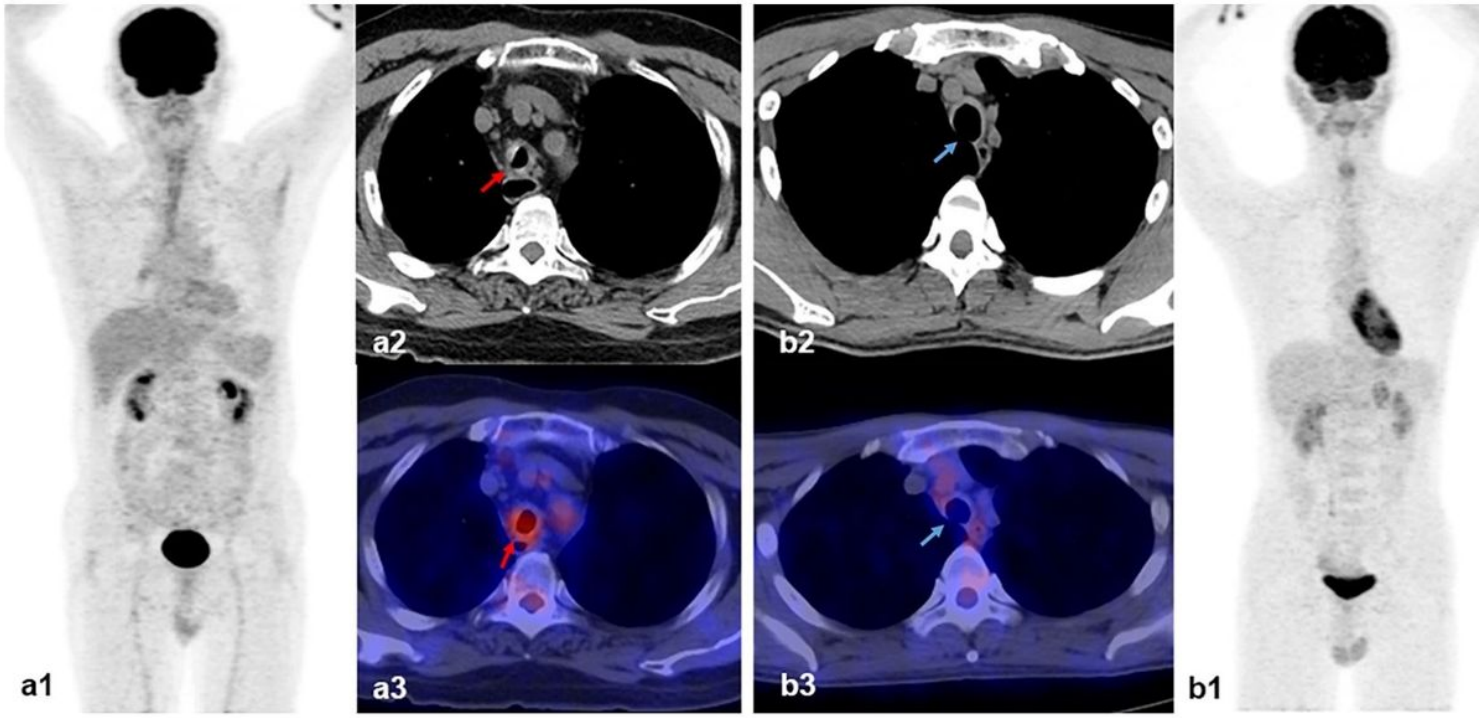

Figure 4

A 58-year-old man (a1-3) presented with cough for 9 months and suffered shortness of breath for a second time in recent days. MIP (a1) and fusion imaging (a3) demonstrated a ring-like increase of FDG uptake in the trachea. The corresponding CT (a2) showed circumferential thickening of the wall (red arrows). Figures on the right show a 36-year-old man who manifested as consistent shortness of breath for 6 months (b1-3). Although chest CT (b2) showed slight thickening of the anterior and lateral walls of the trachea, the uptake was not definite (b3). Note that the posterior wall was spared of thickening (blue arrows).

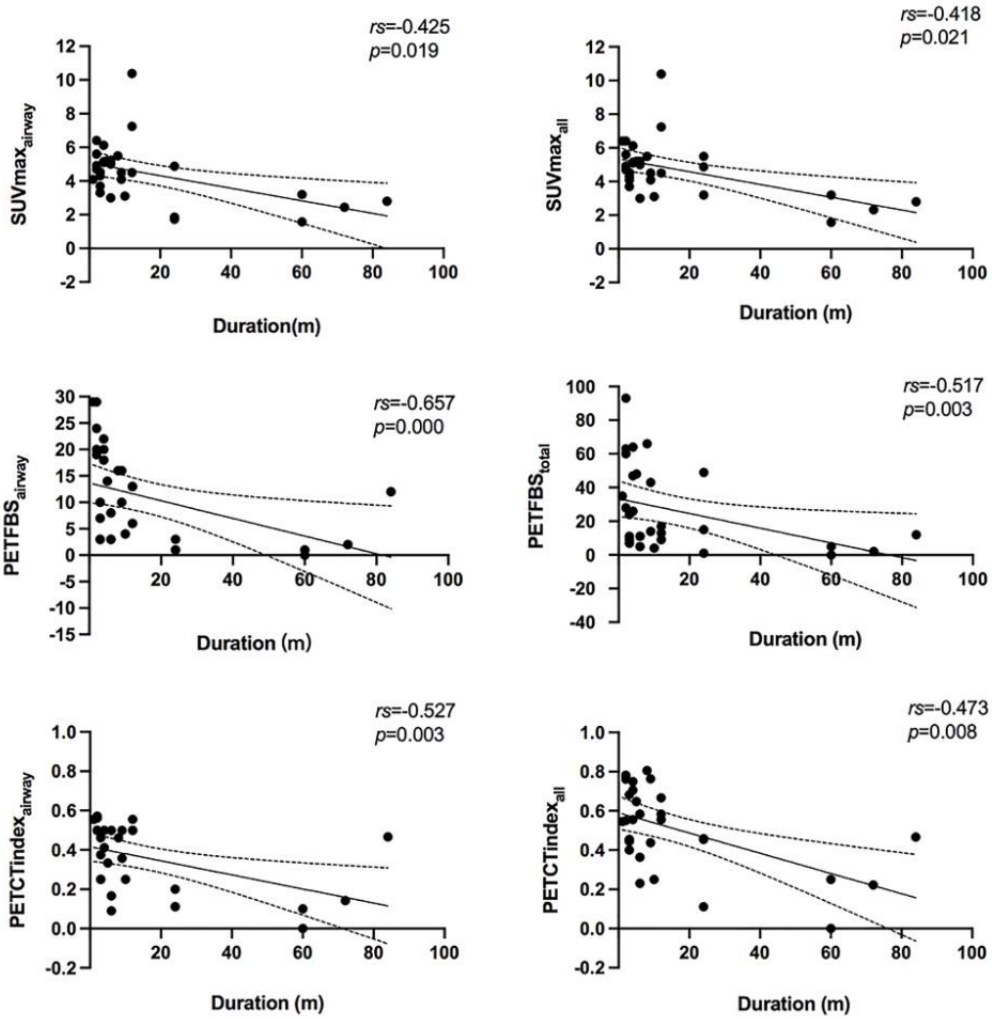

Figure 5

Relationship of disease duration and airway/whole-body PET parameters. The longer duration, the lower FDG uptake. The Spearman correlation coefficient was superior to that of the $PETFBS_{airway}$.

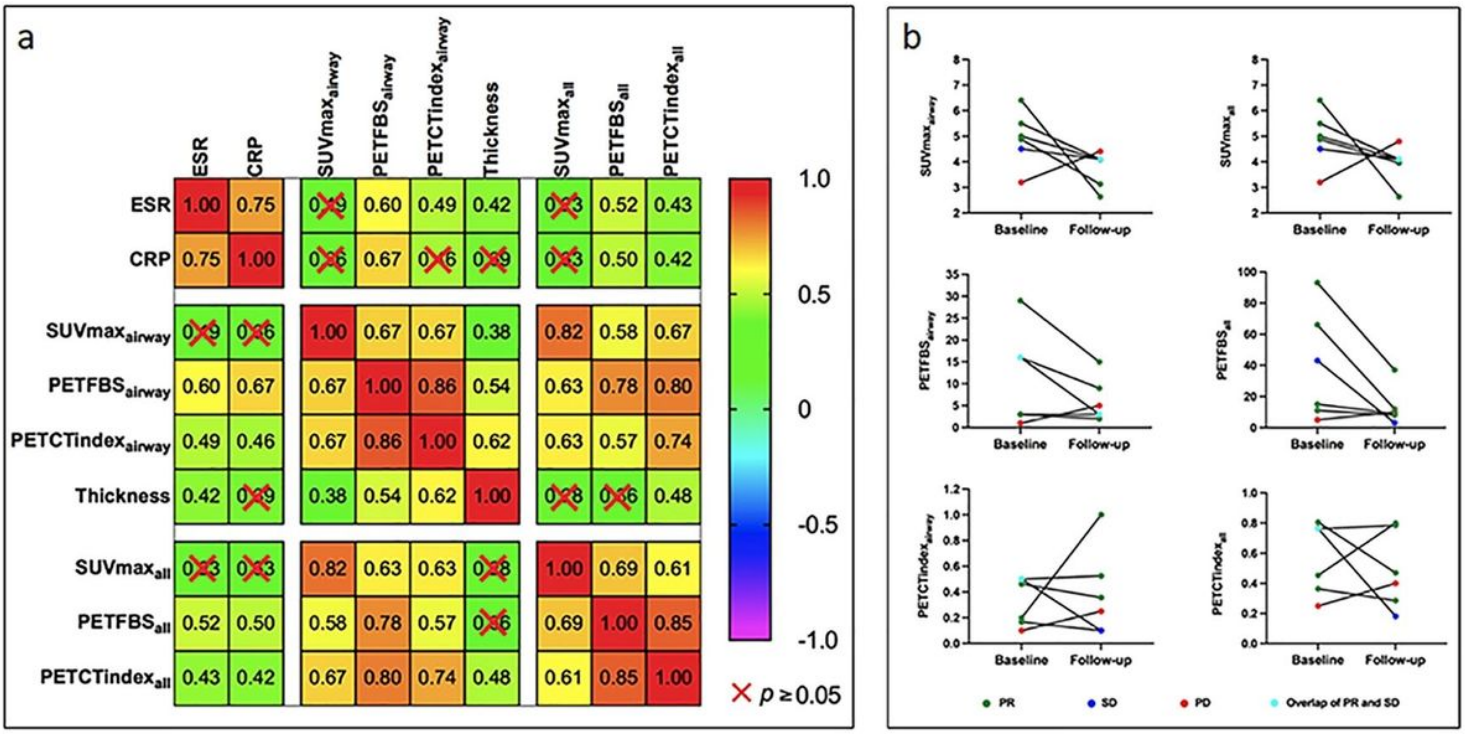

Figure 6

(a) Spearman correlation matrix between nine quantitative criteria. ESR and CRP showed the highest coefficient with $PETFBS_{airway}$. (b) Change of follow-up PET/CT in 6 patients was demonstrated. All but one patient who was considered PR on PET/CT but SD clinically were consistent with the clinical evaluation.

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