Quantitative ^{67}Ga-citrate SPECT/CT for evaluating disease activity in patients with interstitial lung disease

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Abstract

Objective: To determine whether results of a standardized uptake value (SUV)-based semi-quantitative analytic method for gallium-67 (^{67}Ga)-citrate single photon emission tomography/computed tomography (SPECT/CT) reflects disease activity in patients with interstitial lung disease. **Subjects and Methods:** Gallium-67-citrate SPECT/CT was used to evaluate disease activity in 24 patients with interstitial pneumonia on clinical grounds at a single institution from June 2018 to August 2020. SUV in a given volume of interest over the bilateral pulmonary parenchyma was calculated using a dosimetry software package. Correlations of maximum SUV (SUVmax) and mean SUV (SUVmean) with clinical factors, including KL-6, lactate dehydrogenase (LDH), and C-reactive protein (CRP), were evaluated in all 24, as well as in 15 patients with spirometry results using Pearson's rank correlation test. **Results:** The mean bilateral pulmonary SUVmax value showed a moderately significant correlation with KL-6 (Pearson's correlation coefficient r=0.51, P=0.012) and LDH (r=0.51, P=0.010), a weak non-significant correlation with DLCO% (r=-0.26, P=0.34), and no correlation with CRP (r=-0.01, P=0.94), FVC% (r=0.11, P=0.71), or FEV1.0% (r=0.14, P=0.62). Eleven patients with high KL-6 (≥1000U/mL) were defined as having disease activity. Maximum SUV sensitivity, specificity, and accuracy for predicting interstitial lung disease activity were 72.7%, 76.9%, and 75.0%, respectively, with a best cut-off value of 3.78. **Conclusion:** Semi-quantitative values obtained with ^{67}Ga-citrate SPECT/CT showed a moderate correlation with KL-6 and moderate diagnostic performance for predicting disease activity of interstitial lung disease. It is rather unlikely that quantitative ^{67}Ga-citrate SPECT/CT will have a role into the algorithm of interstitial lung disease.

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Introduction

Interstitial lung disease (ILD), a type of chronic progressive pulmonary disease, is characterized by both interstitial inflammation and fibrotic changes. Glucocorticoids (prednisone) in association with immunosuppressive therapy (cyclophosphamide, azathioprine, cyclosporine and mycophenolate) have been widely used and new antifibrotic drug (nintedanib and pirfenidone) is often adopted. Careful evaluation and management are critically important for maintaining quality of life and reducing mortality in affected individuals. Irrespective of ILD type, disease severity is generally evaluated using pulmonary function testing, while disease extension is determined with chest high-resolution computed tomography (HRCT), and inflammation and disease progression by laboratory test results, such as measurements of C-reactive protein (CRP), lactate dehydrogenase (LDH), sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6), surfactant protein A (SP-A), and surfactant protein D (SP-D) levels [1].

Prognostic and disease activity markers are clinically important. Lactate dehydrogenase and KL-6 are used as markers to evaluate the disease activity of ILD, while HRCT is an essential clinical imaging modality for evaluating ILD, though it provides scant indication regarding disease activity. A surgical lung biopsy can be stressful for the patient and the results obtained may not accurately represent the whole lung. Thus, other non-invasive measures of lung inflammation in ILD patients that could be used to predict disease activity are anticipated. Gallium-67 (^{67}Ga)-citrate scintigraphy is a traditional molecular imaging method employed to evaluate degree of whole-body inflammation and infection, and remains a clinically relevant imaging modality in these fields. In addition, recent advances including integration of CT for attenuation correction together with sophisticated reconstruction techniques have enabled semi-quantitative measurements with single photon emission computed tomography/computed tomography (SPECT/CT) that are considered suitable for derivation of standardized uptake value

(SUV) [2-5]. Thus, we speculated that results obtained with ^{67}Ga-citrate SPECT/CT used to assess the degree of inflammation could provide predictive information regarding disease activity in cases of ILD and evaluated the potential role of semi-quantitative values thus obtained for elucidation of associated disease activity in affected patients.

Subjects and Methods

Patients

Our institutional review board granted approval for this retrospective review of clinical and imaging data, and waived the need for obtaining informed consent from the subjects. Twenty-six patients with ILD who underwent ^{67}Ga-citrate scintigraphy using SPECT/CT for evaluation of disease activity in the period on clinical grounds from June 2018 to August 2020. Two patients were excluded from the study because they showed pneumonia, not disease activity of ILD. Data of 24 patients (7 males, 17 females; mean age 65.6± 14.1 years; range 36-91 years),which included those with dermatomyositis/polymyositis (n=10), rheumatoid arthritis (n=6), anti-neutrophil cytoplasmic antibody(ANCA)-associated vasculitis (n=3), idiopathic pulmonary fibrosis (IPF) (n= 2), systemic sclerosis (n=2), and Sjögren's syndrome (n=1), were found to eligible for our study. Patient characteristics are shown in Table 1. All underwent laboratory examinations including LDH (normal <225U/L), KL-6 (normal <500 U/ml), and CRP (normal <0.3mg/dL),while 15 patients received a spirometry examination, including percentage of forced vital capacity (FVC%, normal ≥70%), percentage of forced expiratory volume 1.0 (FEV1.0%, normal≥70%), and percentage of diffusing capacity for carbon monoxide (DLCO%, normal ≥80%) within two weeks before or after the ^{67}Ga-citrate scintigraphy examination. Based on comprehensive assessments including clinical manifestations, laboratory data, and spirometry test results, patients with elevated KL-6 (≥1000U/mL) were defined as having active ILD [6].

Table 1. *Patient characteristics.*

Characteristics	N	Percentage (%)
Total Number	24	
Age (years)	65.6±14.1 (range 36-91)	
Sex (male:female)	7:17	
Underlying disease of ILD		
Dermatomyositis/ polymyositis	10	41.7
Rheumatoid arthritis	6	25.0
ANCA-associated vasculitis	3	12.5
IPF	2	8.3
Systemic sclerosis	2	8.3
Sjögren's syndrome	1	4.2
KL-6 (U/ml)	1045.2±665.4 (range 241-2656)	
LDH (U/L)	235.9±77.3 (range 137-458)	
CRP (mg/dl)	1.03±1.21 (range 0.01-4.57)	
FVC%	77.8±23.3 (range 29.6-114.2)	
FEV1.0%	82.3±23.6 (range 23.5-119.2)	
DLCO%	57.3±19.8 (range 19.8-91.2)	

All data are shown as the mean±SD, unless otherwise indicated. ILD: interstitial lung disease, ANCA: anti-neutrophil cytoplasmic antibody, IPF: idiopathic pulmonary fibrosis, KL-6: sialylated carbohydrate antigen Krebs von den Lungen-6, LDH: lactate dehydrogenase, CRP: C-reactive protein, FVC%: percentage of forced vital capacity, FEV1.0%: percentage of forced expiratory volume 1.0, DLCO%: percentage of diffusing capacity for carbon monoxide

^{67}Ga-citrate scintigraphy

Planar ^{67}Ga-citrate scintigraphy was performed at 48 hours following intravenous administration of ^{67}Ga-citrate with 74MBq using a SPECT/CT scanner (NM/CT670; GE Healthcare, Pittsburgh, Pa) equipped with a low-energy high-resolution collimator. A hybrid system was employed to acquire quantitative SPECT/CT images. For CT, images were initially obtained using the following parameters: tube voltage, 120kV; tube current, 40-80mA with "autoMa; GE Healthcare" function and noise level of 35; X-ray collimation, 20mm (16×1.25mm); table speed, 55mm/second; table feed, 27.5mm per rotation; tube rotation time, 0.5 seconds; pitch, 1.375:1; and matrix, 512×512. Computed tomography images were reconstructed into 3.75-mm thick sections with an adaptive statistical iterative reconstruction algorithm (ASiR; GE Healthcare). Next, SPECT images were acquired using an energy peak of 140.5KeV with a 7.5% window (130-151KeV), step-and-shot mode acquisition (15 seconds per step, 60 steps per detector) with a 6° angular increment, and a body contour scanning option. Single photon emission computed tomography acquisitions were obtained with three angular increments. An extra window was used for scatter correction and set at 120KeV with a 5% window (114-126KeV). For SPECT, images were reconstructed with an iterative ordered subset expectation maximization algorithm (10 ite-

rations, 10 subsets) using CT-based attenuation correction, scatter correction, and resolution recovery performed with software provided by the vendor (Volumetrix MI; GE Healthcare). A post-reconstruction filter was also applied (Gauss filter; frequency of 0.48, order of 10). Following reconstruction, images were set on a 128×128 matrix, with a section thickness of 4.42mm and 1.0 zoom factor.

Image analysis

To calculate SUV, the SPECT/CT system was first calibrated using a dose calibrator for determination of system sensitivity, then the converting factor for radioactivity from measured counts was determined. Standardized uptake value in a given volume of interest (VOI) was indirectly calculated from the percentage of injected dose, obtained using a dosimetry software package (Q. Metrix; GE Healthcare, Pittsburgh, Pa). To derive the percentage of injected dose in a certain VOI using the dosimetry software, the following information was entered in advance: pre-injection radioactivity in the syringe and measurement time, post-injection residual radioactivity in the syringe and measurement time, time of injection into the patient, body weight of the patient, and system sensitivity. Using a dedicated workstation (Geni EXeleris; GE Healthcare, Pittsburgh, Pa), CT, SPECT, and SPECT/CT images were displayed by the dosimetry software. With the transaxial and coronal CT images utilized for anatomical reference, a VOI was drawn over the right and left pulmonary parenchyma, which was automatically reflected on the SPECT/CT fusion images, then the dosimetry software provided multiple quantitative data for a given VOI. Maximum SUV (SUVmax) was defined as the maximum concentration in the target lesion, determined using the following equation: maximum radioactivity/voxel volume/injected radioactivity/body weight, while mean SUV (SUVmean) was determined using the following equation: total radioactivity/VOI volume/injected radioactivity/body weight.

Statistical analysis

Relationships between SUVmax and SUVmean, as well as clinical indications, including KL-6, LDH, CRP, FVC%, and DLCO%, were assessed with Pearson's rank correlation coefficient. The strengths of the correlations were determined using conventional statistical criteria, with 0-0.19 regarded as very weak, 0.2-0.39 as weak, 0.40-0.59 as moderate, 0.6-0.79 as strong, and 0.8-1.0 as very strong. An unpaired t-test was applied for comparisons of SUVmax and SUVmean values between patients with higher (≥1000U/mL) and lower (<1000U/mL) KL-6. A receiver operating characteristic (ROC) curve was produced to determine optimal SUVmax and SUVmean cut-off values providing the best discrimination between patients with higher and lower KL-6. P-values less than 0.05 were considered to indicate a statistically significant difference. All statistical analyses were performed using the SAS software package, version 9.3 (SAS Institute).

Results

The average ± standard deviation (SD) of SUVmax and SUVmean values for the right lung were 3.69±0.84 (range, 1.85-5.43) and 1.21±0.48 (0.45-2.20), respectively, and for the left lung were 3.63±0.83 (2.37-5.82) and 1.32±0.54 (0.50-2.93), respectively. The mean values for bilateral pulmonary SUVmax and SUVmean were 3.66±0.77 (2.51-5.63) and 1.26±0.50 (0.50-2.49), respectively. Findings of a representative case are presented in Figure 1.

The mean value for bilateral pulmonary SUVmax showed a moderately significant correlation with KL-6 (Pearson's correlation coefficient r=0.51, P=0.012) and LDH (r=0.51, P=0.010), a weak non-significant correlation with DLCO% (r=-0.26, P=0.34), and no correlation with CRP (r=-0.01, P=0.94), FVC% (r=0.11, P=0.71), or FEV1.0% (r=0.14, P=0.62) (Figure 2) (Table 2). The mean value for bilateral SUVmean also showed a moderately significant correlation with KL-6 (r=0.50, P=0.014) and LDH (r=0.42, P=0.039), a weak non-significant correlation with DLCO% (r=-0.34, P=0.22), and no correlation with CRP (r=-0.05, P=0.92), FVC% (r=-0.024, p=0.93), or FEV1.0% (r=0.037, P=0.90) (Figure 3) (Table 2).

For the higher (≥1000U/mL) KL-6 group (n=11), mean SUVmax was 4.06±0.78 (2.74-5.63), while that for the lower (<1000U/mL) KL-6 group (n=13) was 3.33±0.59 (2.51-4.56), which was significantly different (P=0.015). In addition, mean SUVmean for those groups was 1.56±0.52 (0.74-2.49) and 1.01±0.32 (0.50-1.52), again a significant difference (P=0.0048). For SUVmax, sensitivity, specificity, and accuracy for predicting interstitial lung disease activity were 72.7% (8/11), 76.9% (10/13), and 75.0% (18/24), respectively, with a best cut-off value of 3.78, while those for SUVmean were 81.8% (9/11), 76.9% (10/13), and 79.2% (19/24), respectively, with a best cut-off value of 1.22.

Discussion

This is the first known study to present findings showing effective clinical application of quantitative ^{67}Ga-citrate SPECT/CT for evaluating disease activity in patients with ILD. In the series analyzed, there were no significant differences noted between pulmonary SUVmax and SUVmean for imaging biomarker use.

Single photon emission computed tomography/CT, a state-of-the-art modality that produces objective quantitative data, is known as a powerful investigative tool in clinical practice. Based on results obtained with robust algorithms for CT-based attenuation correction, scatter correction, and resolution recovery, SPECT/CT generates imaging voxels, denoted as units of radioactivity per volume, i.e., kilobecquerels (kBq)/mL. That is fundamentally different as compared to traditional nuclear imaging methods, such as planar scintigraphy, SPECT, and non-quantitative SPECT/CT, each of which uses counts per second to produce imaging units. Lesion radioactivity can be normalized for determination of injected radioactivity with quantitative SPECT/CT, resulting in quantitative parameter values, such as percent injected dose and SUV [2, 7, 8]. In their report, Zeintl et al. (2010) [7] noted that advanced SPECT/CT technology can facilitate quantitative technetium-99m (^{99m}Tc) SPECT imaging with excellent accuracy in both phantom (error <3.6%) and

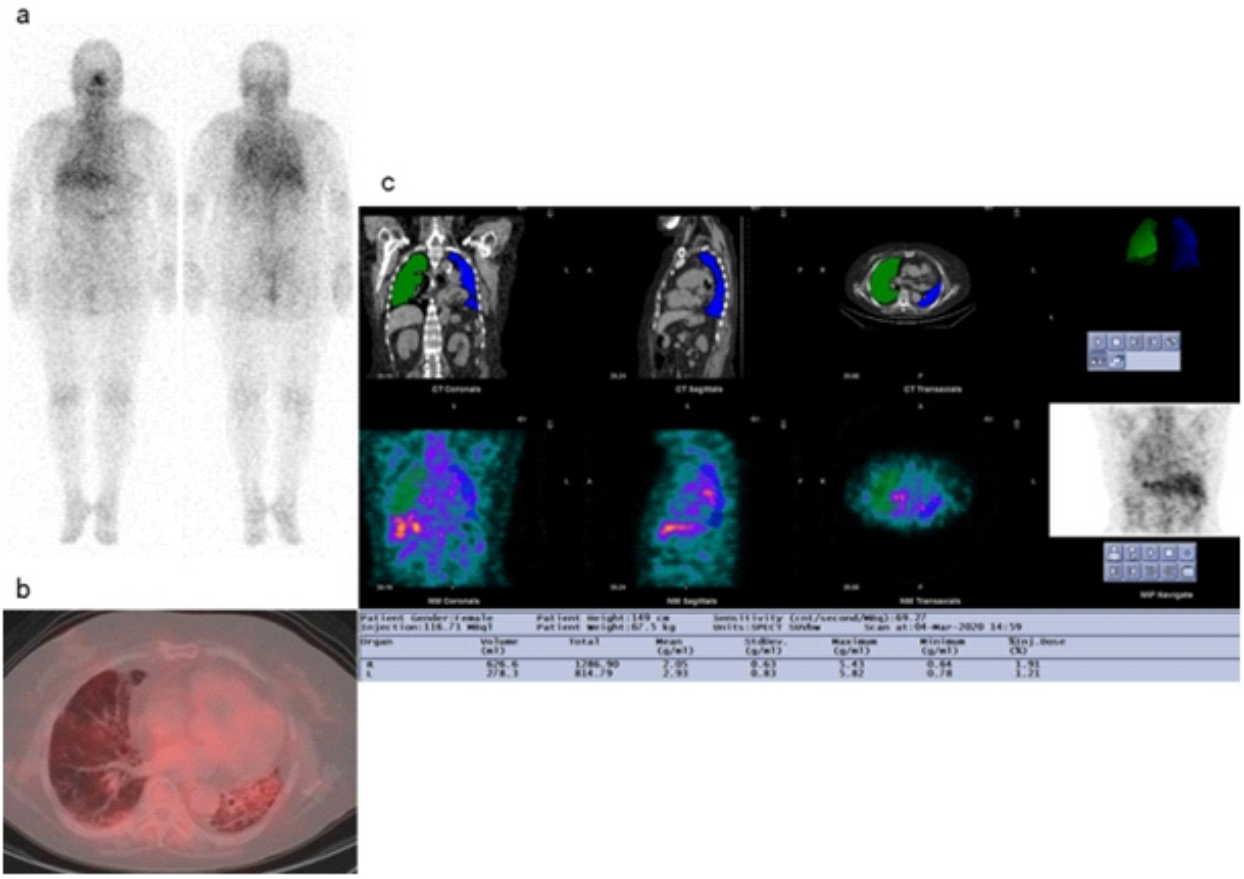

Figure 1. A 77-year-old female with active interstitial pneumonia showing high SUV and laboratory, and low spirometry values. a. Planar ^{67}Ga-citrate scintigraphy showing abnormal ^{67}Ga-citrate uptake in the bilateral lungs. b. ^{67}Ga-citrate SPECT/CT showing abnormal ^{67}Ga-citrate uptake, indicating bilateral interstitial pneumonia. c. The right and left pulmonary SUVmax, and mean bilateral pulmonary SUVmax values were, 5.43, 5.82, and 5.63, respectively, while right and left pulmonary SUVmean, and mean bilateral pulmonary SUVmean values were 2.05, 2.93, and 2.49, respectively. KL-6, LDH, and CRP were 1809U/mL, 352U/L, and 0.53mg/dL, respectively, and FVC, FEV1.0%, and DLCO% were 55.5%, 76.6%, and 31.1%, respectively.

Table 2. *Correlation between SUV (SUVmax and SUVmean) and clinical values.*

	SUVmax		SUVmean	
	Pearson's rank correlation coefficient (r value)	**P value**	**Pearson's rank correlation coefficient (r value)**	**P value**
KL-6	0.51	0.012	0.5	0.014
LDH	0.51	0.01	0.42	0.039
CRP	-0.01	0.94	-0.05	0.92
FVC%	0.11	0.71	-0.024	0.93
FEV1.0%	0.14	0.62	0.037	0.90
DLCO%	-0.26	0.34	-0.34	0.22

KL-6: sialylated carbohydrate antigen Krebs von den Lungen-6, LDH: lactate dehydrogenase, CRP: C-reactive protein, FVC%: percentage of forced vital capacity, FEV1.0%: percentage of forced expiratory volume 1.0, DLCO%: percentage of diffusing capacity for carbon monoxide

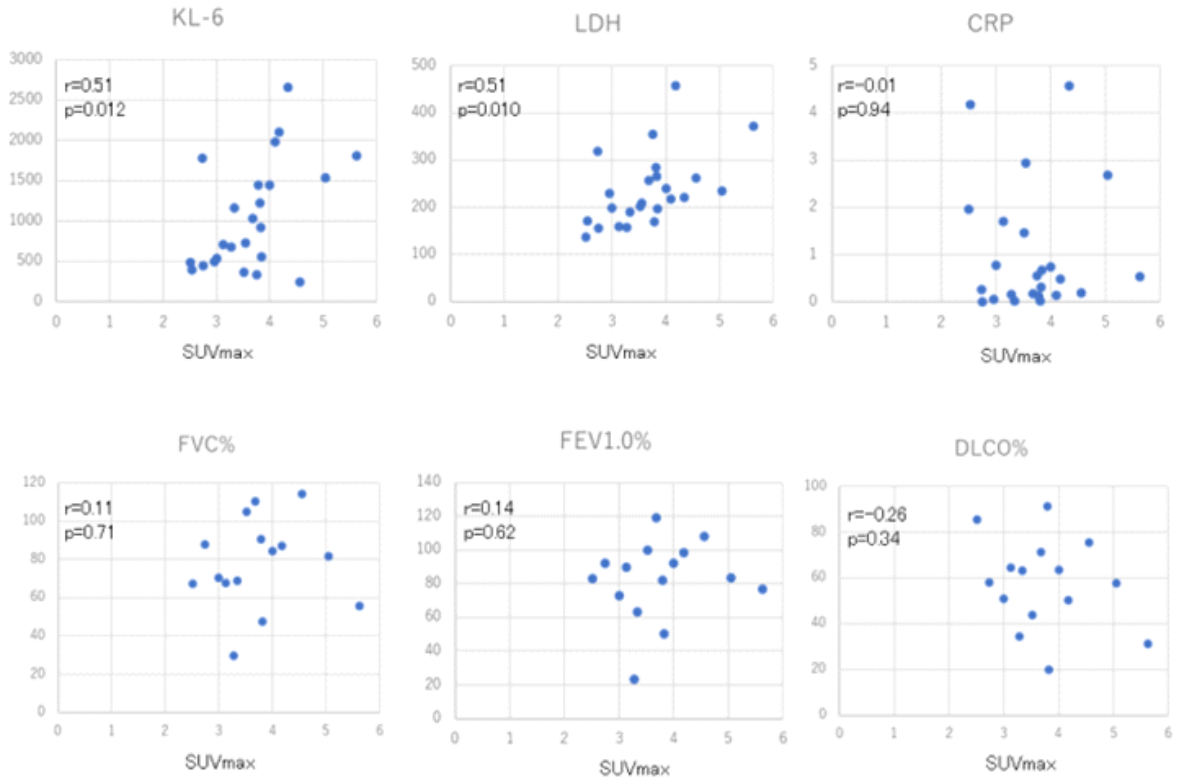

Figure 2. Correlationsof SUVmaxwith clinical values.The mean bilateral pulmonary SUVmaxvalue showed a moderately significant correlation with KL-6 (Pearson's correlation coefficientr=0.51, P=0.012) and LDH (r=0.51, P=0.010), a weak non-significant correlation with DLCO% (r=-0.26, P=0.34), and no correlation with CRP (r=-0.01, P=0.94), FVC% (r=0.11, P=0.71), or FEV1.0% (r=0.14, P=0.62).

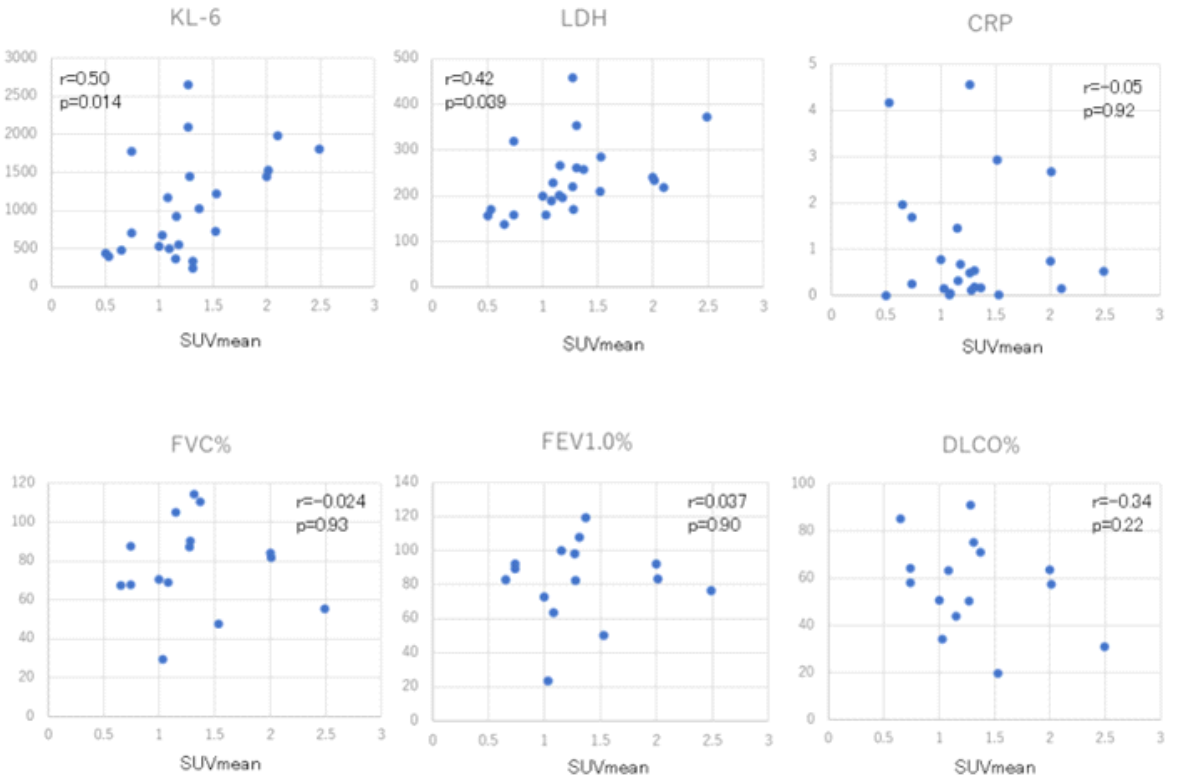

Figure 3. Correlations of SUVmean with clinical values. The mean bilateral SUVmean value showed a moderately significant correlation with KL-6 (Pearson's correlation coefficient r=0.50, P=0.014) and LDH (r=0.42, P=0.039), a weak non-significant correlation with DLCO% (r=-0.34, P=0.22), and no correlation with CRP (r=-0.05, P=0.92), FVC% (r=-0.024, P=0.93), or FEV1.0% (r=0.037, P=0.90).

patient (error <1.1%) studies. Furthermore, Gnesin et al. (2016) [8] performed a phantom study and found that both absolute and concentration of activity results determined with quantitative ^{99m}Tc SPECT/CT were within 10% of the expected values. Kitajima K et al. (2021) [4] evaluated primary bone neoplasms using by quantitative bone SPECT/CT with ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) and reported that mean SUVmax of 19 benign (5 osteoid osteomas, 4 bone giant cell tumor, 4 osteofibrous dysplasia, 3 intraosseous ganglion, 2 aneurysmal bone cyst, 1 intraosseous hemangioma) and 5 malignant (2 osteosarcoma, 1 periosteal osteosarcoma, 1 malignancy in bone giant cell tumor, 1 Ewing sarcoma) primary bone neoplasms were 6.89± 3.26 (range 3.9-15.13) and 10.31±3.19 (5.0-13.45) respectively, with statistically significant difference (P=0.048). Kuji et al. (2017)[9] evaluated normal vertebral body, skeletal degenerative change, and bone metastasis SUVs obtained in analyses of 170 prostate cancer patients undergoing bone SPECT/CT with ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP). Their results showed SUVmax values of 7.58±2.42 for thoracic normal and 8.12±2.24 for lumbar normal vertebral bodies, and 16.73±6.74 for skeletal degenerative changes and 40.90±33.46 for bone metastasis. That for the bone metastasis group was significantly greater as compared to the other three groups (P<0.001). In ROC analyses performed to demonstrate the diagnostic accuracy of SUVmax for discrimination of bone metastasis from skeletal degenerative changes in hot foci, in patient-based mode the area under the ROC curve was 0.840, while that was 0.932 in lesion-based mode.

To the best of our knowledge, two studies have been presented that include discussion of semi-quantitative values obtained with ^{67}Ga-citrate SPECT/CT [5, 10]. In the latter, Grijim et al. (2005) [10] evaluated semi-quantitative ^{67}Ga-citrate scintigraphy in regard to its clinical usefulness as an indicator of response to corticosteroid treatment as well as prognosis after that in patients with idiopathic interstitial pneumonia. Their results in patients with IPF or fibrotic nonspecific interstitial pneumonia (NSIP) demonstrated that despite increased levels of ^{67}Ga-citrate uptake at the baseline, there was no correlation of pulmonary ^{67}Ga-citrate uptake or change in ^{67}Ga-citrate uptake with 1-year change in percentage of %FVC. Toriihara et al. (2018) [5] used mean SUV for ^{67}Ga-citrate SPECT/CT examinations and noted a correlation with blood test results in representative organs. Additionally, their findings demonstrated that physiological uptake in ^{67}Ga-citrate SPECT/CT can be represented as mean SUV, which was not significantly correlated with corresponding blood test results.

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is known to be accumulated not only in malignant tumors but also in active inflammatory lesions, including young fibroblasts, vessel endothelial cells, and macrophages. Thus, several groups have evaluated the clinical utility of SUV with ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) resultsobtained in ILD cases for prediction of disease activity, severity, or prognosis [11-15]. Uehara et al. (2016) [14] found that SUVmax values for 69 patients with ILD-related connective tissue disease were significantly higher in an active as compared to an inactive phase (active n=32, 2.16±1.04; inactive n=37, 1.69±0.84;P=0.022). In a study of 22 patients with dermatomyositis, Motegi et al. (2019) [15] demonstrated that SUVmax for interstitial lung disease was significantly positively correlated with serum KL-6 (r=0.476, P<0.05) but not with CRP (r=-0.142, P=0.53). The results of those two investigations that utilized ^{18}F-FDG PET/CT examinations were very similar to our results obtained with ^{67}Ga-citrate SPECT/CT.

The present study has some limitations, such as the relatively low number of patients enrolled from a single institution. Additionally, bias regarding patient selection may have been present because of the retrospective design. Although histological confirmation of the results is lacking, utilization of an invasive procedure to investigate lesions would not have been ethical. Furthermore, pulmonary function examinations including %FVC and %DLCO were not conducted in all of the cases. A laboratory examination of SP-D was performed in only three cases, thus those parameters could not be evaluated in this series. Finally, ^{67}Ga-citrate scintigraphy looks "out-of-date" in the era of ^{18}F-FDG and other PET tracers. In recent years, to image inflammation new PET radiotracers such as chemokine receptor type 4 (CXCR4)-di-rected tracers, C-C chemokine receptor type 2 (CXCR2) li-gand, synthetic somatostatin analogues, probes containing arginylglycylaspartic acid (RGD), probes biding to alpha-v beta-3 integrin (αvβ3), and fibroblast activation protein-α (FAP)-directed traces have been adapted [16].

In conclusion, the present findings indicate that semi-quantitative values obtained with ^{67}Ga-citrate SPECT/CT have a moderate correlation with KL-6 and moderate diagnostic performance for predicting disease activity of interstitial lung disease. It is rather unlikely that quantitative ^{67}Ga-citrate SPECT/CT will have a role into the algorithm of interstitial lung disease.

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The authors declare that they have no conflicts of interest.

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