The lungs were on fire: a pilot study of ^{18}F-FDG PET/CT in idiopathic-inflammatory-myopathy-related interstitial lung disease

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Abstract

Background: Interstitial lung disease (ILD) and its rapid progression (RP) were main contributors to unfavorable outcome of idiopathic inflammatory myopathy (IIM) patients. This study aimed at identifying the clinical value of PET/CT scan in IIM-ILD patients as well as constructing a predicting model for RP-ILD.

Methods: Adult IIM-ILD patients who were hospitalized at four divisions of the First Affiliated Hospital, Zhejiang University School of Medicine (FAHZJU) from Jannuary 1st 2017 to December 31st 2020 were reviewed. PET/CT scan as well as other factors of patients who met the inclusion and exclusion criteria were collected and analyzed.

Results: A total of 61 IIM-ILD patients were finally enrolled into this study. Twenty-one patients (34.4%) developed RP-ILD and 24 patients (39.3%) died in follow-up. After false discovery rate (FDR) correction, percent-predicted diffusing capacity of the lung for carbon monoxide (DLCO%, P=0.014), bilateral lung mean standard uptake value (SUVmean, P=0.014) and abnormal mediastinal lymph node (P=0.045) were significantly different in comparison between RP-ILD and non-RP-ILD groups. A “DLM” model was hereby established by including the above three values to predict RP-ILD with a cutoff value of ≥2 and an area under the curve (AUC) of 0.905. Higher bilateral lung SUVmean (P=0.019) and spleen SUVmean (P=0.011) were observed in IIM-ILD patients who died within three months, and a moderate correlation was recognized between the two values.

Conclusions: Elevated bilateral lung SUVmean and abnormal mediastinal lymph node were associated with RP-ILD in IIM-ILD patients. The “DLM” model was valuable in predicting RP-ILD and demanded further evaluation.

Introduction

Interstitial lung disease (ILD) is a frequent complication in patients with idiopathic inflammatory myopathy, featuring a predominance of non-specific interstitial pneumonia (NSIP) pattern in histopathological findings [1-3]. A comparably large proportion of idiopathic-inflammatory-myopathy-related ILD (IIM-ILD) tended to be rapidly progressive (RP) and refractory to the conventional immunosuppressive therapy, making it challenging for clinical management of IIM-ILD [4]. In recent studies, the survival of IIM patients with ILD, RP-ILD in particular, is far from satisfactory. To be specific, the mortality rate of IIM-ILD patients varied from 19.0% to 27.0% in follow-up, and a three-month mortality rate of over 30.0% was identified in RP-ILD [5-7]. Therefore it is of vital importance to search for efficient biomarkers or tools for predicting RP-ILD and unfavorable outcome.

Activation and infiltration of immune cells as well as release of cytokines were found to participate in the development of idiopathic pulmonary fibrosis (IPF), connective-tissue-disease-related ILD (CTD-ILD) and Corona Virus Disease 2019 (COVID-19), etc. [8-11] Since elevated ^{18}F-fluorodeoxyglucose (FDG) uptake in PET/CT scan was capable of revealing focal immune activation, a series of studies have focused on the

clinical value of PET/CT scan in these diseases. In systemic-sclerosis-related ILD (SSc-ILD), pulmonary FDG uptake was significantly increased and correlated with severity of ILD [13, 14]. Besides, elevation of pulmonary FDG uptake also predicted progression of SSc-ILD [14]. In IIM-ILD, Dr Morita first reported an IIM-ILD patient who presented high pulmonary FDG uptake and subsequently died of RP-ILD [15]. Afterwards two small cohort study initially identified that FDG uptake (maximum standard uptake value, SUVmax) of lung was correlated with ILD severity and might predict occurrence of RP-ILD [16-17]. However, the sample sizes were too small, and the included organs were only lungs and muscles. Meanwhile the correlation between abnormal FDG uptake and survival of IIM-ILD patients remain unclear. A systemic evaluation of FDG uptake in IIM-ILD patients was demanded to acquire a broader view on the clinical value of PET/CT scan in IIM-ILD.

A systemic evaluation of FDG uptake in a larger cohort of IIM-ILD patients was thus implemented to clarify the predictive value of FDG uptake in multiple organs for RP-ILD as well as unfavorable outcome. The mean value of region of interest (ROI) instead of the maximum value at a single pixel was calculated to avoid interference and acquire a more representative FDG uptake of the targeted organ. In addition, we intended to initially construct a predicting model for RP-ILD or unfavorable outcome in IIM-ILD patients by incorporating the statistically significant values in PET/CT scan, lung function testing, etc. into consideration.

Patients And Methods

Patients

A retrospective cohort study was conducted at the inpatient department of Qingchun, Chengzhan, Zhijiang and Yuhang divisions of the First Affiliated Hospital, Zhejiang University School of Medicine (FAHZJU). After acquiring the approval from the Institutional Review Board (IRB) of FAHZJU (Reference Number: 2021-194) and written informed consent from all the patients involved, in accordance with the *Declaration of Helsinki*, a case search was retrospectively conducted in the inpatient electronic medical record (EMR) system with the International Classification of Diseases, tenth version (ICD-10) codes for dermatomyositis (DM), polymyositis (PM) and amyopathic dermatomyositis (ADM), ranging from January 1st, 2017 to December 31st, 2020. The inclusion criteria of this study were: 1) age over 18 years old; 2) the definite/probable diagnosis of DM, PM or ADM satisfied the 2017 ACR/EULAR classification criteria, as confirmed by two experienced rheumatologists (Heng Cao and Bei Xu) [18]; 3) ILD on high-resolution computed tomography (HRCT) within the first week of admission, including usual interstitial pneumonia (UIP) pattern and non-UIP patterns (NSIP, cryptogenic organizing pneumonia, co-existence of more than one CT pattern), as confirmed by experienced radiologist and respirologist (Yinuo Liu and Bingjue Ye); 4) PET/CT scan performed during hospitalization. Exclusion criteria were: 1) clarified overlap syndromes with other connective tissue diseases (CTDs); 2) myopathy related to thyroid dysfunction, strenuous exercise, inherited metabolic disorders, drug-induced myositis (lamivudine, statins, Chinese herbal medicine, etc.), etc.3) hospitalization for reasons unrelated to myositis and its complications, such as fracture, pregnancy, acquired immunodeficiency syndrome, cataract, etc. due to lack of demanded

medical records for this study; 4) newly-identified or unremitted malignancies; 5) loss to follow-up without death from any cause within three months after hospitalization.

Data collection

Data of all the enrolled patients were retrospectively collected by referring to the EMR system of FAHZJU. Clinical records including demographic information, course of disease, duration of diagnosis delay, disease activity assessment, complications, radiological/laboratory detections, lung function testing, immunosuppressive medications were acquired and analyzed. Survival data were acquired from the follow-up documents. To be specific, IIM patients were followed from hospitalization until the end of follow-up. For patients who perished during hospitalization, dates of death were clearly documented in the EMR system. For patients who were discharged, a routine return visit was arranged two weeks after discharge. In addition to the regular inpatient or outpatient visits, a concise telephone interview was performed three months after discharge, and at an annual frequency afterwards. The end of follow-up could be owing to death from any cause, loss to follow-up, or closure of follow-up for the purpose of this study (March 31st, 2021).

Baseline disease activity assessment, lung HRCT scan and lung function testing were carried out within the first week of hospitalization. On-admission IIM disease activity was routinely assessed using the Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT) [19]. ILD and its rapid progression were confirmed by experienced respirologist and radiologist (Bingjue Ye and Yinuo Liu) using lung HRCTs. Cases with definite or probable UIP pattern were identified based on their classic HRCT manifestation: the presence of basal-dominant reticular opacities and predominantly basal and subpleural distribution of honeycomb lesions, with multiple equal-sized cystic lesions of two to ten mm diameter with a thick wall [20]. A subgroup of RP-ILD patients was considered as those presenting with progressive dyspnea and progressive hypoxemia, acute worsening of interstitial change on the chest radiograph within 1 month after hospitalization or onset of respiratory symptoms [21-23]. The included IIM-ILD patients were hereby divided into RP-ILD group and non-RP-ILD group (control group). Pulmonary hypertension was a rough decision based on the pulmonary artery pressure≥ 25mmHg as measured by echocardiography. All of the included patients received potent immunosuppressive medications: (1) systemic prednisolone (PSL) or methylprednisolone (mPSL) with a maximum dosage ≥ 1 mg/kg/d (calculated by prednisolone); (2) combined therapy of PSL/mPSL, disease modifying anti-rheumatic drugs (DMARDs) or Janus kinase (JAK) inhibitors, with or without intravenous immunoglobulin (IVIG). The DMARDs used in these patients included Mycophenolate, Tacrolimus, Cyclosporine, Methotrexate, Thalidomide, Hydroxychloroquine and Cyclophosphamide. The JAK inhibitors mainly referred to Tofatinib and Baritinib.

The profiles of 12 myositis-specific antibodies (MSAs, anti-MDA5, anti-TIF1γ, anti-Jo-1, anti-OJ, anti-EJ, anti-PL-12, anti-PL-7, anti-Mi-2α, anti-Mi-2β, anti-NXP2, anti-SRP and anti-SAE1) and 4 myositits-associated antibodies (MAAs, anti-Ku, anti-PM-Scl75, anti-PM-Scl100 and anti-Ro-52) were assessed by an imunoblotting assay utilizing the EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (IgG)

commercial line blot assay (Euroimmun, Lübeck, Germany) encompassing a membrane strip with the 16 autoantigens in light of the manufacturer's instructions. To fulfill the testing, serum samples were routinely acquired from suspected IIM patients within the first week of hospitalization.

Whole-body CT and PET, which were performed with a combined PET/CT scanner (Biograph, Sensation 16, Siemens systems), covered a region ranging from the meatus of the ear to the mid thigh. Patients fasted overnight or for at least 6 hours prior to the PET/CT detection. Blood glucose levels were confirmed to be within normal limits before the injection of 4.0MBq/kg of [18F]FDG. Patients rested for 30min so as to minimize non-specific FDG uptake in muscles. Imaging acquisition was systematically implemented at 60 min post-injection. SUV (standard uptake value) was calculated by the following formula: SUV (g/ml) = regional radioactivity concentration (Bq/ml) / [injected dose (Bq)/body weight (g)]. ROI (20mm diameter) was manually placed by a single trained radiologist (Yinuo, Liu) at the region with the highest FDG uptake in liver, spleen, bone marrow (thoracic, T10-12, lumbar, L2-L4) [24], esophagus, stomach, small intestine, colon/rectum, bilateral lung, bilateral cerebellum, bilateral proximal muscles (namely trapezius, deltoid, biceps, iliopsoas, gluteus medius, gluteus maximus and quadriceps) [25], excluding the region prominently influenced by FDG uptake in other anatomical structures. In order to avoid noise and acquire the value representing a certain volume of targeted organs, SUV was calculated as the mean value of ROI (SUVmean) instead of the maximum value at a single pixel [25]. For bilaterally distributed organs, the SUVmean was documented as the maximum SUVmean value of the symmetrical sides. Abnormal hilar or mediastinal lymph nodes were defined as those with swelling and elevated FDG uptake. The radiologist was blinded to the complications and outcome of the included patients when evaluating the SUVmean value of each and every targeted organ.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (*Chicago,* IL*, USA*), Graphpad Prism 8.0 and R 3.6.1. In comparison between patients with RP-ILD and patients in control group, independent sample t-test was utilized to compare normally distributed continuous variables. Mann-Whitney U test was used to compare skewed continuous variables or ordinal categorical variables. Chi-square test and Fisher's exact test were applied to compare unordered categorical variables. P values in comparisons were adjusted by false discovery rate (FDR) correction, utilizing p.adjust function in R.3.6.1, to acquire adjusted p values and minimize type I error. The correlation between two continuous variables was quantified with the Pearson linear analysis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of continuous variables. Survival in different groups was assessed by the Kaplan-Meier method with log-rank test. Cox proportional hazards regression analyses were subsequently adopted to identify the effect of clinical factors on the time to death from any cause. Explanatory factors with $P < 0.05$ in the univariate Cox proportional hazards regression analyses would be entered into the multivariate analyses. All tests were two-sided, and $P < 0.05$ was deemed statistically significant.

Results

From January 1st, 2017 to December 31st, 2020, 274 adult IIM-ILD patients were admitted to the Qingchun, Chengzhan, Zhijiang and Yuhang divisions of FAHZJU. Among them, 61 patients satisfied the inclusion/exclusion criteria and was finally included into the study (Additional file 1), encompassing 40 with DM, 9 with PM and 12 with ADM. 25 were males (41.0%) and the mean age of all the patients included was 56.72 ± 11.28 years old. Twenty-four patients (39.3%) died in follow-up and the medium follow-up time was 11.90 (4.00, 23.80) months. Among the included patients, 21 patients (34.4%) developed RP-ILD (Figure 1). The other 40 patients without RP-ILD constituted the control group. All of the RP-ILD events were identified after implementation of PET/CT scan. IIM patients with RP-ILD were found to suffer from worse survival (P=0.005, Figure 2A) with nine RP-ILD patients (42.9%) died within three months after hospitalization.

An unadjusted comparison between IIM-ILD patients with or without RP-ILD identified that patients who later developed RP-ILD had more complication of pulmonary bacterial infection (P=0.036) and gastrointestinal hemorrhage (P=0.044), higher MYOACT score (P=0.006), higher bilateral lung SUVmean (P<0.001, Figure 2B), more abnormal mediastinal (P=0.002) and hilar (P=0.018) lymph nodes, lower total lung capacity (TLC, P=0.049), lower percent-predicted diffusing capacity of the lung for carbon monoxide (DLCO%, P<0.001, Figure 2C) and positivity of anti-MDA5 antibody (P=0.016). However, after FDR correction, only the significance of DLCO% (P=0.014), bilateral lung SUVmean (P=0.014) and abnormal mediastinal lymph node (P=0.045) remained. (Table 1) No significant correlation was identified among the three clinical factors (P=0.491 and r=-0.090 for bilateral lung SUVmean and DLCO%, P=0.243 for bilateral lung SUVmean and abnormal mediastinal lymph node, P=0.077 for DLCO% and abnormal mediastinal lymph node, Additional file 2). Utilizing ROC curve analysis, the optimal cut-off value of the bilateral lung SUVmean for RP-ILD was >0.454, with a sensitivity of 95.2% and a specificity of 62.5%. The area under the curve (AUC) was 0.805 (Figure 2D). Meanwhile the optimal cut-off value of DLCO% for RP-ILD was <49.0%, with a sensitivity of 87.5%, a specificity of 66.7% and an AUC of 0.802 (Figure 2E).

Table 1 Comparisons of multiple factors between RP-ILD and non-RP-ILD groups

Factors	RP-ILD(21)	Non-RP-ILD(40)	P value	P-adjusted
Age(y)	54.86±11.72	57.70±11.06	0.354	0.824
Sex(male/female)	8/13	17/23	0.740	0.987
Course of disease(m)	2.00(1.00, 2.75)	2.25(1.00,5.00)	0.253	0.748
Duration of diagnosis delay(m)	1.50(0.50,2.00)	1.00(1.00,3.00)	0.274	0.756
Clinical manifestations or complications				
Pulmonary bacterial infection	7(33.3%)	4(10.0%)	0.036	0.347
Pulmonary fungal infection	5(23.8%)	4(10.0%)	0.253	0.748
Tuberculosis infection	0(0.0%)	0(0.0%)	NA	NA
EBV infection	6(28.6%)	5(12.5%)	0.164	0.605
CMV infection	2(9.5%)	0(0.0%)	0.115	0.559
Carcinoma	1(4.8%)	6(15.0%)	0.405	0.824
Gastrointestinal hemorrhage	4(19.0%)	1(2.5%)	0.044	0.347
UIP pattern	3(14.3%)	4(10.0%)	0.683	0.942
Pneumomediastinum	1(4.8%)	1(2.5%)	1.000	1.000
Pulmonary hypertension	3(14.3%)	4(10.0%)	0.683	0.942
Laboratory finding				
Ferritin(ng/ml)	612.50(302.05,2110.25)	664.05(314.40,2061.23)	0.495	0.863
ESR(mm/h)	16.00(6.50,32.00)	17.50(9.50,42.00)	0.466	0.857
CRP(mg/L)	5.40(3.10, 19.80)	6.35(3.00,36.73)	0.660	0.942
ALT(U/L)	37.00(22.50,99.50)	91.50(33.75,212.50)	0.051	0.347
AST(U/L)	45.00(33.00,97.00)	54.50(34.00,235.50)	0.224	0.725
LDH(U/L)	329.00(275.50,478.50)	323.00(247.75,461.50)	0.897	1.000
CK(U/L)	84.00(50.50,255.00)	86.00(44.25,415.25)	0.838	1.000
Disease activity				
MYOACT score	13.00(9.00,15.50)	9.00(7.00,10.75)	0.006	0.102
Lung function testing				
FVC%(%)	65.33±20.08	71.86±15.61	0.165	0.605
FEV1%(%)	64.85±19.40	74.42±18.25	0.062	0.383
FEV1/FVC	0.81(0.75,0.85)	0.81(0.77,0.85)	0.849	1.000
TLC(L)	3.43±1.01	3.98±1.02	0.049	0.347
DLCO%(%)	50.29±15.58	66.92±16.67	<0.001	0.014
^{18}F-FDG PET/CT scan findings				
Bilateral lung SUVmean	0.60±0.15	0.45±0.14	<0.001	0.014
Abnormal mediastinal lymph node	14(66.7%)	10(25.0%)	0.002	0.045
Abnormal hilar lymph node	11(52.4%)	9(22.5%)	0.018	0.204
Liver SUVmean	1.83±0.34	1.73±0.47	0.412	0.824
Spleen SUVmean	2.02±0.50	1.82±0.46	0.126	0.571
Bone marrow SUVmean	1.72±0.50	1.62±0.44	0.402	0.824
Cardiac SUVmean	1.38(1.00,2.03)	1.60(1.12,2.39)	0.379	0.824
Esophagus SUVmean	1.51(1.19,1.83)	1.34(1.07,1.74)	0.213	0.724
Stomach SUVmean	0.69(0.49,1.00)	0.71(0.57,0.83)	0.927	1.000
Small intestine SUVmean	1.05±0.33	1.03±0.32	0.878	1.000
Colon and rectum SUVmean	1.07(0.80,1.32)	1.02(0.83,1.20)	0.693	0.942
Bilateral cerebellum SUVmean	5.17±1.26	5.24±1.61	0.863	1.000
Bilateral trapezius SUVmean	0.82(0.70,0.96)	0.79(0.68,1.00)	0.585	0.942
Bilateral deltoid SUVmean	0.71(0.58,1.27)	0.78(0.61,1.09)	0.590	0.942
Bilateral biceps SUVmean	0.75(0.67,1.01)	0.77(0.60,1.10)	0.879	1.000
Bilateral ilioposas SUVmean	1.10±0.36	1.12±0.36	0.850	1.000
Bilateral gluteus maximus SUVmean	0.85±0.27	0.79±0.32	0.462	0.857
Bilateral gluteus medius SUVmean	0.92±0.29	0.98±0.29	0.473	0.857
Bilateral quadriceps SUVmean	0.78(0.62,0.96)	0.82(0.69,1.05)	0.370	0.824
Myositis-specific antibodies & Myositis-associated antibodies				
Anti-MDA5	13(61.9%)	12(30.0%)	0.016	0.204
Anti-PL-7	4(19.0%)	2(5.0%)	0.169	0.605
Anti-PL-12	1(4.8%)	1(2.5%)	1.000	1.000
Anti-EJ	0(0.0%)	1(2.5%)	1.000	1.000
Anti-OJ	0(0.0%)	1(2.5%)	1.000	1.000
Anti-Jo-1	2(9.5%)	3(7.5%)	1.000	1.000
Anti-TIF1γ	1(4.8%)	3(7.5%)	1.000	1.000
Anti-Mi-2α	0(0.0%)	2(5.0%)	0.541	0.920
Anti-Mi-2β	0(0.0%)	4(10.0%)	0.289	0.756
Anti-SAE1	0(0.0%)	5(12.5%)	0.154	0.605
Anti-NXP2	1(4.8%)	6(15.0%)	0.405	0.824
Anti-SRP	1(4.8%)	2(5.0%)	1.000	1.000
Anti-Ku	1(4.8%)	1(2.5%)	1.000	1.000
Anti-PM-Scl75	1(4.8%)	2(5.0%)	1.000	1.000
Anti-PM-Scl100	0(0.0%)	0(0.0%)	NA	NA
Anti-Ro-52	14(66.7%)	17(42.5%)	0.073	0.414
Therapies				
Steroid monotherapy	6(28.6%)	14(35.0%)	0.611	0.942
Steroid+DMARDs	7(33.3%)	19(47.5%)	0.288	0.756
Steroid+IVIG	2(9.5%)	2(5.0%)	0.602	0.942
Steroid+DMARDs+IVIG	3(14.3%)	4(10.0%)	0.683	0.942
Steroid+JAK inhibitor	3(14.3%)	1(2.5%)	0.113	0.559
IIM subtypes				
DM	13(61.9%)	27(67.5%)	0.662	0.942
PM	2(9.5%)	7(17.5%)	0.479	0.857
ADM	6(28.6%)	6(15.0%)	0.309	0.778

RP-ILD: Rapidly progressive interstitial lung disease; P-adjusted: Adjusted P value after false discovery rate correction; y: years; m: months; NA: Not available; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; UIP pattern: Usual interstitial pneumonia pattern; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ALT: Alaninetransaminase; AST: Aspartate transaminase; LDH: Lactate dehydrogenase; CK: Creatine kinase; MYOACT: Myositis Disease Activity Assessment Visual Analogue Scales; FVC%: Percent-predicted forced vital capacity; FEV1%: Percent-predicted forced expiratory volume in one second; FEV1/FVC: Ratio of FEV1 over FVC; TLC: Total lung capacity; DLCO%: Percent-predicted diffusing capacity of the lung for carbon monoxide; FDG: Fluorodeoxyglucose; SUVmean: mean standard

uptake value; DMARDs: Disease-modifying anti-rheumatic drugs; IVIG: Intravenous immunoglobulin; JAK: Janus kinase; IIM: Idiopathic inflammatory myopathy; DM: dermatomyositis; PM: Polymyositis; ADM: Amyopathic dermatomyositis.

To develop a scoring system for prediction of RP-ILD, we rounded up the cutoff values of bilateral SUVmean and DLCO% to >0.450 and <50.0%, respectively. Each were allotted one point. Identification of abnormal mediastinal lymph node was also allotted one point. Each included patient was then attributed a cumulative score (maximum score of three, minimum score of zero). The scoring system was named "DLM" using the initials of DLCO%, lung and mediastinum. Afterwards, the predictive value of DLM model was evaluated in the 61 patients. None of the 15 patients with a minimum possible score of zero developed RP-ILD. In contrast, all of the nine patients with a maximum possible score of three were found to suffer from RP-ILD in the future (Table 2, Figure 3A). Together with the subsequent ROC curve analysis (Figure 3B), we revealed a cutoff value of ≥2, AUC of 0.905, sensitivity of 85.7%, specificity of 82.5%， positive predictive value (PPV) of 72.0%, negative predictive value (NPV) of 91.7% and accuracy of 83.6%.

Table 2 Distribution of RP-ILD and non-RP-ILD in IIM-ILD patients with different DLM score

DLM Score	Total patients (N)	RP-ILD %(N)	Non-RP-ILD %(N)
0	15	0.0%(0)	100.0%(15)
1	21	14.3%(3)	85.7%(18)
2	16	56.3%(9)	43.7%(7)
3	9	100.0%(9)	0.0%(0)

RP-ILD: Rapidly progressive interstitial lung disease; IIM-ILD: Idiopathic-inflammatory-myopathy-related interstitial lung disease; N：Number.

To explore the predictive value of PET/CT scan in survival, the univariate Cox proportional hazards regression analyses identified pulmonary bacterial infection (P<0.001), RP-ILD (P=0.008), MYOACT score (P<0.001), DLCO% (P=0.016), bilateral lung SUVmean (P=0.007), spleen SUVmean (P=0.008) and use of steroid+IVIG (P=0.015) were significantly correlated with survival in follow-up After FDR correction, however, only pulmonary bacterial infection (P<0.001) and MYOACT score (P<0.001) were significantly associated with survival of these patients. (Additional file 3). The following multivariate Cox proportional hazards regression analysis also identified pulmonary bacterial infection (P=0.014) and MYOACT score (P<0.001) as factors significantly related to survival of IIM-ILD patients (Additional file 4). Furthermore, IIM-ILD patients who died within three months were found to have higher bilateral lung SUVmean (P=0.019, Figure 4A) and higher spleen SUVmean (P=0.011, Figure 4B). A moderate correlation was recognized between spleen SUVmean and bilateral lung SUVmean (P=0.006, r=0.346, Figure 4C).

Nevertheless, in RP-ILD subgroups, bilateral lung SUVmean (P=0.598, Additional file 5) and spleen SUVmean (P=0.161, Additional file 5) were not recognized to be significantly different in patients who died within three months or survived beyond this threshold.

Discussion

To the best of our knowledge, this is the largest cohort to investigate the clinical value of pulmonary FDG uptake in IIM-ILD patients, and the first study to systemically explore FDG uptake of extra-pulmonary organs (liver, spleen, digestive tract, etc.) in IIM-ILD patients. The pulmonary FDG uptake was significantly higher in IIM-ILD patients who were later diagnosed with RP-ILD than that in patients without RP-ILD. More mediastinal and hilar (only before FDR corretion) lymph node abnormality were as well identified in the PET/CT scan of IIM-ILD patients with RP-ILD. Together with DLCO% in pulmonary function testing, pulmonary FDG uptake and abnormality of mediastinal lymph node was used to construct a functional predicting tool (DLM model) for RP-ILD in IIM patients. In addition, elevated pulmonary FDG uptake and spleen FDG uptake were associated with unfavorable outcome of these patients before FDR correction and multivariate regression. A moderate correlation was found between pulmonary FDG uptake and spleen FDG uptake.

Apart from oncologic imaging, ^{18}F-FDG PET/CT was also found to reflect immune cells activation in spleen and malignant tissues [26, 27]. After reviewing preceding literatures, elevated pulmonary FDG uptake could also be taken as an indicator for focal immune activation. In bleomycin-induced pulmonary fibrosis mice model, the early stage of FDG uptake increase was probably related to the early recruitment and activation of leukocytes, meanwhile the later and persistent elevation of FDG uptake might be associated with aerobic glycolysis of myofibroblasts [13, 28, 29]. Savelli and his colleagues proposed ^{18}F-PET/CT might image and quantify the macrophage activity in pulmonary interstitial infiltrates of COVID-19 pneumonia [30]. Furthermore, activation and recruitment of neutrophils also increased focal ^{18}F-FDG uptake in inflammatory lung diseases [31]. The elevated ^{18}F-FDG uptake could therefore serve as a marker for focal and global inflammatory activation and elevated metabolism in bilateral lungs. In addition, two antifibrotic drugs, namely nintedanib and pirfenidone, were found to significantly decrease pulmonary FDG uptake in bleomycin-treated mice, indicating the value of PET/CT scan in evaluating response to antifibrotic medications [32, 33]. However, the evaluating role of PET/CT scan demanded further validation in IPF and CTD-ILD patients.

After initially confirming the role of FDG uptake in reflecting focal immune and metabolistic activation, we used the retrospective cohort to identify the clinical value of PET/CT scan on RP-ILD in IIM-ILD patients. Both increased pulmonary FDG uptake and abnormal mediastinal lymph node were identified to be significantly correlated with RP-ILD in IIM-ILD patients. Compared with the conventional HRCT, PET/CT scan seemed to be more intuitive in predicting RP-ILD. In clinical practice, PET/CT scan was widely probed into among IPF patients [34]. Umeda et al. proposed that the positive retention index of SUV, based on SUV obtained after one-hour and three-hour imaging in 50 patients, efficiently predicted early progression of pulmonary function impairment [35]. In patients suffering from lung cancer, elevated

pulmonary FDG uptake was associated with acute exacerbation of ILD after chemotherapy or surgery [36-38]. In Ssc-ILD patients, pulmonary FDG uptake was correlated with ILD severity [14]. Together with abnormal mediastinal/hilar lymph node, it was as well identified to be associated with progression of ILD within two years [14]. The predictive value of pulmonary FDG uptake for ILD progression crossed the boundary of IPF, tumor-associated ILD and CTD-ILD, and deserves to be further verified in more ILD spectrum and larger cohort.

Before FDR correction, pulmonary FDG uptake was also found to be correlated with survival of IIM-ILD patients. The outcome-predicting value of pulmonary FDG uptake has been proposed in IPF. Umeda et al. also suggested the association between pulmonary FDG uptake and survival of IPF patients [35]. Meanwhile Fraioli and his colleagues proposed including pulmonary FDG uptake into the conventional GAP (gender, age and physiology) model would significantly increase the model's ability in outcome prediction [39]. In CTD-ILD, preceding study indicated that increased spleen FDG uptake could be seen in autoimmune-related ILD patients refractory to the potent rituximab therapy [40]. Through Pearson linear analysis, we also revealed a moderate correlation between spleen SUVmean and bilateral lung SUVmean. The spleen is the largest lymphoid organ containing specific subsets of myeloid cells and lymphocytes, which are already known to be involved in the development of multiple CTDs. We hereby hypothesized that there might exist a linkage between spleen and lung during the development of CTD-ILD. In traditional Chinese medicine, spleen is the organ to produce and replenish Qi, which tonifies and nourishes lung [41]. It will be interesting and meaningful to identify a cross-talk between spleen and lung from the perspective of modern medicine. However, only higher disease activity and complication of pulmonary infection remain statistically significant after FDR correction and multivariate analysis, which was consistent with the reports of preceding studies [42, 43].

RP-ILD is a severe and fatal complication in IIM patients, it was thus necessary to search for early predicting tools so as to carry out a timely and potent therapeutic regimen for patients with high risk for RP-ILD. Previous studies indicated anti-MDA5 antibody, anti-Ro52 antibody, DLCO%, serum ferritin, etc. were correlated with development of RP-ILD [44, 45]. After FDR correction, bilateral lung SUVmean, abnormal mediastinal lymph node and DLCO% were found to be significantly different between patients with RP-ILD and control group. The three clinical factors were tested independent of each other and were hereby incorporated to form the DLM model. The DLM model was comparably satisfying in AUC, sensitivity, specificity, PPV, NPV and accuracy. However, due to the scarcity of IIM-ILD patients receiving PET/CT scan, we failed to construct another cohort of IIM-ILD patients for verification of DLM score.

There existed multiple limitations in this study. Selection bias occurred since patients with fever, signs of cytopenia, higher disease activity, dyspnea tended to receive PET/CT scan to exclude malignancy or relapse of malignancy. Due to the retrospective nature, we failed to enroll more clinical factors like Kreb Von Den Lungen-6, etc. into this study. The scarcity of IIM patients made it impossible to verify the predictive value of DLM model in a new cohort. Healthy people or IIM patients without ILD seldom receive PET/CT scan, made it impossible to construct a healthy control group or take IIM patients without ILD as control. To make the predicting model easy to construct, bilateral lung SUVmean was calculated in one

site with highest FDG uptake instead of multiple sites. Despite all the limitations, we sought to identify the clinical value of PET/CT scan in IIM-ILD, initially construct a scoring system for prediction of RP-ILD, and shed some light on future research on IIM-ILD.

Conclusions

Elevated pulmonary FDG uptake, abnormal mediastinal lymph node and decreased DLCO% were significantly correlated with RP-ILD in IIM-ILD patients. A DLM model was hereby constructed and initially proved efficient in predicting RP-ILD in these patients. Higher disease activity and complication of bacterial infection was significantly related to unfavorable outcome. Besides, IIM-ILD patients with higher pulmonary and spleen FDG uptake (correlated) showed a tendency to suffer from unfavorable outcome, indicating a systemic hyperinflammatory status and a possible linkage between the two sites.

List Of Abbreviations

ILD: Interstitial lung disease;

NSIP: Non-specific interstitial pneumonia;

IIM-ILD: Idiopathic-inflammatory-myopathy-related ILD;

RP: Rapidly progressive;

IPF: Idiopathic pulmonary fibrosis;

CTD-ILD: Connective-tissue-disease-related ILD;

COVID-19: Corona Virus Disease 2019;

FDG: Fluorodeoxyglucose;

SSc-ILD: Systemic-sclerosis-related ILD;

SUV: Standard uptake value;

ROI: Region of interest;

FAHZJU: The First Affiliated Hospital, Zhejiang University School of Medicine;

IRB: Institutional Review Board;

EMR: Electronic medical record;

ICD-10: International Classification of Diseases, tenth version;

DM: Dermatomyositis;

PM: Polymyositis;

ADM: Amyopathic dermatomyositis;

HRCT: High-resolution computed tomography;

UIP: Usual interstitial pneumonia;

CTD: Connective tissue disease;

MYOACT: Myositis Disease Activity Assessment Visual Analogue Scales;

PSL: Prednisolone;

mPSL: Methylprednisolone;

DMARDs: Disease modifying anti-rheumatic drugs;

JAK: Janus kinase;

IVIG: Intravenous immunoglobulin;

FDR: False discovery rate;

ROC: Receiver operating characteristic;

TLC: Total lung capacity;

DLCO%: Percent-predicted diffusing capacity of the lung for carbon monoxide;

AUC: Area under the curve;

PPV: Positive predictive value;

NPV: Negative predictive value;

GAP: Gender, age and physiology.

Declarations

Ethics approval and consent to participate

The study was approved (2021-194) by the IRB of FAHZJU. All participants signed written informed consent at admission.

Consent for publication

Consents for publication from the patients included were also acquired prior to submission.

Availability of data and materials

The dataset supporting the conclusions of this article is presented as Additional file 6 (seen in additional files of this article).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study design: JLiang, HC and JLin. Data collection: JLiang, YS, YK and YH. Verification of IIM diagnosis: HC and BX. Reevaluation of FDG uptake in multiple organs: YL. Identification of ILD and RP-ILD: YL and BY. Statistical analysis: JLiang. Writing: JLiang and HC. Proof reading: JLiang, HC and JLin. All authors read and approved the final manuscript.

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Figures

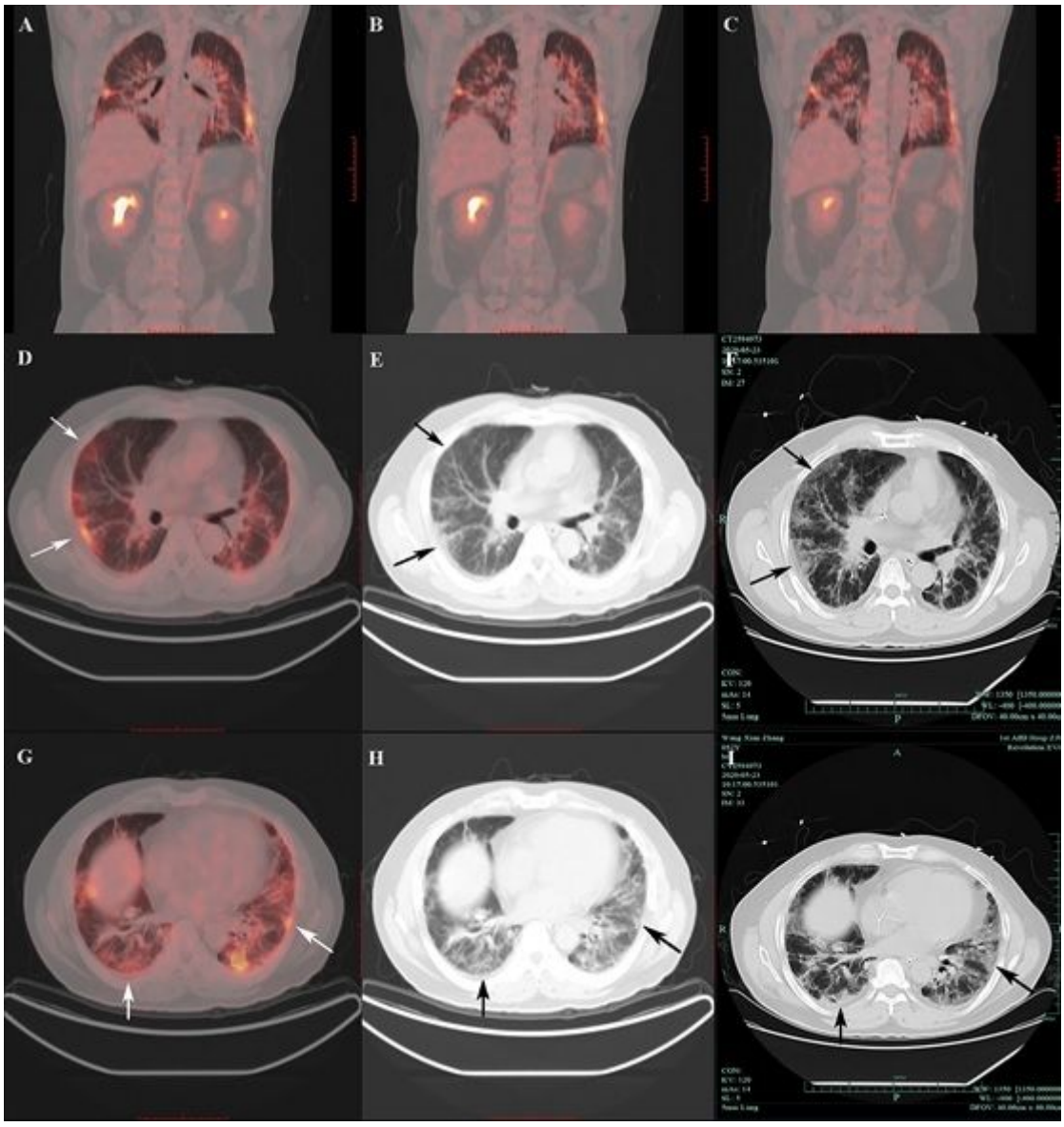

Figure 1

Visual examination of 18F-FDG-PET/CT scan and HRCT of one IIM-ILD patients who developed RP-ILD A to C. Prominently elevated FDG uptake in bilateral lungs of one IIM-ILD patient who later developed RP-ILD. D to F and G to I. Prominently elevated FDG uptake in bilateral lungs of one IIM-ILD patient indicated future RP-ILD in one week (where the arrow pointed) FDG: Fluorodeoxyglucose; HRCT: High resolution CT; IIM-ILD: Idiopathic-inflammatory-myopathy-related interstitial lung disease; RP-ILD: Rapidly progressive interstitial lung disease.

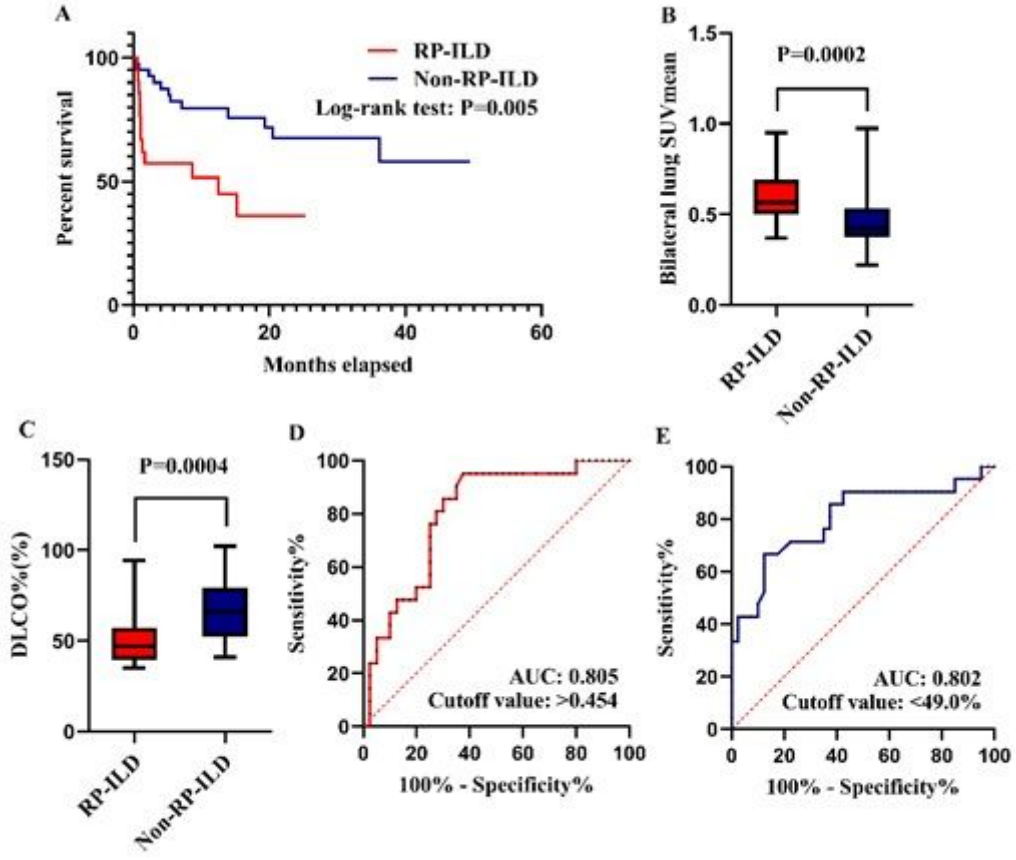

Figure 2

Evaluation of IIM-ILD patients with or without RP-ILD A. Survival of IIM-ILD patients with or without RP-ILD B. Comparison of bilateral lung SUVmean in RP-ILD and non-RP-ILD groups C. Comparison of DLCO% in RP-ILD and non-RP-ILD groups D. ROC curve of bilateral lung SUVmean predicting RP-ILD E. ROC curve of DLCO% predicting RP-ILD IIM-ILD: Idiopathic-inflammatory-myopathy-related interstitial lung disease; RP-ILD: Rapidly progressive interstitial lung disease; SUVmean: mean standard uptake value; DLCO%: Percent-predicted diffusing capacity of the lung for carbon monoxide; ROC: Receiver operating characteristic; AUC: Area under the curve.

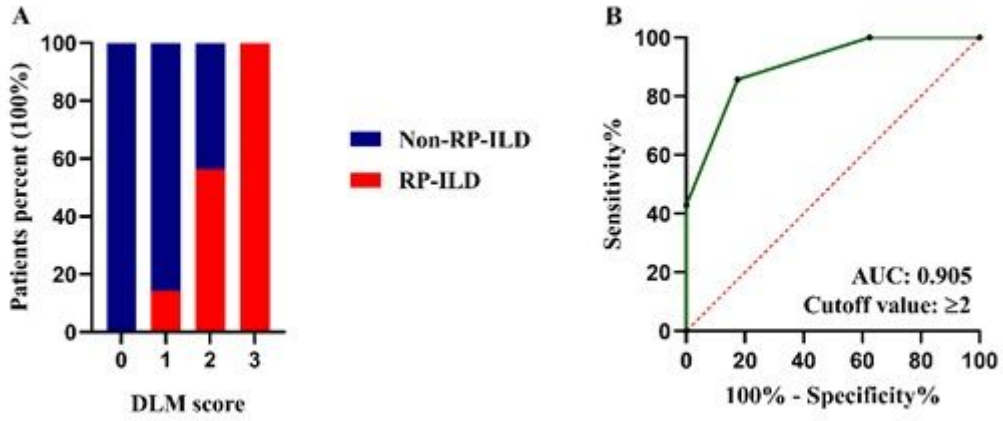

Figure 3

Evaluation of DLM model in predicting RP-ILD in IIM-ILD patients A□Distribution of RP-ILD and non-RP-ILD patients in each DLM score group B□ROC curve of DLM model predicting RP-ILD RP-ILD: Rapidly progressive interstitial lung disease; IIM-ILD: Idiopathic-inflammatory-myopathy-related interstitial lung disease; ROC: Receiver operating characteristic; AUC: Area under the curve.

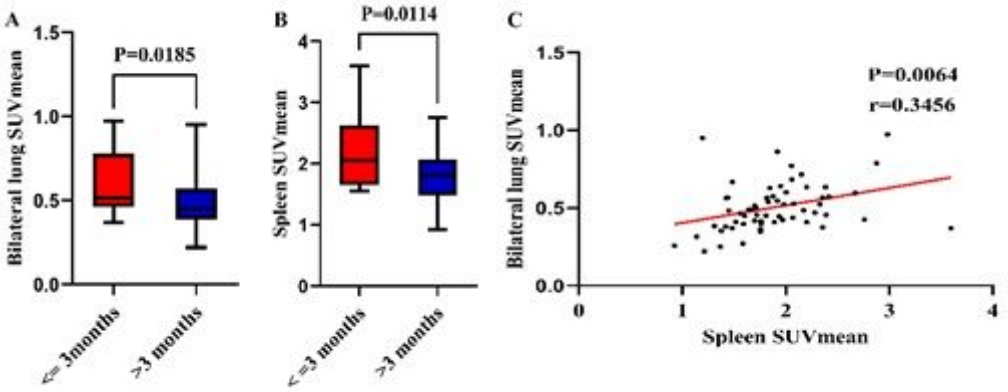

Figure 4

Evaluation of abnormal FDG uptake in IIM-ILD patients with different survival A. Comparison of bilateral lung SUVmean in IIM-ILD patients who died within three months or survived beyond this threshold B. Comparison of spleen SUVmean in IIM-ILD patients who died within three months or survived beyond three months C. Correlation between bilateral lung SUVmean and spleen SUVmean in IIM-ILD patients FDG: Fluorodeoxyglucose; IIM-ILD: Idiopathic-inflammatory-myopathy-related interstitial lung disease; SUVmean: mean standard uptake value.

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