

Peer Review File

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Reviewer A

I think that you conducted research on an interesting topic with a valuable significance in real practice. However, the main result was not the same as you expected as well as many previous studies with a similar topic, i.e., SUV max on PET-CT and acute exacerbation(AE) after pulmonary resection in lung cancer with interstitial lung disease (ILD), were reported. (References. Maniwa et al. Surg Today (2014) 44:494–498; Yamamichi et al. J Thorac Cardiovasc Surg 2020;159:1111-8; Fukunaga et al. European Journal of Radiology 135 (2021) 109477; Kagimoto et al. Ann Thorac Surg 2021;112:264-70; Oishi et al. respiratory investigation 59 (2021) 106e113)

Major comments:

Comment 1. First, as for included subjects, was there any patient who was treated neoadjuvant chemotherapy or radiotherapy before the surgery? In addition, how long did the patients have the interstitial lung disease (ILD) and which medications were taken for ILD. These detailed information might be clues to explain the conflict result and those contents would be added in the method and the result section.

Reply 1: Thank you for your thoughtful comments and suggestions. As neoadjuvant LC therapy, only one patient received neoadjuvant chemotherapy and did not develop pAE-ILD or AE-ILD after 30 days postoperatively. Additionally, we could not examine the duration of ILD because the timing of ILD onset was unknown in many cases in the medical records. Finally, we included information on preoperative steroid use in Tables 1 and 2 with respect to medications for ILD and additionally reviewed preoperative pirfenidone use. In our study, pirfenidone administration also had no effect on pAE-ILD. The discussion regarding pirfenidone has been added to the Method, Results, and Discussion sections in the manuscript and in Tables 1 and 2.

Changes in the text:

Page 8, lines 135–139: ‘Their baseline demographic and clinical parameters before lung resection were obtained from medical records, and the following parameters being included: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking status, medical history of ILD, histology, pathological stage, laboratory test results, pulmonary function, and surgical procedure type’.

Page 11, lines 206–207: ‘Among patients with a preoperative history of ILD, 9 (7.6%) and 21 (18.0%) patients used steroids and pirfenidone, respectively’.

Page 14, lines 256–257: ‘; however, this study did not demonstrate the efficacy of pirfenidone in preventing pAE-ILD’.

Table 1. Patient characteristics

		N = 117	%
Age, years	Median (range)	71 (39-86)	
Sex	Male/Female	103/14	88.0/12.0
ECOG PS	0–1/2	114/3	97.4/2.6
Smoking status	Yes/No	112/5	95.7/4.3
Histology	Ad/Sq/Sm/other	49/47/9/12	41.9/40.2/7.7/10.3
pStage	0/ I/ II/III/IV	4/73/17/21/2	3.4/62.4/14.5/17.9/1.7
ILD pattern	UIP/non-UIP	27/90	23.1/76.9
LDH, U/l	Median (range)	202.5 (132–350)	
KL-6†, U/ml	Median (range)	487.0 (149–717)	
%FVC, %	Median (range)	95.1 (55.2–136.3)	
%DLco‡, %	Median (range)	64.8 (40.6–98.6)	
ILD-GAP score‡	Median (range)	1.0 (-2–5)	
Surgical procedure	Lobectomy		
	/Segmentectomy /Partial resection	96/2/19	82.1/1.7/16.2
Preoperative steroid use	Yes/No	9 /108	7.6/92.3
Preoperative pirfenidone use	Yes/No	21/96	18.0/82.0
History of AE	Yes/No	0/117	0.0/100.0
RS for predicting AE after pulmonary resection†	Median (range)	7.0 (0–14)	
SUV _{max} of contralateral interstitial lesion	Median (range)	1.61 (0.82–3.70)	

Table 2. Comparison of clinicopathological factors between the pAE-ILD and non-pAE-ILD groups.

		Non-pAE-ILD (N = 109)		pAE-ILD (N = 8)		P-value
		N	%	N	%	
Age, years	Median (range)	71.0 (39–86)		77.5 (66–84)		0.014
Sex	Male/Female	95/14	87.2/12.8	8/0	100.0/0.0	0.349
ECOG PS	0–1/2	106/3	97.2/2.8	8/0	100.0/0.0	0.807
Smoking status	Yes/No	104/5	95.4/4.6	8/0	100.0/0.0	0.697
Histology	NSCLC/SCLC	100/9	91.7/8.3	8/0	100.0/0.0	0.516
pStage	0– II/III–IV	89/20	81.7/18.3	5/3	62.5/37.5	0.189
ILD	UIP/non-UIP	22/87	20.2/79.8	5/3	62.5/37.5	0.016
LDH, U/l	Median (range)	203.0 (132–350)		151.0 (149–228)		0.059
KL-6†, U/ml	Median (range)	461.0 (149–1855)		680.5 (409–2019)		0.080
%FVC, %	Median (range)	96.2 (55.2–136.3)		90.1 (72.9–125.2)		0.315
%DLco‡, %	Median (range)	64.8 (40.6–98.6)		75.8 (48.0–104.1)		0.897
ILD-GAP score‡	<1/≥1	19/81	19.0/81.0	0/8	0.0/100.0	0.201
Surgical producer	Lobectomy/ Limited surgery	88/21	80.7/19.3	8/0	100.0/0.0	0.194
Preoperative steroid use	Yes/No	9/100	8.3/91.7	0/8	0.0/100.0	0.516
Preoperative pirfenidone use	Yes/No	19/90	17.4/82.6	2/6	25.0/75.0	0.438
RS for predicting AE after pulmonary resection†	0–10/11–14	85/18	82.5/17.5	3/5	37.5/62.5	0.009
SUV _{max} of contralateral interstitial lesion	Median (range)	1.61 (0.82–3.70)		1.62 (1.40–2.05)		0.944

Comment 2. Second, how about other parameters, not just SUVmax in noncancerous lesion would be checked to predict AE of ILD in lung cancer with ILD? A recent published article (Reference. Yoon et al. BMC Pulm Med (2021) 21:294) showed that among SUVs, SUVRTF is the best parameter as predictive factor in postop.AE in idiopathic pulmonary fibrosis after lung surgery. They measured other SUVs besides SUVmax to compensate for the SUV differences between subjects or to compensate for the air component in the lung tissue.

Reply 2: Thank you for your thoughtful comments and suggestions. As we addressed your point in our previous study (1), ¹⁸F-FDG uptake in patients with IPF undergoing ¹⁸F-FDG PET/CT could be measured using various methods, including SUVRTF as reported in previous studies; however, measuring SUV_{max} would be a simpler method compared to these other approaches and could be useful in real-world clinical practice. Although we could not perform other measurements in this study, we plan to investigate them in future large-scale studies.

<reference>

(1) Akaike K, Saruwatari K, Oda S, et al. Predictive value of (18)F-FDG PET/CT for acute exacerbation of interstitial lung disease in patients with lung cancer and interstitial lung disease treated with chemotherapy. *Int J Clin Oncol* 2020;25:691-90.

Comment 3. Third, you mentioned shortly a preventive therapy for pAE of ILD in lung ca with ILD in the discussion section (Line 249~). To help readers give knowledge of managing this fatal situation, I suggest that other managements besides pirfenidone would be added.

Reply 3: Thank you for your suggestion. Regarding the management of pAE-ILD prevention, in the present study, limited surgery had no effect on pAE-ILD; however, previous reports showed that limited surgery reduced the frequency of pAE-ILD. Therefore, we added the following sentence regarding limited surgery to the discussion section in the manuscript.

Changes in the text: Page 14, lines 260–262: ‘Although our study did not demonstrate a significant difference, Sato et al. reported that limited surgery was associated with a lower frequency of pAE-ILD. In LC patients with ILD, limited surgery could be a useful method of preventing pAE-ILD’.

Comment 4. Lastly, in the discussion section (Line 269~), you addressed the conflict result in your article, just compared with your previous article. However, the above-mentioned articles had a more similar topic with this manuscript, so you should explain reasons about the different results from those researches.

Reply 4: Thank you for bringing this to our attention. We agree with your comment. We believe that two possible factors, namely the different types of triggers for AE-ILD and the duration of observation, could affect this discrepancy. Hence, we discussed the two factors in the discussion section in the manuscript. Please refer to the following (Page 15–17, Line 288–302).

Minor comments:

Comment 1. Line 105 “in high-risk LC with ILD” the meaning of this phrase is ambiguous, so clarify the sentence.

Reply 1: Thank you for bringing this to our attention. According to your suggestion, we corrected the text and deleted the following terms ‘high risk’ from the Introduction section in the manuscript.

Changes in the text: Page 6, lines 105 ‘... in LC patients with ILD...’

Comment 2. Line 418, Edit the reference following the style guideline of this journal.

Reply 2: Thank you for indicating this. We accordingly corrected the reference as follows.

Changes in the text: Page 24, lines 444–446 ‘Win T, Screamon NJ, Porter JC, et al. Pulmonary (18)F-FDG uptake helps refine current risk stratification in idiopathic pulmonary fibrosis (IPF). *Eur J Nucl Med Mol Imaging* 2018;45:806-15’.

Reviewer B

The authors retrospectively investigated whether SUVmax values in contralateral interstitial lesions could be a predictor of acute exacerbations within 30 days postoperatively in lung cancer patients with comorbid interstitial lung disease undergoing lung resection. In spite of a negative study, the reviewer believe that the contents of this study is novel and interesting.

Major comments

Comment 1. In this study, the values of SUVmax were measured in contralateral interstitial lesions to evaluate disease activity in ILD. Please describe the reason why contralateral rather than ipsilateral was chosen as the target of evaluation.

Reply 1: Thank you for your thoughtful comments and suggestions. As we addressed your point in our previous study (1), when patients present with primary lung cancer in interstitial shadows, accurate measurement of ^{18}F -FDG uptake is difficult because the boundary between the lung cancer and interstitial lung lesions is often indistinguishable. Accordingly, measuring the SUV_{max} of contralateral interstitial lesions is more appropriate than measuring that of ipsilateral interstitial lesions. Thus, we performed analyses based on the SUV_{max} of contralateral lesions.

<reference>

(1) Akaike K, Saruwatari K, Oda S, et al. Predictive value of (18)F-FDG PET/CT for acute exacerbation of interstitial lung disease in patients with lung cancer and interstitial lung disease treated with chemotherapy. *Int J Clin Oncol* 2020;25:691-90.

Comment 2. Because of the heterogeneity of ILDs such as idiopathic pulmonary fibrosis, contralateral interstitial lesions may not always reflect the disease activity such as higher or highest SUVmax. The analysis with maximal SUVmax in lung areas with interstitial shadows may be very interesting.

Reply 2: Thank you for the pertinent comment, with which we agree.

However, in our previous study, we also examined the SUV_{max} of the ipsilateral interstitial lesions and all interstitial lesions regardless of the side, as well as contralateral interstitial lesion, in the chemotherapy-related AE-ILD investigation (1). In that study, we found that the SUV_{max} of contralateral lesions but not ipsilateral interstitial lesions trended toward being significantly associated with AE-ILD in LC patients with ILD who were treated with chemotherapy.

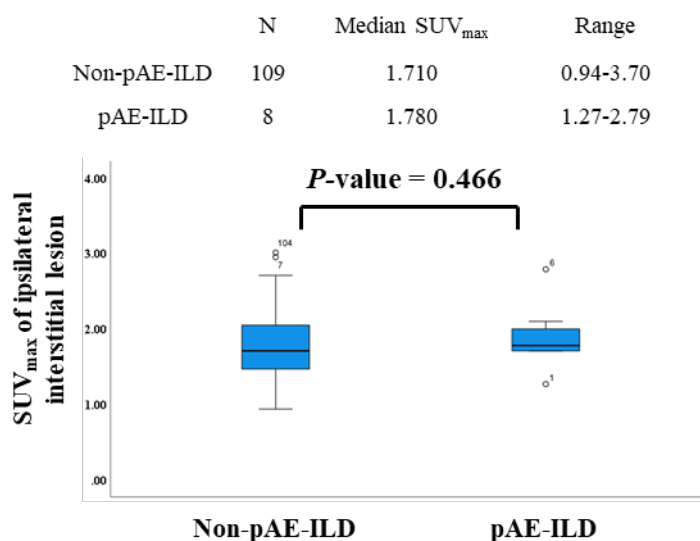
However, based on your suggestion, we examined the SUV_{max} of the ipsilateral interstitial

lesion and added the results. Unfortunately, the SUV_{max} of ipsilateral interstitial lesions was not associated with pAE-ILD. Please refer to the following figure.

<reference>

(1) Akaike K, Saruwatari K, Oda S, et al. Predictive value of (18)F-FDG PET/CT for acute exacerbation of interstitial lung disease in patients with lung cancer and interstitial lung disease treated with chemotherapy. *Int J Clin Oncol* 2020;25:691-90.

figure. Correlation between SUV_{max} of ipsilateral interstitial lesions and the incidence of pAE-ILD.



Comment 3. Please add preoperative evaluators and methods as well as AE-ILD in the imaging of ILD. Also, please consider adding intraobserver variability.

Reply 3: Thank you for bringing this to our attention. We have accordingly added and corrected the following sentence in the methods section of the manuscript.

Changes in the text: Page 9, lines 152–153 and 165–170: ‘ILD was diagnosed based on evidence of diffuse parenchymal and interstitial lung abnormalities on chest CT and’, and ‘CT findings were considered concordant when both pulmonologists reached the same results. When they reached different results, CT scans were re-examined, and the final findings were agreed upon by consensus between the two pulmonologists’.

Comment 4. Please add information on preoperative use of antifibrotic drugs In Table 1,

if possible.

Reply 4: Thank you for bringing this to our attention. Based on your comment, we have included pirfenidone in Table 1. In our study, pirfenidone administration also had no effect on pAE-ILD.

Changes in the text: Table 1

Table 1. Patient characteristics

		N = 117	%
Age, years	Median (range)	71 (39-86)	
Sex	Male/Female	103/14	88.0/12.0
ECOG PS	0–1/2	114/3	97.4/2.6
Smoking status	Yes/No	112/5	95.7/4.3
Histology	Ad/Sq/Sm/other	49/47/9/12	41.9/40.2/7.7/10.3
pStage	0/ I/ II/III/IV	4/73/17/21/2	3.4/62.4/14.5/17.9/1.7
ILD pattern	UIP/non-UIP	27/90	23.1/76.9
LDH, U/l	Median (range)	202.5 (132–350)	
KL-6†, U/ml	Median (range)	487.0 (149–717)	
%FVC, %	Median (range)	95.1 (55.2–136.3)	
%DLco‡, %	Median (range)	64.8 (40.6–98.6)	
ILD-GAP score‡	Median (range)	1.0 (-2–5)	
	Lobectomy		
Surgical procedure	/Segmentectomy	96/2/19	82.1/1.7/16.2
	/Partial resection		
Preoperative steroid use	Yes/No	9 /108	7.6/92.3
Preoperative pirfenidone use	Yes/No	21/96	18.0/82.0
History of AE	Yes/No	0/117	0.0/100.0
RS for predicting AE after pulmonary resection†	Median (range)	7.0 (0–14)	
SUV _{max} of	Median (range)	1.61 (0.82–3.70)	

contralateral interstitial
lesion

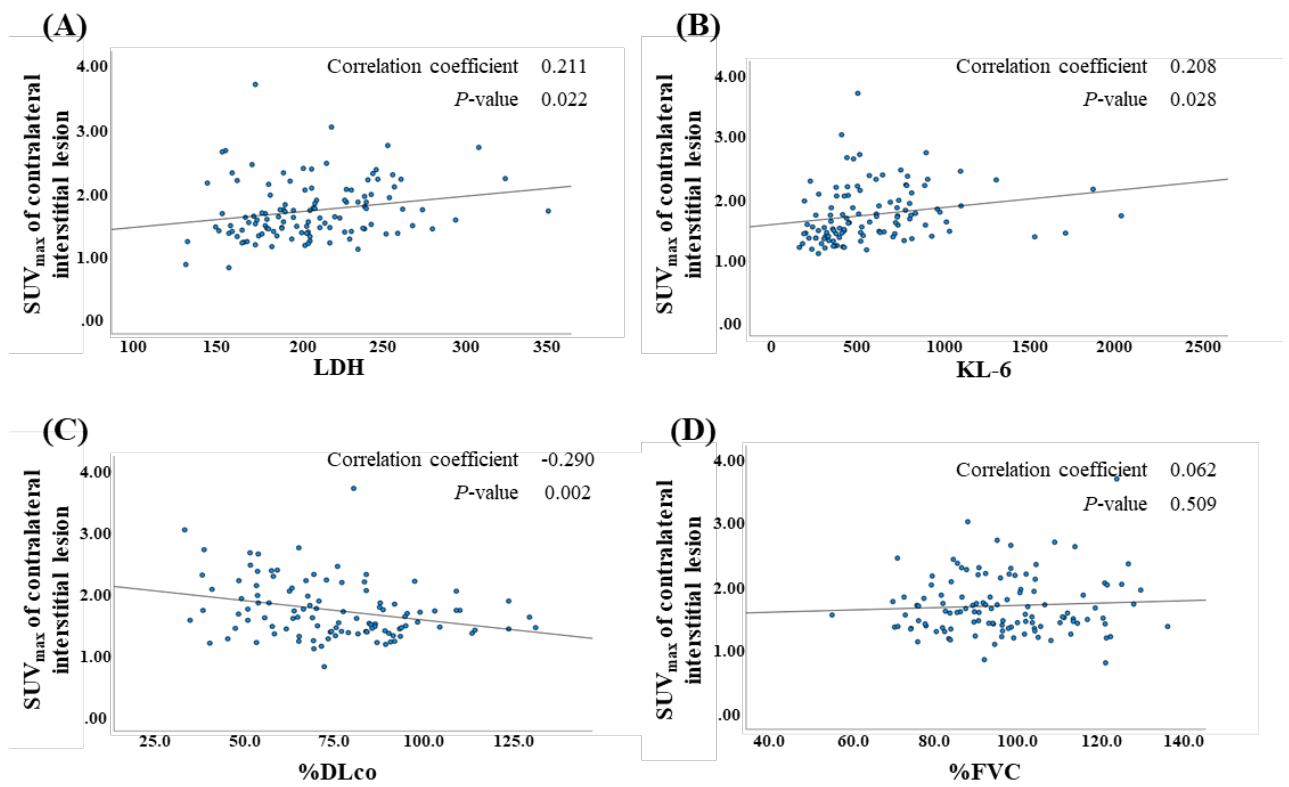
Minor comments

Comment 1. In Figure 3 (b) and (c), the vertical axis is unreadable.

Reply 1: Thank you for pointing this out. Figure 3 was accordingly corrected.

Changes in the text: Figure 3

Figure 3.



Reviewer C

This paper was written by Dr Akaike et al, demonstrating that SUVmax was not a predictor of postoperative AE of ILD after pulmonary resection, but may be a predictive tool for the correlation with ILD severity. This paper is well written and self-explanatory. However, minor issue has been raised as follow;

Major comments

Comment 1. Regarding the relationship between PET SUVmax and postoperative AE of ILD, two previous studies (Yamamichi T, JTCVS, 2020 and Kagimoto A, ATS, 2020) have been reported, both of which demonstrated the SUVmax of ILD lesions as the predictive factor for postoperative AE of ILD, and those results were not consistent with the current study. Authors should discuss these conflicting results and clarify its reason.

Reply 1: Thank you for your comments and suggestions. The discrepancy between our results and those of previous similar studies was believed to be due to patient background. In contrast, Umeda et al. demonstrated that the SUV_{max} in ILD is more concentrated in the UIP pattern with a honeycomb cyst region (1). In the current study, the proportion of ILD patients with the UIP pattern was 23.1%, which was extremely low compared with that mentioned in the following previous reports: the report by Yamamichi et al. was limited to IPF patients with the UIP pattern (2) and the report by Kagimoto et al. included many ILD patients with a probable and definite UIP pattern, accounting for 80.8% (3). Additionally, the median %DLco was 64.8% in this study, which was better than that in a previous report by Kagimoto et al. These two factors may have affected the results of the current study. Accordingly, we added and corrected the following sentence in the discussion section of the manuscript.

<reference>

(1) Akaike K, Saruwatari K, Oda S, et al. Predictive value of (18)F-FDG PET/CT for acute exacerbation of interstitial lung disease in patients with lung cancer and interstitial lung disease treated with chemotherapy. *Int J Clin Oncol* 2020;25:691-90.

(2) Yamamichi T, Shimada Y, Masuno R, et al. Association between F-18 fluorodeoxyglucose uptake of noncancerous lung area and acute exacerbation of interstitial pneumonia in patients with lung cancer after resection. *J Thorac Cardiovasc Surg* 2020;159:1111-8.e2.

(3) Kagimoto A, Tsutani Y, Handa Y, et al. Prediction of acute exacerbation of interstitial pneumonia using visual evaluation of PET. *Ann Thorac Surg* 2021;112:264-70.

Changes in the text: Page 15, lines 280–289 ‘However, there were no significant differences in the correlation between the SUV_{max} of contralateral interstitial lesions and pAE-ILD, in contrast to previous similar reports (24,25) and our previous study on LC

patients with ILD treated with chemotherapy (10). The reason for the discrepancy in the former observation is believed to be the higher ^{18}F -FDG accumulation in interstitial lesions of ILD patients with the UIP pattern with honeycomb cysts than in ILD patients with the non-UIP pattern, as reported by Umeda et al. (26). Compared to previous reports, our study may have included more mild cases with fewer UIP patterns on chest CT and fewer instances of low pulmonary function, such as higher %DLco. Additionally, two possible reasons may explain the discrepancy between our current and previous results:?

Reviewer D

The authors investigated the significance of SUVmax of interstitial lesions on postoperative and concluded it was not a predictor of the event.

About this field, Japanese nation-wide database study by Dr. Sato et al. developed risk scoring system for the prediction of AE. Unfortunately, it is difficult for us to find new findings or value in this study to add to the previous report.

Major comments

Comment 1. In the study, Postoperative AE was occurred only in eight patients and it is difficult to prove statistical significance for this small number of events. If it was proved, the authors need to solve the problem of confounding with various other factors.

Reply 1: Thank you for this comment and suggestion. As indicated, this was a single-centre, small-scale study; thus, there were limitations in proving statistical significance. We have stated this in the limitation section. In the future, we plan to investigate confounding factors in large-scale studies. The changes are made on Page 17, Line 318–326.

Comment 2. The authors showed positive correlation between SUVmax and LDH, KL-6, %DLCO and %FVC in Figure 3. However, measuring these elements is relatively easy and we do not need to speculate them from SUVmax of interstitial lesions in our practice. Therefore, it has little clinical importance.

Reply 2: Thank you for your valuable comment. As you pointed out, it is relatively easy to assess factors such as KL-6 and pulmonary function test, and it may not be meaningful to investigate the association between SUV_{max} and these elements in the real-world clinical practice. However, in this study, although SUV_{max} was not associated with pAE-ILD, SUV_{max} was associated with AE-ILD 30 days postoperatively. Therefore, we have described the association of SUV_{max} with these elements to corroborate that SUV_{max} reflects the disease activity of ILD. We would appreciate your consideration.

Comment 3. Among the results which the authors described, however, most notable finding was that SUVmax of interstitial lesions was associated with postoperative AE in the remote postoperative period.

Small number of events, but statistically significant difference shown.

There are few studies on AE in the remote period after lung surgery. I recommend the

author should focus on the late-onset event and re-investigate about it.

Other factors which potentially affect AE in the remote period need to be also estimated with SUV_{max} of interstitial lesions.

Reply 3: Thank you for this comment. In this study, we additionally compared SUV_{max} between the AE-ILD and non-AE-ILD groups after 30 days postoperatively. SUV_{max} was significantly higher in the AE-ILD group than in the non-AE-ILD group, and this result was included in Supplementary Figure 3.

As shown in the table below, we additionally examined postoperative chemotherapy and chemotherapy at postoperative recurrence for confounders to AE-ILD during this observation period after 30 days postoperatively and found no significant differences between the AE-ILD and non-AE-ILD groups. In the future, we plan to investigate the relationship between late-onset AE-ILD and SUV_{max} and the confounders to AE-ILD in large-scale studies.

Comparison of clinicopathological factors between the AE-ILD and non-AE-ILD groups after 30 days postoperatively

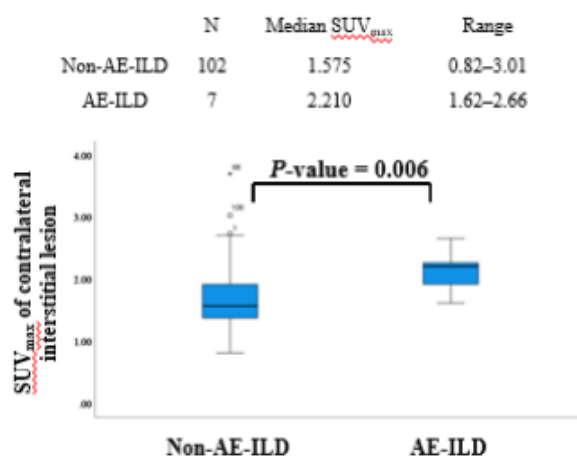
		Non-AE-ILD (N = 102)		AE-ILD (N = 7)		P-value
		N	%	N	%	
Postoperative chemotherapy	Yes/No	9/93	8.8/91.2	2/5	28.6/71.4	0.147
Chemotherapy at postoperative recurrence of lung cancer	Yes/No	10/92	9.8/90.2	2/5	28.6/71.4	0.171

ILD interstitial lung disease, AE acute exacerbation

Changes in the text: Page 12, lines 234–236 ‘Additionally, the median SUV_{max} of contralateral interstitial lesions in the AE-ILD group after 30 days postoperatively was significantly higher than that in the non-AE-ILD group (2.210 vs 1.575, P = 0.006; Supplementary Figure 3)’.

Changes in Supplementary Figure 3

Supplementary figure 3. Correlation between SUV_{max} of contralateral interstitial lesions and the incidence of AE-ILD after 30 days postoperatively.



Note to the Editor

Finally, since we noticed unclear sentence, we additionally corrected and changed the following the gray highlighted words in the sentences:

Abstract section

Page 4, lines 69-73: ‘**Methods:** Overall, 117 consecutive lung cancer patients with interstitial lung disease who underwent pulmonary resection between August 2010 and April 2019 at the Kumamoto University Hospital were retrospectively analysed for the association between the maximum standardized uptake value of the contralateral interstitial lesions and interstitial lung disease parameters.’

Page 4-5, lines 84-87: ‘and the incidence rate of acute exacerbation of interstitial lung disease was significantly higher in the high maximum standardized uptake value group (≥ 1.61) than in the low maximum standardised uptake value group (< 1.61) (12.7% vs. 0%, $P = 0.002$, Gray’s test).’

Page 5, lines 88-91: ‘**Conclusions:** Maximum standardized uptake value was not a predictor of postoperative acute exacerbation of interstitial lung disease in lung cancer patients with interstitial lung disease after pulmonary resection, but could be a predictive tool of an association with interstitial lung disease severity and activity markers.’

Methods section

Page 8, lines 135-139: ‘Their baseline demographic and clinical parameters before lung resection were obtained from medical records, and the following parameters being included: age, sex, Eastern Cooperative Oncology Group (ECOG) performance Status (PS), smoking status, medical history of ILD, histology, pathological stage, laboratory test results, pulmonary function, and surgical procedure type.’

Page 9, lines 161-162: ‘new bilateral alveolar infiltrates regardless of the extent of the segment on CT findings,’

Page 10, lines 178-180: ‘The highest ^{18}F -FDG uptake was measured by a circular region-of-interest with a fixed diameter of approximately 30 mm on PET images corresponding to the interstitial lesion region on CT and defined as SUV_{max} (Figure 1).’

Results section

Page 11, lines 197-200: ‘The ECOG PS was 0-1 in 114 patients (97.4%) and 112 (95.7%) patients were smokers. In the histological type, adenocarcinoma, squamous cell carcinoma, and small cell carcinoma accounted for 49 (41.9%), 47 (40.2%), and nine (7.7%) patients, respectively.’

Discussion section

Page 13, lines 239-241: ‘This study aimed to examine whether SUV_{max} (calculated from the ^{18}F -FDG PET/CT images) of contralateral interstitial lesions was a predictive factor for pAE-ILD in LC patients with ILD who underwent pulmonary resection.’.

Page 13, lines 246-249: ‘This result suggests that SUV_{max} of contralateral interstitial lesions may be a marker of the severity and activity of ILD, and supports the decision to perform surgery for LC in those patients, considering the risk of developing AE-ILD in the future.’.

Page 16, lines 300-302: ‘AE-ILD was detected in long-follow-up periods (the occurrence of AE-ILD from the first administration of chemotherapy to the time of death regardless of the cause or the last follow-up).’.

Page 16-17, lines 307-311: ‘The mechanism of ^{18}F -FDG accumulation in interstitial lesions may involve fibroblast cells stimulated by transforming growth factor- β (TGF- β). Previous reports had demonstrated that the TGF- β -stimulated fibroblast cells have increased glucose transporter-1 at the cell membrane and active metabolism, which leads to increased ^{18}F -FDG uptake in interstitial lesions on PET image.’.

Page 17, lines 311-314: ‘Additionally, TGF- β -stimulated fibroblast cells not only produce excessive collagen type-1, which contributes to the progression of pulmonary fibrosis, but also release cytokines, such as IL-6, and produce inflammatory changes in the lung microenvironment.’.

Page 17, lines 315-317: ‘Thus, the ^{18}F -FDG accumulation in interstitial lesions might represent an increase in TGF- β -stimulated fibroblast cells, which might reflect a pulmonary microenvironment with increased fibrosis and inflammation.’.

Page 17, lines 318-320: ‘This study had several limitations. First, this study was retrospectively conducted at a single institution among the Japanese population only. Moreover, there was a risk of bias because of the nature of the retrospective study.’.

Page 17, lines 323-326: ‘Third, several clinical variables such as LDH and KL-6 were elevated because of the activity of interstitial pneumonia and cancer progression. Therefore, the study results should be interpreted with caution, and large-scale, multi-centre, prospective studies are required to analyse these findings.’.

Figure section

Figure 1 and 2: we changed ‘(a), (b), (c), and (d)’ to ‘(A), (B), (C), and (D)’.