BMC Pulmonary Medicine

RESEARCH

Open Access

Predictors for acute exacerbation of interstitial pneumonia following lung cancer surgery: a multicenter study

Lijie Yin[1], Rui Xu[1], Xiaojian Liu[1], Liping Fu[1*] and Guangliang Qiang[2*]

Abstract

Background Acute exacerbation (AE) of interstitial lung disease (ILD) is one of the most serious complications during perioperative period of lung cancer resection. This study aimed to investigate the correlation between preoperative 2- deoxy-2-[18F]fluoro-D-glucose (^{18}F-FDG) PET/CT findings and AE in lung cancer patients with ILD.

Methods We retrospectively reviewed the data of 210 patients who underwent lung resection for non-small cell lung cancer. Relationships between clinical data and PET images and AE were evaluated. The patients were divided into an AE(+) and an AE(-) group for multivariate logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was conducted and the area under curve (AUC) was used to assess the predictive values.

Results Among 210 patients, 48 (22.8%) were diagnosed with ILD based on chest CT. Among them, 9 patients (18.75%) developed AE after lung resection and were defined as AE(+) group. The course of ILD was longer in AE(+) group compared to AE(-) group. More patients in AE(+) group had a history of AE and chronic obstructive pulmonary disease (COPD) than in AE(-) group. The maximum standardized uptake value (SUVmax) of the noncancerous interstitial pneumonia (IP) area and cancers in AE(+) group was significantly higher compared to AE(-) group. Univariate logistic regression analysis showed that AE, COPD, SUVmax of the noncancerous IP area, SUVmax of cancer, surgical method were significantly correlated with AE. The course of ILD[OR(95%CI) 2.919; $P=0.032$], SUVmax of the noncancerous IP area[OR(95%CI) 7.630;$P=0.012$] and D-Dimer level[OR(95%CI) 38.39;$P=0.041$] were identified as independent predictors for AE in patients with ILD after lung cancer surgery. When the three indicators were combined, we found significantly better predictive performance for postoperative AE than that of SUVmax of the noncancerous IP area alone [0.963 (95% CI 0.914-1.00); sensitivity, 100%, specificity 87.2%, $P<0.001$ vs. 0.875 (95% CI 0.789 ~ 0.960); sensitivity, 88.9%, specificity, 76.9%, $P=0.001$; difference in AUC = 0.088, Z = 1.987, $P=0.04$].

Conclusion The combination of the course of ILD, SUVmax of the noncancerous IP area and D-Dimer levels has high predictive value for the occurrence of AE in patients with concomitant interstitial lesions.

Keywords PET-CT, Interstitial lung disease, Risk factors, Lung cancer, Acute exacerbation

*Correspondence:
Liping Fu
flp39@163.com
Guangliang Qiang
pkudd@126.com

[1]Department of Nuclear Medicine, China-Japan Friendship Hospital, Beijing, China
[2]Department of Thoracic Surgery, Peking University Third Hospital, Beijing, China

Introduction

Interstitial lung disease (ILD) is a general term for a group of diffuse lung diseases that mainly involve the lung interstitium and alveolar cavity, leading to the impairment of alveolar-capillary functional units. ILD is characterized by progressive exacerbation of breathing difficulties, restrictive ventilation dysfunction, and diffuse dysfunction. ILD has been shown to share similar risk factors and pathophysiological mechanisms with lung cancer [1, 2]. Notably, ILD is frequently observed in patients with lung cancer, and it is important to develop strategies for the treatment of ILD [3, 4].

AE of ILD (AE-ILD) is one of the most serious complications during the perioperative period of lung cancer with ILD (LC-ILD). Procedures such as bronchoscopy, endoscopic treatment, lung resection, chest radiation therapy, and some medications have been identified as potential triggers for AE-ILD. A multicenter retrospective study reported that the incidence of postoperative AE-ILD in lung cancer patients with ILD was 9.3% with 95% confidence interval (CI) of 8.0-10.8, and AE-ILD was characterized by rapidly progressing dyspnea and audible Velcro rales in the lungs [5]. High-resolution computed tomography (HRCT) shows new ground-glass opacities and/or consolidations superimposed on usual interstitial pneumonia (UIP), often necessitating treatment with high-dose glucocorticoid or combined immunosuppressive therapy, with a mortality rate as high as 30–100% [5–7]. Therefore, identifying the risk factors for AE-ILD following lung cancer resection is of great significance for surgeons to weigh the pros and cons of surgery and prevent postoperative AE. Although previous studies have identified some risk factors for AE-ILD following lung cancer resection, such as surgical methods, lung function, gender, tumor location, CT features, ^{18}F-FDG maximum standardized uptake value (SUVmax) of the noncancerous interstitial pneumonia (IP) area, and the perioperative changes in neutrophil-to-lymphocyte ratio (ΔNLR), the conclusions remain inconsistent [6–8]. Moreover, there are currently limited literatures on the predictive value of various factors for AE occurrence. Therefore, in this study we aimed to investigate whether the visual evaluation of FDG accumulation in the noncancerous IP area is a predictive factor for AE-ILD after lung resection and whether the combination of multiple predictive factors enhances the predictive accuracy for adverse events.

Patients and methods

Patients

We retrospectively reviewed the data of 210 patients who underwent lung resection for non-small cell lung cancer between November 2020 and October 2023. All ILD was diagnosed by high-resolution computed tomography (HRCT). The diagnostic criteria for idiopathic ILD were the 2013 American Thoracic Society and European Respiratory Society Idiopathic Interstitial Pneumonia statement and related updates, including an update regarding the diagnosis of IPF that was released in 2018 [9, 10]. The diagnosis of secondary ILD was based on in a multidisciplinary collaboration, usually including physicians in the departments of respiratory, rheumatology, thoracic surgery, radiology, pathology, and lung biopsy was performed when necessary to identify the etiology of ILD. All patients underwent preoperative ^{18}F-FDG PET/CT scans for lung cancer staging following the protocol described below. The maximum standardized uptake value (SUVmax) of each interstitial lesion, which we identified on the CT images of patients with ILD, was measured using a circular region-of-interest with a fixed diameter of almost 30 mm on PET images, and the value of the lesion where 18F-FDG uptake was the highest was defined as the SUVmax [11, 12]. ^{18}F-FDG PET/ CT images were interpreted independently by two radiologists. We collected data for preoperative demographics, pathological characteristics of tumors, laboratory indicators, complications, and the incidence of AE. AE was diagnosed according to the diagnostic criteria proposed by Collard et al. [13].

^{18}F-FDG PET/CT protocol

Integrated 18F-FDG PET/CT imaging was performed using the Siemens Biograph Vision 600 scanner (Siemens AG, Erlangen, Germany). Patient fasted for 4–6 h, and their height, weight, and blood glucose concentration were measured before receiving an intravenous injection of 185–370 MBq (5–10 mCi) FDG. Approximately 3.7 MBq (0.1 mCi) per kg of body weight of FDG was injected through an antecubital vein, with a dose of 333 MBq (9 mCi) for patients weighing over 90 kg. ^{18}F-FDG was produced by Beijing Atomic High Tech Co., Ltd., with a radiochemical purity of >95%.

Following injection, the patients lay flat for 1 h in a quiet and dark environment and then underwent whole-body PET/CT imaging. Imaging was performed with the patient in a supine position, both arms raised, and involved a CT localization acquisition (tube current: 35 mA, tube voltage: 120 kV), followed by CT and PET acquisitions (SS mode) from the lower edge of the eye socket to the upper middle thigh range. For CT acquisition, automatic tube current regulation technology was utilized, with a tube voltage of 120 kV, a layer thickness of 3.0 mm, and a pitch of 1.0. The SS mode PET collection time for each bed was 1.5 min. PET images were reconstructed using iterative algorithms (ordered subset expectation maximization [OSEM] algorithm, 2 iterations, 5 subsets, matrix 440×440).

Statistical analysis

Statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, Illinois, USA) and MedCalc for Windows, Version 14.8.1 (MedCalc Software, Mariakerke, Belgium). A P-value < 0.05 was considered statistically significant. Data were expressed as mean ± standard deviation. Student's t-test or Welch's t-test was used for parametric data. Mann-Whitney U test was used for nonparametric data. Fisher's exact test or the chi-square test was performed for categorical values. Logistic regression analysis was used to identify the predictive factors for AE of the noncancerous IP area after lung cancer surgery. PET/CT and clinical variables with P values less than 0.05 in the univariate analyses were included in the multivariate analyses. Receiver operating characteristic (ROC) curve was generated using the predicted probability obtained from the logistic regression model, and the area under curve (AUC) was used to assess the predictive values of FDG PET/CT imaging and clinical variables. Statistical significance of the improvement in AUC after adding an explanatory factor was evaluated using the Delong test [14].

Results

Patient characteristics and imaging features

A total of 210 patients underwent pulmonary resection of non-small cell lung cancer. Among them, 48 patients (22.8%) were diagnosed with ILD based on chest CT findings, including 37 (77.1%) males and 11 (22.9%) females, with a mean age of 66.9 ± 7.8 years and a median age of 67 years. Following lung resection, 9 patients (18.75%) developed AE (AE(+) group) while 48 patients (81.25%) did not develop AE (AE(-) group). According to the WHO 2021 pathological classification [15], there were 30 cases of adenocarcinoma, 14 cases of squamous cell carcinoma, and 4 other cases (2 cases of sarcomatoid carcinoma and 2 cases of large cell neuroendocrine carcinoma). Figure 1 presents a typical case of a 55-year-old man who showed high SUVmax (5,8) in the ILD area in the preoperative18F-FDG PET/CT scan. The patient

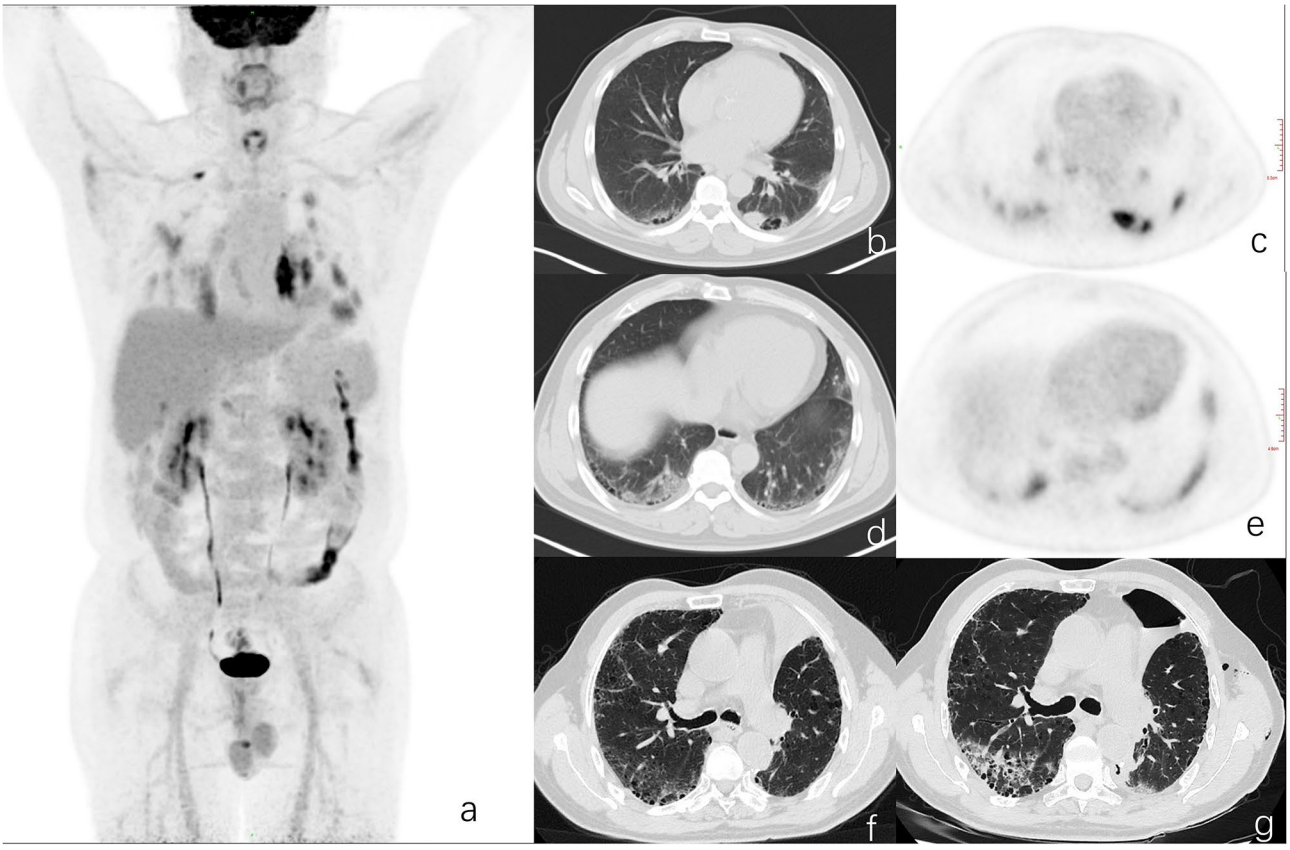

Fig. 1 A typical case with high FDG uptake in the idiopathic interstitial pneumonia area on 18 F-FDG PET/CT. The patient was a 55-year-old man who underwent left lower lobectomy with lymph node dissection via video-assisted thoracoscopic surgery for adenocarcinoma and respiratory distress on postoperative day 40 due to postoperative acute exacerbation. (**a**) A MIP PET image. (**b**, **d**) preoperative chest CT.(**c**, **e**) preoperative 18 F-FDG PET/CT. (**f**, **g**) preoperative and postoperative day 40 image. Preoperative chest CT showed peripheral reticular opacities and ground glass located in the lung bases(white arrow). Hight FDG uptakes were observed in the areas, and the maximum standardized uptake value (SUVmax) was 5.8. The lung tumor was located in the left lower lobe and 18 F-FDG uptake matched to the location was observed(black arrow). Newly formed reticular opacities were observed not only in the left lung base but also in the left upper lobe as well as in the right residual lobes(arrow head)

underwent right lower lobectomy with lymph node dissection via video-assisted thoracoscopic surgery for adenocarcinoma. The post operative pathological diagnosis of ILD was usual interstitial pneumonia (UIP). He developed postoperative AE on post operative day 40.

91.7% (44/48) of the patients were diagnosed with idiopathic ILD of unknown etiology, including 35 cases of IPF, 8 cases of NSIP, and 1 case of desquamative interstitial pneumonia. One case of patient was diagnosed with hypersensitivity pneumonitis. 6.2% (3/48) of the patients were diagnosed with CTD-ILD, including rheumatoid arthritis in 2 cases, Sjogren syndrome in 2 cases. The clinical, PET, and pathological characteristics of the patients are shown in Tables 1 and 2.

Notably, the course of ILD of AE (+) group was longer than that of AE (-) group. More patients in the AE (+) group had a history of AE and COPD than in the AE (-) group. The SUVmax of the noncancerous IP area and cancers in the AE (+) group were significantly higher compared with the AE (-) group. There were no significant differences in age, gender, smoking pack-years, Type and extent of ILD, body mass index (BMI), pathological type, clinical staging of lung cancer, inflammatory markers, or the perioperative changes between AE (+) and AE (-) groups.

Predictive factors for AE

We performed multivariate logistic regression analysis for clinical and PET/CT variables that were significantly associated with conversion status in the univariate analysis. In univariate analysis, we found that factors such as AE, COPD, SUVmax of the noncancerous IP area, SUVmax of cancer, surgical method were significantly correlated with AE. After the adjustment for other clinical and imaging features, the course of ILD, SUVmax of the noncancerous IP area and D-Dimer were identified as the independent predictors for AE in ILD patients after lung cancer surgery. The results are shown in Table 3.

Table 1 Patient's clinical characteristics

Characteristic	AE(-) (*n* = 39)	AE(+) (*n* = 9)	T Value	χ2	Z Value	*P* value
Age(y)	66.83 ± 7.2	68.73 ± 7.9	-0.457			0.653
				0.021		0.885
≥ 65	25	6				
< 65	14	3				
Sex				2.915		0.088
Female	10	0				
Male	29	9				
Smoking history				1.114		0.286
No	11	1				
Yes	28	8				
Preoperative comorbidity						
History of AE				9.063		0.003*
No	38	6				
Yes	1	3				
COPD				14.928		<0.001*
No	37	4				
Yes	2	5				
Asthma				1.338		0.247
No	38	8				
Yes	1	1				
Type of ILD				1.747		0.627
IPF	27	8				
NISP	7	1				
CTD-ILD	3	0				
Other types	2	0				
Extent of ILD				2.462		0.117
Localized distribution	28	4				
Diffuse distribution	11	5				
Course of ILD	0.7 ± 1.4	5.0 ± 9.6	-2.757			0.008*
BMI	24.2 ± 3.5	23.6 ± 3.0	0.490			0.628

BMI: body mass index; COPD: chronic obstructive pulmonary disease; ILD: Interstitial lung disease

*Statistical significance

Table 2 Preoperative pulmonary PET/CT and Laboratory Data and surgical information

Characteristic	AE(-) (*n* = 39)	AE(+) (*n* = 9)	T Value	χ2	Z Value	*P* value
SUVmax of the noncancerous IP area	1.6 ± 0.8	3.2 ± 1.4	-6.004			<0.001*
SUVmax of cancer	8.9 ± 6.6	14.9 ± 6.5	-3.178			0.002*
Inflammatory marker						
NLR(Preoperative)	3.04 ± 2.37	3.84 ± 3.5			-0.409	0.682
PLR(Preoperative)	132.10 ± 53.82	144.71 ± 91.74			-0.066	0.947
NLR(Postoperative)	13.02 ± 7.75	9.85 ± 7.07			-1.149	0.251
PLR(Postoperative)	235.34 ± 143.62	233.26 ± 133.68			-0.066	0.947
△NLR	9.97 ± 8.43	6.01 ± 4.98			-1.677	0.093
△PLR	103.24 ± 102.71	87.54 ± 86.32			-0.145	0.885
D-Dimer(mg/dl)	0.48 ± 0.5	1.01 ± 0.9			-2.756	0.006*
Surgical operative method				12.03		0.150
Lung wedge resection	21	1				
Lobectomy	18	7				
pneumonectomy	0	1				
Histologic subtype				1.958		0.581
Adenocarcinoma	24	6				
Squamous cell carcinoma	12	2				
Large cell carcinoma	1	1				
Sarcomatoid carcinoma	2	0				
Clinical stage				0.561		0.967
IA1	6	1				
IA2	8	2				
IA3	12	2				
IB	7	2				
IIA	6	2				

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; IP: interstitial pneumonia

*Statistical significance

The ROC curve was constructed with the predicted probability obtained from the logistic regression to compare the predictive value of the course of ILD, SUVmax of the noncancerous IP area and D-Dimer. As shown in Fig. 2, the AUCs for the course of ILD, SUVmax of the noncancerous IP area, and D-Dimer in predicting postoperative AE were [0.764 (95% CI 0.640 ~ 0.887); sensitivity, 88.9, specificity, 46.2, $P=0.001$], [0.875 (95% CI 0.789 ~ 0.960); sensitivity, 88.9, specificity, 76.9, $P=0.001$], and [0.685 (95% CI 0.538 ~ 0.833); sensitivity, 66.7, specificity, 69.2, $P=0.001$], respectively. The optimal threshold values used for the models were as follows: for SUVmax of the noncancerous IP area, 1.85 or greater; for the course of ILD, 0.2 months or greater; for D-Dimer, 0.48 mg/dl or greater. The AUC for the combination of these three indicators was [0.963 (95% CI 0.914-1.00); sensitivity, 100, specificity 87.2, $P<0.001$]. This AUC was significantly superior to that of SUVmax of the noncancerous IP area (difference in AUC = 0.088, Z = 1.987, $P=0.04$, as assessed by DeLong test) (Fig. 3). It is suggested that in patients with concomitant interstitial lesions, the combination of the course of interstitial lung disease, SUVmax of the noncancerous IP area and D-Dimer has high predictive value for the occurrence of AE.

Discussion

In this study we investigated whether FDG PET/CT scans could provide added predictive value to other predictive factors in predicting the occurrence of AE. Multivariate analysis revealed that the course of ILD, SUVmax of the noncancerous IP area and D-Dimer were risk factors for AE-ILD following lung cancer resection. In addition, ROC curve analysis showed that a combination of the three factors outperformed each factor alone in predicting the occurrence of AE.

Lung cancer patients with ILDs undergoing pulmonary resection often develop postoperative AE of interstitial pneumonia [16]. Postoperative AE-ILD is defined as ILD that occurs within 30 days after surgery and cannot be explained by lung infections or other diseases, characterized by symptoms including progressive dyspnea, increasing interstitial shadows on chest CT or X-ray, and a decrease in blood oxygen partial pressure by >10 mmHg [6, 17]. Sato et al. [16] developed a risk score system to assess individual risk for AE. In this system, the history of preoperative AE was proved to be the most

Table 3 Univariate and multivariate logistic analysis of the predictors of AE after lung cancer surgery

Variable	Univariate					Multivariate				
	β	S.E.	Wald	OR(95%CI)	*P* Value	β	S.E.	Wald	OR(95%CI)	*P* value
Age(y)	0.008	0.047	0.029	1.008(0.919 ~ 1.106)	0.864					
Sex	-1.015	1.122	0.818	0.363(0.040 ~ 3.270)	0.366					
Smoking history	1.145	1.119	1.048	3.143(0.351 ~ 28.159)	0.306					
History of AE	2.944	1.235	5.68	19(1.68 ~ 213.975)	0.017*	1.762	1.477	1.422	5.823(0.322~105.350)	0.233
COPD	3.141	0.988	10.097	23.125(3.332 ~ 160.490)	0.001*	-2.725	1.925	2.004	0.066(0.002~2.851)	0.066
Asthma	1.558	1.467	1.129	4.75(0.268 ~ 84.175)	0.288					
Type of ILD	-1.096	0.942	1.353	0.334(0.053 ~ 2.119)	0.245					
Extent of ILD	1.157	0.759	2.323	3.182(0.718 ~ 14.094)	0.127					
Course of(m)ILD	0.522	0.224	5.436	1,685(1.087 ~ 2.613)	0.020*	1.071	0.501	4.577	2.919(1.094~7.789)	0.032*
BMI	-0.059	0.119	0.248	0.943(0.747 ~ 0.119)	0.618					
SUVmax of the non-cancerous IP area	1.251	0.438	8.148	3.493(1.480 ~ 9.245)	0.004*	2.032	0.808	6.318	7.630(1.565~37.206)	0.012*
SUVmax of cancer	0.111	0.057	10.651	1.117(0.999 ~ 1.249)	0.042*	0.081	0.101	0.652	1.085(0.891~1.321)	0.419
NLR (Preoperative)	0.058	0.093	0.389	1.060(0.883 ~ 1.271)	0.533					
PLR (Preoperative)	0.003	0.006	0.308	1.003(0.992 ~ 1.014)	0.579					
NLR (Postoperative)	-0.078	0.070	1.248	0.925(0.807 ~ 1.061)	0.264					
PLR (Postoperative)	0.000	0.003	0.004	1.000(0.995 ~ 1.005)	0.953					
△NLR	-0.081	0.061	1.783	0.922(0.819 ~ 1.039)	0.182					
△PLR	-0.001	0.004	0.135	0.999(0.992 ~ 1.006)	0.713					
D-Dimer (mg/dl)	1.569	0.638	6.052	4.801(1.376 ~ 16.754)	0.014*	3.648	1.787	4.167	38.39(1.157~1274.442)	0.041*
Surgical operative method	2.380	1.072	4.927	10.803(1.321 ~ 88.347)	0.026*	7.457	5.134	2.109	1731.87(0.074 ~ 4062.747)	0.146
Histologic subtype	-0.123	0.511	0.058	0.884(0.325 ~ 2.405)	0.809					
Clinical stages	0.151	0.291	0.271	1.163(0.658 ~ 2.057)	0.602					

*Statistical significance

weighted factor. While the etiology of AE remains partially understood, known risk factors and triggers include advanced disease, infection, and a previous history of AE [18, 19]. Our findings highlighted that those with history of AE in their course of disease were highly likely to develop AE after pulmonary resection (3/4). Although the history of AE was not identified as a predictor for AE in our study (OR: 5.823; 95% CI: 0.322–105.35; $P=0.233$), careful consideration should be given to the surgical indication for this group of patients, considering the notably poor prognosis associated with a history of AE.

Diffuse pulmonary interstitial disease is a group of diseases characterized by chronic inflammation and interstitial fibrosis, mainly involving the alveolar wall and adjacent supportive structures. Most ILD lesions involve not only the lung interstitium, but also the lung parenchyma (alveolar cavity, alveolar epithelial cells), pulmonary capillary endothelial cells, and bronchioles. As a result, pulmonary parenchymal changes such as alveolitis and protein leakage from the alveolar cavity may occur. When the inflammation of the alveolar wall further develops, it affects the interstitial tissue and leads to irreversible pulmonary interstitial fibrosis (PIF) [20]. An important subset of patients with fibrotic ILD experiences a decline in lung function with progressive symptoms, poor response to treatment, and reduced quality of life [21]. Furthermore, lung function tends to deteriorate in patients with idiopathic pulmonary fibrosis despite treatment [2].

It is widely recognized that low forced vital capacity, low diffusion capacity, and baseline hypoxemia are the most consistent risk factor for the exacerbation of IPF [22]. Due to the retrospective nature of this study, we did not follow up on lung function parameters in all patients. However, we observed that the patients in the AE(+) group had a longer history of ILD than the AE(-) group. It is possible that some patients with long-term ILD in our study should be classified as having progressive fibrosing ILD (PF-ILD) and have poor lung function, suggesting that the history of ILD may serve as a predictive factor for AE. However, this needs further confirmation by future studies with larger sample size.

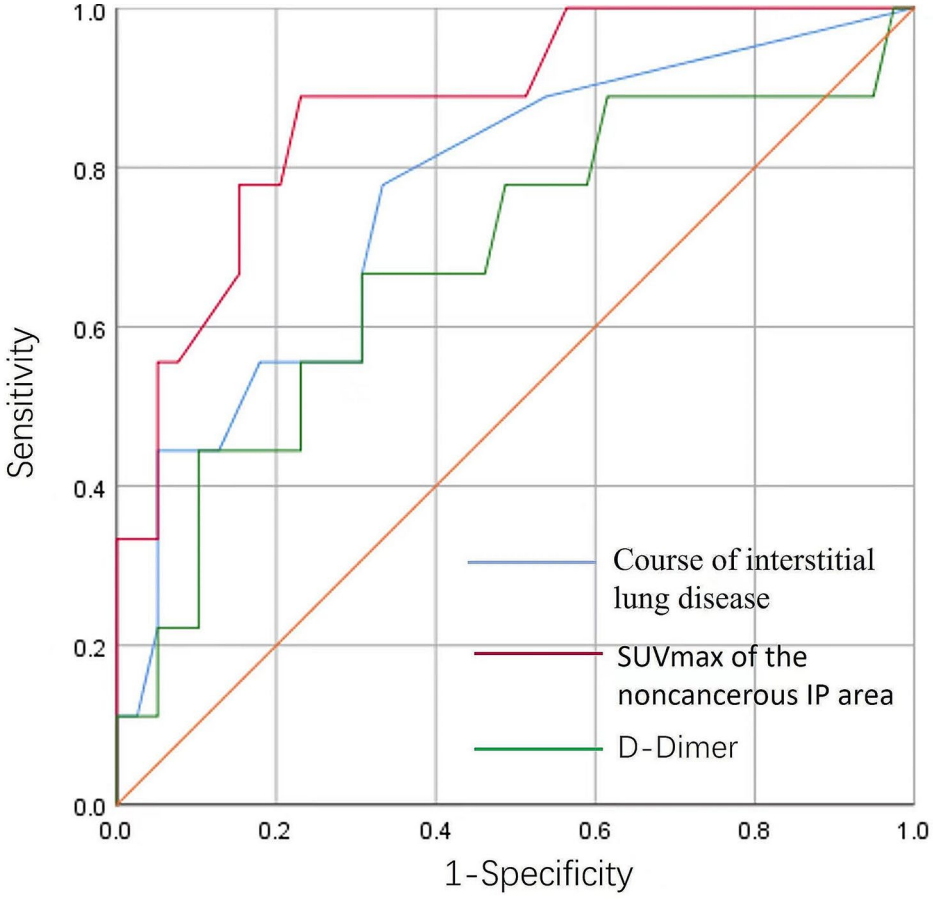

Fig. 2 AUCs for the course of ILD, SUVmax of the noncancerous IP area, and D-Dimer in predicting postoperative AE.

PET imaging, as a functional imaging modality, can reflect the physiological, pathological, and biochemical metabolic changes in human tissues. 18 F-FDG is a glucose analogue imaging agent widely used in PET/CT imaging of tumors and inflammatory diseases. Increased uptake of 18 F-FDG in patients with pulmonary fibrosis is caused by fibrotic lung injury, which leads to neovascularization and an increase in red blood cells and inflammatory cells (neutrophils and macrophages) [12]. Both red blood cells and inflammatory cells express glucose transporter 1, resulting in increased glucose metabolism in fibrotic lungs [23]. Kagimoto et al. [8] demonstrated that the accumulation of FDG in the IP area was a significant risk factor for AE of IP. Similarly, Oishi et al. found that in the AE(+) group, the SUVmax of F-FDG in the idiopathic interstitial pneumonia (IIP) area was significantly higher compared with that in the AE(-) group [24]. Akaike et al. reported that the SUV of contralateral interstitial lesions trended towards significant association with the onset of AE-ILD [22]. In our study, we found that the SUVmax of the noncancerous IP area in the AE(+) group was significantly higher compared with the AE(-) group (3.2±1.4 vs.1.6±0.8, $P<0.001$). Univariable logistic regression analyses showed that the SUVmax of the noncancerous IP area trended towards significant association with the onset of AE-ILD [OR: 7.63, 95% CI: 1.565–37.206, $P=0.012$]. The AUC of the SUVmax of the noncancerous IP area for AE were [0.875 (95% CI 0.789 ~ 0.960); sensitivity, 88.9, specificity, 76.9, $P=0.001$]. Although the SUVmax of cancer was higher with vs. without AE-ILD, it was not the predictive factors for AE-ILD. Consistent with current literature, squamous cell carcinoma (SCC) is the most common histologic subtype in patients with IPF [25], but our study showed that most common histology was adenocarcinoma, followed by SCC, same as the findings reported by Héluain et al. [26]. Previous study indicated significantly higher glucose transporter 1 expression in SCC compared to adenocarcinoma, in both primary tumors and lymph node metastasis [27]. Additionally, the mean SUVmax of the tumors was significantly higher in SCC lesions than in AC lesions [28, 29]. In our study, there were 30 patients with ACC (6 with AE) and 14 patients with SCC (2 with AE). The histologic subtype subtypes of AE(+) and AE(-) groups were not statistically significant, which may be the reason why SUVmax of cancer was not a predictive factor for AE.

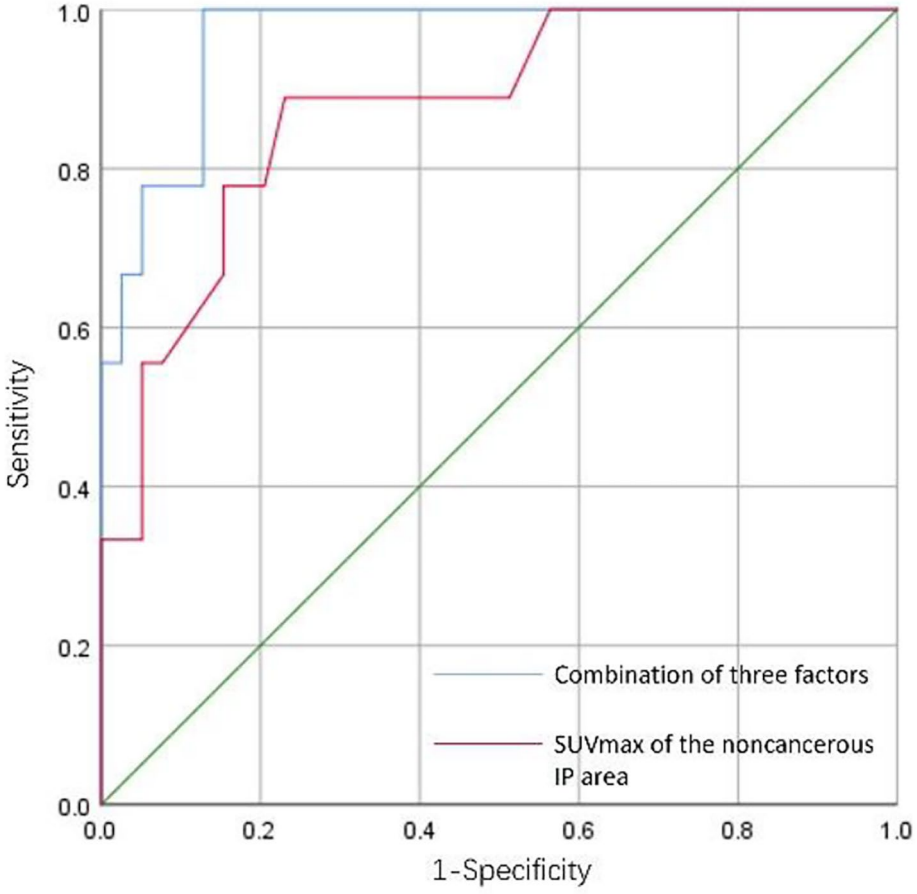

Fig. 3 AUCs for the combination of the course of ILD, SUVmax of the noncancerous IP area, and D-Dimer vs. SUVmax of the noncancerous IP area in predicting postoperative AE.

The symptoms of ILD are usually accompanied by vascular damage and strong reactions to various inflammations. Recently, the bidirectional relationship between inflammation and thrombosis is well established [30]. Due to the procoagulant factors in the endothelial tissue of the human body, the endothelial cells are usually exposed to the outside after damage, and the coagulation system is gradually activated [31]. During the activation process, the value of D-Dimer will continuously increase. Several studies indicate that a high D-Dimer level is associated with an increased risk of developing AE within three months of measurement [32, 33]. Ishikawa et al. showed that elevated D-Dimer level was a risk factor for the development of AE-ILD [32]. In our cohort, we observed that ILD patients tend to have comorbidities such as COPD. Increasing evidence suggests a hypercoagulable state in COPD, involving changes in a variety of coagulation factors, including a sudden increase in blood D-Dimmer levels [34, 35]. Similarly, in our study D-Dimer level in the AE(+) group was higher than that in the AE(-) group and D-Dimer emerged as an important predictive factor for AE (OR: 38.29), with the mean D-dimer values in the AE(+) and AE(-) groups being 1.01 ± 0.9 and 0.48 ± 0.5 mg/L, respectively, with an optimal cut off point of 0.56 mg/L.

In our study, the course of ILD, SUVmax of the noncancerous IP area, and D-Dimer were associated with AE in patients with ILD post-surgery. The AUC values for the course of ILD, SUVmax of the noncancerous IP area, and D-Dimer for predicting postoperative AE were 0.764, 0.875, and 0.685, respectively. The AUC of SUVmax of the noncancerous IP area as a predictive factor for predicting AE occurrence was slightly higher than that in previous studies [7, 36]. Our study conducted a ROC curve analysis to compare PET scans alone and the combination of three factors (the course of ILD, SUVmax of the noncancerous IP area, and D-Dimer) for predicting AE. It revealed that the combination of these three factors had better predictive performance than PET alone, particularly by improving specificity and sensitivity. Our findings demonstrate that in patients with concomitant interstitial lesions, the combination of the course of ILD, SUVmax of the noncancerous IP area and D-Dimer has high predictive value for predicting the occurrence of AE.

This study has some limitations. First, all the included studies were retrospective in nature, so there may be some bias that cannot reflect the actual situation of all patients. Second, the sample size was small, potentially resulting in a lack of precision, widening 95% CIs in risk estimates. The number of AE(+) patients was only nine. The small sample size may also contribute to the non-significance of previously established predictor factors in multivariate analysis in this study. The sample size of this study is small and does not meet the requirements of EPV (Event Per Variable). Therefore, the results may not be robust enough. However, considering that patients with AE are relatively rare and the results have some interpretability, they will still be presented. Further studies are needed to confirm the reliability of our results.

Conclusion

In conclusion, the course of ILD, SUVmax of the noncancerous IP area and D-Dimer levels are predictive factors for AE in patients with ILD undergoing lung cancer surgery. Considering these three factors may help reduce the risk of AE in these patients.

Author contributions

Conception and design: Yin LJ; (II) Administrative support: Qiang GL, Fu LP; (III) Provision of study materials or patients: Liu XJ, Qiang GL; (IV) Collection and assembly of data: Yin LJ, Xu R; (V) Data analysis and interpretation: Yin LJ, Qiang GL, Fu LP; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Funding

This work was supported by the Key Clinical Projects of Peking University Third Hospital (Grant No. BYSYRCYJ2023001).

Data availability

The data that support the findings of this study are available from the authors but restrictions apply to the availability of these data, which were used under license from the Ethics Committee of Peking University Third Hospital for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from Peking University Third Hospital.

Declarations

Ethical approval

This study was approved by Ethics Committee of Peking University Third Hospital and conducted in accordance with the 2000 Declaration of Helsinki. Due to the observational nature of this study, the need for informed consent was waived by the Ethics Committee of Peking University Third Hospital in accordance with the local legislation and institutional requirements.

Consent

N/A.

Competing interests

The authors declare no competing interests.

Received: 7 May 2024 / Accepted: 22 July 2024
Published online: 01 August 2024

References

1. Artinian V, Kvale PA. Cancer and interstitial lung disease. Curr Opin Pulm Med. 2004;10(5):425–34.
2. Richeldi L, Collard HR, Jones MG. Idiopathic Pulmonary Fibros Lancet. 2017;389(10082):1941–52.
3. Choi WI, et al. Interstitial lung Disease and Lung Cancer Development: a 5-Year Nationwide Population-based study. Cancer Res Treat. 2018;50(2):374–81.
4. Barczi E, et al. Impact of interstitial lung disease and simultaneous lung cancer on therapeutic possibilities and survival. Thorac Cancer. 2020;11(7):1911–7.
5. Sato T, et al. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. J Thorac Cardiovasc Surg. 2014;147(5):1604–e16113.
6. Hao X, et al. Risk factors for acute exacerbation of interstitial lung disease following lung cancer resection: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2022;34(5):744–52.
7. Ozawa Y, et al. Preoperative CT findings for Predicting Acute Exacerbation of interstitial pneumonia after Lung Cancer surgery: a Multicenter Case-Control Study. AJR Am J Roentgenol. 2021;217(4):859–69.
8. Kagimoto A, et al. Prediction of Acute Exacerbation of interstitial pneumonia using visual evaluation of PET. Ann Thorac Surg. 2021;112(1):264–70.
9. Raghu G, et al. Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44–68.
10. Travis WD, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733–48.
11. Akaike K, 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(4):681–90.
12. Yoon HY, et al. The value of (18)F-FDG PET/CT in evaluating Disease Severity and Prognosis in Idiopathic Pulmonary Fibrosis patients. J Korean Med Sci. 2021;36(41):e257.
13. Collard HR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2007;176(7):636–43.
14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837–45.
15. Nicholson AG, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. J Thorac Oncol. 2022;17(3):362–87.
16. Sato T, et al. A simple risk scoring system for predicting acute exacerbation of interstitial pneumonia after pulmonary resection in lung cancer patients. Gen Thorac Cardiovasc Surg. 2015;63(3):164–72.
17. Homma S, et al. Japanese guideline for the treatment of idiopathic pulmonary fibrosis. Respir Investig. 2018;56(4):268–91.
18. Kim HH, et al. Clinical impact of pre-existing acute exacerbation in patients with interstitial lung disease who underwent lung transplantation. Respir Res. 2023;24(1):307.
19. Song JW, et al. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. 2011;37(2):356–63.
20. Barkas GI, Daniil Z, Kotsiou OS. The role of small Airway Disease in Pulmonary Fibrotic diseases. J Pers Med, 2023. 13(11).
21. Wong AW, Ryerson CJ, Guler SA. Progression of fibrosing interstitial lung disease. Respir Res. 2020;21(1):32.
22. Atkins CP, Loke YK, Wilson AM. Outcomes in idiopathic pulmonary fibrosis: a meta-analysis from placebo controlled trials. Respir Med. 2014;108(2):376–87.
23. El-Chemaly S, et al. Glucose transporter-1 distribution in fibrotic lung disease: association with [^{18}F]-2-fluoro-2-deoxyglucose-PET scan uptake, inflammation, and neovascularization. Chest. 2013;143(6):1685–91.
24. Oishi H, et al. Correlation between preoperative (18)F-FDG PET/CT findings and postoperative short-term prognosis in lung cancer patients with idiopathic interstitial pneumonia after lung resection. Respir Investig. 2021;59(1):106–13.
25. Tzouvelekis A, et al. Lung cancer in patients with idiopathic pulmonary fibrosis. A retrospective multicenter study in Greece. Pulm Pharmacol Ther. 2020;60:101880.
26. Héluain V, et al. Clinical and molecular analysis of lung cancers associated with fibrosing interstitial lung disease. Respir Med Res. 2023;83:100946.

27. Kokeza J et al. The Effect of GLUT1 and HIF-1α expressions on glucose uptake and patient survival in Non-small-cell Lung Carcinoma. Int J Mol Sci, 2023. 24(13).
28. Liu X, et al. Role of multiple dual-phase (18)F-FDG PET/CT metabolic parameters in differentiating adenocarcinomas from squamous cell carcinomas of the lung. Heliyon. 2023;9(10):e20180.
29. Meng N, et al. Quantitative parameters of static imaging and fast kinetics imaging in (18)F-FDG total-body PET/CT for the assessment of histological feature of pulmonary lesions. Quant Imaging Med Surg. 2023;13(9):5579–92.
30. Dutt N, et al. Mortality and its predictors in COVID-19 patients with pre-existing interstitial lung disease. Cureus. 2022;14(8):e27759.
31. Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood. 2019;133(9):906–18.
32. Ishikawa G, et al. Elevated serum D-dimer level is associated with an increased risk of acute exacerbation in interstitial lung disease. Respir Med. 2017;128:78–84.
33. Isshiki T, et al. Recombinant human soluble thrombomodulin treatment for acute exacerbation of idiopathic pulmonary fibrosis: a retrospective study. Respiration. 2015;89(3):201–7.
34. Zheng LL, et al. Correlation of Coagulation Dysfunction with infection and Hypercapnia in Acute Exacerbation of COPD patients. Infect Drug Resist. 2023;16:5387–94.
35. Balaguer C, et al. Effects of simvastatin in chronic obstructive pulmonary disease: results of a pilot, randomized, placebo-controlled clinical trial. Contemp Clin Trials Commun. 2016;2:91–6.
36. Shi S, et al. Correlation between serum bilirubin levels and the severity as well as the prognosis of idiopathic pulmonary fibrosis. Chron Respir Dis. 2020;17:1479973120957676.

Publisher's Note