【 ORIGINAL ARTICLE 】

Predictive Factors for Pneumomediastinum During Management of Connective Tissue Disease-related Interstitial Lung Disease: A Retrospective Study

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Abstract:

Objective   To identify factors associated with pneumomediastinum during management of connective tissue disease (CTD)-related interstitial lung disease (ILD).

Methods   Patients diagnosed with pneumomediastinum after the initiation of corticosteroid therapy for their CTD-ILD were enrolled. The baseline characteristics of patients who developed pneumomediastinum after the initiation of corticosteroid therapy (n=13, all occurring within 120 days) were compared to those of patients who did not develop pneumomediastinum (n=49). A multivariate logistic regression analysis was performed to identify factors associated with pneumomediastinum. A receiver operating characteristic (ROC) curve analysis was also performed to assess the predictive performance.

Results   The body mass index (BMI) [odds ratio (OR) (95% confidence interval (CI)) 0.482 (0.272-0.853)] and serum lactate dehydrogenase (LDH) [OR (95% CI) 1.013 (1-1.025)] levels at baseline were identified as independent factors associated with pneumomediastinum after corticosteroid initiation. The optimal cut-off points of the BMI and LDH levels for predicting pneumomediastinum development, as estimated by the Youden index, were 20.2 kg/m^2 and 378 U/L, respectively. LDH showed a sensitivity of 61.5% and the highest specificity of 87.8%. Importantly, combining these markers resulted in the highest sensitivity of 100% and a specificity of 71.4%.

Conclusion   A low BMI and high serum LDH levels at baseline are useful predictive factors for pneumomediastinum development in CTD-ILD patients.

Key words: pneumomediastinum, air leak syndrome, connective tissue disease, interstitial lung disease, dermatomyositis

Introduction

Pneumomediastinum is defined as the presence of air in the mediastinum with either no primary pathology or as a result of trauma, intrathoracic infections, or aerodigestive tract perforation (1). In addition, pneumomediastinum is associated with a variety of structural lung diseases (2) and patients with idiopathic pulmonary fibrosis (IPF), one of the most common forms of interstitial lung disease (ILD), are at risk (3). Mechanistically, alveolar disruption allows air to enter the interstitial space, leading to dissection along peribronchial sheaths that extends into the mediastinum (3, 4).

In rheumatology, pneumomediastinum has been described

as a rare complication, usually occurring in the presence of ILD (5), and several studies have recently addressed its clinical features in ILD associated with dermatomyositis (DM) and polymyositis (PM) (6-9). Although less frequent than in DM/PM, pneumomediastinum in other connective tissue disease (CTD)-related ILD (CTD-ILD), such as rheumatoid arthritis (RA) (10, 11), systemic lupus erythematosus (SLE) (12) and systemic sclerosis (SSc) (13), has been described in a few case reports. Controversy exists as to whether or not the development of pneumomediastinum itself in these comorbid cases is a prognostic factor. In a recent retrospective cohort study of 25 CTD-pneumomediastinum patients, occurrence was associated with a low cumulative survival rate (1 year: 52%, 2 years: 40%) (5); in contrast, Yoshida et al. (7) investigated the prognosis of pneumomediastinum in DM and reported that the direct cause of death was actually respiratory failure resulting from progressive ILD or infection. They thus concluded that pneumomediastinum itself is never a poor prognostic factor in DM.

The pathogenesis of pneumomediastinum in CTD-ILD might be similar to that in IPF, but unlike cases of IPF, patients with CTD are mainly treated with corticosteroids, the weakening effect of which is likely to contribute to the onset or persistence of pneumomediastinum (14). In fact, the onset of pneumomediastinum in CTD coincides almost directly with corticosteroid therapy, especially after initiation or increasing dosages. Zhang et al. (15) reported 28 patients with CTD complicated by pneumomediastinum, of whom 26 (93%) developed it after steroid therapy. Similarly, among DM patients with pneumomediastinum, the onset was observed during corticosteroid therapy in the majority of cases (19/21; 90%) (7). However, to our knowledge, no published studies have focused on patients after the initiation of corticosteroid therapy for CTD-ILD and investigated the clinical manifestations according to the development of pneumomediastinum.

Therefore, in this study, we retrospectively compared the clinical characteristics between CTD-ILD patients who developed pneumomediastinum after the initiation of corticosteroid therapy and those who did not to identify the factors associated with the pathogenesis of pneumomediastinum in CTD-ILD.

Materials and Methods

Patients

Patients with CTD-ILD who were admitted to the rheumatology department of the University of Tsukuba Hospital between December 1, 2014, and November 31, 2019, and initiated corticosteroid therapy for ILD were screened. Patients with the following conditions were excluded from this study: (1) drug-induced ILD or (2) pure RA-associated organizing pneumonia (RA-OP) without any major CTD marker autoantibody other than anti-cyclic citrullinated pep-

tide antibody; the latter exclusion criterion was devised because there had been no reports of pneumomediastinum in RA-OP, and some of these patients were assumed to have received treatment in an outpatient setting.

The underlying CTD diagnoses were defined according to the current rheumatologic classification criteria for RA (16), DM/PM (17), clinically amyopathic DM (CADM) (18), SSc (19, 20), Sjögren's syndrome (SS) (21, 22), SLE (23, 24), mixed connective tissue disease (MCTD) (25) and microscopic polyangiitis (MPA) (26, 27). Chest computed tomography (CT) was performed for the evaluation of ILD before corticosteroid therapy. Similarly, except for a single case (substituted with chest X-ray), pneumomediastinum was confirmed by high-resolution CT (HRCT). Patients with increased serum Krebs von den Lungen-6 (KL-6) levels and progression on imaging findings were treated according to the discretion of individual physicians with regard to respiratory symptoms, serological markers, imaging findings and pulmonary function tests. Patients with other organ involvement were also included.

The candidate participants were 78 patients with CTD-ILD, and the flow diagram of the selection process is shown in Fig. 1. Air leak syndrome (ALS) includes conditions such as interstitial emphysema, pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema and systemic air embolism. In this study, a total of 15 patients with ALS were identified, and 2 of these patients - 1 patient with pneumothorax and 1 patient with pneumothorax and subcutaneous emphysema without pneumomediastinum - were excluded. The pneumomediastinum group consisted of 13 patients, while the control group included patients who had been admitted during the same period and initiated corticosteroid therapy for ILD but did not develop any ALS during a minimum of 120 days of follow-up after the initiation of corticosteroids. Of the 63 patients without ALS, 14 were excluded due to death (n=7) or failure to receive follow-up (n=7) for at least 120 days. A total of 49 patients were thus enrolled in the control group, and for the 3 control patients who had multiple treatment episodes during the study period, only the first episode was analyzed. We set 120 days as the minimum follow-up period because all pneumomediastinum episodes occurred within 120 days.

This study was approved by the ethics committee of the University of Tsukuba Hospital (approval number: H29-154). The need for written informed consent was waived by the opt-out method on the website of the University of Tsukuba Hospital (http://www.md.tsukuba.ac.jp/clinical-med/rheumatology/) because of the retrospective and observational design that used only clinical data obtained in daily clinical practice.

Study variables

Baseline characteristics and treatments were evaluated and compared between patients with and without pneumomediastinum. All clinical data were extracted from electronic
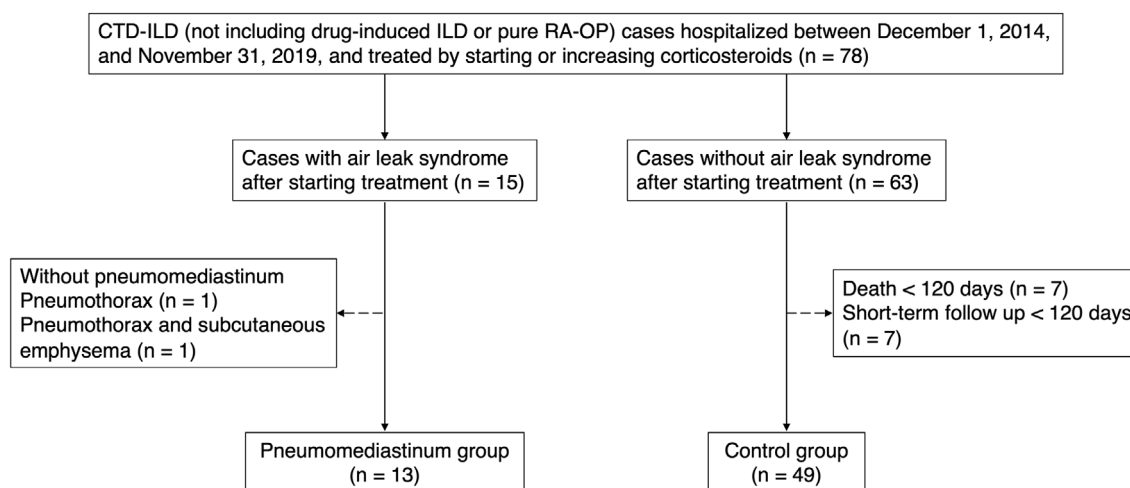
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┌─────────────────────────────────────────────────────────────────────────┐
│ CTD-ILD (not including drug-induced ILD or pure RA-OP) cases hospitalized │
│ between December 1, 2014, and November 31, 2019, and treated by starting  │
│ or increasing corticosteroids (n = 78)                                    │
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┌──────────────────────────────┐        ┌──────────────────────────────┐
│ Cases with air leak syndrome  │        │ Cases without air leak       │
│ after starting treatment      │        │ syndrome after starting      │
│ (n = 15)                      │        │ treatment (n = 63)           │
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│ Without pneumomediastinum      │        │ Death < 120 days (n = 7)     │
│ Pneumothorax (n = 1)          │        │ Short-term follow up < 120   │
│ Pneumothorax and subcutaneous │        │ days (n = 7)                 │
│ emphysema (n = 1)             │        │                              │
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┌──────────────────────────────┐        ┌──────────────────────────────┐
│ Pneumomediastinum group        │        │ Control group                │
│ (n = 13)                      │        │ (n = 49)                     │
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Figure 1. Flow diagram of the patient selection process. CTD-ILD: connective tissue disease-associated interstitial lung disease, RA-OP: rheumatoid arthritis-associated organizing pneumonia, air leak syndrome: interstitial emphysema, pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema and systemic air embolism

medical records, particularly the following demographic and clinical information at baseline (start of corticosteroid therapy): age, sex, body mass index (BMI; weight in kilograms divided by the square of the height in meters), underlying CTD, CTD and ILD disease duration, smoking status, respiratory symptoms and serum laboratory tests [KL-6, lactate dehydrogenase (LDH), albumin (Alb), immunoglobulin G (IgG) and C-reactive protein (CRP)]. We collected additional data on the partial pressure of arterial oxygen on room air (PaO$_2$) and pulmonary function tests, including the forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO), for the 6-month period before treatment initiation. The FVC and DLCO are expressed as percentages of the predicted values.

HRCT with 2.0-mm collimation at 2.0-mm intervals was performed without a gap. After HRCT images were reviewed by one or two experienced radiologists, ILD was diagnosed and evaluated by the consensus of at least two rheumatologists. Defined abnormalities were 1) ground-glass opacity, 2) consolidation, 3) traction bronchiectasis, 4) reticulation and 5) honeycombing, in accordance with the recommendations of the Nomenclature Committee of the Fleischner Society (28).

All patients were initially treated with prednisolone or intravenous methylprednisolone (mPSL) pulse therapy (500-1,000 mg/day for 3 days) followed by prednisolone. The concomitant use of immunosuppressive drugs, such as intravenous cyclophosphamide (IVCY) (500-1,000 mg/body), cyclosporine (CyA), tacrolimus (TAC), mycophenolate mofetil (MMF) and/or azathioprine (AZP) within 4 weeks, was recorded if administered.

Statistical analyses

Continuous variables were expressed as the mean±standard deviation (SD) if they had a normal distribution or the median with interquartile range (IQR) if they did not have a normal distribution. Categorical variables were summarized as proportions (%). In addition, continuous variables were compared by the Mann-Whitney U test, and categorical variables were compared using the χ^2 or Fisher exact tests. A multivariate logistic regression analysis was also performed to assess predictive factors associated with pneumomediastinum.

To address missing data, we applied multiple imputation by chained equation (29); the prevalences of missing baseline data of PaO$_2$, FVC and DLCO were 32%, 26%, and 31%, respectively, while others were 0%. In addition, receiver operating characteristic (ROC) curve analyses were performed to assess the predictive performances of potential predictive factors. The optimal cut-off points were determined by using the Youden index (30). Sensitivity, specificity and 95% confidence intervals (CI) were calculated for the derived predictive rules. Finally, pneumomediastinum-free survival curves were estimated by the Kaplan-Meier method with log-rank testing performed for comparisons. All p-values were two-sided and considered to be statistically significant when less than 0.05.

Results

Clinical characteristics of CTD-ILD patients with and without pneumomediastinum

Comparisons of the baseline clinical characteristics between patients with (n=13) and without (n=49) development of pneumomediastinum after the initiation of corticosteroid therapy are summarized in Table 1. The mean age of patients with pneumomediastinum at the initiation of corticosteroid therapy for CTD-ILD was 63.3±10.1 years old, and 62% of patients were women, which did not statistically differ from the control group. In contrast, the BMI was significantly lower in patients with pneumomediastinum than in

Table 1. Clinical Characteristics of Patients with and without Pneumomediastinum at the Initiation of Corticosteroid Therapy for Connective Tissue Disease-associated Interstitial Lung Disease.

	Pneumomediastinum group (n=13)	Control group (n=49)	p
Age, mean (SD) years	63.3 (10.1)	59.8 (12.4)	0.32
Sex			0.32
Female, n (%)	8 (62)	37 (76)	
Male, n (%)	5 (38)	12 (24)	
BMI, mean (SD) kg/m^2	20.5 (3)	23.3 (3.9)	0.02
CTD			
RA, n (%)	4 (31)	7 (14)	0.22
DM/PM, n (%)	4 (31)	19 (39)	0.75
CADM, n (%)	4/13 (31)	3/49 (6)	0.03
SSc, n (%)	0	6 (12)	0.33
SS, n (%)	2 (15)	5 (10)	0.63
SLE, n (%)	1 (8)	2 (4)	0.51
MCTD, n (%)	1 (8)	2 (4)	0.51
MPA, n (%)	1 (8)	0	0.21
Overlap syndrome, n (%)	0	8 (16)	0.19
		(RA+PM 2, RA+DM 1, PM+SS 1, PM+SSc 1, SSc+MPA 1, RA+SSc+MPA 1, PM+SSc+SS 1)	
Interval between the first CTD diagnosis and intensification of therapy, median (IQR) months	14 (0-156)	1 (0-91)	0.31
Interval between the first detection of ILD and intensification of therapy, median (IQR) months	7 (3-25)	4 (1-20)	0.38
Smoking status			0.69
Never, n (%)	8 (62)	30 (61)	
Former, n (%)	3 (23)	15 (31)	
Current, n (%)	2 (15)	4 (8)	
Symptoms			
Cough, n (%)	6 (46)	24 (49)	1
Dyspnea, n (%)	10 (77)	22 (45)	0.06
Chest pain, n (%)	0	1 (2)	1
None, n (%)	1(8)	13 (27)	0.26
Laboratory findings			
KL-6, mean (SD) U/mL	1,606 (787)	1,321 (818)	0.19
LDH, mean (SD) U/L	388 (159)	275 (105)	0.02
Alb, mean (SD) g/dL	3.1 (0.6)	3.4 (0.6)	0.28
IgG, mean (SD) mg/dL	1496 (747)	1,821 (705)	0.11
CRP, mean (SD) mg/dL	3.44 (4.65)	1.73 (2.74)	0.36
PaO$_2$, mean (SD) mmHg[a]	66.9 (5.1)	80.5 (13.2)	0.001*
Pulmonary function tests			
%FVC, mean (SD)[b]	59 (20)	70.8 (15.7)	0.19*
%DLCO, mean (SD)[c]	35.9 (10.4)	60.4 (17.9)	0.006*
Imaging pattern			
Ground-glass opacity, n (%)	7 (54)	36 (73)	0.19
Consolidation, n (%)	4 (31)	12 (24)	0.73
Traction bronchiectasis, n (%)	9 (69)	36 (73)	0.74
Reticulation, n (%)	11 (85)	38 (78)	0.72
Honeycombing, n (%)	4 (31)	9 (18)	0.44
Initial corticosteroids			
PSL, mean (SD) mg	45.4 (12.5)	43.9 (11.6)	0.71
mPSL pulse therapy, n (%)	6 (46)	4 (8)	0.004
Treatment within 4 weeks			
Immunosuppressive agents			
IVCY, n (%)	4 (31)	5 (10)	0.08
CyA, n (%)	5 (38)	4 (8)	0.02
TAC, n (%)	1 (8)	12 (24)	0.27
MMF, n (%)	1 (8)	0	0.21
AZP, n (%)	0	1 (2)	1

[a] Data available for 42 (pneumomediastinum 8, control 34) patients, [b] Data available for 46 (pneumomediastinum 5, control 41) patients, [c] Data available for 43 (pneumomediastinum 3, control 40) patients. * p values derived through multiple imputation analysis.

SD: standard deviation, IQR: interquartile range, BMI: body mass index, CTD: connective tissue disease, RA: rheumatoid arthritis, DM/PM: dermatomyositis/polymyositis, CADM: clinically amyopathic dermatomyositis, SSc: systemic sclerosis, SS: Sjögren's syndrome, SLE: systemic lupus erythematosus, MCTD: mixed connective tissue disease, MPA: microscopic polyangiitis, ILD: interstitial lung disease, KL-6: Krebs von den Lungen-6, LDH: lactate dehydrogenase, Alb: albumin, IgG: immunoglobulin G, CRP: C-reactive protein, PaO$_2$: partial pressure of arterial oxygen on room air, %FVC: percent predicted forced vital capacity, %DLCO: percent predicted diffusing capacity for carbon monoxide, PSL: prednisolone, mPSL pulse therapy: intravenous methylprednisolone pulse therapy (500-1,000 mg/day for 3 days), IVCY: intravenous cyclophosphamide (500-1,000 mg/body), CyA: cyclosporine, TAC: tacrolimus, MMF: mycophenolate mofetil, AZP: azathioprine

those without it (20.5±3 kg/m^2 vs. 23.3±3.9 kg/m^2, p=0.02). The most common underlying CTDs in the pneumomediastinum group were RA in 4 patients (31%) and PM/DM in 4 patients (31%), all of which consisted of CADM, followed by SS in 2 patients (15%), SLE in 1 patient (8%), MCTD in 1 patient (8%) and MPA in 1 patient (8%). Only the proportion of CADM was significantly higher than in the control group. There were no significant differences in the CTD and ILD disease duration and smoking status between the groups, but in patients with pneumomediastinum, 77% (10 patients) had dyspnea, which was more frequent than in those without pneumomediastinum.

Although the KL-6, LDH and CRP levels were higher and Alb and IgG levels lower in patients with pneumomediastinum than in those without it, only the difference in LDH was significant (p=0.02). Analyses of multiple imputed data showed that PaO$_2$ and %DLCO were significantly lower in the pneumomediastinum group than in the control group (p= 0.001 and p=0.006, respectively), and %FVC was lower to a non-significant degree.

The major imaging features of ILD in patients with pneumomediastinum were reticulation (11/13 patients, 85%), traction bronchiectasis (9/13 patients, 69%) and ground-glass opacity (7/13 patients, 54%), findings that were similar to those in patients without pneumomediastinum. No patient underwent a lung biopsy for a histological analysis.

The initial dose of prednisolone was similar between groups. Of the 13 patients with pneumomediastinum, 6 (46%) received mPSL pulse therapy as the initial treatment, a significantly higher rate than in control patients (4/49 patients, 8%) (p=0.004), while IVCY was administered to 4 patients with pneumomediastinum. CyA was the most commonly preferred immunosuppressive agent in patients with pneumomediastinum (5/13 patients, 38%), while TAC was the most commonly preferred in control patients (12/49 patients, 24%). CyA was administered significantly more often in the pneumomediastinum group than in the control group (p=0.02), whereas MMF and AZP were rarely used in either group.

Clinical course and outcome of patients with pneumomediastinum

The detailed characteristics of the 13 patients who developed pneumomediastinum after the initiation of corticosteroid therapy are summarized in Table 2. The median time-to-onset of pneumomediastinum was 28 days (IQR 19-54). All patients had a comorbid ALS, the most frequent being subcutaneous emphysema (10/13 patients, 77%) and pneumothorax (6/13 patients, 46%), while interstitial emphysema, pneumopericardium, pneumoperitoneum and systemic air embolism were not observed. The mean daily dose of prednisolone at the onset of pneumomediastinum was 39.6±14.9 mg. No patients were receiving mPSL pulse therapy, but 6 received immunosuppressive agents (IVCY and CyA: 3 patients; IVCY and TAC: 1 patient; CyA and MMF:1 patient; and CyA: 1 patient).

The treatment and outcomes for ALS are shown in Table 3. Although most patients (9/13 patients, 69%) were observed without specific treatment, 3 required ventilation support. For two of these patients, support was mandated because of respiratory failure before the onset of pneumomediastinum, but additional treatment was not required after the event. Invasive approaches, including chest drain, pleurodesis or operation, were performed in two patients, although these interventions were for pneumothorax, not pneumomediastinum. No relapses of pneumomediastinum were observed.

At a mean follow-up time of 748±709 days after the initiation of corticosteroid therapy, 9 patients were alive, and 4 had died from respiratory failure associated with ILD, although pneumomediastinum itself was not directly associated with these deaths. The cumulative survival rate was 68.4% (95% CI 42.6-94.1%), and the cumulative survival curve is shown in Fig. 2. Furthermore, the cumulative survival rate at 120 days was compared with that in the modified control group without pneumomediastinum. The modified group included the original control group (n=49) and non-survivors who died within 120 days (n=7) without pneumomediastinum. The cumulative survival curves are shown in Supplementary material. The log-rank test showed no statistically significant difference in the survival between the 2 groups (p=0.35).

Factors associated with the development of pneumomediastinum

A multivariate logistic regression analysis was conducted to evaluate the predictive factors significantly associated with the development of pneumomediastinum. We selected the BMI, CADM, LDH, PaO$_2$, %DLCO, mPSL pulse therapy and CyA as explanatory variables based on the presence of a significant difference (p<0.05) in these factors between the pneumomediastinum and control groups in Table 1. Model 1 included the BMI, CADM, LDH, PaO$_2$ and mPSL pulse therapy, and Model 2 included the BMI, LDH, % DLCO, mPSL pulse therapy and CyA.

Model 1 showed that the BMI [odds ratio (OR) (95% CI) 0.482 (0.272-0.853)] and LDH [OR (95% CI) 1.013 (1-1.025)] were significantly associated with the development of pneumomediastinum, whereas CADM [OR (95% CI) 9.223 (0.428-198.970)], PaO$_2$ [OR (95% CI) 0.967 (0.859-1.088)] and mPSL pulse therapy [OR (95% CI) 13.062 (0.928-183.780)] were not associated (Table 4). Model 2 revealed that none of the explanatory variables were statistically significant, although patients with a low BMI and high LDH tended to develop pneumomediastinum [OR (95% CI) 0.642 (0.35-1.179) and 1.014 (0.999-1.029), respectively] (Table 4).

ROC curve and optimal cut-off values for the BMI and LDH level

ROC curve analyses were performed to evaluate the usefulness of the BMI and LDH level in predicting the devel-

Table 2.　Characteristics of the 13 Patients who Developed Pneumomediastinum after Initiating Corticosteroid Therapy.

Patients	Age (years)	Sex	CTD	Interval between the initiation of CS therapy and the development of pneumomediastinum (days)	BMI (kg/m²)	LDH (U/L)	Comorbid ALS	Initial CS		Treatment at the diagnosis of pneumomediastinum		
								PSL (mg/day)	mPSL pulse therapy (mg/day)	PSL (mg/day)	mPSL pulse therapy (mg/day)	IS
1	48	M	CADM	55	24.2	635	subcutaneous emphysema	60	1,000	45		IVCY+CyA
2	68	F	MPA	13	21.3	490	subcutaneous emphysema	50	1,000	50		
3	44	F	CADM	56	19.6	378	pneumothorax, subcutaneous emphysema	30		25		IVCY+TAC
4	65	F	SLE	54	20.7	397	subcutaneous emphysema	45		35		
5	58	M	RA	28	21.9	399	pneumothorax	60	1,000	60		IVCY+CyA
6	64	F	SS	19	16.8	177	pneumothorax, subcutaneous emphysema	30		30		
7	72	F	MCTD	28	20.2	247	subcutaneous emphysema	40		30		
8	71	M	RA	21	20	315	pneumothorax	50		40		
9	70	M	RA	14	24.3	486	pneumothorax, subcutaneous emphysema	60	1,000	60		
10	72	F	RA	19	25.6	639	subcutaneous emphysema	60	1,000	60		
11	52	M	CADM	49	17.5	204	subcutaneous emphysema	30		25		CyA+MMF
12	77	F	SS	113	15.2	182	pneumothorax	30		15		CyA
13	62	F	CADM	32	19.2	501	subcutaneous emphysema	45	1,000	40		IVCY+CyA

M: male, F: female, CTD: connective tissue disease, CADM: clinically amyopathic dermatomyositis, MPA: microscopic polyangiitis, SLE: systemic lupus erythematosus, RA: rheumatoid arthritis, SS: Sjögren's syndrome, MCTD: mixed connective tissue disease, CS: corticosteroids, BMI: body mass index, LDH: lactate dehydrogenase, ALS: air leak syndrome including interstitial emphysema, pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema and systemic air embolism, PSL: prednisolone, mPSL pulse therapy: intravenous methylprednisolone pulse therapy (500-1,000 mg/day for 3 days), IS: immunosuppressive agents, IVCY: intravenous cyclophosphamide (500-1,000 mg/body), CyA: cyclosporine, TAC: tacrolimus, MMF: mycophenolate mofetil

Table 3.　Summary of the Treatment for Air Leak Syndrome and Its Outcome.

Patients	Age (years)	Sex	CTD	Treatment for air leak syndrome					Recurrence of pneumomediastinum	Outcome	Cause of death	Follow-up duration (days)
				Observation	Chest drain	Pleurodesis	Operation	Ventilator				
1	48	M	CADM	+	-	-	-	-	no	alive		1,988
2	68	F	MPA	-	-	-	-	+*	no	deceased	ILD	71
3	44	F	CADM	+	-	-	-	-	no	alive		1,760
4	65	F	SLE	+	-	-	-	-	no	alive		1,762
5	58	M	RA	-	+	+	+	-	no	alive		502
6	64	F	SS	+	-	-	-	-	no	alive		1,196
7	72	F	MCTD	+	-	-	-	-	no	alive		659
8	71	M	RA	+	-	-	-	-	no	alive		888
9	70	M	RA	-	+	-	-	+	no	deceased	ILD	71
10	72	F	RA	-	-	-	-	+*	no	deceased	ILD	23
11	52	M	CADM	+	-	-	-	-	no	alive		358
12	77	F	SS	+	-	-	-	-	no	deceased	ILD	261
13	62	F	CADM	+	-	-	-	-	no	alive		188

* use before the diagnosis of pneumomediastinum. M: male, F: female, CTD: connective tissue disease, CADM: clinically amyopathic dermatomyositis, MPA: microscopic polyangiitis, SLE: systemic lupus erythematosus, RA: rheumatoid arthritis, SS: Sjögren's syndrome, MCTD: mixed connective tissue disease, air leak syndrome: interstitial emphysema, pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema and systemic air embolism, ILD: interstitial lung disease
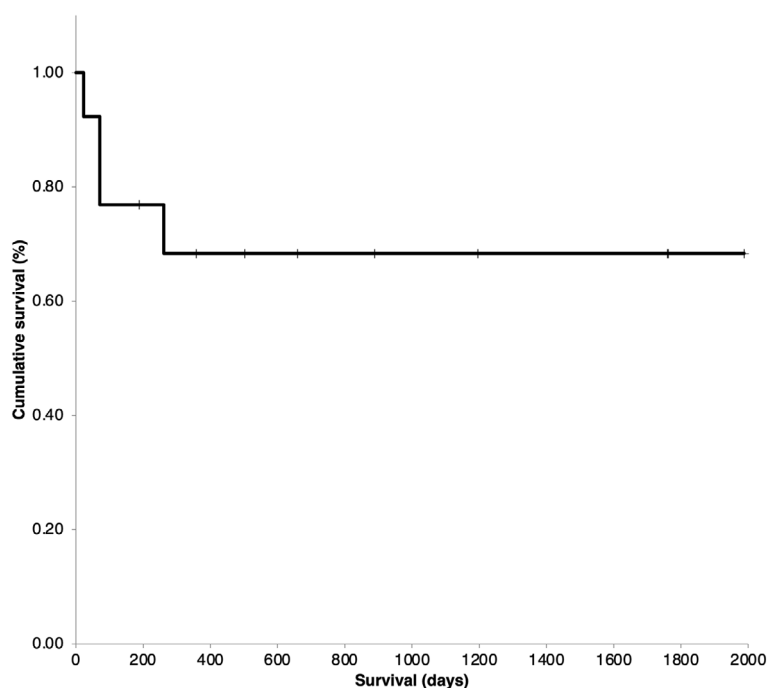
Figure 2. Kaplan-Meier survival curve for 13 patients who developed pneumomediastinum after the initiation of corticosteroid therapy.

Table 4. Results of a Multivariate Logistic Regression Analysis of the Factors Associated with Development of Pneumomediastinum after the Initiation of Corticosteroid Therapy for Connective Tissue Disease-associated Interstitial Lung Disease.

Model 1	OR	95% CI	p
BMI	0.482	0.272-0.853	0.013
CADM	9.223	0.428-198.970	0.153
LDH	1.013	1-1.025	0.048
PaO2	0.967	0.859-1.088	0.562
mPSL pulse therapy	13.062	0.928-183.780	0.056

Model 2	OR	95% CI	p
BMI	0.642	0.35-1.179	0.149
LDH	1.014	0.999-1.029	0.067
%DLCO	0.899	0.774-1.044	0.157
mPSL pulse therapy	7.266	0.077-689.886	0.383
CyA	5.578	0.222-140.161	0.289

BMI: body mass index, CADM: clinically amyopathic dermatomyositis, LDH: lactate dehydrogenase, PaO2: partial pressure of arterial oxygen on room air, mPSL pulse therapy, intravenous methylprednisolone pulse therapy (500-1,000 mg/day for 3 days), %DLCO: percent predicted diffusing capacity for carbon monoxide, CyA: cyclosporine, OR: odds ratio, CI: confidence interval

opment of pneumomediastinum, and estimated ROC curves are presented in Fig. 3. These results indicated that both the BMI and LDH level were effective for predicting the development of pneumomediastinum, as the area under the curve (AUC) for BMI was 0.711 (95% CI 0.541-0.881), while that for LDH was 0.709 (95% CI 0.516-0.901). The optimal cut-off values of the BMI and LDH level, as derived by the Youden index, were 20.2 kg/m^2 and 378 U/L, respectively. The sensitivity, specificity and accuracy of the BMI, LDH level and the combination thereof are shown in Table 5. The sensitivities of the BMI alone and LDH level alone were 53.9% and 61.5%, respectively, and their specificities were 83.7% and 87.8%, respectively. When the markers were combined by adding the LDH level to the BMI, the sensitivity and specificity of the BMI and/or LDH level became 100% and 71.4%, respectively, indicating that the LDH level alone had the highest specificity, while the combination of the BMI and LDH level had the highest sensitivity.

Subsequently, groups were created based on the optimal cut-off values derived from the ROC analysis. Pneumomediastinum-free survival rates were estimated using the Kaplan-Meier method and compared between the different groups. The log-rank tests for the Kaplan-Meier curves showed that patients with a low BMI alone (≤20.2 kg/m^2), high LDH level alone (≥378 U/L) or either a low BMI and/or high LDH level (≤20.2 kg/m^2 and/or ≥378 U/L) were significantly more likely to develop pneumomediastinum after the initiation of corticosteroid therapy than those with a high BMI alone (>20.2 kg/m^2) (p=0.005), low LDH level alone (<378 U/L) (p<0.001) or both a high BMI and low LDH level (>20.2 kg/m^2 and <378 U/L) (p<0.001) (Fig. 4).

Discussion

This is the first study investigating factors associated with pneumomediastinum during management of CTD-ILD that specifically focused on patients with ILD receiving corticosteroid therapy. In this study, the BMI and serum LDH levels at baseline were identified as independent factors as-
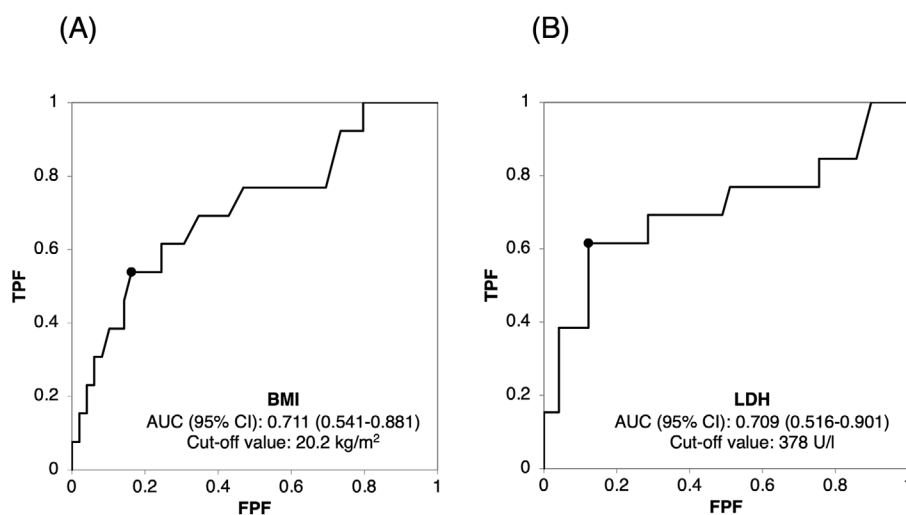
Figure 3. Receiver operating characteristic (ROC) curve analyses of the BMI (A) and LDH level (B) in patients with and without pneumomediastinum in CTD-ILD. The Youden index was used to estimate the optimal cut-off point. BMI: body mass index, LDH: lactate dehydrogenase, CTD-ILD: connective tissue disease-associated interstitial lung disease, AUC: area under ROC curve, CI: confidence interval, FPF: false positive fraction, TPF: true positive fraction

Table 5. Sensitivity, Specificity and Accuracy of Baseline Characteristics in Predicting Pneumomediastinum after the Initiation of Corticosteroid Therapy for Connective Tissue Disease-associated Interstitial Lung Disease.

	cut-off value	sensitivity (95% CI)	specificity (95% CI)	accuracy (95% CI)
BMI (kg/m^2)	≤20.2	53.9 (25.1, 80.8)	83.7 (70.3, 92.7)	77.4 (65, 87.1)
LDH (U/L)	≥378	61.5 (31.6, 86.1)	87.8 (75.2, 95.4)	82.3 (70.5, 90.8)
BMI (kg/m^2) and/or LDH (U/L)	≤20.2/≥378	100	71.4 (56.7, 83.4)	77.4 (65, 87.1)

BMI: body mass index, LDH: lactate dehydrogenase, CI: confidence interval

sociated with pneumomediastinum after the initiation of corticosteroid therapy. The optimal cut-off point estimates of the BMI and LDH levels for predicting the development of pneumomediastinum were 20.2 kg/m^2 and 378 U/L, respectively. LDH provided a sensitivity of 61.5% and the highest specificity at 87.8%. Importantly, combining the two markers by adding the LDH level to the BMI resulted in the highest sensitivity of 100%, although its specificity was 71.4%. This indicated that the combination of a low BMI and/or high LDH levels at baseline was useful for predicting pneumomediastinum after the initiation of corticosteroid therapy.

Three important findings were obtained from this study. First, a low BMI and high LDH level at baseline were significant predictors for pneumomediastinum after the initiation of corticosteroid therapy for CTD-ILD, whereas CADM was not. These results enable the risk stratification and early detection of pneumomediastinum patients requiring management of CTD-ILD. Both the BMI and LDH level are clinically utilizable markers, but neither has been reported as a pneumomediastinum risk factor in the field of rheumatology. Because of the rarity of CTD patients presenting with comorbid pneumomediastinum, there are only a few statistically established risk factors, and well-known clinical char-

acteristics of pneumomediastinum in CTD are mainly based on published case reports. Within the literature, only two studies have reported statistically significant predictors of pneumomediastinum. In one study, cutaneous ulcers were found to be an independent risk factor for the development of pneumomediastinum in DM (9), while a systematic meta-analysis found that high anti-MDA5 antibody levels had an increased OR for pneumomediastinum among DM patients (31).

Second, we provided insight into the association between a low BMI and/or high LDH levels at baseline and the development of pneumomediastinum. A low BMI indicates starvation or malnutrition, leading to atrophic changes in connective tissue within the alveoli. This is evidenced by animal studies in which caloric restriction caused a significant decrease in lung tissue elasticity (32), alveolar wall thinning and alveolar loss (33). Indeed, in a clinical setting, the relationship between a low BMI and the risk of pneumomediastinum has been well established (34, 35), especially in anorexia nervosa patients (even excluding vomiting), suggesting that pneumomediastinum may constitute a complication of an underweight status (36). However, the BMI values and severity of patients in our study were not comparable to those of anorexia nervosa patients despite
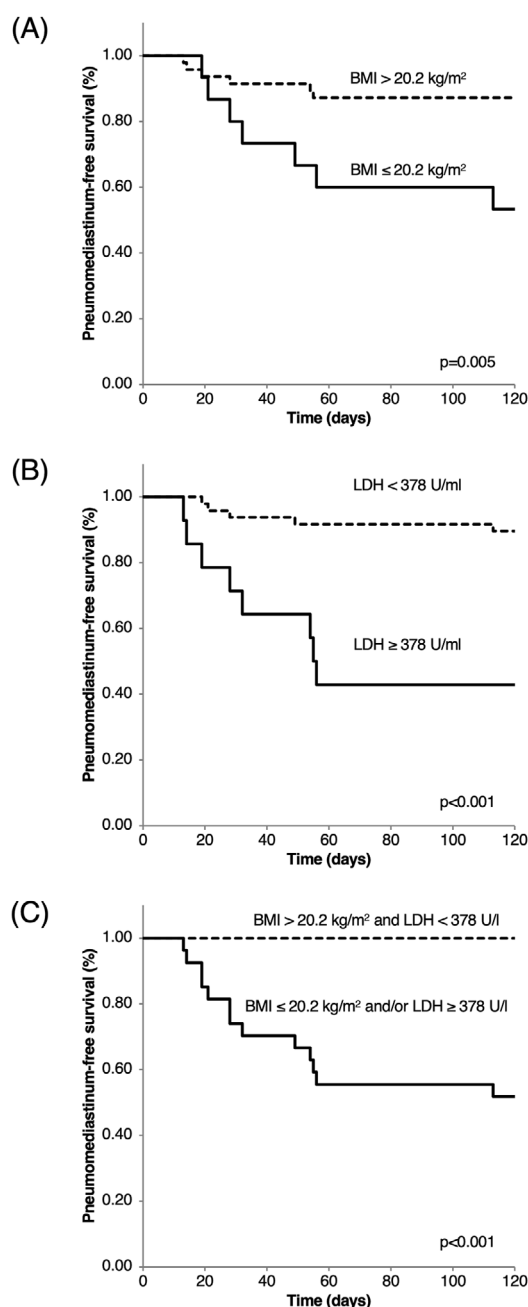
Figure 4.   Kaplan-Meier curves for groups created based on the optimal cut-off value derived by an ROC analysis. The time to the development of pneumomediastinum after the initiation of corticosteroid therapy was described for the BMI alone (A), LDH level alone (B), and combination of the BMI and LDH level (C). ROC: receiver operating characteristic, BMI: body mass index, LDH: lactate dehydrogenase

their underweight status. Low BMI patients with CTD-ILD who have potential soft tissue weakness are presumably at risk of alveolar wall rupture. In contrast, regarding high LDH levels, Chu et al. (37) reported that high peak LDH levels were associated with the development of pneumomediastinum in patients with severe acute respiratory syndrome. LDH is ubiquitous within the body, and because of this non-specificity, little evidence exists regarding whether or not LDH levels are positively correlated with CTD-ILD activity or severity. However, several pulmonary disorders,

including ILD, are known to increase serum LDH levels via cell damage, inflammation or both (38). Notably, since the first report was published in 1968 (39), serum LDH has been a traditional biomarker for ILD. Collectively, evidence suggests that not only a low BMI but also high LDH levels at baseline signify potential alveolar wall weakening due to damage or inflammation. In the present study, the levels of KL-6, a biomarker for evaluating the severity of CTD-ILD with high sensitivity and specificity (40), were not significantly different between the two groups. However, the PaO_2 and %DLCO values were significantly lower in patients with pneumomediastinum than in those without it. A previous study found that the serum KL-6 levels peak after starting treatment and then decrease gradually to baseline (41). Unlike PaO_2 and %DLCO, the serum KL-6 levels at baseline would not reflect ongoing lung injury and fibrosis.

Third, we can now offer suggestions on how to prevent the development of pneumomediastinum during management of CTD-ILD. Based on our results, patients with a low BMI and/or high LDH levels at baseline may have soft tissue weakness, including within the alveolar walls, and may be predisposed to develop pneumomediastinum. Within the literature, several underlying mechanisms of pneumomediastinum with regard to the tissue status have already been proposed. Yamanishi et al. (14) reported that weakening of the interstitial lung tissue from steroids may contribute to pneumomediastinum pathogenesis, and another report found that increases in the air cystic space as a result of interstitial pneumonia and fibrosis may increase the risk of pneumomediastinum (42). Furthermore, alveolar ruptures associated with an elevated alveolar pressure or damage (due to infection or aspiration) are the most common causes of pneumomediastinum (1, 43).

In the present study, associated factors that all pneumomediastinum patients had in common were either a low BMI and/or high LDH levels, the use of corticosteroids and underlying ILD indicated for treatment. Although these unchangeable factors resulted in pneumomediastinum, after the initiation of corticosteroid therapy, we were able to take ablative measures for other factors that increased the alveolar pressure or damaged the alveoli. We therefore propose the following approaches: 1) when using ventilator support (e.g., in acute exacerbation of ILD), it is reasonable to minimize pressure settings; 2) cough suppressants (when needed) are also recommended for reducing alveolar pressure; and 3) treatment strategies vary according to the clinical situation of each individual, although immunosuppression remains the mainstay of treatment for ILD (44). Even in ILD patients with a low BMI and/or high LDH levels, if needed, mPSL pulse therapy is recommended to avoid a fatal outcome. It is essential to reduce the disease activity or inflammation with the aim of preventing progression to fibrosis, and importantly, combination therapy with immunosuppressive agents allows for the tapering of corticosteroids. It is speculated that these approaches may help prevent the development of pneumomediastinum in CTD-ILD patients, especially in

those with a low BMI and/or high LDH levels at baseline. Despite the fact that pneumomediastinum itself is unlikely to cause death, it imposes a huge burden on patients in terms of symptoms, the need for bed rest, interference with activities of daily living and a prolonged duration of hospitalization. Thus, identifying patients at particularly high risk and taking measures to prevent it are extremely important.

Several limitations associated with the present study warrant mention. First, we were unable to fully describe the usefulness of the BMI and LDH as definitive prognostic factors because of the retrospective design. Second (and consistent with previous reports), even though it was evident that CADM accounts for the majority of pneumomediastinum with DM, CADM itself was not an independent significant factor in this study. This lack of significance in the multivariable analysis may be due to the low proportion of CADM patients in the pneumomediastinum group, which consisted of 9 patients (69%) with CTD other than CADM. As the proportion of CADM among all CTD-ILD patients was less precise, it could thus not be definitively argued that CADM was not a risk factor for developing pneumomediastinum. Third, this study focused on hospitalized patients, so mild patients might have been excluded from the analysis. Finally, the treatment choice and evaluations performed were entirely dependent on the discretion of the individual physicians, which may have led to biased results. Further prospective, large-scale studies will be needed to confirm our findings.

In conclusion, this study showed that a low BMI and high serum LDH levels at baseline were useful predictive factors for the development of pneumomediastinum during corticosteroid therapy for CTD-ILD, as the highest sensitivity was obtained by combining these two markers. ILD patients with these factors should be treated more cautiously, such as by reducing the alveolar pressure and administering immunosuppressive agents, to spare patients from treatment with corticosteroids, which can contribute to pneumomediastinum pathogenesis.

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