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ORIGINAL RESEARCH

The Risk Factors of Exacerbation in Interstitial Pneumonia With Autoimmune Features: A Single-Center Observational Cohort Study

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ABSTRACT

Objectives: To investigate the long-term outcomes, including risk factors, for exacerbation between monotherapy and combination therapy in patients with interstitial pneumonia with autoimmune features (IPAF).

Methods: We assessed 672 patients between April 2009 and March 2019 who were evaluated using high-resolution computed tomography (HRCT) of the chest. We applied the IPAF criteria. Fifty-two patients who visited our department for at least 6 months were diagnosed with IPAF. Clinical, laboratory, and imaging data were collected from medical records and statistically analyzed.

Results: Among the 52 cases of IPAF, we compared the characteristics at diagnosis between treated (n = 28) and untreated patients (n = 24). The exacerbation rates were 42.9% (n = 12) and 8.3% (n = 2) (P = 0.0051), respectively. Among the treated patients, smoking history, high titer of KL-6, and the duration from diagnosis to the start of treatment were significant risk factors for exacerbation (P = 0.0062, 0.011, and 0.019, respectively). The number of risk factors was significantly and positively associated with exacerbation rate (P = 0.0053). Among the treated patients, glucocorticoid (GC) monotherapy was used in 13 cases, and GC and immunosuppressant (IS) combination therapy was used in 14 patients. There was no significant difference in the treatment methods between patients with and without risk factors (P = 0.47). When comparing the long-term outcomes between the monotherapy and combination therapy groups, the 3-year non-exacerbation rates were 72.9 and 45.9% (P = 0.020), respectively.

Conclusions: IPAF patients with risk factors had a high exacerbation rate, regardless of the type of treatment. New interventions aimed at preventing exacerbations in these patients are required.

Keywords: Interstitial pneumonia with autoimmune features; Long-term outcomes; Prognosis; Risk factors; Treatment methods

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Key Summary Points

Why carry out this study?

The prognosis of IPAF varies among studies. Nonetheless, no study has compared the long-term outcome, and the efficacy and safety profiles of different treatment methods for IPAF have not been reported.

We investigated the long-term outcomes, including risk factors, for exacerbation between monotherapy and combination therapy in patients with IPAF

What was learned from the study?

The exacerbation rate of IPAF patients with risk factors was high, regardless of treatment.

It is important to start treatment early.

New interventions aimed at preventing exacerbations in these patients are required.

INTRODUCTION

Some patients with idiopathic interstitial pneumonia (IIP) may have features of connective tissue disease (CTD) [1]. In the past, this disorder was referred to as undifferentiated connective tissue disease-associated interstitial lung disease (UCTD-ILD), lung-dominant CTD, or autoimmune-featured ILD [2–4]. There were discrepancies in the inclusion criteria among published reports. Therefore, the term interstitial pneumonia with autoimmune features (IPAF) has been proposed to define patients with ILD with autoimmune features but who do not meet the established CTD criteria by the European Respiratory Society (ERS)/American Thoracic Society (ATS) in 2015 to unify the inclusion criteria. These advocated criteria are composed of three domains: clinical, serological, and morphological [5] (Table 1).

The prognosis of IPAF varies among studies. According to one study [1], IPAF is associated with worse survival than CTD-ILD while showing slightly better survival than idiopathic pulmonary fibrosis (IPF). Other studies showed no significant difference between IPAF and IPF [6], and IPAF survival was better than IIP survival and similar to CTD-ILD survival [7]. To date, no study has compared the long-term outcome or the efficacy and safety profiles of different treatment methods for IPAF.

This study investigated the long-term outcomes, including risk factors, for exacerbation between monotherapy and combination therapy in patients with IPAF.

METHODS

Patients

In this observational cohort study, the data of 672 patients who visited the Division of Pulmonary Medicine, Allergy, and Rheumatology, Iwate Medical University Hospital, between April 2009 and March 2019 and were evaluated by chest high-resolution computed tomography (HRCT) scans were submitted to the IPAF criteria. All procedures were approved by the medical ethics committee of Iwate Medical University Hospital (registration no. MH2018-505) and followed the tenets of the Declaration of Helsinki. This is a retrospective study and written consent is not required. The method of disclosure to patients is as follows. The method of disclosure to patients will be explained in writing at the outpatient clinic of the Department of Respiratory, Allergy, and Collagen Diseases, and subjects will be given the opportunity to refuse the use of their data.

Assessment of IPAF

Chest HRCT scans were assessed by a trained radiologist and pulmonologist looking for adherence to the guidelines for IPF [8] and the ATS/ERS statement of IIP 2013 [9]. Then, a trained rheumatologist classified patients as IPAF if they met the IPAF criteria. We defined

'exacerbation' as an acute, clinically significant respiratory deterioration characterized by evidence of new ground-glass opacification, consolidation, or reticulation on HRCT occurring less than 1 month before starting or increasing of glucocorticoid (GC) and/or immunosuppressant (IS) [10]. We defined 'severity of interstitial pneumonia' by a three-point scale (stage I–III) according to a partially modified from the guidelines for systemic sclerosis of the Japanese Dermatological Association [11], as follows: "stage I, disease extent on HRCT $\leq$ 20%; stage II, disease extent on HRCT $>$ 20% without oxygen therapy; stage III, disease extent on HRCT $>$ 20% with oxygen therapy". We also defined 'treated patients' as patients treated at our department for the first time, although they had never been treated.

Statistical Analysis

The association of prognostic factors suggesting exacerbation to clinical, laboratory, and radiographic information at baseline characteristics was analyzed using Fisher's exact test, the Wilcoxon rank-sum test, or the Kruskal–Wallis test. We compared these variables between groups using the Chi-square test. Results were considered significant at $P < 0.05$. Baseline variables ($P < 0.05$) in univariate analysis were included in the multivariable models. Kaplan–Meier curves and log-rank tests were used to compare non-exacerbation rates between the groups. Results were considered significant at $P < 0.05$. All statistical analyses were performed using JMP software v. 13.2.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics of IPAF

Sixty-eight cases (17.1%, among all patients excluding without ILD) were clinically, serologically, and morphologically diagnosed as IPAF. Among them, 52 patients who visited our department for at least 6 months were enrolled (Supplementary Material). Of the 52 cases of IPAF, the exacerbation rate was 27% (n = 14), including 3.8% (n = 2) mortality. The clinical characteristics of the 52 patients are shown in Table 2. The mean age at diagnosis was 63.6 $\pm$ 13.9 years, and 55.8% were women. The mean observation period was 45.0 $\pm$ 34.6 months. The proportion of current or past smoking was 46.2% (n = 24). The proportion of severity of interstitial pneumonia was 55.8% (n = 29) with stage I, 32.7% (n = 17) with stage II and 11.5% (n = 6) with stage III, respectively. In the baseline values of pulmonary function test, which was conducted on a small number of patients, mean percentage of predicted forced vital capacity (%FVC) was within the normal range (80.2 $\pm$ 19.5) and mean percentage of predicted diffusing capacity of the lung for carbon monoxide (%DLCO) was a mild reduction (73.0 $\pm$ 17.5). There were relatively few severe interstitial pneumonia cases. On HRCT, the proportion of morphological pattern was 11.5% (n = 6) with UIP, 78.8% (n = 41) with NSIP, 7.7% (n = 4) with OP and 1.9% (n = 1) with NSIP with OP overlap, respectively. Almost all of the patients had NSIP patterns. The proportions of diagnostic domains in IPAF were 48.1, 36.5, 88.5, and 36.5% for the clinical and serological domain, clinical and morphological domain, serological and morphological domain, and all domains, respectively. The features within each IPAF domain were follows. The most frequently identified clinical findings were arthritis or morning stiffness (28.8%), followed by Raynaud's phenomenon (19.2%) and unexplained digital edema (15.4%). The most frequently identified serological findings were ANA positive $\geq$ 320 (36.5%) and anti-Ro (SS-A) positive (36.5%). The most frequently identified morphological finding was NSIP pattern by HRCT (78.8%) while only one patient showed pericardial effusion or pericardial thickening within multicompartment involvement.

We compared the baseline characteristics between patients with IPAF, CTD-ILD, and IIP (Supplementary Material). The mean age and titer of Krebs von den Lungen-6 (KL-6) at diagnosis in the IPAF group were significantly higher than those in the CTD group (P = 0.018 and 0.019, respectively). The proportion of

Table 1 Classification criteria for interstitial pneumonia with autoimmune features (5)

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and,

2. Exclusion of alternative etiologies and,

3. Does not meet criteria of a defined connective tissue disease and,

4. At least one feature from at least two of these domains

A. Clinical domain	B. Serologic domain	C. Morphologic domain
1. Distal digital fissuring (i.e., "mechanic hands")	1. ANA $\geq$ 1:320 titer, diffuse, speckled, homogeneous patterns or a. ANA nucleolar pattern (any titer) or b. ANA centromere pattern (any titer)	1. Suggestive radiology patterns by HRCT (see text for descriptions):
2. Distal digital tip ulceration	2. Rheumatoid factor $\geq$ 2 $\times$ upper limit of normal	a. NSIP
3. Inflammatory arthritis or polyarticular morning joint stiffness $\geq$ 60 min	3. Anti-CCP	b. OP
4. Palmar telangiectasia	4. Anti-dsDNA	c. NSIP with OP overlap
5. Raynaud's phenomenon	5. Anti-Ro (SS-A)	d. LIP
6. Unexplained digital edema	6. Anti-La (SS-B)	2. Histopathology patterns or features by surgical lung biopsy:
7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)	7. Anti-ribonucleoprotein	a. NSIP
	8. Anti-Smith	b. OP
	9. Anti-topoisomerase (Scl-70)	c. NSIP with OP overlap
	10. Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)	d. LIP
	11. Anti-PM-Scl 12. Anti-MDA-5	e. Interstitial lymphoid aggregates with germinal centers
		f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
		3. Multi-compartment involvement (in addition to interstitial pneumonia):
		a. Unexplained pleural effusion or thickening
		b. Unexplained pericardial effusion or thickening
		c. Unexplained intrinsic airways disease[a] (by PFT, imaging or pathology)
		d. Unexplained pulmonary vasculopathy

HRCT high-resolution computed tomography, *ANA* antinuclear antibody, *NSIP* non-specific interstitial pneumonia, *OP* organizing pneumonia, *LIP* lymphoid interstitial pneumonia, *PFT* pulmonary function testing

[a] Includes airflow obstruction, bronchiolitis, or bronchiectasis

Table 2 Baseline characteristics and prognostic factors for exacerbation in 52 patients with IPAF

Variable	Total (n = 52)	Exacerbation		P value
		(−) (n = 38)	(+) (n = 14)	
Female sex, % (n)	55.8 (29)	52.6 (20)	64.3 (9)	0.45
Age, years (n)	63.6 ± 13.9 (52)	63.1 ± 14.5	64.9 ± 12.2	0.74
Observed duration, months (n)	45.0 ± 34.6 (52)	41.9 ± 35.4	53.5 ± 32.2	0.11
Smoking, % (n)	46.2 (24)	34.2 (13)	78.6 (11)	0.0044**
FVC % pred, (n)	80.2 ± 19.5 (34/52)	78.4 ± 18.1 (24/38)	84.4 ± 23.2 (10/14)	0.76
D_{LCO} % pred, (n)	73.0 ± 17.5 (16/52)	71.2 ± 16.9 (11/38)	76.9 ± 20.0 (5/14)	0.61
KL-6, U/ml (n)	812 (378–1301) (52)	618 (282–1067)	1299 (784–2516)	0.0017**
SP-D, ng/ml (n)	196 (86.9–300.8) (46/52)	104 (68.3–176)	224 (102–344) (32/38)	0.040*
Stage I, % (n)	55.8 (29)	86.2 (25)	13.8 (4)	
Stage II, % (n)	32.7 (17)	70.6 (12)	29.4 (5)	0.080
Stage III, % (n)	11.5 (6)	66.7 (4)	33.3 (2)	
Death, % (n)	3.8 (2)			
Exacerbation, % (n)	26.9 (14)			
Duration from diagnosis to the start of treatment, months (n)	7.6 ± 13.6 (28)	4.4 ± 12.4 (16)	11.8 ± 14.5 (12)	0.019*
Treatment, % (n)	53.8 (28)	42.1 (16)	85.7 (12)	0.0051**
Glucocorticoid[a] use, % (n)	51.9 (27)	39.5 (15)	85.7 (14)	0.0031**
Immunosuppressant use, % (n)	28.8 (15)	21.1 (8)	50.0 (7)	0.041*
Combined, % (n)	26.9 (14)	18.4 (7)	50.0 (7)	0.023*
Clinical domain				
Mechanic's hands, % (n)	7.7 (4)	5.3 (2)	14.3 (2)	0.28
Distal digital tip ulceration, % (n)	0 (0)	0 (0)	0 (0)	NA
Arthritis or morning stiffness, % (n)	28.8 (15)	29.0 (11)	28.6 (4)	0.98
Palmar telangiectasia, % (n)	0 (0)	0 (0)	0 (0)	NA
Raynaud's phenomenon, % (n)	19.2 (10)	18.4 (7)	21.4 (3)	0.81
Unexplained digital oedema, % (n)	15.4 (8)	13.2 (5)	21.4 (3)	0.46
Gottron's sign, % (n)	3.8 (2)	5.3 (2)	0 (0)	0.38
Serological domain				
ANA positive ≥ 320, % (n)	36.5 (19)	31.6 (12)	50.0 (7)	0.22

Table 2 continued

Variable	Total (n = 52)	Exacerbation		P value
		(−) (n = 38)	(+) (n = 14)	
ANA nucleolar, % (n)	17.3 (9)	18.4 (7)	14.3 (2)	0.73
ANA centromere, % (n)	9.6 (5)	10.5 (4)	7.1 (1)	0.71
RF titer > 2 × upper limited of normal, % (n)	11.5 (6)	15.8 (6)	0 (0)	0.11
Anti-CCP positive, % (n)	5.8 (3)	7.9 (3)	0 (0)	0.28
Anti-dsDNA positive, % (n)	3.8 (2)	2.6 (1)	7.1 (1)	0.45
Anti-Ro (SS-A) positive, % (n)	36.5 (19)	31.6 (12)	50.0 (7)	0.22
Anti-La (SS-B) positive, % (n)	7.7 (4)	7.9 (3)	7.1 (1)	0.93
Anti-RNP positive, % (n)	15.4 (8)	15.8 (6)	14.3 (2)	0.89
Anti-Sm positive, % (n)	5.8 (3)	5.3 (2)	7.1 (1)	0.80
Anti-topoisomerase (Scl-70) positive, % (n)	7.7 (4)	10.5 (4)	0 (0)	0.21
Anti-tRNA synthetase (ARS) positive, % (n)	11.5 (6)	10.5 (4)	14.3 (2)	0.71
Anti-PM-Scl positive, % (n)	NA	NA	NA	NA
Anti-MDA-5 positive, % (n)	0 (0)	0 (0)	0 (0)	NA
Morphological domain				
UIP, % (n)	11.5 (6)	13.2 (5)	7.1 (1)	0.55
NSIP, % (n)	78.8 (41)	78.9 (30)	78.6 (11)	0.98
OP, % (n)	7.7 (4)	7.9 (3)	7.1 (1)	0.93
NSIP with OP overlap, % (n)	1.9 (1)	0 (0)	7.1 (1)	0.096
LIP, % (n)	0 (0)	0 (0)	0 (0)	NA
Multicompartment involvement				
Pleural effusion or pleural thickening, % (n)	0 (0)	0 (0)	0 (0)	NA
Pericardial effusion or pericardial thickening, % (n)	1.9 (1)	0 (0)	7.1 (1)	0.096
Intrinsic airway disease	0 (0)	0 (0)	0 (0)	NA

Table 2 continued

Variable	Total (n = 52)	Exacerbation		P value
		(−) (n = 38)	(+) (n = 14)	
Pulmonary vasculopathy	0 (0)	0 (0)	0 (0)	NA

Data represent the median (IQR), the mean ± SD, or % (number); P values were calculated using the Fisher's exact test, the Wilcoxon rank-sum test or Kruskal–Wallis test. The observed duration was calculated from the diagnosis to the point of the last follow-up between April 2009 and March 2019

DLCO % pred percent predicted diffusion capacity for carbon monoxide, *FVC % pred* percent predicted forced vital capacity, *KL-6* Krebs von den Lungen 6, *SP-D* surfactant protein-D, *ANA* anti-nuclear antibody, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptide, *dsDNA* double-stranded DNA, *RNP* ribonucleoprotein, *Sm* smith, *Scl* scleroderma, *tRNA* transfer RNA, *PM* polymyositis, *MDA-5* melanoma differentiation antigen 5, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *UIP* usual pneumonia, *LIP* lymphoid interstitial pneumonia

[a] As prednisolone

*P value < 0.05

**P value < 0.01

Table 3 Multivariate logistic regression model for prognostic factors for exacerbation in 52 patients with IPAF

	Odds ratio [95% CI]	P value
Smoking, %	6.65 [0.98–45.2]	0.037*
KL-6 ≥ 1542 U/ml	39.8 [2.62–603]	0.0011**
SP-D ≥ 118 ng/ml	15.7 [1.41–174]	0.0080**
Duration from diagnosis to the start of treatment ≥ 1 month	8.67 [1.53–49.2]	0.0148*

*P-value < 0.05, **P-value < 0.01

KL-6 Krebs von den Lungen 6, *SP-D* surfactant protein-D

treated patients with IPAF, including those treated with IS, was significantly lower than that with CTD-ILD (P = 0.0001). Comparing the long-term outcomes among patients with IPAF, CTD-ILD, and IIP, the 3-year non-exacerbation rates were 71.8, 67.5, and 47.2%, respectively (Supplementary Material). There was no significant difference in long-term outcomes between patients with IPAF and CTD-ILD (P = 0.61).

Prognostic Factors for Exacerbation of IPAF

We divided IPAF patients into two groups: those with exacerbation and those without exacerbation. We evaluated risk factors for exacerbation. On univariate analysis, smoking history, high titer of KL-6, high titer of pulmonary surfactant protein-D (SP-D), duration from diagnosis to the start of treatment, and treatment with oral GC and/or IS use were significantly elevated in the exacerbation group (Table 2). On multivariate analysis, smoking history, high titer of KL-6 and SP-D, duration from diagnosis to the start of treatment, and treatment with oral GC and/or IS were significantly elevated in the exacerbation group. In the multivariate logistic regression model, exacerbation of IPAF was significantly associated with smoking history, high titers of KL-6 and SP-D, and the duration from diagnosis to the start of treatment (Table 3).

Characteristics of Treated and Untreated IPAF

Among the 52 patients with IPAF, 28 were treated with GC and/or IS therapy. The

Table 4 Baseline characteristics and prognostic factors for exacerbation in patients with IPAF with or without treatment

Variable	Treatment		*P* value	Treatment (−) (*n* = 24)		*P* value
				Exacerbation		
	(−) (*n* = 24)	(+) (*n* = 28)		(−) (22)	(+) (2)	
Female sex, % (*n*)	50.0 (12)	60.7 (17)	0.44	50.0 (11)	50.0 (1)	1.0
Age, years (*n*)	67.0 ± 12.8 (24)	60.7 ± 14.2 (28)	0.10	67.1 ± 13.4 (22)	66.5 ± 3.5 (2)	0.60
Observed duration, months (*n*)	38.4 ± 36.2 (24)	50.7 ± 32.8 (28)	0.081	39.2 ± 37.7 (22)	29.5 ± 3.5 (2)	0.88
Smoking, % (*n*)	37.5 (9)	53.6 (15)	0.25	36.4 (8)	50.0 (1)	0.70
KL-6, U/ml (*n*)	734.3 ± 534.9 (24)	1288 ± 1011 (28)	0.042*	725.3 ± 555.2 (22)	833.5 ± 294.9 (2)	0.53
SP-D, ng/ml (*n*)	251.5 ± 177.3 (19)	200.5 ± 162.8 (27)	0.32	270.3 ± 178.1 (17)	91.2 ± 30.8 (2)	0.14
Stage I, % (*n*)	65.5 (19)	34.5 (10)		89.5 (17)	10.5 (2)	
Stage II, % (*n*)	23.5 (4)	76.5 (13)	0.0015**	100 (4)	0 (0)	0.24
Stage III, % (*n*)	16.7 (1)	83.3 (5)		100 (1)	0 (0)	
CRP, mg/dl (*n*)	0.41 ± 1.04 (24)	0.73 ± 1.65 (28)	0.78	0.44 ± 1.08 (22)	0.10 ± 0.00 (2)	0.21
Ferritin, ng/ml (*n*)	227.9 ± 153.4 (7)	294.8 ± 323.0 (7)	0.85	227.9 ± 153.3 (7)	NA (0)	NA
Clinical domain						
Mechanic's hands, % (*n*)	0 (0)	14.3 (4)	0.054	0 (0)	0 (0)	NA
Distal digital tip ulceration, % (*n*)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Arthritis or morning stiffness, % (*n*)	12.5 (3)	42.9 (12)	0.016*	13.6 (3)	0 (0)	0.58
Palmar telangiectasia, % (*n*)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Raynaud's phenomenon, % (*n*)	25.0 (6)	14.3 (4)	0.96	27.3 (6)	0 (0)	0.39
Unexplained digital edema, % (*n*)	16.7 (4)	14.3 (4)	0.81	18.2 (4)	0 (0)	0.51
Gottron's sign, % (*n*)	0 (0)	7.1 (2)	0.18	0 (0)	0 (0)	NA
Serological domain						
ANA positive ≥ 320, % (*n*)	29.2 (7)	42.9 (12)	0.31	31.8 (7)	0 (0)	0.34
Centromere, % (*n*)	16.7 (4)	3.6 (1)	0.11	18.2 (4)	0 (0)	0.51
Nucleolar, % (*n*)	25.0 (6)	10.7 (3)	0.17	22.7 (5)	50.0 (1)	0.39
RF titer > × 2 upper limited normal, % (*n*)	20.8 (5)	3.6 (1)	0.052	22.7 (5)	0 (0)	0.45

Table 4 continued

Variable	Treatment		*P* value	Treatment (−) (*n* = 24)		*P* value
				Exacerbation		
	(−) (*n* = 24)	(+) (*n* = 28)		(−) (22)	(+) (2)	
Anti-CCP positive (+), % (*n*)	8.3 (2)	3.6 (1)	0.46	9.1 (2)	0 (0)	0.66
Anti-dsDNA positive, % (*n*)	4.2 (1)	3.6 (1)	0.91	4.6 (1)	0 (0)	0.76
Anti-Ro (SS-A) positive, % (*n*)	20.8 (5)	50.0 (14)	0.030*	22.7 (5)	0 (0)	0.45
Anti-La (SS-B) positive, % (*n*)	8.3 (2)	7.1 (2)	0.87	9.1 (2)	0 (0)	0.66
Anti-RNP positive, % (*n*)	20.8 (5)	10.7 (3)	0.31	22.7 (5)	0 (0)	0.45
Anti-Sm positive, % (*n*)	8.3 (2)	3.6 (1)	0.46	4.6 (1)	50.0 (1)	0.026*
Anti-topoisomerase (Scl-70) positive, % (*n*)	16.7 (4)	0 (0)	0.025*	18.2 (4)	0 (0)	0.51
Anti-tRNA synthetase positive, % (*n*)	0 (0)	21.4 (6)	0.016*	0 (0)	0 (0)	NA
Anti-MDA-5 positive, % (*n*)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Morphological domain						
NSIP, % (*n*)	79.2 (19)	78.6 (22)	0.96	77.3 (17)	100 (2)	0.45
OP, % (*n*)	4.2 (1)	10.7 (3)	0.38	4.6 (1)	0 (0)	0.76
NSIP + OP, % (*n*)	0 (0)	3.6 (1)	0.35	0 (0)	0 (0)	NA
UIP, % (*n*)	16.7 (4)	7.1 (2)	0.28	18.2 (4)	0 (0)	0.51
LIP, % (*n*)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Multicompartment involvement						
Pleural effusion or thickening, % (*n*)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Pericardial effusion or thickening, % (*n*)	0 (0)	3.6 (1)	0.35	0 (0)	0 (0)	NA
Intrinsic airways disease, % (*n*)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Pulmonary vasculopathy, % (*n*)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Duration from diagnosis to the start of treatment, months (*n*)	NA	7.6 ± 13.6 (28)	NA	NA	NA	NA
Risk factors ≥ 2, % (*n*)	NA	75.0 (21)	NA	NA	NA	NA
Glucocorticoid[a] dose at the start of treatment, mg/day	NA	31.3 ± 15.0 (27/28)	NA	NA	NA	NA
Glucocorticoid[a] dose at last visit, mg/day	NA	8.6 ± 5.5 (27/28)	NA	NA	NA	NA

Table 4 continued

Variable	Treatment		*P* value	Treatment (−) (*n* = 24)		*P* value
				Exacerbation		
	(−) (*n* = 24)	(+) (*n* = 28)		(−) (22)	(+) (2)	
AE, % (*n*)	NA	39.3 (11)	NA	NA	NA	NA
Severe AE, % (*n*)	NA	10.7 (3)	NA	NA	NA	NA

Variable	Treatment (+) (*n* = 28)					
	Exacerbation		*P* value	Type of treatment		*P* value
	(−) (16)	(+) (12)		Mono (13)	Combination (14)	
Female sex, % (*n*)	43.8 (7)	33.3 (4)	0.58	61.5 (8)	57.1 (8)	0.82
Age, years (*n*)	57.7 ± 14.6 (16)	64.7 ± 13.2 (12)	0.19	65.2 ± 14.1 (13)	56.5 ± 14.1 (14)	0.10
Observed duration, months (*n*)	45.6 ± 32.7 (16)	57.5 ± 33.2 (12)	0.23	56.9 ± 39.5 (13)	41.1 ± 21.2 (14)	0.29
Smoking, % (*n*)	31.3 (5)	83.3 (10)	0.0062**	61.5 (8)	50.0 (7)	0.55
KL-6, U/ml (*n*)	885.9 ± 778.0 (16)	1825 ± 1065 (12)	0.011*	1139 ± 1093 (13)	1479 ± 958.9 (14)	0.14
SP-D, ng/ml (*n*)	227.9 ± 170.3 (15/16)	166.2 ± 153.1 (12)	0.081	202.5 ± 123.2 (12/13)	206.9 ± 197.8 (14)	0.64
Stage I, % (*n*)	80.0 (8)	20.0 (2)		50.0 (5)	50.0 (5)	
Stage II, % (*n*)	61.5 (8)	38.5 (5)	0.18	58.3 (7)	41.7 (5)	0.41
Stage III, % (*n*)	60.0 (3)	40.0 (2)		40.0 (2)	60.0 (3)	
CRP, mg/dl (*n*)	0.88 ± 2.04 (16)	0.53 ± 0.97 (12)	0.80	0.85 ± 1.95 (13)	0.67 ± 1.45 (14)	0.42
Ferritin, ng/ml (*n*)	392.2 ± 416.5 (4/16)	164.9 ± 91.4 (3/12)	0.29	173.7 (1/13)	315.0 ± 348.9 (6/14)	1.00
Clinical domain						
Mechanic's hands, % (*n*)	12.5 (2)	16.7 (2)	0.76	0 (0)	28.6 (4)	0.037*
Distal digital tip ulceration, % (*n*)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Arthritis or morning stiffness, % (*n*)	50.0 (8)	33.3 (4)	0.38	30.8 (4)	50.0 (7)	0.31
Palmar telangiectasia, % (*n*)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Raynaud's phenomenon, % (*n*)	6.3 (1)	25.0 (3)	0.16	15.4 (2)	14.3 (2)	0.94
Unexplained digital edema, % (*n*)	6.3 (1)	25.0 (3)	0.16	7.1 (1)	20.0 (3)	0.31

Table 4 continued

Variable	Treatment (+) (n = 28)					
	Exacerbation		*P* value	Type of treatment		*P* value
	(−) (16)	(+) (12)		Mono (13)	Combination (14)	
Gottron's sign, % (n)	12.5 (2)	0 (0)	0.20	0 (0)	14.3 (2)	0.16
Serological domain						
ANA positive ≥ 320, % (n)	31.3 (5)	58.3 (7)	0.15	46.2 (6)	42.9 (6)	0.86
Centromere, % (n)	0 (0)	8.3 (1)	0.24	7.7 (1)	0 (0)	0.29
Nucleolar, % (n)	12.5 (2)	8.3 (1)	0.72	15.4 (2)	7.1 (1)	0.50
RF titer > × 2 upper limited normal, % (n)	6.3 (1)	0 (0)	0.38	0 (0)	7.1 (1)	0.33
Anti-CCP positive (+), % (n)	6.3 (1)	0 (0)	0.38	0 (0)	7.1 (1)	0.33
Anti-dsDNA positive, % (n)	0 (0)	8.3 (1)	0.24	0 (0)	7.1 (1)	0.33
Anti-Ro (SS-A) positive, % (n)	43.8 (7)	58.3 (7)	0.45	76.9 (10)	28.6 (4)	0.012*
Anti-La (SS-B) positive, % (n)	6.3 (1)	8.3 (1)	0.83	15.4 (2)	0 (0)	0.13
Anti-RNP positive, % (n)	6.3 (1)	16.7 (2)	0.38	7.7 (1)	7.1 (1)	0.96
Anti-Sm positive, % (n)	6.3 (1)	0 (0)	0.38	0 (0)	7.1 (1)	0.33
Anti-topoisomerase (Scl-70) positive, % (n)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Anti-tRNA synthetase positive, % (n)	25 (4)	16.7 (2)	0.59	7.7 (1)	35.7 (5)	0.08
Anti-MDA-5 positive, % (n)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Morphological domain						
NSIP, % (n)	81.3 (13)	75.0 (9)	0.69	76.9 (10)	85.7 (12)	0.56
OP, % (n)	12.5 (2)	8.3 (1)	0.72	15.4 (2)	7.1 (1)	0.50
NSIP + OP, % (n)	0 (0)	8.3 (1)	0.24	7.7 (1)	0 (0)	0.29
UIP, % (n)	6.3 (1)	8.3 (1)	0.83	0 (0)	7.1 (1)	0.33
LIP, % (n)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Multicompartment involvement						
Pleural effusion or thickening, % (n)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Pericardial effusion or thickening, % (n)	0 (0)	8.3 (1)	0.24	0 (0)	7.1 (1)	0.33

Table 4 continued

Variable	Treatment (+) (n = 28)					
	Exacerbation		P value	Type of treatment		P value
	(−) (16)	(+) (12)		Mono (13)	Combination (14)	
Intrinsic airways disease, % (n)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Pulmonary vasculopathy, % (n)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Duration from diagnosis to the start of treatment, months (n)	4.4 ± 12.4 (16)	11.8 ± 14.5 (12)	0.019*	7.3 ± 14.5 (13)	8.4 ± 13.5 (14)	0.41
Risk factors ≥ 2, % (n)	56.3 (9)	100 (12)	0.0020**	7.7 (1)	42.9 (6)	0.030*
Glucocorticoid[a] dose at the start of treatment, mg/day	35.3 ± 16.0 (15/16)	26.3 ± 12.6 (12)	0.10	30.4 ± 13.0 (13)	32.1 ± 17.2 (14)	0.96
Glucocorticoid[a] dose at last visit, mg/day	7.6 ± 5.1 (15/16)	9.9 ± 6.0 (14)	0.30	9.2 ± 7.2	8.1 ± 3.6	0.98
AE, % (n)	25.0 (4)	58.3 (7)	0.074	30.8 (4)	50.0 (7)	0.31
Severe AE, % (n)	12.5 (2)	8.3 (1)	0.72	23.1 (3)	0 (0)	0.057

Data represent the median (IQR), the mean ± SD or % (number), P values were calculated using the Fisher's exact test, the Wilcoxon rank-sum test or Kruskal–Wallis test. The observed duration was calculated from the diagnosis to the point of the last follow-up between April 2009 and March 2019

KL-6 Krebs von den Lungen 6, *SP-D* surfactant protein-D, *ANA* anti-nuclear antibody, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptide, *dsDNA* double-stranded DNA, *RNP* ribonucleoprotein, *Sm* smith, *Scl* scleroderma, *tRNA* transfer RNA, *MDA-5* melanoma differentiation antigen 5, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *UIP* usual pneumonia, *LIP* lymphoid interstitial pneumonia, *AE* adverse events

[a] As prednisolone

*P value < 0.05

**P value < 0.01

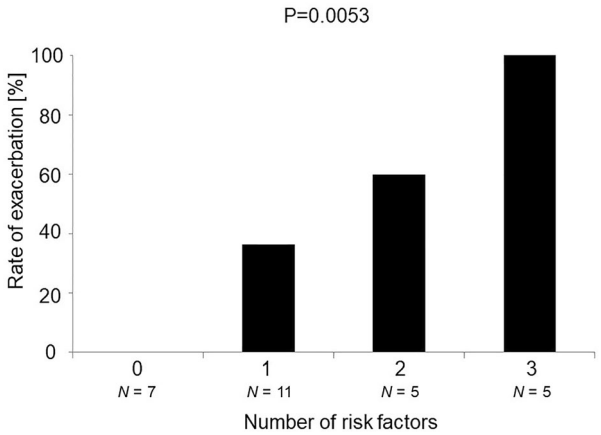

Fig. 1 Cumulative rate of exacerbation in 28 treated patients with IPAF. The positivity of three risk factors, namely smoking history, high titer of KL-6, and the duration from diagnosis to the start of treatment, were counted. *P* values were calculated using the Kruskal–Wallis test

proportions of each therapy were 51.9% ($n = 27$) for GC and 28.8% ($n = 15$), respectively. One patient was treated with IS only (Table 2). The remaining 24 patients were not treated. We compared the characteristics at diagnosis between the treated ($n = 28$) and untreated ($n = 24$) groups (Table 4). The treated group was significantly positively associated with titer of KL-6 and severity of interstitial pneumonia ($P = 0.042$ and 0.0015, respectively) (Table 4). The treated group was also significantly associated with arthritis, anti-SS-A antibody positivity, and anti-ARS antibody positivity ($P = 0.016$, 0.03, and 0.016, respectively) characterized by

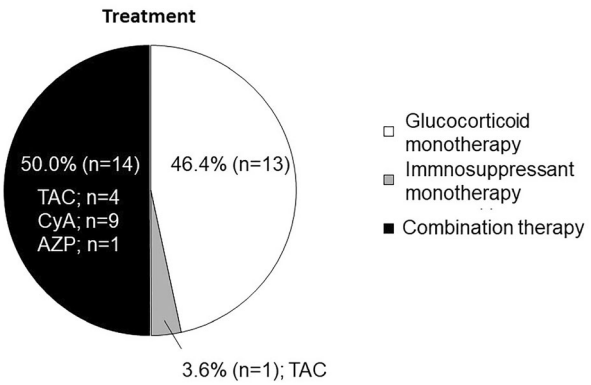

Fig. 2 IPAF treatment type. The GC monotherapy subgroup included 13 participants (46.4%). Immunosuppressant monotherapy (tacrolimus) was administered to one patient (3.6%). Immunosuppressants included tacrolimus, cyclosporine, and azathioprine (29%, $n = 4$; 64%, $n = 9$; and 7%, $n = 1$) in the GC + IS combination therapy group

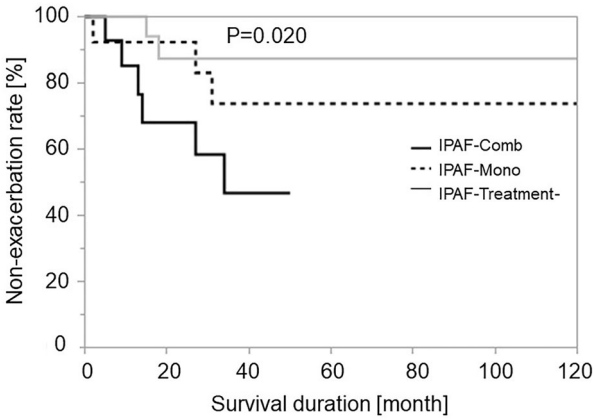

Fig. 3 Kaplan–Meier survival curves in each treatment for IPAF. Interstitial pneumonia with autoimmune features (IPAF) with monotherapy ($n = 13$), combined therapy ($n = 14$), and without treatment ($n = 24$). IPAF-Combo vs. IPAF-Mono; $P = 0.020$, IPAF-Combo vs. IPAF-untreated; $P = 0.00070$, IPAF-Mono vs. IPAF-untreated; $P = 0.0088$

polymyositis/dermatomyositis (Table 4). In contrast, anti-Scl-70 antibody positivity was significantly higher ($P = 0.025$), characterized by systemic scleroderma (Table 4).

Prognostic Factors for Exacerbation of Treated IPAF

Among the 28 patients treated with IPAF, the exacerbation rate was 42.9% ($n = 12$) (Table 4). We evaluated the risk factors for exacerbation in the treated groups. Smoking history, high KL-6 titer, and the duration from diagnosis to the start of treatment (> 1 month) were significant risk factors for exacerbation ($P = 0.0062$, 0.011, and 0.019, respectively) (Table 4). The number of risk factors was positively and significantly associated with the exacerbation rate ($P = 0.0053$) (Fig. 1).

Treatment Method and the Long-Term Outcome in IPAF

We divided the treated group into two subgroups: those treated with monotherapy (GC) and those treated with combination therapy (GC and IS). GC monotherapy was administered in 46.4% ($n = 13$), and GC + IS combination therapy was administered in 50% ($n = 14$) of the treatments. The combination therapy group was significantly associated with 'mechanic's hands' ($P = 0.037$) (Table 4). In contrast, anti-SS-A antibody positivity was significantly higher ($P = 0.012$) (Table 4). Combination therapy was significantly higher in patients with more than two risk factors than monotherapy ($P = 0.030$) (Table 4). GC dose at the start of treatment in the monotherapy and combination therapy groups was 30.4 ± 13.0 mg/day and 32.1 ± 17.2 mg/day, compared with 9.2 ± 7.2 mg/day and 8.1 ± 3.6 mg/day at the last visit, showing no significant difference between groups ($P = 0.96$ and 0.98, respectively) (Table 4). The immunosuppressants included calcineurin inhibitors tacrolimus and cyclosporine (29%, $n = 4$; 64%, $n = 9$). Azathioprine was administered to one patient (Fig. 2). There was no significant difference in the rate of exacerbations among patients with IS ($P = 0.16$). Comparing the long-term outcomes between the monotherapy and combination therapy groups, it turned out that the 3-year non-exacerbation rates were 72.9 and 45.9%, respectively ($P = 0.020$) (Fig. 3). The combination therapy group had a significantly worse prognosis than the monotherapy group, and the rate of severe adverse events (SAE) requiring hospitalization due to infections such as pneumonia was 23.1 and 0%, respectively ($P = 0.057$) (Table 4). The combination therapy group tended to have fewer SAEs.

DISCUSSION

This study found that the risk factors for exacerbation of IPAF were smoking history, high titer of KL-6, and high titer of SP-D. Particularly in the treated group, smoking history, high titer of KL-6, and the duration from diagnosis to the start of treatment were significantly associated with exacerbations. Regarding long-term outcomes, IPAF was better than IIP and similar to CTD-ILD. This is comparable to the results of a previous study [7]. Patients with IPAF with risk factors had a high exacerbation rate regardless of treatment; however, there was no significant difference between the monotherapy and combination therapy groups.

Older age, male sex, ever-smokers, radiological and/or pathological UIP pattern, %FVC, and %DLCO have been reported as risk factors for exacerbation [1, 6, 7, 12, 13]. In our study, ever-smoking was a risk factor for exacerbation, similar to previous reports [1, 6, 7, 12, 13]. In contrast, older age, male sex, and radiological UIP pattern were not risk factors for exacerbation in our study. Regarding %FVC and %DLCO, the rates of these examinations were only 57 and 26%, respectively, so their association with exacerbation could not be assessed. Our study revealed that KL-6 and SP-D were risk factors for exacerbation. KL-6 and SP-D are active markers of interstitial pneumonia in Japan. Although one study reported KL-6 as a poor prognostic factor in IPAF [13], SP-D has not been reported previously. A high SP-D titer at diagnosis was a poor prognostic factor in patients with IIP [14]. SP-D has never been

reported as a poor prognostic factor in patients with IPAF, but we speculated that SP-D might predict a poor prognosis. When treated with IPAF, a high SP-D titer was not a risk factor for exacerbation. Our study also revealed that the duration from diagnosis to the start of treatment was a risk factor for exacerbation. These findings suggest that early diagnosis and early start of treatment are necessary. We speculated that the start of treatment as early as possible may improve the prognosis.

To date, there have been no promising treatments. GC with or without IS, such as mycophenolate mofetil, azathioprine, calcineurin inhibitors, or rituximab, has been used for CTD treatment [15–25]. However, no studies have comprehensively described the long-term outcomes of patients with IPAF by comparing different treatment methods. Our study compared the efficacy and safety profiles of GC monotherapy and GC + IS combination therapy. The reduction in GC dose was not significantly different between monotherapy and combination therapy. In the combination therapy group, 'mechanic's hands' was significantly higher. This suggests 'anti-ARS antibody syndrome' [26–28] and has a favorable response to GC [29]. Therefore, we speculated that this was why there was no significant difference in the reduction of GC dose between monotherapy and combination therapy groups, regardless of the addition of IS. Although there was no significant difference in the duration from diagnosis to the start of treatment, the GC dose at the start of treatment, and the last visit between the two groups, the combination therapy group had significantly worse long-term outcomes than the monotherapy group. We speculated that this was because the combination therapy group had more risk factors than the monotherapy group. On the other hand, age at diagnosis, GC dose at the start of treatment, and the last visit were not significantly different between the two groups. Despite the use of IS in combination, SAE tended to be lower in the combination therapy group. This may be because IS was administered to patients who were judged to be tolerant of IS.

This study has some limitations. First, this is a single-center retrospective observational cohort study, which makes selection bias and limits generalizability. However, many previous studies were also single-center retrospective studies [1, 6, 7, 13, 30, 31]. Second, we evaluated the small number of IPAF patients. Therefore, we may not be able to evaluate the effect of some variables accurately. However, the number of IPAF patients in this study is not different from previous studies [6, 30, 31]. Third, this study did not examine the risk of exacerbations related to lung function (%FVC and %DLCO) because we could not collect the data on pulmonary function tests for all patients from their medical records, as the data were collected from actual clinical practice.

In conclusion, our study revealed that patients with IPAF with more than two risk factors had a high exacerbation rate regardless of treatment. Moreover, the later the start of treatment, the worse the prognosis. Therefore, it is important to start treatment early. To the best of our knowledge, this is the first report comparing the significance of the effectiveness of IPAF treatment between monotherapy and combination therapy. Further studies should clarify new interventions aimed at preventing exacerbations in these patients.

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Disclosures. Katsuya Suzuki and Tsutomu Takeuchi have nothing to disclosure. Okinori Murata has changed affiliation: Division of Allergy and Rheumatology, Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Japan. Makoto Maemondo has changed affiliation: Division of Pulmonary Medicine, Department of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Japan.

Compliance with Ethics Guidelines. All procedures were approved by the Medical Ethics Committee of Iwate Medical University Hospital (registration no. MH2018-505) and adhered to the tenets of the Declaration of Helsinki. This is a retrospective study and written consent is not required. The method of disclosure to patients is as follows. The method of disclosure to patients will be explained in writing at the outpatient clinic of the Department of Respiratory, Allergy, and Collagen Diseases, and subjects will be given the opportunity to refuse the use of their data.

Data Availability. All data generated or analyzed during this study are included in this published article or as supplementary information files.

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