Original Article

Compatible with fibrotic hypersensitivity pneumonitis on high-resolution computed tomography: from the ATS/JRS/ALAT 2020 hypersensitivity pneumonitis guidelines

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Background: In compatible with fibrotic hypersensitivity pneumonitis (HP) of the computed tomography (CT) classification using the American Thoracic Society (ATS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) HP guidelines, the lung fibrosis pattern was classified as either a usual interstitial pneumonia (UIP) pattern or a diffuse ground-glass opacity (GGO) pattern with subtle fibrosis. We investigated whether patients with the same imaging classification had different disease progression. We also attempted to reclassify these patients using the CHEST HP guidelines.

Methods: Patients with fibrotic HP who had compatible CT pattern in the ATS/JRS/ALAT classification were investigated retrospectively.

Results: With 62 patients in the UIP pattern group and 25 patients in the diffuse GGO pattern group, 87 patients with fibrotic HP had compatible pattern on CT. Annual forced vital capacity changes in the UIP pattern group and diffuse GGO pattern group were –2.7% and +3.3% (P=0.004), respectively. The 5-year survival rates in the UIP pattern group and diffuse GGO pattern group were 86% and 100% (P=0.02). In UIP pattern group in the ATS/JRS/ALAT classification, 27% patients were classified as typical fibrotic HP pattern in the CHEST guidelines. In the diffuse GGO pattern group, 52% patients were classified as typical pattern of fibrotic HP. In the CHEST guidelines, more patients in the GGO pattern were classified as typical pattern compared with those in the UIP pattern (P=0.02).

Conclusions: The two patterns in compatible with fibrotic HP of CT classification using the ATS/JRS/ALAT HP guidelines had different disease progression. Typical patterns were more frequent in the CHEST guidelines than the ATS/JRS/ALAT guidelines.

Keywords: Chronic hypersensitivity pneumonitis (chronic HP); high-resolution computed tomography classification (HRCT classification); hypersensitivity pneumonitis guidelines (HP guidelines); fibrotic hypersensitivity pneumonitis (fibrotic HP)

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Introduction

Hypersensitivity pneumonitis (HP) is a disease caused by repeated inhalation of inciting antigens, resulting in the inflammation and fibrosis of the alveolar walls and bronchiole, mainly due to lymphocytic infiltration. Histopathological findings and high-resolution computed tomography (HRCT) scan findings are often similar between patients with fibrotic HP and those patients with idiopathic pulmonary fibrosis (IPF). Moreover, approximately half of the patients diagnosed with IPF in the 2011 IPF guidelines had their diagnoses changed from IPF to chronic HP after a 6-year follow-up (1). Therefore, fibrotic HP was very difficult to differentiate from IPF.

The American Thoracic Society (ATS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) HP guidelines was published in 2020. The diagnostic confidence of fibrotic HP is calculated from a matrix table based mainly on the HRCT findings, presence of exposure, histopathology, and bronchoalveolar lavage (BAL) findings. Furthermore, the HRCT findings are divided into typical fibrotic HP, compatible with fibrotic HP, and indeterminate for fibrotic HP (2).

According to the ATS/JRS/ALAT guidelines, in compatible with fibrotic HP, the lung fibrosis pattern was classified as either a usual interstitial pneumonia (UIP) pattern according to the 2018 IPF guidelines or a diffuse ground-glass opacity (GGO) pattern with subtle fibrosis. The UIP pattern on HRCT was a poor prognostic factor in patients with fibrotic HP, whereas the GGO pattern was not (3). UIP and GGO patterns classified in the same category, "compatible with fibrotic HP" could have different disease behavior (4). In addition, the distribution of fibrosis in the ATS/JRS/ALAT HP guidelines for typical fibrotic HP on HRCT is axially and craniocaudally random. A few patients show a homogeneous distribution of shadows, and the HRCT findings in many patients could be categorized as compatible with fibrotic HP. Therefore, it is important to understand the patients classified as compatible with fibrotic HP on HRCT. In this study, we compared the disease progression in patients with fibrotic HP who had compatible pattern with fibrotic HP of the HRCT classification in accordance with the ATS/JRS/ALAT guidelines (2). Moreover, using the CHEST guidelines (5), the patients with fibrotic HP who had compatible pattern with fibrotic HP of the HRCT classification in accordance with the ATS/JRS/ALAT guidelines were reclassified, and the impact of the CHEST guidelines was investigated. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1845/rc).

Highlight box

Key findings

- A usual interstitial pneumonia (UIP) and a diffuse ground-glass opacity (GGO) patterns in compatible with fibrotic hypersensitivity pneumonitis (HP) of high-resolution computed tomography (HRCT) classification using the American Thoracic Society (ATS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) HP guidelines had different disease progression.

What is known and what is new?

- In compatible with fibrotic HP of HRCT classification using the ATS/JRS/ALAT HP guidelines, the 5-year survival rates in the UIP pattern group and diffuse GGO pattern group were 86% and 100%.
- In the CHEST guidelines, more patients in the diffuse GGO pattern in accordance with the ATS/JRS/ALAT HRCT classification were classified as typical pattern compared with those in the UIP pattern.

What is the implication, and what should change now?

- HRCT classification and diagnostic confidence in HP guidelines are not predictive of prognosis.

Methods

Study subjects

This study was a single-center, retrospective study. The patients were included using the following criteria: patients who underwent surgical lung biopsy or transbronchial lung cryobiopsy between January 2015 and December 2019 at our hospital, those who were pathologically diagnosed with fibrotic HP by a pathologist (T.T.) specializing in HP, those who were diagnosed as fibrotic HP by multidisciplinary discussion team, those who were classified as compatible with fibrotic HP in the HRCT classification of the official ATS/JRS/ALAT HP guidelines (2), and those who had forced vital capacity (FVC) measured 1 year after diagnosis. The changes in pulmonary function test and interstitial pneumonia markers, prognosis, onset of acute exacerbation, and treatments were investigated in the target patients. Moreover, the ratio of patients meeting the progressive fibrosing interstitial lung disease (PF-ILD) criteria during the clinical course was investigated. The criteria for PF-ILD were defined as meeting the following within 1 year

from enrollment: a relative decrease in FVC ≥10% and any two of the following: a relative decrease in FVC of 5–10%, an increase in fibrosis on HRCT findings, or worsening of respiratory symptoms (6,7). Respiratory symptoms were determined from the medical records. The percentage of newly proposed progressive pulmonary fibrosis (PPF) in the 2022 IPF guidelines was also surveyed (4). The criteria for PPF were defined as meeting the following within 1 year from enrollment: any two of the following: physiological evidence of disease progression with an absolute decrease in FVC of 5% or in diffusing capacity of lung for carbon monoxide (DLco) of 10%, a radiological evidence of disease progression on HRCT findings, or worsening of respiratory symptoms.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Kanagawa Cardiovascular and Respiratory Disease Center on 27 October 2021 (No. KCRC-21-0028), and individual consent for this retrospective analysis was waived. Each patient's information was anonymized prior to all analyses.

HRCT findings

The imaging protocol for HRCT was supine, deep-inhalation, unspaced, 0.5-mm thin-slice CT of the entire lung field (Aquilion ONE or Aquilion Precision). In patients classified as compatible with fibrotic HP based on the ATS/JRS/ALAT HP guidelines (2), patients with a UIP pattern according to the 2018 IPF guidelines were defined as the UIP pattern group, and patients with a diffuse GGO pattern with subtle fibrosis were defined as the diffuse GGO pattern group. A respiratory physician (S.K.) and a respiratory physician (R.O.) specializing in ILD judged the HRCT independently, and if they disagreed on the pattern classification, they discussed the HRCT pattern together. In patients where the two respiratory physicians could not reach agreement after discussion, a chest radiologist judged the HRCT.

Treatments

The patients whose inciting antigen was identified by inhalation challenge test or antigen avoidance test avoided the inciting antigen. Furthermore, the patients were instructed to discard down jackets and feather quilts, to clean their house, or to change their residence if necessary, depending on the inciting antigen. In patients whose disease progressed despite antigen avoidance or in those whose inciting antigen was unidentified, steroids, immunosuppressants, and antifibrotic agents were often used. The type, dosage, and timing of treatment were optimized by the attending physician according to each patient's condition.

Statistical analysis

The Fisher's exact test and chi-square test was used to compare the categorical variables, and the unpaired *t*-test was used to compare the continuous variables of the patient's background. Furthermore, the analysis of covariance was used to compare the changes in the lung function test and interstitial pneumonia markers at 1 and 2 years after diagnosis in the UIP pattern and diffuse GGO pattern groups. The log-rank test was used to compare survival and duration of events. In addition, the Cox hazard regression analysis was used to select predictors of death, acute exacerbation, and initiation of long-term oxygen therapy (LTOT). Multivariate Cox hazard regression analysis was performed for parameters that were $P<0.05$ in univariate Cox hazard regression analysis. Then, all data were analyzed using R version 3.61 with R studio and BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). Any missing data were not complemented.

Results

Baseline characteristics

Consecutively, 87 patients met the criteria, with 62 patients in the UIP pattern group and 25 patients in the diffuse GGO pattern group (*Figure 1*). In *Figure 2A*,*2B*, GGOs distributed predominantly in the lower lobe were judged as the diffuse GGO pattern group with compatible with fibrotic HP according to the ATS/JRS/ALAT guidelines. In *Figure 2C*, the ATS/JRS/ALAT guidelines considered the UIP pattern group as compatible with fibrotic HP. The two groups had no significant differences in age, gender, FVC, diffusing capacity of lung for carbon monoxide (DLco), and pathological findings; the UIP pattern group had a lower Krebs von den Lungen-6 (KL-6) level and a lower percentage of lymphocyte in BAL fluid compared with the diffuse GGO pattern group. All patients in the UIP pattern group did not have any treatments at baseline; conversely, two patients in the diffuse GGO pattern group received steroids (*Table 1*). Neither group was treated with immunosuppressants or antifibrotic drugs at baseline.

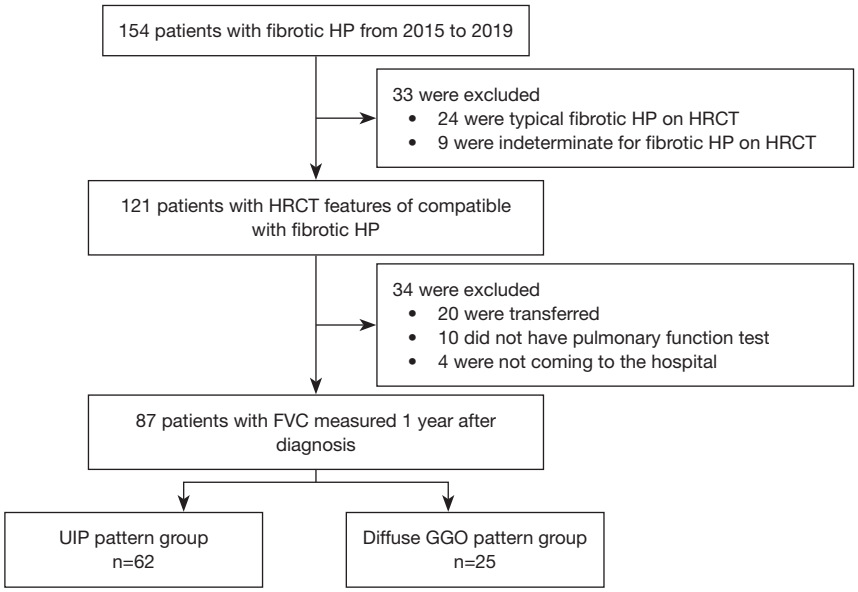

Figure 1 Flow chart of the selection process in this study. HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; FVC, forced vital capacity; UIP, usual interstitial pneumonia; GGO, ground-glass opacity.

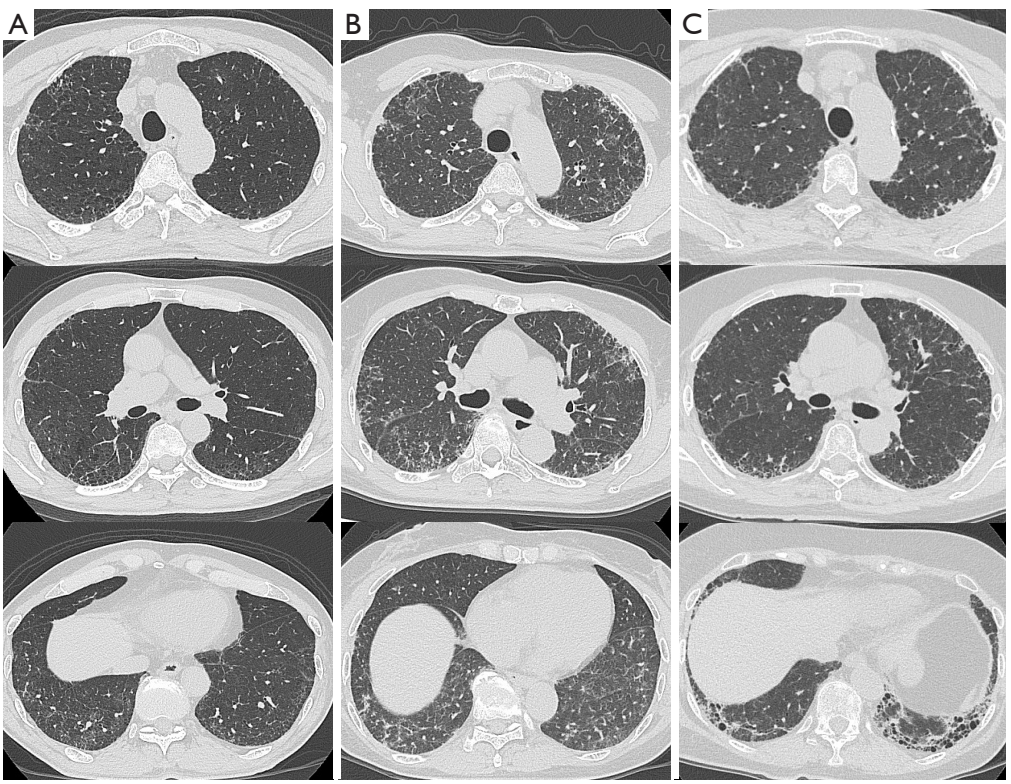

Figure 2 High-resolution computed tomography findings of three patients. According to the ATS/JRS/ALAT guidelines, (A,B) the diffuse ground-glass opacity pattern with compatible with fibrotic HP; (C) the usual interstitial pneumonia pattern as compatible with fibrotic HP. ATS, American Thoracic Society; JRS, Japanese Respiratory Society; ALAT, Latin American Thoracic Association; HP, hypersensitivity pneumonitis.

Table 1 Baseline characteristics

Parameters	UIP pattern group (n=62)	Diffuse GGO pattern group (n=25)	P value
Age (years)	67.4±7.1	68.8±7.4	0.39
Sex (male/female)	44/18	12/13	0.05
BMI (kg/m^2)	23.8±3.4	23.4±3.6	0.71
Surgical lung biopsy	30 (48.4)	12 (48.0)	>0.99
Cryobiopsy	32 (51.6)	13 (52.0)	>0.99
Never smoker (yes/no)	18/44	15/10	0.01
WBC (/μL)	6,180±1,630	6,500±2,680	0.48
LDH (U/L)	217±42	223±47	0.62
CRP (mg/dL)	0.21±0.31	0.31±0.58	0.30
KL-6 (U/mL)	1,365±1,404	2,119±2,441	0.07
SP-D (ng/mL)	327±221	341±194	0.77
FVC %predicted (%)	90.8±17.0	86.1±17.5	0.25
DLco %predicted (%)	79.1±21.2	80.0±20.7	0.85
BAL macrophages (%)	62±24	38±24	<0.001
BAL lymphocytes (%)	32±25	51±27	0.009
Poorly formed non-necrotizing granulomas	38 (61.3)	20 (80.0)	0.13
Airway-centered fibrosis	38 (61.3)	18 (72.0)	0.39
Steroid before diagnosis	0 (0.0)	2 (3.2)	>0.99

Data are presented as n (%) or mean ± standard deviation. The numbers of patients who underwent BAL were 52 in the UIP pattern group and 19 in the diffuse GGO pattern group. UIP, usual interstitial pneumonia; GGO, ground-glass opacity; BMI, body mass index; WBC, white blood cell; LDH, lactate dehydrogenase; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; FVC, forced vital capacity; DLco, diffusing capacity of lung for carbon monoxide; BAL, bronchoalveolar lavage.

Clinical course and treatments

The mean observation period after the diagnosis for all patients was 37.5 months. There was no significant difference between the proportion of patients who received steroids, tacrolimus, or antifibrotic agents by 1 year after diagnosis between the patients in the UIP pattern and diffuse GGO pattern groups (*Table 2*). The mean dose for the 11 PSL users in the UIP group was 17.1±9.1 mg/day, compared to 21.7±11.5 mg/day in the four patients with diffuse GGO pattern (P=0.27). In the UIP pattern group, the FVC and DLco changes were greater than those in the diffuse GGO pattern group during 1 year after the diagnosis (P=0.004 and P=0.01, respectively). The 2-year changes in FVC and KL-6 were also significantly different between the UIP pattern group and diffuse GGO pattern group (P=0.02 and P=0.002, respectively) (*Figure 3*). Within 1 year after the diagnosis, 23 patients (37%) in the UIP pattern group and 3 patients (12%) in the diffuse GGO pattern group had met the diagnostic criteria for PF-ILD, with a statistical significance (P=0.02). Within 1 year after diagnosis, PPF criteria were met in 44% of the UIP pattern group and 12% of the diffuse GGO pattern group (P=0.006). The incidence rates of acute exacerbation within 1 year were 4.8% in the UIP pattern group and 0% in the diffuse GGO pattern group. Nine patients died in the UIP pattern group (P=0.02) (*Figure 4A*), whereas all patients in the diffuse GGO pattern group survived for 5 years. The 3-year event rates were 27.4% in the UIP pattern group and 4.0% in the diffuse GGO pattern group, where events were defined as death, acute exacerbation, or LTOT (P=0.01) (*Figure 4B*). A multiple logistic regression analysis indicated that the UIP pattern on HRCT were independently associated with death, acute exacerbation, and induction of LTOT (*Table 3*). In *Figure 5*, the course of representative HRCT images of the diffuse GGO pattern group and the UIP pattern group was showed.

Table 2 Treatments during 1 year from diagnosis

Treatments	UIP pattern group (n=62)	Diffuse GGO pattern group (n=25)	P value
Steroid	11 (17.7)	6 (24.0)	0.55
Steroid dosage (mg/day)	17.1±9.1	21.7±11.5	0.27
Time to steroid administration (months)	5.8±4.9	2.3±1.6	0.66
Tacrolimus	3 (4.8)	2 (8.0)	0.62
Antifibrotic agents	9 (14.5)	1 (4.0)	0.26

Data are presented as n (%) or mean ± standard deviation. UIP, usual interstitial pneumonia; GGO, ground-glass opacity.

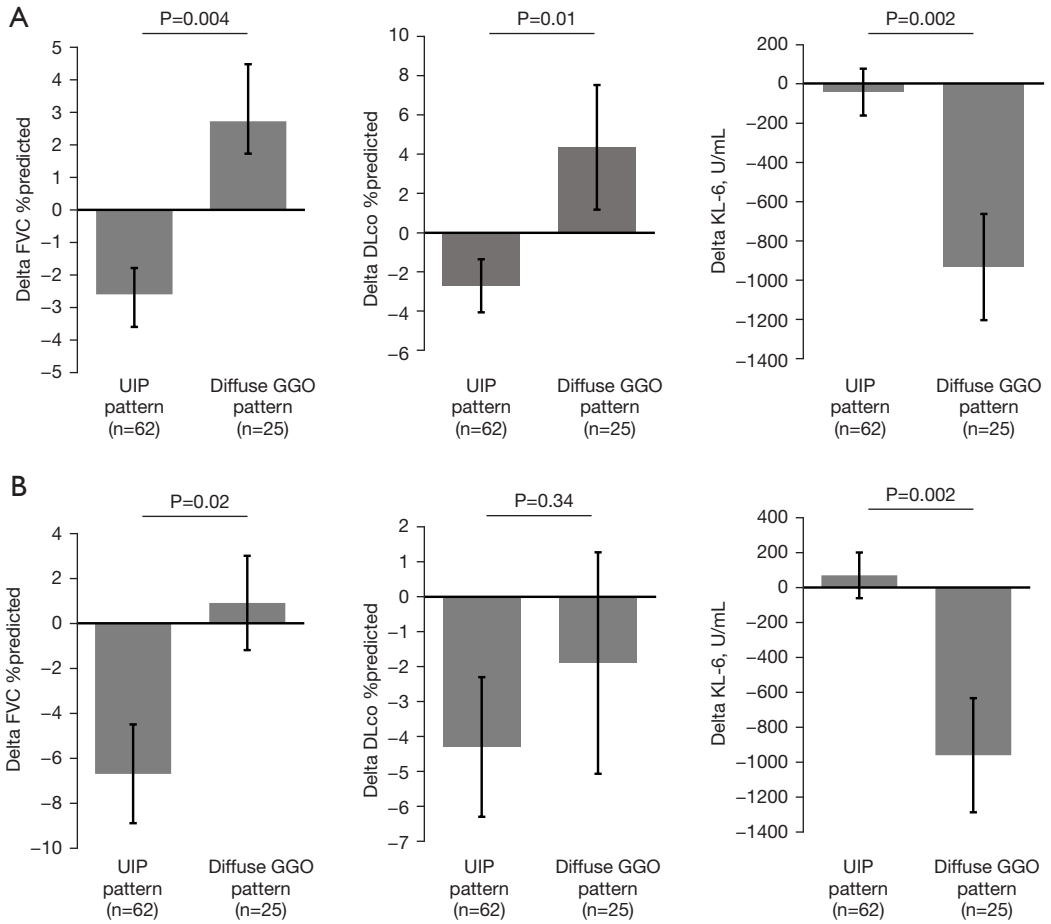

Figure 3 Mean changes in FVC, DLco, and KL-6 1 year after the diagnosis (A) and 2 years after the diagnosis (B). The P value for FVC change was calculated using ANCOVA with a fibrotic pattern in HRCT as a factor and FVC and KL-6 as covariates at diagnosis. The P value for DLco change was calculated using ANCOVA with a fibrotic pattern in HRCT as a factor and DLco and KL-6 as covariates at diagnosis. The P value for KL-6 change was calculated using ANCOVA with a fibrotic pattern in HRCT as a factor and DLco and KL-6 as covariates at diagnosis. FVC, forced vital capacity; DLco, diffusing capacity of lung for carbon monoxide; KL-6, Krebs von den Lungen-6; UIP, usual interstitial pneumonia; GGO, ground-glass opacity; ANCOVA, analysis of covariance; HRCT, high-resolution computed tomography.

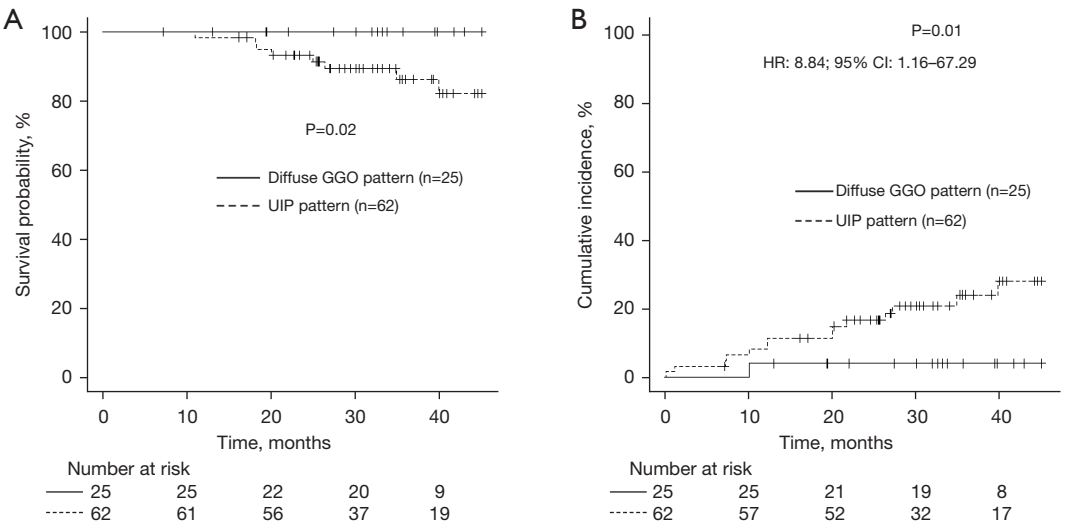

Figure 4 Comparison of clinical course of the diffuse GGO pattern and the UIP pattern. (A) Overall survival curve between the diffuse GGO pattern and the UIP pattern; (B) the event curve of death, acute exacerbation, or initiation of long-term oxygen therapy. The P values were calculated using a log-rank test. GGO, ground-glass opacity; UIP, usual interstitial pneumonia; HR, hazard ratio; CI, confidence interval.

Table 3 Predictors of the disease progression to death, acute exacerbation, and induction of LTOT in patients with fibrotic HP

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.02 (0.95–1.09)	0.66		
Male	0.78 (0.30–1.99)	0.60		
Never smoker	0.87 (0.33–2.33)	0.78		
KL-6 (U/mL)	1.00 (1.00–1.00)	0.49		
SP-D (ng/mL)	1.00 (1.00–1.00)	0.36		
BAL lymphocytes (%)	0.99 (0.97–1.01)	0.37		
FVC %predicted (%)	0.96 (0.94–0.99)	0.02	0.99 (0.95–1.02)	0.41
DLco %predicted (%)	0.97 (0.95–0.99)	0.004	0.98 (0.94–1.01)	0.16
Desaturation in the 6-min walk test (%)	1.18 (1.05–1.34)	0.006	1.12 (0.95–1.02)	0.12
The UIP patten group	8.84 (1.16–67.29)	0.03	10.43 (1.18–92.07)	0.03

LTOT, long-term oxygen therapy; HP, hypersensitivity pneumonitis; HR, hazard ratio; CI, confidence interval; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; BAL, bronchoalveolar lavage; FVC, forced vital capacity; DLco, diffusing capacity of lung for carbon monoxide; UIP, usual interstitial pneumonia.

Reclassification with the HRCT classification of the CHEST HP guidelines in 2021

In the 62 patients with UIP pattern, in accordance with the ATS/JRS/ALAT HRCT classification (2), 17 patients (27%) were classified as typical fibrotic HP and 45 patients (73%) were classified as compatible with fibrotic HP according to the HRCT classification of the CHEST HP guidelines (5). In the 25 patients with the diffuse GGO pattern, in accordance with the ATS/JRS/ALAT HRCT classification (2), 13 patients (52%) were classified as typical fibrotic HP and 12 patients (48%) were classified as compatible with fibrotic

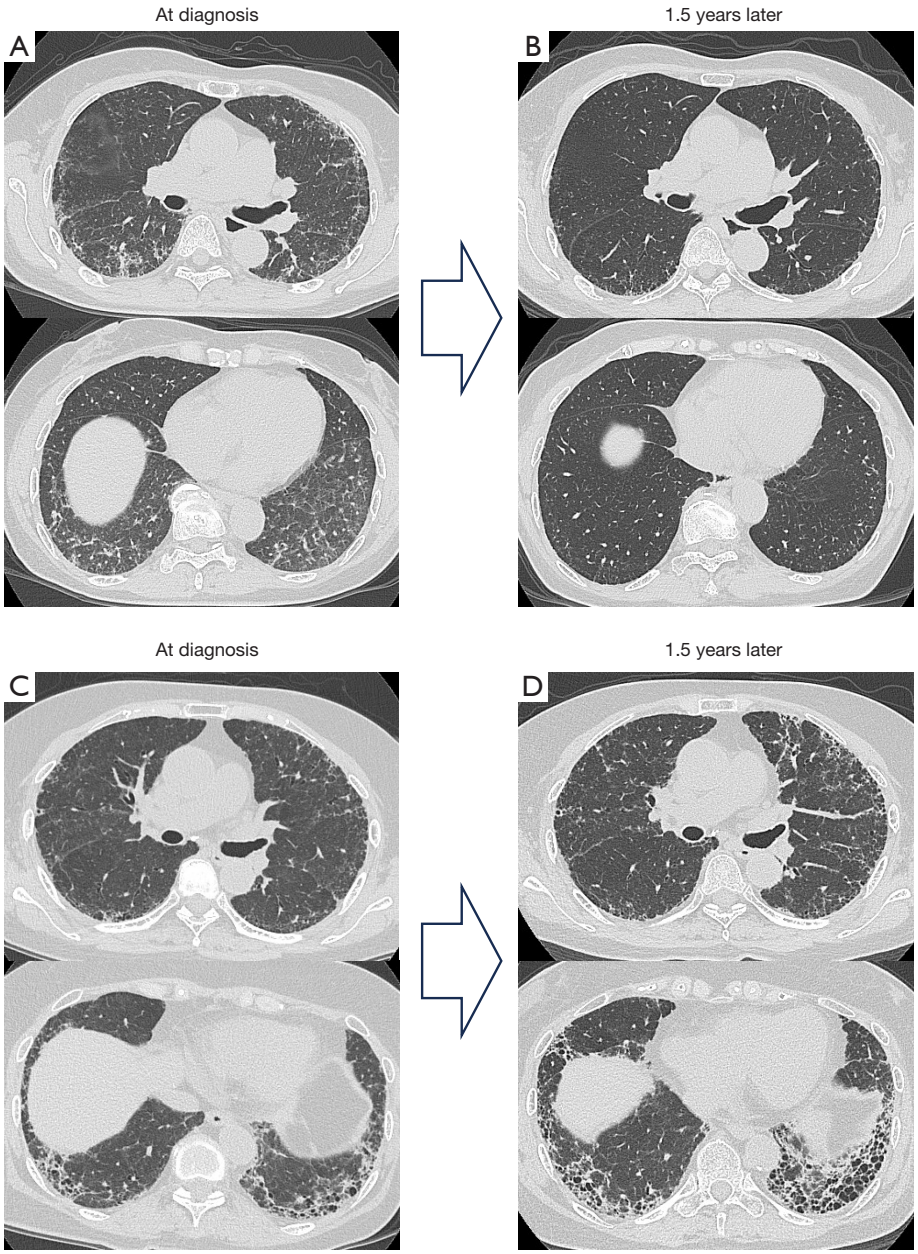

Figure 5 High-resolution computed tomography in patients with compatible with fibrotic HP. (A,B) A patient in the diffuse ground-glass opacity pattern group; (C,D) a patient in the usual interstitial pneumonia pattern group. HP, hypersensitivity pneumonitis.

HP. In accordance with the CHEST HP guidelines (5), more patients with the GGO pattern in ATS/JRS/ALAT guidelines were classified as typical pattern in CHEST guidelines compared with those with the UIP pattern in ATS/JRS/ALAT guidelines (P=0.02). In *Figure 2A*, GGOs distributed predominantly in the lower lobes were judged as GGO pattern group in compatible with fibrotic HP according to the ATS/JRS/ALAT guidelines, and compatible with fibrotic HP according to the CHEST guidelines. In *Figure 2B*, the ATS/JRS/ALAT guidelines considered the GGO pattern group as compatible with fibrotic HP; GGOs was present in all lung zone of subpleural areas, which was considered as typical fibrotic HP according to the CHEST guidelines. In *Figure 2C*, the ATS/JRS/ALAT

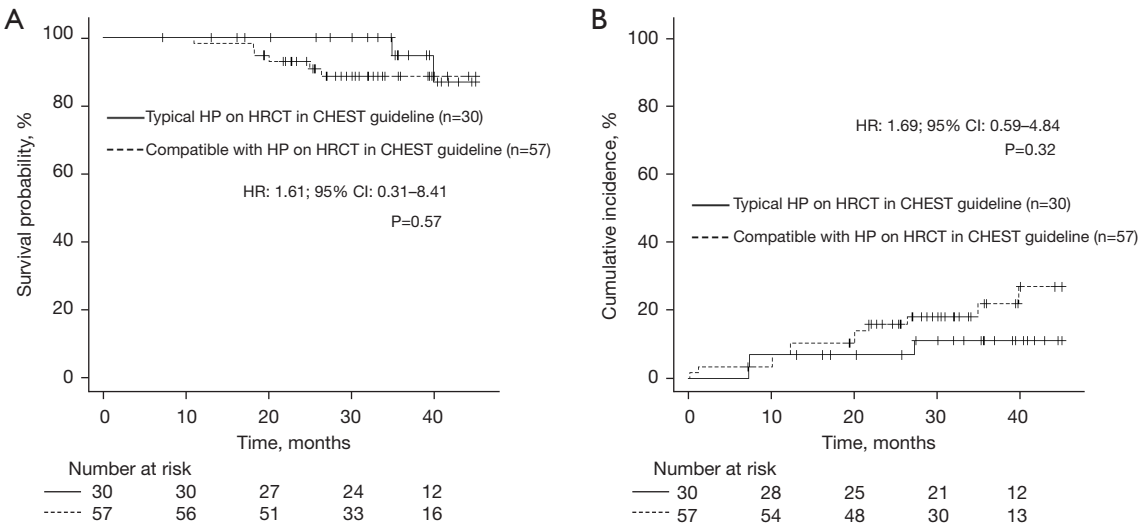

Figure 6 Based on CHEST guidelines classification, comparison of clinical course of typical HP and compatible with HP on HRCT. (A) Overall survival curve; (B) the event curve of death, acute exacerbation, or initiation of long-term oxygen therapy. HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; HR, hazard ratio; CI, confidence interval.

guidelines considered the UIP pattern group as compatible with fibrotic HP, while the CHEST guidelines considered it as typical fibrotic HP due to the presence of centrilobular nodules of GGO in all lung zones. After the reclassification with the HRCT classification of the CHEST HP guidelines, no significant difference in overall survival was observed between typical HP and compatible with HP on HRCT in CHEST guidelines [HR =1.61; 95% confidence interval (CI): 0.31–8.41; P=0.57] (*Figure 6A*). Where events were defined as death, acute exacerbation, or LTOT, no significant difference in events was observed between two groups (HR =1.69; 95% CI: 0.59–4.84; P=0.32) (*Figure 6B*). The changes in FVC and KL-6 were compared between typical HP pattern in CHEST guidelines and compatible with fibrotic HP pattern in CHEST guidelines. The FVC changes in the typical and compatible groups in CHEST guidelines after 1 year were −0.1% and −1.3% (P=0.52), respectively. Furthermore, the FVC changes in the typical and compatible groups after 2 years were −4.3% and −5.3% (P=0.77), respectively. Regarding the change of KL-6 levels over 2 years, the patients with typical HP pattern in CHEST guidelines improved by 871 U/mL, whereas those with compatible with fibrotic HP pattern worsened by 82 U/mL (P<0.001).

Discussion

In patients with compatible with fibrotic HP of the CT classification using the ATS/JRS/ALAT HP guidelines, a larger decrease in FVC and smaller improvement of KL-6 values were observed in the UIP pattern group compared with the diffuse GGO pattern group using the ATS/JRS/ALAT fibrotic HP guidelines. Moreover, the UIP pattern group had more events of death, acute exacerbation, and induction of LTOT compared with the diffuse GGO pattern group.

The patients with compatible with fibrotic HP in the ATS/JRS/ALAT HRCT classification seemed to have different prognoses because of the significant changes in FVC and DLco after the first year of diagnosis between the UIP pattern group and diffuse GGO pattern group, as observed in this study. A decrease in FVC ≥10% and DLco ≥15% within 12 months in patients with chronic HP were reported to be poor prognostic factors (8,9). Therefore, prognostic factors FVC and DLco for fibrotic HP were important. The KL-6 level in patients with chronic HP was significantly elevated at acute exacerbation (10), and a decrease in KL-6 levels ≥10% after 2 weeks of antigen avoidance was associated with survival (11). Therefore, the annual KL-6 level change was one of the candidates for a prognostic factor in patients with fibrotic HP. In this study, a difference in KL-6 level change was also observed between the UIP pattern group and diffuse GGO pattern group. The UIP pattern group could have a worse disease prognosis than the diffuse GGO pattern group using the ATS/JRS/ALAT fibrotic HP guidelines based on the

changes of the FVC and KL-6 level.

In this study, more patients in the UIP pattern group were diagnosed with PF-ILD or PPF during the first year after diagnosis compared with those in the diffuse GGO pattern group. In the INBUILD study, fibrotic HP was placed within the newly proposed phenotype of PF-ILD. Except for IPF, the fibrotic HP was the most common disease diagnosed in 173 patients (26%). Faverio *et al.* reported that 81% of the 75 ILD patients were diagnosed by meeting the diagnostic criteria of FVC ≥10% (12). Therefore, to examine annual changes in FVC, was particularly useful in patients with fibrotic HP. In this study, only 13% of the patients were prescribed with nintedanib because many patients were included before the approval of nintedanib. Nintedanib was shown to be effective in reducing the FVC decline in the INBUILD study (7). The patients with UIP pattern in compatible with fibrotic HP had the rapid decline of FVC; routine short-term checks for changes in FVC are necessary after the diagnosis.

The prognosis of chronic/fibrotic HP was approximately 5–8 years (13,14). When investigating the fibrotic HP, a long-term observation was needed. Although this study did not have a long enough period of time to fully ascertain the prognosis, significant differences in the log-rank test of the survival curve were found between the two groups. Moreover, the events of death, acute exacerbation, and initiation of LTOT differed between the two groups. In patients with compatible pattern on HRCT, The UIP pattern group was an independent predictor of the events in multivariate Cox hazard regression analysis as well as FVC, DLco, and desaturation in the 6-min walk test, which were consistent with previous studies in patients with all fibrotic HP (8,15-17). Regarding HRCT findings, the UIP pattern or honeycomb in HRCT findings was associated with a poor prognosis and the increased frequency of acute exacerbations, with median survival as short as 2.8 years, which was similar to the prognosis of patients with IPF (3,18,19). Meanwhile, the presence of GGO has been associated with better survival compared with the absence of GGO (1,20). Based on this study and previous reports, it could not be appropriate to use the ATS/JRS/ALAT HRCT classification of fibrotic HP to predict disease progression. The PF-ILD and PPF classifications, which are classifications based on disease behavior, not ILD diagnosis, could be more appropriate for predicting disease progression.

When the patients were reclassified using the HRCT classification in accordance with the 2021 CHEST HP guidelines (5), 30% of the patients in the UIP pattern group in the ATS/JRS/ALAT HP guidelines were classified as typical HP and more than half of the patients in the diffuse GGO pattern group were classified as typical HP in the CHEST HP guidelines from our results. Buendia-Roldan *et al.* reported that the number of patients diagnosed with HP with high confidence was 26 (18%) in the ATS/JRS/ALAT guidelines and 94 (65%) in the CHEST HP guidelines, when comparing the two guidelines in 144 patients with HP, including 100 patients with fibrotic HP (21). The CHEST guidelines had less stringent HRCT finding criteria for typical fibrotic HP compared with the ATS/JRS/ALAT guidelines. Therefore, when the CHEST HP guidelines was used, a higher percentage of the patients were classified as typical fibrotic HP in patients with compatible with fibrotic HP of the CT classification using the ATS/JRS/ALAT HP guidelines. In this study, the diagnostic confidence of the CHEST HP guidelines was low in its ability to discriminate overall survival and events of death, acute exacerbation, or initiation of LTOT; however, this study included only patients with compatible with fibrotic HP of the CT classification using the ATS/JRS/ALAT HP guidelines.

This study had several limitations. First, this study had a single-center, retrospective design, which was a major bias in patient selection. Consecutive patients were enrolled to reduce the bias in this study. Second, this study excluded patients who did not undergo lung function tests 1 year after the diagnosis, which had a likelihood of underestimating the FVC decline. The main reason for the exclusion of patients in this study was the lack of regular outpatient visits due to referral to other hospitals, rather than the lack of pulmonary function tests 1 year after the diagnosis. Furthermore, they could not be checked regularly at our hospital because some patients were referred to our hospital only for histopathological examinations. Third, the decision to initiate treatments was made by the attending physicians. However, no difference in frequency of treatment existed between the UIP pattern group and diffuse GGO pattern group within 1 year after diagnosis. Fourth, the HRCT classification was mainly performed by two respiratory physicians, not chest radiologist. Bias existed because two of the respiratory physicians (S.K. and R.O.) were key members of the study.

Conclusions

In the 2020 ATS/JRS/ALAT HP guidelines, the UIP pattern group and diffuse GGO pattern group in compatible with fibrotic HP had different disease progression from

the results of FVC, DLco, KL-6, and prognosis. The classification of diagnostic confidence seems to be separated from the prognostic classification. Not small differences in CT classification were observed in the two guidelines in patients with compatible with fibrotic HP in ATS/JRS/ALAT guidelines.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1845/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Kanagawa Cardiovascular and Respiratory Disease Center on 27 October 2021 (No. KCRC-21-0028), and individual consent for this retrospective analysis was waived.

References

1. Morell F, Villar A, Montero MÁ, et al. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. Lancet Respir Med 2013;1:685-94.
2. Raghu G, Remy-Jardin M, Ryerson CJ, et al. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2020;202:e36-69.
3. Salisbury ML, Gu T, Murray S, et al. Hypersensitivity Pneumonitis: Radiologic Phenotypes Are Associated With Distinct Survival Time and Pulmonary Function Trajectory. Chest 2019;155:699-711.
4. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022;205:e18-47.
5. Fernández Pérez ER, Travis WD, Lynch DA, et al. Diagnosis and Evaluation of Hypersensitivity Pneumonitis: CHEST Guideline and Expert Panel Report. Chest 2021;160:e97-e156.
6. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med 2019;381:1718-27.
7. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med 2020;8:453-60.
8. Gimenez A, Storrer K, Kuranishi L, et al. Change in FVC and survival in chronic fibrotic hypersensitivity pneumonitis. Thorax 2018;73:391-2.
9. Horimasu Y, Ishikawa N, Iwamoto H, et al. Clinical and molecular features of rapidly progressive chronic hypersensitivity pneumonitis. Sarcoidosis Vasc Diffuse Lung Dis 2017;34:48-57.
10. Okamoto T, Fujii M, Furusawa H, et al. The usefulness of KL-6 and SP-D for the diagnosis and management of chronic hypersensitivity pneumonitis. Respir Med 2015;109:1576-81.

11. Hanzawa S, Tateishi T, Ishizuka M, et al. Changes in serum KL-6 levels during short-term strict antigen avoidance are associated with the prognosis of patients with fibrotic hypersensitivity pneumonitis caused by avian antigens. Respir Investig 2020;58:457-64.
12. Faverio P, Piluso M, De Giacomi F, et al. Progressive Fibrosing Interstitial Lung Diseases: Prevalence and Characterization in Two Italian Referral Centers. Respiration 2020;99:838-45.
13. Kypreos M, Batra K, Glazer CS, et al. Impact of number and type of identified antigen on transplant-free survival in hypersensitivity pneumonitis. PLoS One 2022;17:e0273544.
14. Okuda R, Takemura T, Misumi T, et al. Acute Exacerbation and Proposed Criteria for Progressive Pulmonary Fibrosis in Patients with Fibrotic Hypersensitivity Pneumonitis and Idiopathic Pulmonary Fibrosis. Respiration 2023;102:803-12.
15. Watanabe M, Horimasu Y, Iwamoto H, et al. C-C Motif Chemokine Ligand 15 May Be a Useful Biomarker for Predicting the Prognosis of Patients with Chronic Hypersensitivity Pneumonitis. Respiration 2019;98:212-20.
16. Trushenko NV, Suvorova OA, Pershina ES, et al. Predictors of Progression and Mortality in Patients with Chronic Hypersensitivity Pneumonitis: Retrospective Analysis of Registry of Fibrosing Interstitial Lung Diseases. Life (Basel) 2023;13:467.
17. Adegunsoye A, Oldham JM, Bellam SK, et al. Computed Tomography Honeycombing Identifies a Progressive Fibrotic Phenotype with Increased Mortality across Diverse Interstitial Lung Diseases. Ann Am Thorac Soc 2019;16:580-8.
18. Choe J, Chae EJ, Kim YJ, et al. Serial changes of CT findings in patients with chronic hypersensitivity pneumonitis: imaging trajectories and predictors of fibrotic progression and acute exacerbation. Eur Radiol 2021;31:3993-4003.
19. Kang J, Kim YJ, Choe J, et al. Acute exacerbation of fibrotic hypersensitivity pneumonitis: incidence and outcomes. Respir Res 2021;22:152.
20. Chung JH, Zhan X, Cao M, et al. Presence of Air Trapping and Mosaic Attenuation on Chest Computed Tomography Predicts Survival in Chronic Hypersensitivity Pneumonitis. Ann Am Thorac Soc 2017;14:1533-8.
21. Buendia-Roldan I, Aguilar-Duran H, Johannson KA, et al. Comparing the Performance of Two Recommended Criteria for Establishing a Diagnosis for Hypersensitivity Pneumonitis. Am J Respir Crit Care Med 2021;204:865-8.

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