

The Efficacy of Corticosteroid Therapy in Fibrotic Hypersensitivity Pneumonitis: A Propensity Score-matched Cohort Analysis

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Research article

Keywords: fibrotic hypersensitivity pneumonitis, propensity score matching, corticosteroid

Posted Date: November 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-99702/v1>

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Version of Record: A version of this preprint was published at BMC Pulmonary Medicine on July 19th, 2021. See the published version at <https://doi.org/10.1186/s12890-021-01608-1>.

RESEARCH ARTICLE

The efficacy of corticosteroid therapy in fibrotic hypersensitivity pneumonitis: a propensity score-matched cohort analysis

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Abstract

Background:: Fibrotic hypersensitivity pneumonitis (HP) is a chronic interstitial lung disease caused by allergic responses to repeated exposures to a causative antigen. Therapeutic evidence of corticosteroid for fibrotic HP remains lacking, although corticosteroid is recognized as a major treatment option. The purpose of this study was to evaluate the efficacy of corticosteroid for patients with fibrotic HP in a propensity score-matched cohort.

Methods:: Retrospective medical record review from 2005 to 2019 in a single center was conducted to identify 144 patients with fibrotic HP. Semiquantitative scores of lung abnormalities on HRCT were evaluated. Patients with corticosteroid treatment (PDN group) and without the treatment (non-PDN group) were matched using a propensity score method. Survival rates and serial changes in pulmonary function, and annual changes in HRCT scores were compared between pair-matched patients.

Results:: In the matched analysis, 30 of the PDN group were matched with 30 of the non-PDN group, the majority of which comprised ILD without extensive fibrosis. The survival rate was significantly better in the PDN group ($P = 0.032$ for the stratified Cox proportional hazards model; HR, 0.250). Absolute changes in %FVC at 6, 12, and 24 months from baseline were significantly better in the PDN group. Fewer cases experienced annual deterioration in HRCT scores in the non-PDN group for ground-glass attenuation, consolidation, reticulation, traction bronchiectasis and honeycombing.

Conclusions:: Fibrotic HP without extensive fibrosis may receive benefits from corticosteroid treatment in terms of improvements in survival rate and pulmonary function decline and inhibition of fibrotic progression. We propose that early initiation of corticosteroid be considered for fibrotic HP when worsening fibrosis is observed.

Keywords: fibrotic hypersensitivity pneumonitis; propensity score matching; corticosteroid

Background

Hypersensitivity pneumonitis (HP) is an immune-mediated lung disease caused by repeated exposure to a sensitized antigen. HP is traditionally classified as acute or chronic form [1]. Currently, the classification is described more specifically as nonfibrotic HP or fibrotic HP, given the clinical-radiologic-pathologic correlation

that is linked to clinical outcomes [2]. Compared with nonfibrotic HP having favorable prognosis, the clinical behavior of fibrotic HP may mimic that of idiopathic pulmonary fibrosis, resulting in high mortality [3, 4].

For pharmacological treatment for fibrotic HP, corticosteroid is considered as the mainstay of treatment. Given the pathogenesis of HP as an immune-mediated disease, corticosteroid as an anti-inflammatory agent is a reasonable treatment option. However, the evidence to guide corticosteroid treatment for fibrotic HP is still based on observational data and expert opinion [5]. The effectiveness of corticosteroid has been reported only in acute farmer's lung [6]. A recent report regarding the effectiveness of corticosteroid for fibrotic HP failed to demonstrate clinical benefits on pulmonary function and survival for patients treated with corticosteroid compared with untreated patients [7]. In this previous study, underlying characteristic differences between corticosteroid-treated and untreated groups in fibrotic HP remained to be considered to compare treatment outcomes between groups. A clinical question that remains to be solved is whether corticosteroid enables an alteration of the clinical course of fibrotic HP.

Therefore, this study was conducted to demonstrate the efficacy of corticosteroid for fibrotic HP by matching baseline characteristics of patients treated and untreated with corticosteroid and comparing clinical outcomes. We aimed to propose candidates who benefit from corticosteroid treatment in patients with fibrotic HP.

Methods

Patients selection and data collection

Retrospective medical record reviews of consecutive patients with interstitial lung disease (ILD) who were hospitalized in our center between January 2005 and December 2019, were conducted to identify 144 patients with fibrotic HP. The patient recruitment flow diagram is shown in Figure 1. The diagnosis of HP was validated with a positive result of inhalation challenge test and/or pathological analysis of surgical lung biopsy, autopsy or transbronchial lung biopsy, on the basis of Yoshizawa's criteria [8, 9, 10, 11, 12]. Presence of fibrosis was based on high-resolution computed tomography (HRCT) findings, including reticulation, traction bronchiectasis, and honeycombing. Diagnostic confidence of fibrotic HP according to the guideline from the American Thoracic Society was reviewed for all 144 patients [2], which revealed the majority of patients in our cohort were diagnosed with moderate to definite confidence: definite, 51; high, 37; moderate, 42; low, 12; not excluded, 2. In the entire cohort, 107 with prednisolone (PDN) treatment (PDN group) and the remaining 37 patients without treatment (non-PDN group) were identified. Thirty of the PDN group were matched with 30 of the non-PDN group using a propensity score-matching method. The present study conformed to the Declaration of Helsinki and was approved by the institutional review board at Tokyo Medical and Dental University (M2019-206). Written informed consent was waived due to the retrospective nature of this study.

Clinical data of the eligible patients were obtained from medical records. Baseline data were reviewed on either the date of initiating corticosteroid for the PDN group or the date of diagnosis for the non-PDN group. The absolute decline of percent-predicted forced vital capacity (%FVC) 12 months before registration was

extrapolated from %FVC data retrieved in 6-18 months prior to the registration date. As follow-up pulmonary function data, the absolute changes in %FVC at 6 ± 3 months, 12 ± 3 months, and 24 ± 3 months were collected. The last observation carried forward method was used to replace missing FVC measurements for censored or dead cases. The observation period was ended at the last visit in five years or until April 2020. Survival period was defined as the time from the date initiating corticosteroid in the PDN group or the date of diagnosis in the non-PDN group, until the date of death from any cause or the last day patients were known to be alive in the observation period.

Missing %FVC data imputed using the last observation carried forward method for censored or dead cases were in no patients at 6 months, 14 patients (13%) at 12 months, and 24 patients (32%) at 24 months in the entire PDN group and no patients at 6 months, 2 patients (5%) at 12 months, and 7 patients (19%) at 24 months in the entire non-PDN group. Missing %FVC data imputed were in no patients at 6 months, 1 patient (3%) at 12 months, and 4 patients (13%) at 24 months in the matched PDN group and no patients at 6 months, 1 patient (3%) at 12 months, and 7 patients (23%) at 24 months in the matched non-PDN group.

Radiographic assessment

Evaluations of HRCT findings at baseline and the 1-year follow-up were performed using Dutka/Vasakova scoring system by grading four levels: 1) Aortic arch, 2) Carina, 3) Maximum diameter of the right ventricle, and 4) Top of the right diaphragmatic dome [13].

HRCT findings were semiquantitatively graded as summarized in Table S1 and Figure S1. HRCT findings were interpreted on the basis of the recommendations of the Nomenclature Committee of the Fleischner Society [14]. The extents of ground-glass attenuation (GGA), consolidation, reticulation, and honeycombing were graded using scores from 0 to 5 on the basis of Kazerooni's method [15], with slight modifications. The extent of traction bronchiectasis was assessed using a score from 0 to 3 as previously described [16, 17]. Bronchiolectasis, predominantly localized more distally in the lung, often within 2-5 mm of the pleura, was excluded from bronchiectasis to more accurately score the extent of bronchiectasis in this study. The presence of mosaic attenuation was recorded. The presence of these HRCT findings and mosaic attenuation was also recorded. A maximum score and the total score for GGA, consolidation, reticulation, honeycombing, and traction bronchiectasis were recorded. A maximum score in any of the lung areas was recorded in order to evaluate the severity of each HRCT finding. The total score was calculated by summing up the scores in 8 areas for each HRCT finding in order to evaluate the change in scores between the PDN group and non-PDN group.

Two pulmonary specialists (TS and ME), blinded to the clinical data, independently scored HRCT features and reached consensus on mismatches. Correlation coefficients for interobserver variation to evaluate the concordance of total and maximum scores of each HRCT finding between readers were all excellent agreements, with Spearman r values ranging from 0.841 to 0.940 ($P < 0.001$).

Statistical analysis

The data were analysed using EZR software (Saitama, Japan, version 2.6-1) [18]. Data are presented as the means (standard deviations [SDs]), medians with interquartile ranges (IQRs), or as numbers of patients and percentages where appropriate. All statistical analyses were performed using All *P*-values were two sided, and *P*-values of 0.05 or less were considered statistically significant. The Bonferroni correction adjusted *P*-values for multiple tests. Correlation coefficients for interobserver variation to evaluate the concordance of total and maximum scores of each HRCT finding between readers were obtained using Spearman's rank correlation coefficient test (*r*). Cumulative rates of mortality were estimated using the Kaplan-Meier method and were compared using the Cox proportional hazard regression model or the stratified Cox proportional hazard regression model.

The propensity score (PS) for the presence of PDN treatment was estimated for each patient with a logistic regression model using baseline patient characteristics. The following characteristics of patients were included in the model: age, sex, smoking history, %FVC, percent predicted expiratory volume in one second (%FEV1), and presence of honeycombing, traction bronchiectasis and mosaic attenuation on HRCT. The presence of these HRCT findings was included because they were previously demonstrated as prognostic factors [4, 19, 20, 21, 22]. PS matching using a 1: 1 nearest-neighbor method without replacement was performed between the PDN and non-PDN groups, with calipers of width equal to 0.25 of the standard deviation of the logit of the PS [23]. This yielded a c-statistic of 0.815, indicating an adequate ability to differentiate between the two groups. Figure S2 illustrates the dot plot of the distribution of propensity scores in both groups.

Results

Baseline patient characteristics

Baseline characteristics in the entire cohort were compared between the PDN group (*n* = 107) and the non-PDN group (*n* = 37), as shown in Table 1. Patients with lower pulmonary function with mean %FVC of 58.2% and more rapid decline in %FVC before registration were included in the PDN group. All HP patients were instructed to avoid exposure to a causative antigen. Corticosteroid was continuously administered from baseline over the observation period in all cases of the treatment group, with a mean initial dose of approximately 0.5 mg/kg daily on a physician-dependent tapering schedule. In baseline HRCT findings (Table 2), traction bronchiectasis and honeycombing was more frequently present, and higher maximum scores for GGA, reticulation, traction bronchiectasis and honeycombing were more frequently observed in the PDN group. Baseline characteristics after matching were compared between the PDN group (*n* = 30) and the non-PDN group (*n* = 30) (Table 1). There were no significant differences in most baseline parameters, including pulmonary function with mean %FVC of approximately 70%, although 12-month %FVC decline before registration was more rapid in the PDN group. In HRCT analysis (Table 2), significant differences between the groups disappeared in the presence of HRCT findings and in the distribution of maximum scores in all HRCT findings. Therefore, baseline characteristics as well as baseline HRCT scores were mostly well-adjusted using propensity scores.

The entire cohort consisted of ILD with more progressed fibrosis, while the matched cohort consisted of ILD with mild to moderate fibrotic progression. Indeed,

29% of cases in the entire cohorts showed reduced %FVC less than 50%, which is the cut-off value for the worst physiology score in the ILD-GAP model [24], while merely 3% of cases in the matched cohort exhibited low %FVC less than 50%. In addition, the distribution of maximum scores revealed that none exhibited maximum reticulation score > 3 (25-<50% in any of lung areas) and maximum traction bronchiectasis score = 3 (Severe) in the matched cohort.

Therapeutic effect on clinical outcomes

Figure 2 illustrated the Kaplan-Meier curves for survival rates between the PDN group and the non-PDN group. In the entire cohort (Figure 2a), the survival rate was significantly worse in the PDN group, with $P = 0.040$ (hazard ratio [HR], 1.878; 95% confidence interval [CI], 1.029-3.426). Conversely, in the matched cohort (Figure 2b), the survival rate was better in the PDN group, with $P = 0.032$ (HR, 0.250; 95% CI, 0.071-0.886). This result demonstrated that corticosteroid improved the survival rate in the matched cohort.

Figure 3 shows the comparison of absolute change in %FVC from baseline (%FVC) between the PDN group and the non-PDN group. In the entire cohort (Figure 3a), the %FVCs in the PDN group vs the non-PDN group were significantly different at 6 months (4.0% vs -3.2%, $P < 0.001$), at 12 months (2.9% vs -5.5%, $P < 0.001$), and at 24 months (0.8% vs -10.3%, $P < 0.001$). Similarly, in the matched cohort (Figure 3b), %FVCs in the PDN group vs non-PDN group were significantly different at 6 months (6.6% vs -3.2%, $P < 0.001$), at 12 months (5.0% vs -4.9%, $P < 0.001$), and at 24 months (0.9% vs -9.4%, $P = 0.001$). These results demonstrated that corticosteroid improved pulmonary function over two years in our cohort.

Table 3 and Figure 4 describe the 1-year changes in total scores from baseline in the matched cohort. In Table 3, significantly fewer patients in the PDN group experienced deteriorated in scores of all HRCT findings. In Figure 3, the scores in the PDN group appeared to improve in of GGA and consolidation, with slow progression in reticulation, traction bronchiectasis, and honeycombing. In contrast, the scores of all HRCT findings appeared to worsen in the non-PDN group. These results indicated that corticosteroid improved the acute inflammatory findings of GGA and consolidation, and inhibited progression of fibrotic components of reticulation, traction bronchiectasis, and honeycombing in our cohort.

Representative pair-matched cases in the matched cohort are illustrated in Figure 5.

Discussion

Our study aimed to support the therapeutic evidence focusing on corticosteroid in patients with fibrotic HP. We demonstrated that corticosteroid improved survival and inhibited radiologic fibrotic progression and FVC decline in the analysis between the matched cohorts with or without corticosteroid that comprised ILD without extensive fibrosis. We propose that patients with fibrotic HP need to be treated with corticosteroid before fibrosis extends severely.

This is the first report that demonstrated the survival benefit of corticosteroid in patients with fibrotic HP. The matching analysis revealed improved survival in the corticosteroid treatment group by using the propensity score method to match

the patient characteristics, including pulmonary function and radiologic presence of fibrosis, which are recognized as prognostic variables of mortality. Indeed, reduced FVC is also recognized as a mortality predictor in fibrotic HP [25]. Honeycombing presence is an established factor of prognostic importance in patients with diverse fibrotic ILDs, including HP [4, 19, 22]. A previous report evaluating the effectiveness of corticosteroid for fibrotic HP failed to demonstrate a survival benefit with corticosteroid using a cohort with lower FVC and a relatively high frequency of honeycomb presence in the treatment group [7]. Consistently, the corticosteroid treatment group of our entire cohort, which similarly consisted of more cases of ILD in a progressed stage, with lower FVC and higher scores of radiologic fibrosis, exhibited a worse survival rate than the corticosteroid untreated group. These underlying characteristic differences between groups seemed to underestimate the effectiveness of treatment. Notably, the matched cohort consisted of many cases of ILD in an earlier stage, with lower scores of fibrosis. Therefore, our results may be applicable only to patients with ILD without extensive fibrosis to expect therapeutic improvement. Whether corticosteroid provides therapeutic benefits for HP patients with extensive fibrosis remains unresolved in this study.

Regarding the radiographic assessment, fibrotic components of reticulation, traction bronchiectasis and honeycombing were surprisingly stabilized in scores after treatment; in addition, acute inflammatory findings of GGA and consolidation improved in scores. In contrast, all these components were deteriorating in most cases in the non-PDN group. This result indicates that corticosteroid may exert a slow progression of fibrosis, which is conceivably formed by immune-mediated inflammation in HP as a target of anti-inflammatory medication. There are several papers describing that traction bronchiectasis and reticulation may occasionally be reversible by treatment, although these fibrotic components typically exhibited worsening over time. In the analysis of nonspecific interstitial pneumonia comparing the extent of HRCT findings between the initial and the later timepoints, some instances of traction bronchiectasis in the early stage were reversible, which was presumably attributed to the collapse of the surrounding peripheral lung parenchyma [26]. In addition, reticulation primarily associated with fibrosis was slightly improved by pharmacological therapy in some cases [27]. It is possible that these fibrotic components could be at least slowed in progression using corticosteroid, which was supported by our results of annual HRCT score changes. We believe that corticosteroid provides a benefit for fibrotic HP in terms of an inhibitory effect on fibrotic progression, as well as an ameliorating effect on acute inflammation.

With respect to pulmonary function improvement, it is plausible that the extended GGA yielded the positive response to pulmonary function in our cohort, which had decreased scores after initiating corticosteroid in many cases. As reported previously, regression of GGA that primarily reflects a lymphocytic inflammation linked to an improvement of pulmonary function in fibrosing lung diseases [28]. Meanwhile, our result was inconsistent with a previous report that addressed an absent effect in fibrotic HP [7]. The inconsistency may be attributed to the duration of the treatment period, as the mean time was half a year in this previous study, while corticosteroid was continuously used over the observation periods in our study. Whether a therapeutic pulmonary function response yields a survival benefit remains unclear, given

that even the PDN group in the entire cohort showed posttreatment improvement in FVC, regardless of high mortality rates. This clinical question needs to be investigated further.

Corticosteroid treatment for fibrotic HP lacks supportive evidence thus far. We demonstrated that the matched cohort of mild to moderate fibrosis showed survival improvement and slower radiologic fibrotic progression with corticosteroid treatment, while the entire cohort, including the population with progressed fibrosis, failed to show a survival benefit on corticosteroid. Therefore, we suggest that corticosteroid treatment needs to be started before fibrotic lesions extend severely. To distinguish mild to moderate fibrosis as a target for therapy from severe fibrosis, baseline variables of %FVC > 50%, maximum reticulation score < 4, and maximum traction bronchiectasis score < 3 provide a clue that covered a majority of the population in our matched cohort. In addition, a population with extended GGA, suggestive of a more abundant inflammatory process, may be a candidate of corticosteroid treatment, as might acute inflammatory HP. In our matching analysis, total GGA score reduced dramatically after treatment, which may have been related to improved outcomes. Supportively, the presence of GGA was associated with improved survival using a multivariate model with adjustment for honeycombing presence in patients with chronic HP [29]. A recent review proposed a sign of active inflammation, including extended GGA, as a clue for introducing immunosuppression therapy in fibrotic HP [5]. Taken together, we suggest that progressive fibrotic HP, yet with mild to moderate fibrosis, additively with the presence of GGA in lung areas, could be a promising candidate for corticosteroid treatment.

For pharmacological options, which corticosteroid or anti-fibrotic agent to select remains to be discussed. In the latest report, nintedanib, a major anti-fibrotic agent, reduced the rate of ILD progression in chronic fibrosing ILDs with progressive phenotype that covered a population of fibrotic HP [30, 31]. However, the primary outcome of this study focused on pulmonary function decline instead of survival difference, which was not statistically identified in the analysis of secondary outcome. Considering the pathogenesis of HP as an immune-mediated disease, corticosteroid as an anti-inflammatory agent is a reasonable treatment option even when fibrotic lesions are dominant findings in lung fields. In this regard, intensive immunosuppression therapy using corticosteroid plus immunosuppressants as a first-line therapy may be worth examining, although the effectiveness of subsequent addition of mycophenolate mofetil or azathioprine failed to achieve positive clinical outcomes [32].

This study has several limitations. First, the matching analysis was conducted in a small-sized cohort. This is mainly because patients with progressed ILD were mostly on a therapeutic intervention, and we failed to collect more non-PDN cases for matching. We plan to conduct a prospective study involving multi-centers in the future. Second, a quantitative scoring system was not adopted in this study; though such systems have been commonly used for more precisely estimating the extent of HRCT abnormalities. Instead, we used a semiquantitative assessment to provide ease of measurement and practical utility for clinicians. Third, the optimal dose and duration of therapy that will affect therapeutic outcomes and the risk of adverse events were not discussed in this study. Mean initial dose of corticosteroid

in our cohort was around 0.5 mg/kg daily on an individual tapering schedule without complete withdrawal over a clinical course, resulting in favorable survival in the matched cohort. Whether lower dose of corticosteroid may differ in outcome may be a question of interest in respect to minimizing the long term adverse effect of the therapy. Finally, the optimal dose and duration of corticosteroid that will affect therapeutic outcomes and the risk of adverse events were not discussed in this study.

Conclusions

This study demonstrated that corticosteroid may favorably alter the clinical course of fibrotic HP in a population without extensive fibrosis in our single-center cohort. Fibrotic HP at an early stage with an observed fibrotic progression may receive the benefits of survival improvement and slower fibrotic progression from corticosteroid treatment. We believe this suggestion will serve as a guide for introducing corticosteroid in clinical practice.

Additional Files

Additional file 1: Figure S1- Semiquantitative scoring for traction bronchiectasis used in this study. Figure S2- A dot plot of the distribution of propensity scores in the PDN group and the non-PDN group. Table S1- Summary of the semiquantitative scoring system for HRCT findings.

Abbreviations

BAL: bronchioalveolar lavage; BW: body weight; CI: confidence interval; CyA: cyclosporine A; CYC: cyclophosphamide; DLco: Diffusion capacity of lung for carbon monoxide; FEV1: Forced expiratory volume in one second; FVC: forced vital capacity; GGA: ground glass attenuation; HP: hypersensitivity pneumonitis; HR: hazard ratio; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; KL-6: Krebs von den Lungen-6; NR: not reached; NTD: nintedanib; PDN: prednisolone; PFD: pirfenidone; PS: propensity score; SD: standard deviation; SP-D: surfactant protein-D; TAC: tacrolimus.

Acknowledgements

Funding There is no funding source for the current study.

Author contributions

ME and TO contributed to the study design, data analysis and interpretation, and the writing of the manuscript. TS, TA, and KT contributed to data analysis and interpretation. YM takes full responsibility for the content of this manuscript, including data and analysis. All authors critically revised the manuscript for intellectual content and approved the final draft.

Availability of data and materials The datasets analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate The present study conformed to the Declaration of Helsinki and was approved by the institutional review board at Tokyo Medical and Dental University (M2019-206). Written informed consent was waived due to the retrospective nature of this study.

Consent for publication Not applicable.

Competing interests YM received lecture fees from Nippon Boehringer Ingelheim and AstraZeneca. The other authors have no conflicts of interest. The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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Tables

Table 1 Baseline characteristics in the entire cohort and in the matched cohort.

	Entire cohort			Matched cohort		
	PDN group n = 107	Non-PDN group n = 37	P-value	PDN group n = 30	Non-PDN group n = 30	P-value
Age, yr	64 [5869]	69 [6173]	0.016	65 [5972]	69 [6172]	0.452
Sex, male	63 (59%)	23 (62%)	0.876	15 (50%)	18 (60%)	0.505
Body weight, kg	57 [4968]	58 [4969]	0.703	56 [4769]	59 [4770]	0.365
Smoking, pack yr	7 [038]	20 [047]	0.575	10 [030]	16 [034]	0.696
Ever smoked	55 (51%)	21 (57%)	0.145	17 (57%)	17 (57%)	0.999
FVC, ml	1890 (640)	2280 (740)	0.003	2260 (700)	2180 (740)	0.484
%FVC, %predicted	58.2 (14.2)	71.0 (15.0)	j 0.001	71.5 (13.2)	67.6 (14.0)	0.217
< 50%	31 (29%)	3 (8%)	0.012	1 (3%)	3 (10%)	0.617
%FVC decline, %predicted						
12-month before registration	13.3 (9.5)	5.2 (5.7)	j 0.001	12.0 (6.2)	5.0 (5.3)	j 0.001
FEV1, ml	1630 (530)	1910 (580)	0.007	1880 (580)	1820 (560)	0.565
%FEV1, %predicted	64.0 (14.2)	77.4 (14.2)	j 0.001	76.3 (11.7)	73.7 (12.2)	0.27
DLco, %	44.5 (18.2)	56.2 (23.7)	0.005	56.7 (14.7)	54.3 (25.6)	0.658
Serum KL-6, U/mL	1540 [11002590]	1070 [7401590]	0.004	1420 [9801960]	1070 [7501860]	0.589
Serum SP-D, ng/mL	276 [176437]	243 [180317]	0.171	225 [130340]	260 [200340]	0.424
BAL lymphocyte, %	17 [839]	16 [539]	0.546	22.9 [10.941.5]	20.5 [5.529.8]	0.52
Antigen†						
Bird-related	78 (73%)	31 (84%)	0.495	24 (80%)	24 (80%)	0.999
Home-related	14 (13%)	3 (8%)		3 (10%)	3 (10%)	
Unknown	15 (14%)	3 (8%)		3 (10%)	3 (10%)	
Treatment						
Anti-fibrotic agent	14 (13%)	8 (22%)	0.288	3 (10%)	7 (23%)	0.149
	PFD 11, NTD 3	PFD 4, NTD 4		PFD 1, NTD 2	PFD 3, NTD 4	
Immunosuppressant	49 (46%): CYA, 33; CYC, 5; TAC, 11	0	-	10 (33%): CYC, 5; CyA, 4; TAC, 1	0	-

Values are given as the number (percentage), mean (SD), or median [25th and 75th percentiles].

P-values were obtained from a two-sided Mann-Whitney U test, the chi-square test, or Fisher's exact test for the comparison between the PDN group and the non-PDN group in the entire cohort.

P-values were obtained from McNemar's test, Wilcoxon signed-rank test, paired t-test, or Fisher's exact test for the comparison between the PDN group and the non-PDN group in the matched cohort. BAL: bronchioalveolar lavage; BW: body weight; CyA: cyclosporine A; CYC:

cyclophosphamide; DLco: Diffusion capacity of lung for carbon monoxide; FEV1: Forced expiratory volume in one second; FVC: forced vital capacity; HP: hypersensitivity pneumonitis; KL-6: Krebs von den Lungen-6; NTD: nintedanib; PDN: prednisolone; PFD: pirfenidone; SD: standard deviation; SP-D: surfactant protein-D; TAC: tacrolimus.

†The causative antigens were deemed as bird-related when an inhalation test using an avian antigen and/or serum antibody to an avian antigen was positive or home-related when an environmental challenge test or serum anti-Trichosporon asahii antibody was positive.

Table 2 Analysis of baseline HRCT findings in the entire cohort and in the matched cohort.

Baseline HRCT findings	Entire cohort		P-value	Matched cohort		P-value
	PDN group n = 107	Non-PDN group n = 37		PDN group n = 30	Non-PDN group n = 30	
Presence of findings						
GGA	107 (100%)	36 (97%)	0.257	30 (100%)	30 (100%)	-
Consolidation	83 (78%)	29 (78%)	0.999	19 (63%)	23 (77%)	0.386
Reticulation	107 (100%)	36 (97%)	0.257	30 (100%)	30 (100%)	-
Traction bronchiectasis	99 (93%)	29 (78%)	0.030	24 (80%)	24 (80%)	0.999
Honeycombing	62 (58%)	14 (38%)	0.055	12 (40%)	12 (40%)	0.999
Mosaic attenuation	60 (56%)	16 (43%)	0.247	17 (57%)	14 (47%)	0.579
Maximum scores, mean						
GGA	2.6	2.2	0.032	2.6	2.2	0.162
0/1/2/3/4/5 [%]	0/5/46/37/10/2	3/19/46/19/11/3	0.021	0/3/53/27/13/3	0/20/53/13/10/3	0.253
Consolidation	1.2	1.1	0.456	1.0	1.1	0.837
0/1/2/3/4/5 [%]	22/42/29/5/2/0	22/54/19/3/3/0	0.675	37/33/23/3/3/0	23/50/20/3/3/0	0.732
Reticulation	2.3	1.9	0.005	2.1	1.9	0.307
0/1/2/3/4/5 [%]	0/10/51/35/4/0	3/19/62/16/0/0	0.001	0/20/53/27/0/0	0/23/63/13/0/0	0.521
Traction bronchiectasis	1.6	1.1	0.001	1.1	1.1	0.878
0/1/2/3 [%]	7/40/42/10	22/51/27/0	< 0.001	20/47/33/0	20/50/30/0	0.999
Honeycombing	1.7	1.4	0.016	1.4	1.4	0.999
0/1/2/3/4/5 [%]	1/40/48/10/1/0	3/59/35/3/0/0	0.012	3/57/33/7/0/0	0/60/37/3/0/0	0.999

Values are given as number (percentage). P-values were obtained from two-sided Mann-Whitney U test, chi-square test, or Fisher's exact test for the comparison between the PDN group and the non-PDN group in the entire cohort. P-values were obtained from McNemar's test, the Wilcoxon signed-rank test, the paired t-test, or Fisher's exact test for the comparison between the PDN group and the non-PDN group in the matched cohort. HP: hypersensitivity pneumonitis; PDN: prednisolone; PFD: pirfenidone; SD: standard deviation.

Table 3 Total HRCT scores in the matched cohort.

Matched cohort	PDN group	Non-PDN group	P-value
Total HRCT scores (Baseline)			
GGA	13 [1017]	10 [714]	0.033
Consolidation	2 [06]	2 [15]	0.593
Reticulation	11 [714]	9 [812]	0.592
Traction bronchiectasis	3 [16]	2 [15]	0.614
Honeycombing	8 [79]	8 [510]	0.779
Total HRCT scores (1-year follow-up)			
GGA	8 [610]	11 [716]	0.031
Consolidation	1 [04]	6 [29]	0.005
Reticulation	11 [814]	14 [1118]	0.018
Traction bronchiectasis	3 [06]	5 [38]	0.077
Honeycombing	8 [711]	9 [813]	0.166
1-year change in total scores, n (deteriorated/nondeteriorated) †			
GGA	(2/26)	(15/13)	<0.001
Consolidation	(4/24)	(21/7)	<0.001
Reticulation	(12/16)	(27/1)	<0.001
Traction bronchiectasis	(10/18)	(24/4)	0.001
Honeycombing	(8/20)	(19/9)	0.008

Total HRCT scores at baseline and the 1-year follow-up, and the 1-year change in total scores in the matched cohort were described. HRCT data were obtained in 28 of 30 patients at the 1-year follow-up. Values are given as number or median [25th and 75th percentiles]. P-values were obtained from the Wilcoxon signed-rank test and McNemar's test. GGA: ground glass attenuation; HRCT: high-resolution computed tomography; PDN: prednisolone.

†The 1-year change in total scores was evaluated dichotomously as deteriorated when a total score at the 1-year follow-up was increased from baseline or nondeteriorated when a total score was the same or decreased.

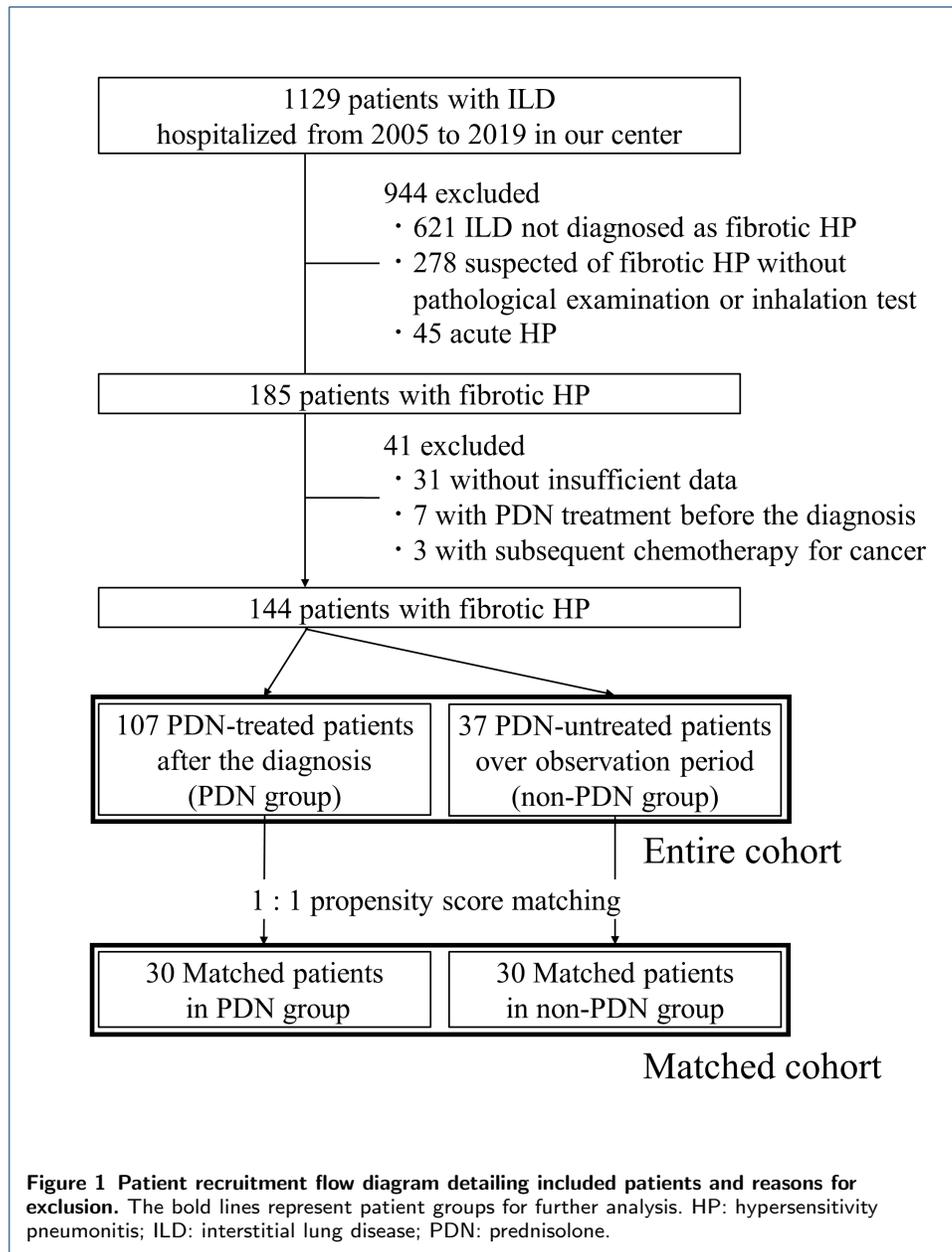
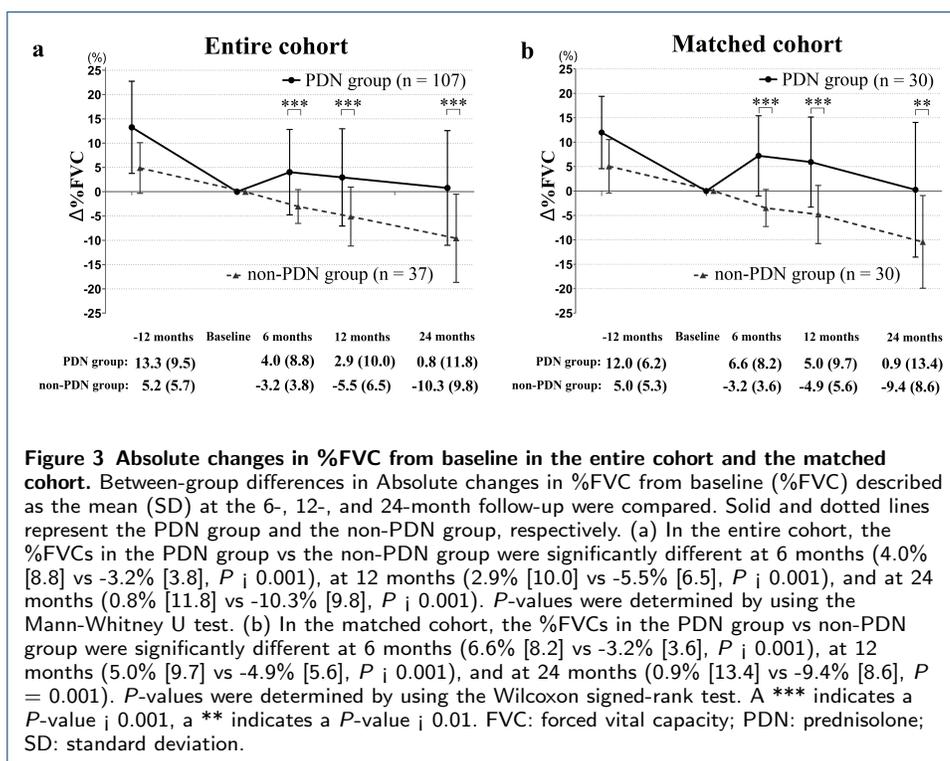
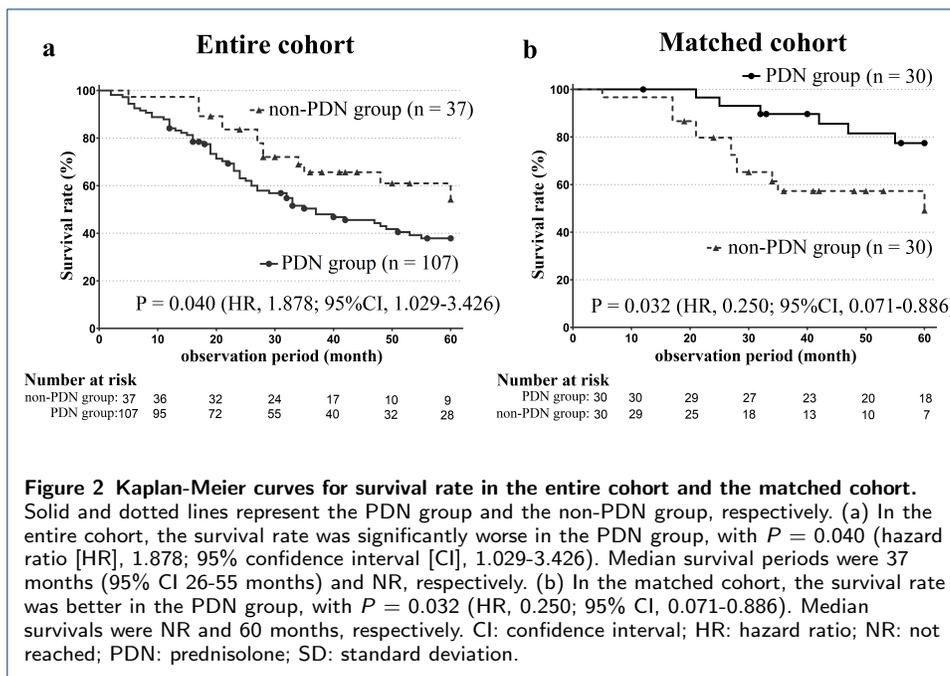
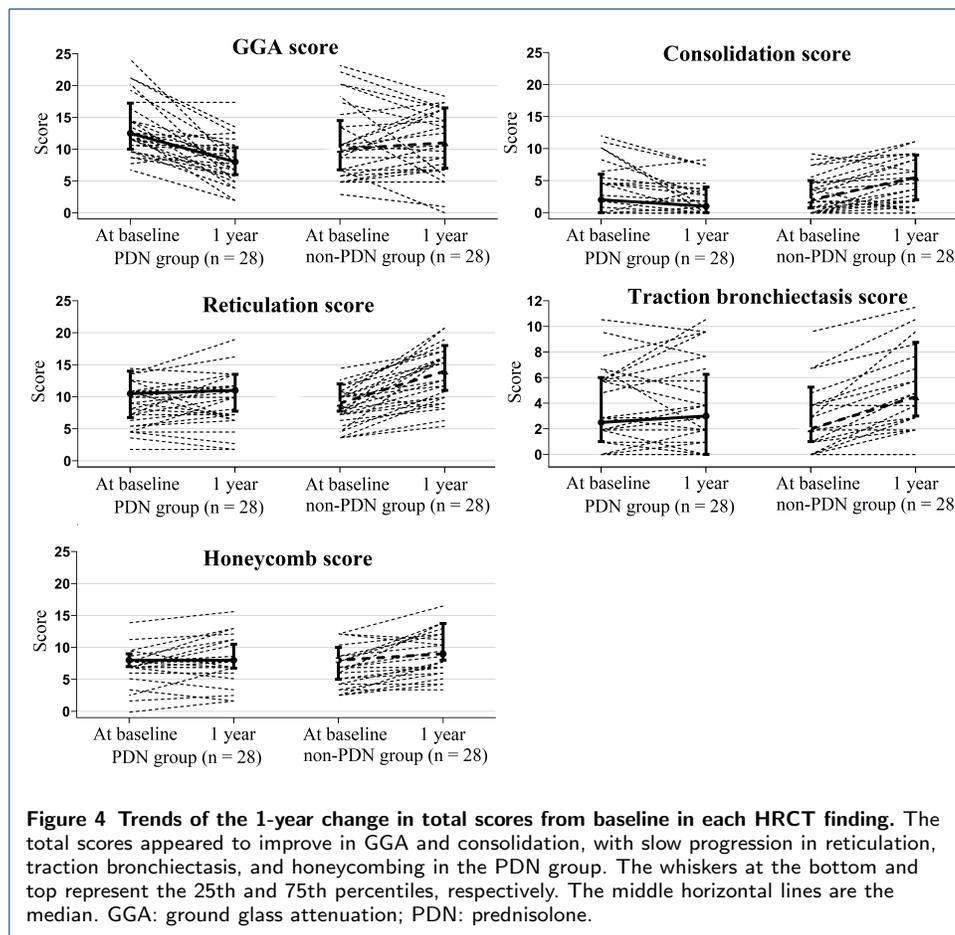


Figure 1 Patient recruitment flow diagram detailing included patients and reasons for exclusion. The bold lines represent patient groups for further analysis. HP: hypersensitivity pneumonitis; ILD: interstitial lung disease; PDN: prednisolone.





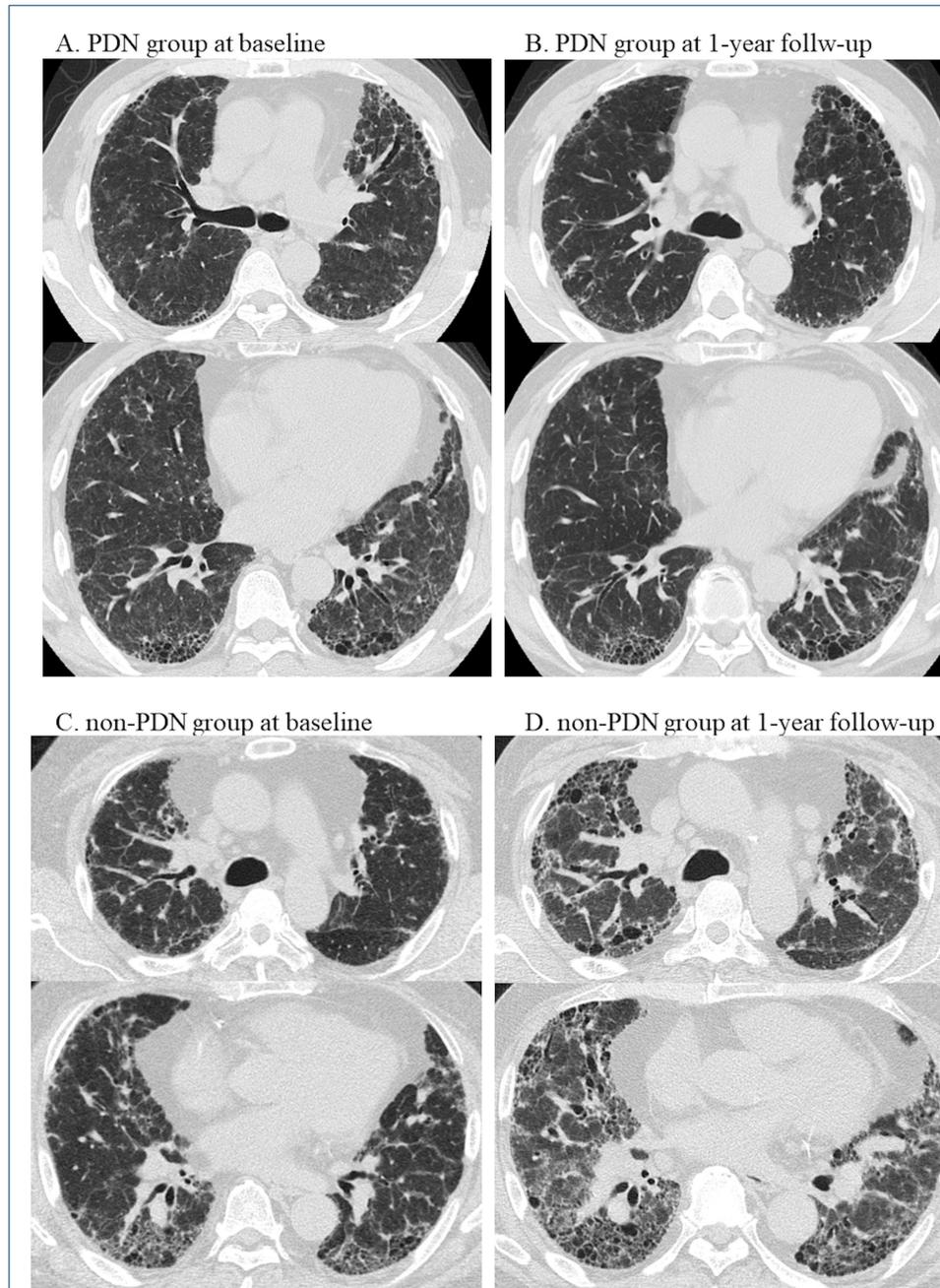


Figure 5 Representative pair-matched cases of patients in the matching analysis. (A)(B) A 63-year-old male with fibrotic bird-related hypersensitivity pneumonitis was treated with prednisolone from baseline till the end of the follow-up period at 60 months. At baseline, the patient's %FVC was 57.9%, the annual %FVC decline before the treatment was 26.1%, and BAL lymphocyte count was 29%. At the 1-year follow-up, the change in %FVC from baseline was +15.9%. Reduced GGA with least fibrotic progression was observed on HRCT over a year. Total scores of HRCT findings (baseline to 1-year follow-up): GGA (22 to 14), consolidation (2 to 0), reticulation (12 to 13), traction bronchiectasis (6 to 8), honeycombing (13 to 14), and mosaic attenuation (2 to 0). (C)(D) A 66-year-old male with fibrotic bird-related hypersensitivity pneumonitis was not accepted for corticosteroid treatment over the clinical course till his date of death at 17 months. At baseline, his %FVC was 46.6%, and the annual FVC decline till the date of diagnosis was 4.7%. At the 1-year follow-up, the change of %FVC from baseline was -12.3%. Outstanding fibrotic progressions were observed on HRCT. The total scores of HRCT findings were as follows: GGA (11 to 18), consolidation (5 to 6), reticulation (16 to 19), traction bronchiectasis (10 to 15), honeycombing (14 to 19), and mosaic attenuation (0 to 0). BAL: bronchoalveolar lavage; %FVC: percent forced vital capacity; GGA: ground glass attenuation; HP: hypersensitivity pneumonitis; HRCT: high-resolution computed tomography.

Figures

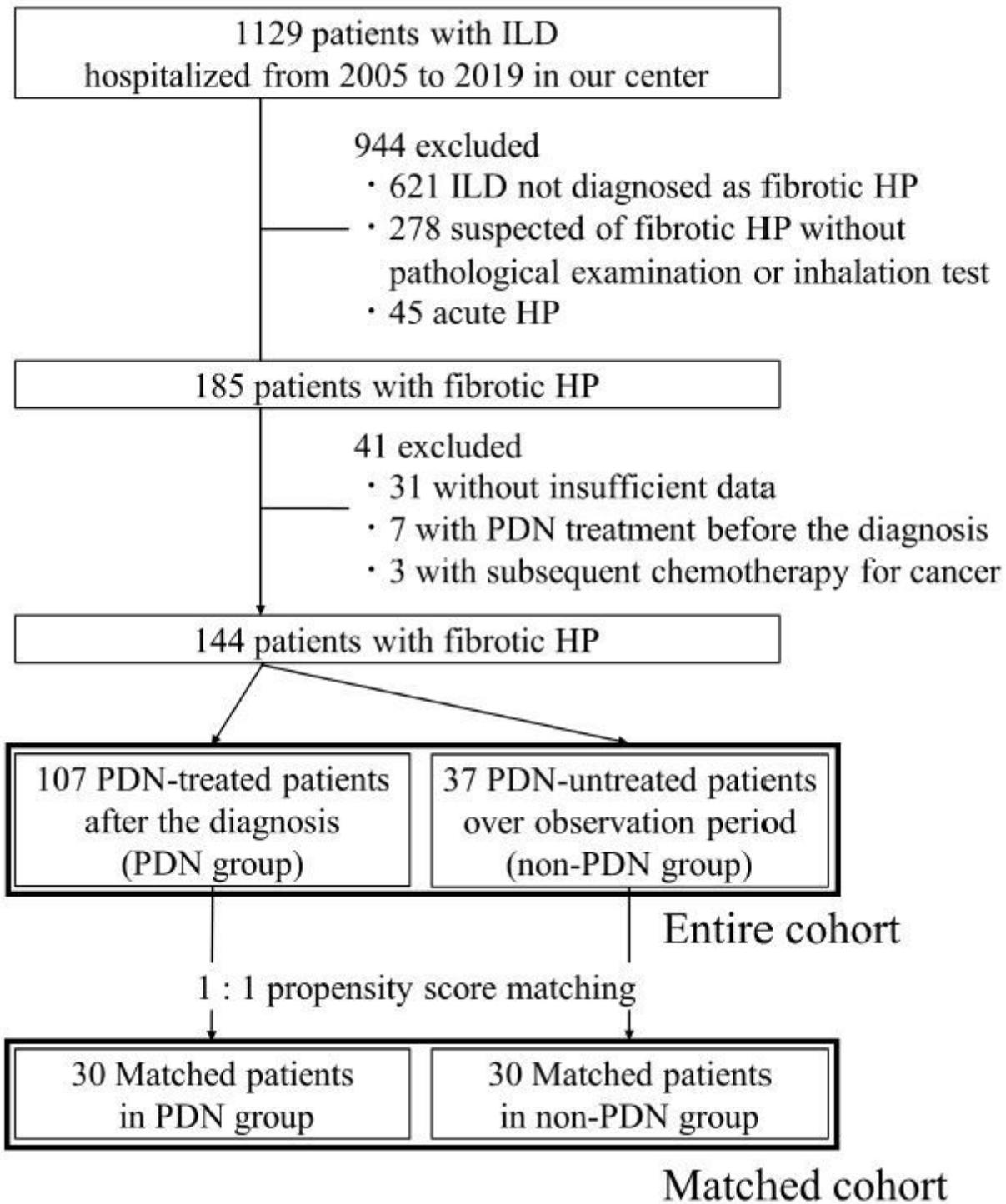


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Patient recruitment flow diagram detailing included patients and reasons for exclusion. The bold lines represent patient groups for further analysis. HP: hypersensitivity pneumonitis; ILD: interstitial lung disease; PDN: prednisolone.

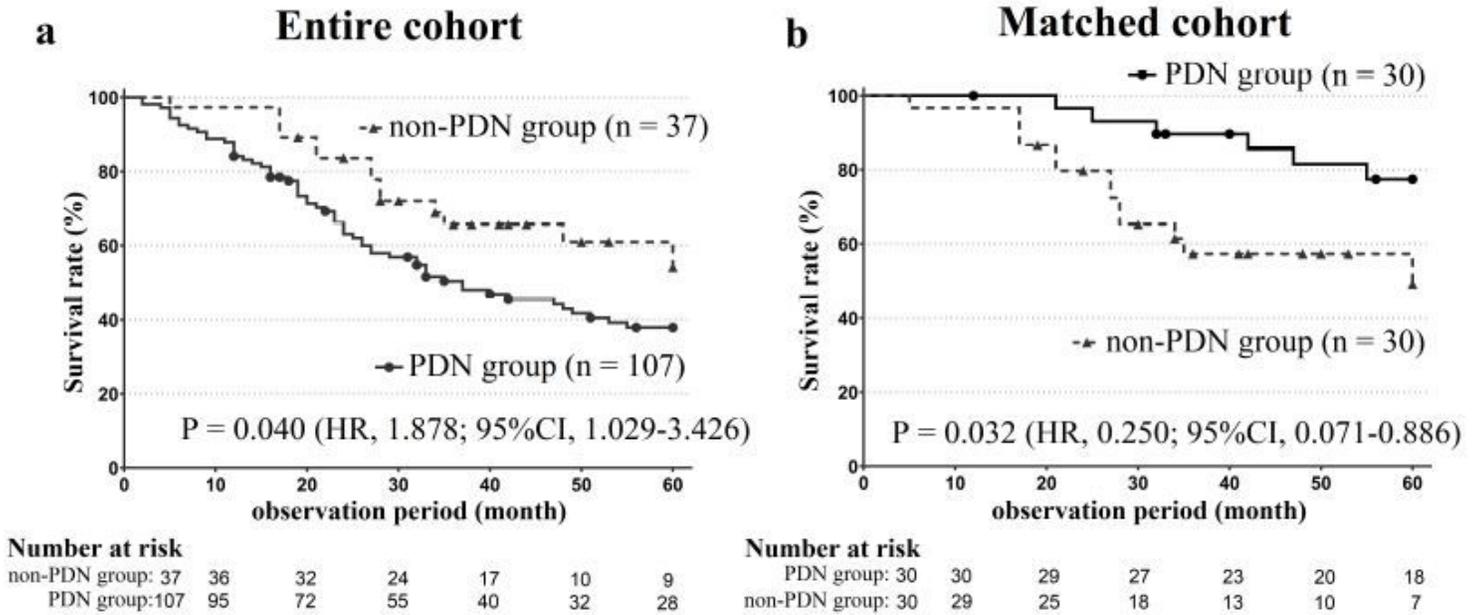


Figure 2

Kaplan-Meier curves for survival rate in the entire cohort and the matched cohort. Solid and dotted lines represent the PDN group and the non-PDN group, respectively. (a) In the entire cohort, the survival rate was significantly worse in the PDN group, with $P = 0.040$ (hazard ratio [HR], 1.878; 95% confidence interval [CI], 1.029-3.426). Median survival periods were 37 months (95% CI 26-55 months) and NR, respectively. (b) In the matched cohort, the survival rate was better in the PDN group, with $P = 0.032$ (HR, 0.250; 95% CI, 0.071-0.886). Median survivals were NR and 60 months, respectively. CI: confidence interval; HR: hazard ratio; NR: not reached; PDN: prednisolone; SD: standard deviation.

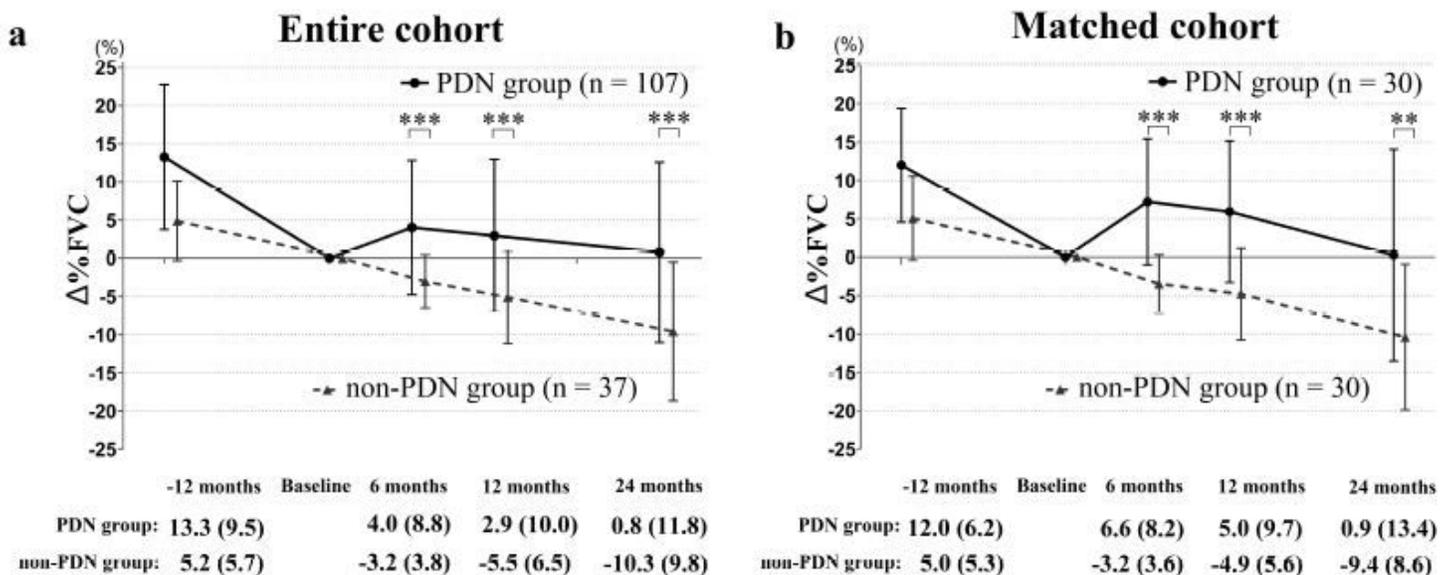


Figure 3

Absolute changes in %FVC from baseline in the entire cohort and the matched cohort. Between-group differences in Absolute changes in %FVC from baseline (%FVC) described as the mean (SD) at the 6-, 12-, and 24-month follow-up were compared. Solid and dotted lines represent the PDN group and the non-PDN group, respectively. (a) In the entire cohort, the %FVCs in the PDN group vs the non-PDN group were significantly different at 6 months (4.0% [8.8] vs -3.2% [3.8], $P < 0.001$), at 12 months (2.9% [10.0] vs -5.5% [6.5], $P < 0.001$), and at 24 months (0.8% [11.8] vs -10.3% [9.8], $P < 0.001$). P-values were determined by using the Mann-Whitney U test. (b) In the matched cohort, the %FVCs in the PDN group vs non-PDN group were significantly different at 6 months (6.6% [8.2] vs -3.2% [3.6], $P < 0.001$), at 12 months (5.0% [9.7] vs -4.9% [5.6], $P < 0.001$), and at 24 months (0.9% [13.4] vs -9.4% [8.6], $P = 0.001$). P-values were determined by using the Wilcoxon signed-rank test. A *** indicates a P-value < 0.001 , a ** indicates a P-value < 0.01 . FVC: forced vital capacity; PDN: prednisolone; SD: standard deviation.

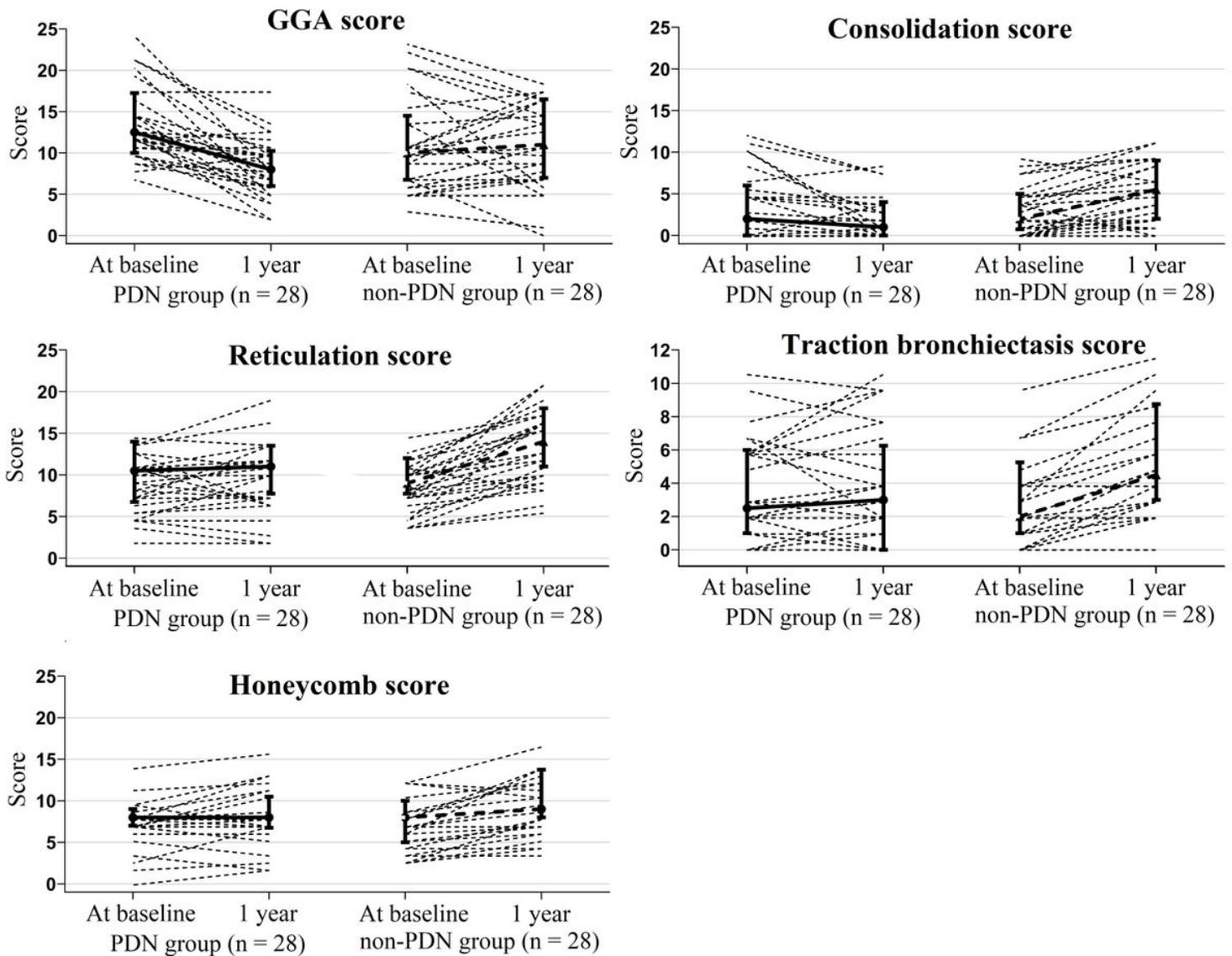


Figure 4

Trends of the 1-year change in total scores from baseline in each HRCT finding. The total scores appeared to improve in GGA and consolidation, with slow progression in reticulation, traction

bronchiectasis, and honeycombing in the PDN group. The whiskers at the bottom and top represent the 25th and 75th percentiles, respectively. The middle horizontal lines are the median. GGA: ground glass attenuation; PDN: prednisolone.

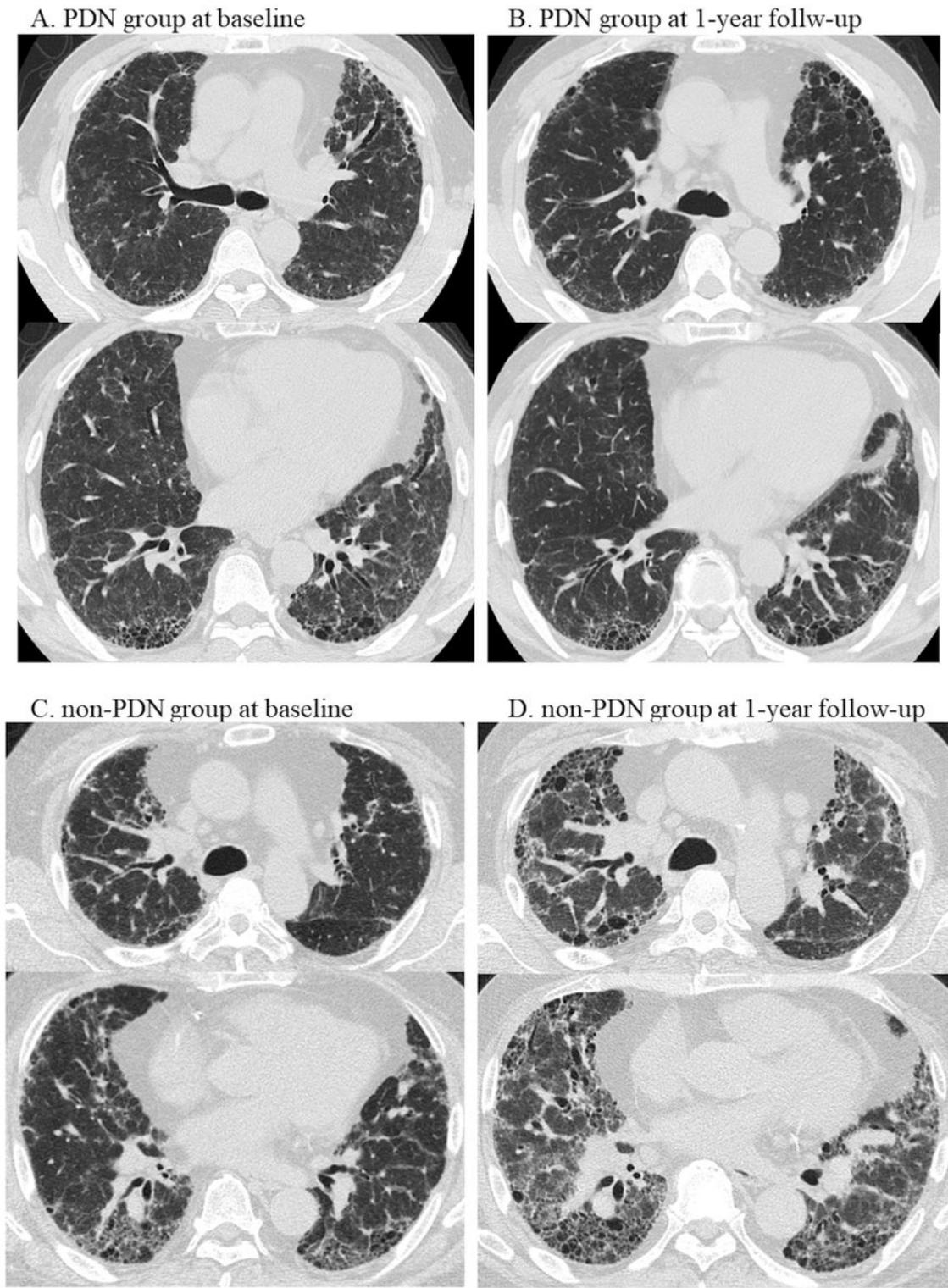


Figure 5

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of the follow-up period at 60 months. At baseline, the patient's %FVC was 57.9%, the annual %FVC decline before the treatment was 26.1%, and BAL lymphocyte count was 29%. At the 1-year follow-up, the change in %FVC from baseline was +15.9%. Reduced GGA with least fibrotic progression was observed on HRCT over a year. Total scores of HRCT findings (baseline to 1-year follow-up): GGA (22 to 14), consolidation (2 to 0), reticulation (12 to 13), traction bronchiectasis (6 to 8), honeycombing (13 to 14), and mosaic attenuation (2 to 0). (C)(D) A 66-year-old male with fibrotic bird-related hypersensitivity pneumonitis was not accepted for corticosteroid treatment over the clinical course till his date of death at 17 months. At baseline, his %FVC was 46.6%, and the annual FVC decline till the date of diagnosis was 4.7%. At the 1-year follow-up, the change of %FVC from baseline was -12.3%. Outstanding fibrotic progressions were observed on HRCT. The total scores of HRCT findings were as follows: GGA (11 to 18), consolidation (5 to 6), reticulation (16 to 19), traction bronchiectasis (10 to 15), honeycombing (14 to 19), and mosaic attenuation (0 to 0). BAL: bronchioalveolar lavage; %FVC: percent forced vital capacity; GGA: ground glass attenuation; HP: hypersensitivity pneumonitis; HRCT: high-resolution computed tomography.

Supplementary Files

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