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3D-CT-derived lung volumes and mortality risk in patients with fibrotic hypersensitivity pneumonitis

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3D-CT, three-dimensional computed tomography; AE, acute exacerbation; BMI, body mass index; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; iPPFE, idiopathic pleuroparenchymal fibroelastosis; KL-6, Krebs von den Lungen-6; LV, lung volume; PFT, pulmonary function test; PPF, progressive pulmonary fibrosis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; SP-D, surfactant protein-D; UIP, usual interstitial pneumonia

ABSTRACT

Background: Hypersensitivity pneumonitis (HP) is a complex and heterogenous interstitial lung disease (ILD) that occurs in susceptible individuals due to certain inhaled antigens. Fibrotic-HP is a major underlying disease of progressive pulmonary fibrosis. Therefore, in addition to the radiological features of HP, quantitatively measuring fibrosis is important to evaluate disease severity and progression. The present study aimed to compare three-dimensional computed tomography (3D-CT)-derived lung volumes (LVs) of patients with HP and determine its association with mortality risk.
Methods: In this retrospective and multicenter cohort study, 126 patients diagnosed with HP (fibrotic, n = 72 and non-fibrotic, n = 54) with a confidence level higher than moderate were enrolled. Each lobe LV was measured using 3D-CT at the time of diagnosis and standardized using predicted forced vital capacity. The 3D-CT LV was compared with those of 42 controls and 140 patients with idiopathic pulmonary fibrosis (IPF).
Results: Compared to patients with fibrotic-HP, the standardized total LV was significantly higher in controls and patients with non-fibrotic-HP and was similar in patients with IPF. Longitudinal analyses demonstrated that approximately half of the patients with fibrotic-HP had an annual decrease in total LV. Decreased total and lower-lobe LVs were associated with shorter survival, and were independently associated with mortality together with ongoing exposure to inciting antigens. A composite model consisting of ongoing exposure to inciting antigens and total or lower-lobe LV successfully classified mortality risk into three groups.
Conclusions: Quantitatively measuring standardized LV can help determine disease severity, progression, and mortality risk in patients with fibrotic-HP.

Introduction

Hypersensitivity pneumonitis (HP) is an immune-related disease that manifests as interstitial lung disease (ILD) in susceptible individuals who develop an exaggerated response to an identified or unidentified antigen.[1–3] As the presence of fibrosis is a critical determinant of prognosis, the latest international guidelines categorize HP as non-fibrotic and fibrotic HP. Patients with non-fibrotic

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HP who avoid ongoing exposure to the inciting agent may have a favorable prognosis and the possibility of stabilization or full recovery. However, patients with fibrotic HP have a poorer prognosis.[1–3] Fibrotic HP is a common cause of progressive pulmonary fibrosis (PPF).[4,5] Moreover, it was the most frequently identified underlying disease in the INBUILD trial.[6]

For the diagnosis of HP, assessment of radiographic features using high-resolution computed tomography (HRCT) and identifying inciting antigens are essential.[1,2] An early study reported that upper zone-predominant fibrosis distinguishes fibrotic HP from idiopathic pulmonary fibrosis (IPF).[7] However, subsequent studies demonstrated that only a small proportion of patients with fibrotic HP (<10%) have upper lung-predominant disease.[8–10] These studies have suggested the heterogeneity and complexity of the progression of fibrosis in patients with HP. Therefore, quantitative measurements of disease progression might be helpful in addition to semi-quantitative assessment of fibrotic changes on HRCT and spirometry measurements in patients with HP.

Recent advances in three-dimensional computed tomography (3D-CT) allow for detailed reconstruction of lung images, which provides accurate lung volume (LV) measurements of the different lobes. Compared with pulmonary function tests (PFTs), there seemed several clinical advantages for 3D-CT analyses; PFTs require active patient participation, and the inability to understand or an unwillingness to follow directions typically leads to submaximal test results.[11] In addition, productive cough and dyspnea on exertion frequently occur in patients with ILD, and pneumothorax and acute exacerbation (AE) can occur during ILD. Spirometry was also difficult in patients with persistent symptoms, advanced respiratory disease, acute respiratory failure, and AE. Conversely, CT images can be obtained with minimal patient effort, such as a full inspiration breath-hold for a few seconds, allowing the assessment of patients with severe respiratory failure. Thus, 3D-CT analyses were considered a safe and patient-friendly method that could be applied to patients with advanced disease or respiratory failure.[12]

Quantitative assessment of standardized 3D-CT LVs has revealed that fibrosis can be distinctly progressed by the underlying disease and at AE, particularly in IPF, rheumatoid arthritis-associated ILD (RA-ILD), and idiopathic pleuroparenchymal fibroelastosis (iPPFE).[13–15] However, no study has quantitatively evaluated lung lobe volumes in patients with fibrotic or non-fibrotic HP. Therefore, herein, we aimed to assess the lung lobe volume loss and its association with mortality risk in patients with fibrotic HP.

Methods

Patients

In this retrospective, multicenter, cohort study, we reviewed 133 consecutive patients who were diagnosed with HP with a more than moderate confidence level based on the 2020 ATS/JRS/ALAT guidelines[1] at Hamamatsu University School of Medicine, Seirei Mikatahara Hospital, and Seirei Hamamatsu General Hospital between January 2007 and December 2022. Seven patients were excluded from this study, which included two patients with CT slices >5 mm thick, three with a history of lung resection or concomitant malignancy, and two with insufficient clinical data regarding PFT. Subsequently, 72 and 54 patients were categorized as fibrotic HP and non-fibrotic HP, respectively[1] (Supplementary Fig. 1). Longitudinal analyses were conducted in 60 patients with fibrotic HP who were available for chest CT 1 year after diagnosis, because CT was not performed in eight patients, three patients were transferred to a different hospital, and one died. We confirmed whether PPF could be diagnosed during longitudinal analysis. Individual patient records were reviewed for suspected causative antigens, such as documented environmental exposure to avian antigens (bird owner, feather or down-containing items, and bird dropping), prior or active exposure to mold or bacterial antigen in the farm environment, home or workplace, or other specifically identifiable exposure items or work history (humidifier, metalwork fluid, isocyanates, and other occupation-related antigens). Avoidance of ongoing exposure to the inciting antigen was defined as follows: For bird-related HP, culling of birds; for residence-related HP, relocation, renovation, or thorough cleaning by a professional; and for occupation-related HP, changing jobs or wearing a dust mask.[16] Ongoing exposure to the inciting antigen was defined as unsuccessful avoidance of ongoing exposure as described above.

The study also included 42 healthy individuals who visited Hamamatsu University Hospital for medical checkups between September 2014 and July 2017. The controls were individuals with age and sex distribution similar to that of the patients with fibrotic HP, and their chest CT scans revealed no obvious ILD. To compare the 3D-CT LVs of patients with HP with those of patients with IPF, 140 consecutive patients with IPF diagnosed at Hamamatsu University Hospital between January 2007 and July 2020 were also included. The data were obtained from a previous study,[13] and the diagnosis of IPF was based on the ATS/ERS/JRS/LATA criteria.[17] The criteria for PPF were based on the 2022 ATS/ERS/JRS/ALAT Clinical Practice Guideline.[4] As this was a retrospective study and worsening respiratory symptoms were difficult to assess, the physiological criteria (absolute decline in FVC of $\geq$5% or a decline in DLCO of $\geq$10%) and radiological criteria for PPF within 1 year of follow-up from diagnosis were assessed.

This study was approved by the ethics committee of Hamamatsu University School of Medicine (20-270) and was conducted in accordance with the approved guidelines. The requirement for patient approval and/or informed consent was waived because of the retrospective study design.

Quantification and standardization of 3D-CT LVs

Electronically stored chest CT images at the time of HP diagnosis were used. All CT images were acquired at the time of HP diagnosis and a year later if a chest CT was available in routine clinical practice. In healthy controls, chest CT scans at the optimum timing were used. Chest CT was performed without intravenous contrast with the patients in the supine position. The patients were instructed to maintain full inspiration breath-hold. The SOMATOM Definition Flash (Siemens Healthcare, Tokyo, Japan) and Aquillion CX (Canon Medical Systems, Tokyo, Japan) CT scanners were used. The CT machine settings were as follows: detector-row configuration acquired as 128 $\times$ 0.6 mm (SOMATOM) and 64 $\times$ 0.5 mm (Aquillion CX) by double sampling, 120 kVp and quality mAs via AEC. A sharp kernel of I70 (SOMATOM) and FC52 (Aquillion CX) were used to create 3D-CT images using 5-mm slices at 5-mm intervals in the lung parenchyma (window level, −600 HU; window width, 1500 HU). SYNAPSE VINCENT version 3 (FUJIFILM Medical Systems, Tokyo, Japan) was used to extract lung fields from CT images, segment the lung lobe segmentation, and analyze the volumes for total lung; bilateral upper and lower lobes; right upper, middle, and lower lobes; and left upper and lower lobes. Digital imaging and communication in medicine data for each patient were anonymously transferred to the software. Using this software, whole-lung extraction from chest CT was automatically quantified by excluding the thoracic wall, mediastinum, large vessels, and airways toward the tertiary bronchi. Lung extraction and lung lobe segmentation were performed using threshold values and anatomical knowledge-based algorithms. The CT values for the entire lung were between −1000 and 0 HU. In addition, threshold-based volumetric CT analysis, in which threshold CT values can be flexibly determined by all users, was used. Standardized LV (%) was calculated by dividing the volume measured

Table 1
Clinical characteristics of patients with fibrotic and non-fibrotic HP.

	Fibrotic HP (n = 72)	Non-fibrotic HP (n = 54)	P value
Age, year	72 [66–75]	66.5 [57.3–73]	0.009
Sex, male/female	48 (66.7%)/24 (33.3%)	30 (55.6%)/24 (44.4%)	0.266
Diagnostic confidence definite/high/moderate	15 (20.8%)/26 (36.1%)/31 (43.1%)	6 (11.1%)/29 (53.7%)/19 (35.2%)	0.108
Observation period, month	34 [16–66]	18 [9–67]	0.164
Never smoker	28 (38.9%)	26 (48.1%)	0.364
Former or current smoker	44 (61.1%)	28 (51.9%)	0.364
BMI, kg/m^2	23.0 [20.8–25.1]	22.1 [20.2–24.4]	0.335
Anti-inflammatory therapy[†]	45 (62.5%)	13 (23.2%)	< 0.001
Anti-fibrotic therapy	10 (13.9%)	0 (0.0%)	0.005
Identified inciting antigens[‡]	52 (72.2%) 26 bird related, 21 residence related, 5 occupation-related	41 (75.9%) 14 residence related, 11 occupation-related, 9 humidifiers, 5 bird related, 2 air-conditioning	0.686
Avoidance of ongoing exposure to antigens[§]	16 (22.2%)	32 (59.3%)	< 0.001
Ongoing exposure to inciting antigens	56 (77.8%)	22 (40.7)	< 0.001
Death[¶]	18 (23.1%) 11 acute exacerbation, 2 respiratory failure, 3 pneumonia, 2 unknown	5 (9.3%) 1 cardiovascular disease, 1 chronic kidney disease, 1 pancreatic cancer, 2 unknown	0.035
Pulmonary Function Test			
FVC, % predicted	76.0 [65.0–90.9]	93.9 [76.8–102.9]	< 0.001
DLCO, %	68.5 [60.4–85.7] (n = 53[‖])	75.2 [55.7–88.2] (n = 46[‖])	0.858
Laboratory			
KL-6, U/mL	1541 [741–2750]	1447 [697–3014]	0.528
SP-D, ng/mL	304 [181–458] (n = 70)	246 [118–424] (n = 52)	0.090

HP, hypersensitivity pneumonitis; BMI, body mass index; FVC, forced vital capacity; DLCO, diffuse capacity of the lung for carbon monoxide; KL-6, Krebs von den Lunge-6; SP-D, surfactant protein-D.

[†] Anti-inflammatory therapy was defined as steroid treatment or steroid treatment and administration of immunosuppressants.

[‡] In fibrotic HP, antigens were bird related in 26 patients, residence related in 21, and occupation-related in 5. In non-fibrotic HP, antigens were residential in 14 patients, occupation-related in 11, humidifiers in 9, bird related in 5, and air-conditioning in 2.

[§] Avoidance of ongoing exposure to inciting antigen was defined as follows: for bird-related HP, culling the birds; for residence-related HP, relocation, renovation, or through cleaning by a professional; for occupation-related HP, changing jobs or wearing a dust mask. Ongoing exposure to inciting antigen was defined unsuccessful avoidance of ongoing exposure as described above.

[¶] The cause of death was defined as all-cause death. The causes of death in fibrotic HP were acute exacerbation in 11 patients, respiratory failure in 2, pneumonia in 3, and unknown in 2. The causes of death in non-fibrotic HP were octopus cardiomyopathy, chronic kidney disease, and late-onset pancreatic cancer in one patient each and unknown in two patients.

[‖] DLCO could not be measured because of dyspnea.

using 3D-CT by the predicted forced vital capacity (FVC-predicted). The reference values of FVC-predicted were defined based on age, sex, height, and ethnicity.[18,19] The change in the standardized LV was calculated as absolute changes (standardized LV volume at baseline−standardized LV volume at 1 year).

Data collection

Clinical characteristics at the time of HP diagnosis (age, sex, physical examination, smoking history, blood test results, and PFT results) were retrieved from patients' medical records. Clinical data recorded 1 year after diagnosis were also retrieved.

A composite model consisting of ongoing exposure to antigen and standardized LV

To assess mortality risk, we created a composite model with ongoing exposure to the inciting antigen and standardized LV. The standardized total LV or standardized lower-lobe LV was used to calculate the risk score using the median points. A simple scoring system was developed. One point each was assigned if the patient was exposed to the inciting antigen and the standardized total LV or standardized lower-lobe LV was less than or equal to the median. Based on the total points, the patients were categorized into the following three groups: mild (0), moderate,[1] and severe.[2] The prediction model was evaluated using Harrell's concordance index (C-index).

Statistics

Categorical variables are presented as numbers (percentages) and continuous variables are presented as means or medians (interquartile ranges [IQR]). The Mann−Whitney U test and Fisher's exact test were used to compare continuous and categorical variables, respectively. Pearson's correlation coefficient was used to determine the relationship between FVC and standardized total LV at the time of fibrotic HP diagnosis. The overall survival time was measured from the date of fibrotic HP diagnosis. Patients were censored if they remained alive until December 31, 2022. Cumulative survival probabilities were estimated using the Kaplan−Meier method and the log-rank test. The cutoff values for standardized LV were assessed using the median. Cox proportional hazards regression analysis was used to identify factors associated with mortality. Among the statistically significant covariates in the univariate analysis, clinically relevant and important variables were selected for the multivariate analysis. All statistical analyses were performed using EZR (version 1.51).[20] All analyses were two-tailed, and statistical significance was set as $p < 0.05$.

Results

Clinical characteristics of the patients at the time of HP diagnosis

Patient characteristics and diagnostic confidence according to the latest ATS/JRS/ALAT guidelines are shown in Table 1 and

Supplementary Figure 2. Patients with fibrotic HP were older than those with non-fibrotic HP. However, no significant difference in was found sex between the two groups. Moreover, 15 (20.8%), 26 (36.1%), and 31 (43.1%) patients were diagnosed with fibrotic HP with “definite,” “high,” and “moderate” confidence, respectively. Meanwhile, 6 (11.1%), 29 (53.7%), and 19 (35.2%) patients were diagnosed with non-fibrotic HP with “definite,” “high,” and “moderate” confidence, respectively. The frequency of identifying inciting antigens was similar between fibrotic and non-fibrotic HP groups. However, less than half of the patients with fibrotic HP successfully avoided ongoing exposure to the inciting antigen (fibrotic vs. non-fibrotic, 22.2% vs. 59.3%). Despite anti-inflammatory and anti-fibrotic treatments being frequently administered to patients with fibrotic HP, 18 (23.1%) died during the observation period. PFTs revealed that the FVC of patients with fibrotic HP was lower than that of patients with non-fibrotic HP (median, 76.0% vs. 93.9%). However, the lung diffusion capacity for carbon monoxide (DLCO) was not significantly different between the fibrotic and non-fibrotic HP groups.

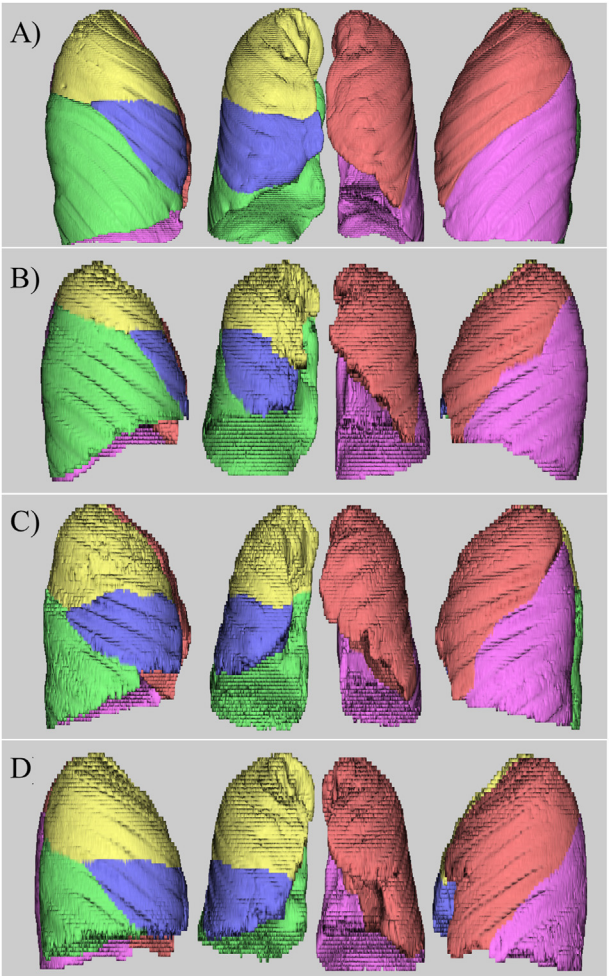

Fig. 1. Three-dimensional computed tomography of the lung images obtained at diagnosis.
Representative segmental lung images of an age- and sex-matched **(A)** control (male, height 164.5 cm, and weight 62.8 kg), **(B)** a patient with non-fibrotic HP (male, height 169.5 cm, and weight 63.7 kg), **(C)** a patient with fibrotic HP (male, height 169.0 cm, weight 68.0 kg), and **(D)** a patient with IPF (male, height 167.1 cm, weight 64.1 kg) at the time of diagnosis. The lungs are color-coded as follows: right upper lobe, yellow; right middle lobe, blue; right lower lobe, green; left upper lobe, red; and left lower lobe, pink.
HP, hypersensitive pneumonitis; IPF, idiopathic pulmonary fibrosis.

Standardized total LV and its correlation with lung physiology

Representative segmental lung images of fibrotic HP, non-fibrotic HP at diagnosis, and age- and sex-matched controls are depicted in Figure 1. The standardized 3D-CT LV measurements are shown in Table 2. The median standardized total LV, upper-lobe LV, and lower-lobe LV in patients with fibrotic HP were 104.1%, 49.8%, and 42.4%, respectively, indicating lower lobe–dominant fibrosis. No difference was noted in the standardized LV by smoking history (data not shown). Compared with patients with non-fibrotic HP and controls, patients with fibrotic HP had significantly decreased upper and lower-lobe LVs and thus a significantly lower total LV. Compared with patients with IPF, patients with fibrotic HP had significantly decreased upper-lobe LVs. Furthermore, the standardized total LV was equivalent between patients with IPF and those with fibrotic HP.

To validate the values of the standardized LV, correlation analyses were performed. The standardized total LV (%) and total LV (L) were significantly associated with the FVC (%) and FVC (L) in patients with fibrotic HP ($r = 0.63$, $p < 0.001$ and $r = 0.82$, $p < 0.001$, respectively) and patients with non-fibrotic HP ($r = 0.56$, $p < 0.01$ and $r = 0.80$, $p < 0.01$, respectively) (Supplementary Fig. 3).

Association between standardized 3D-CT LV and mortality

Because patients with fibrotic HP have a poor prognosis, we evaluated the 3D-CT LV associated with mortality risk in patients with fibrotic HP. Furthermore, we determined whether standardized total LV, standardized upper-lobe LV or standardized lower-lobe LV was associated with mortality. In a comparison of groups with 3D-CT LVs above and below the median, patients with a standardized total LV $\leq$ 104% had significantly shorter survival than those with a standardized total LV >104% (median survival time 47 months vs. not reached, $p = 0.02$; Fig. 2A). Patients with standardized lower-lobe LV $\leq$ 42.4% demonstrated a shorter survival than patients with standardized lower-lobe LV >42.4% (median survival time 68 months vs. not reached, $p < 0.01$; Fig. 2B). However, patients with standardized upper-lobe LV $\leq$ 50% had shorter survival than patients with standardized upper-lobe LV >50%; the difference was not statistically significant (median survival time 84 months vs. 100 months, $p = 0.43$; Fig. 2C).

Univariate and multivariate analyses

Univariate analyses demonstrated that standardized total LV and standardized lower-lobe LV were significant indicators of mortality risk (as continuous and categorial valuables). Furthermore, ongoing exposure to the inciting antigen, even after being identified, was significantly associated with mortality risk in patients with fibrotic HP (hazard ratio >5.00, $p < 0.01$). Multivariate analyses revealed that standardized total LV, standardized lower-lobe LV, and ongoing exposure to the inciting antigen were significantly associated with mortality after adjusting for age (Table 3).

To evaluate mortality risk, patients who met the criteria for PPF, physiological criteria (absolute decline in FVC of $\geq$5% or a decline in DLCO of $\geq$0%), and radiological criteria for PPF within 1 year of follow-up from diagnosis were assessed. Owing to the retrospective nature of the study, worsening respiratory symptoms were not assessed. Among the 72 patients with fibrotic HP, 54 were available for the evaluation of the physiological and radiological criteria for PPF. Subsequently, 14 and 24 patients met the physiological and radiological criteria, respectively, resulting in 9 (16.7%) who met the PPF criteria by fulfilling both the physiological and radiological criteria for PPF. Patients who met the PPF criteria showed a significantly higher mortality risk in univariate analysis (Table 3).

Table 2
Comparison of standardized three-dimensional computed tomography LV in patients with fibrotic HP, non-fibrotic HP, and IPF.

Standardized 3D-CT LV, %	Controls (n = 42)	Non-fibrotic HP at diagnosis (n = 54)	Fibrotic HP at diagnosis (n = 72)	IPF at diagnosis (n = 140)	P value Controls vs. Non-fibrotic HP	P value Controls vs. Fibrotic HP	P value Non-fibrotic HP vs. Fibrotic HP	P value Fibrotic HP vs. IPF
Total lung	142.8 [127.4–153.8]	121.3 [102.1–135.9]	104.1 [89.6–120.5]	108.2 [90.5–123.5]	<0.001	<0.001	<0.001	0.242
Right lung	77.0 [71.1–82.4]	63.7 [55.1–72.3]	57.6 [49.0–65.2]	59.2 [52.0–68.8]	<0.001	<0.001	0.002	0.203
Right upper lobe	31.1 [27.3–34.1]	23.8 [19.5–27.3]	22.8 [17.1–26.2]	25.2 [21.5–29.8]	<0.001	<0.001	0.137	0.001
Right middle lobe	13.9 [12.0–16.4]	11.4 [9.4–14.6]	13.0 [11.0–15.8]	13.5 [10.9–16.0]	0.002	0.215	0.017	0.972
Right lower lobe	32.0 [28.1–35.8]	28.6 [25.4–34.7]	21.7 [16.6–28.4]	20.2 [15.6–24.0]	0.080	<0.001	0.003	0.101
Left lung	65.4 [58.6–72.7]	54.6 [46.3–64.6]	47.2 [38.8–52.6]	50.1 [41.8–58.8]	<0.001	<0.001	<0.001	0.047
Left upper lobe	36.5 [32.9–39.2]	30.2 [25.6–34.7]	26.5 [20.7–33.0]	29.7 [24.8–35.1]	<0.001	<0.001	0.003	0.003
Left lower lobe	29.6 [25.0–32.6]	24.8 [19.4–29.6]	19.6 [14.7–25.0]	19.3 [15.3–23.8]	0.003	<0.001	<0.001	0.994
Upper lobes	66.7 [59.8–72.1]	53.4 [46.5–61.2]	49.8 [37.4–58.7]	54.8 [46.9–63.8]	<0.001	<0.001	0.018	0.001
Lower lobes	61.2 [52.1–67.4]	54.2 [44.7–61.0]	42.4 [32.6–52.5]	39.7 [32.4–48.0]	0.016	<0.001	<0.001	0.707

LV, lung volume; HP, hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis.

Prevalence of the annual decline in the LV in patients with fibrotic HP

We measured the annual changes in the LV to assess the frequency of disease progression in patients with fibrotic HP. Among the 72 patients with fibrotic HP, annual CT was available in 60. Approximately 50% of patients with fibrotic HP had a lower standardized LV, and 22 (36.6%) demonstrated an annual reduction in the standardized total LV of >5% (Fig. 3A). Patients with an annual reduction in the standardized total LV and upper-lobe LV tended to have shorter survival than those without an annual reduction (Fig. 3B). The clinical characteristics of the patients with fibrotic HP according to annual changes in the standardized LV are presented in Supplementary Tables 1–3. Patients with an annual reduction in the standardized LV of >5% (total LV, upper-lobe LV, and lower-lobe LV) tended to have ongoing exposure to inciting antigens and failed to avoid antigen exposure compared to patients with annually increased standardized LV, although the difference was not statistically significant. Especially, the frequencies of patients who met the PPF criteria was higher in patients with an annual decline in the standardized LV.

Predictive model for mortality consisting of ongoing exposure to the inciting antigen and standardized LV

Given that ongoing exposure to the inciting antigen and lower standardized LV were significantly associated with mortality in patients with fibrotic HP, we developed a predictive model of prognosis for patients with fibrotic HP. One point was assigned for each of the following prognostic factors: (1) standardized total LV $\leq$ 104 and ongoing exposure to the inciting antigen or (2) standardized lower-lobe LV $\leq$ 42.4 and ongoing exposure to the inciting antigen. Patients were classified into three groups based on the total point score: 0, mild; 1, moderate; and 2, severe. Kaplan–Meier curves for the assessment of exposure to the inciting antigen with the standardized total or lower-lobe LV categorized patients with fibrotic HP into three groups with distinct survival curves and a high discrimination yield (median survival time: not reached vs. 100 months vs. 47 months, respectively, Fig. 4A; median survival time: not reached vs. not reached vs. 68 months, respectively, Fig. 4B).

Discussion

In this study, we quantitatively measured the LV of patients with fibrotic and non-fibrotic HP using 3D-CT. The LV was significantly reduced in patients with fibrotic HP than in patients with non-fibrotic HP and controls. Additionally, the LV in patients with fibrotic HP was similar to that in patients with IPF. Both cross-sectional and longitudinal analyses demonstrated that a decrease in the total LV was associated with an increase in mortality risk. Multivariate analyses also demonstrated the importance of assessing LV reduction in addition to avoiding ongoing exposure to inciting antigens in patients with fibrotic HP. Collectively, our results suggest that volume loss in the lungs is a fundamental feature in patients with fibrotic HP.

Regarding the distribution of fibrosis, although upper lobe–predominant fibrosis was reported,[7] the latest guidelines state that the majority of fibrosis in fibrotic HP is predominantly axially

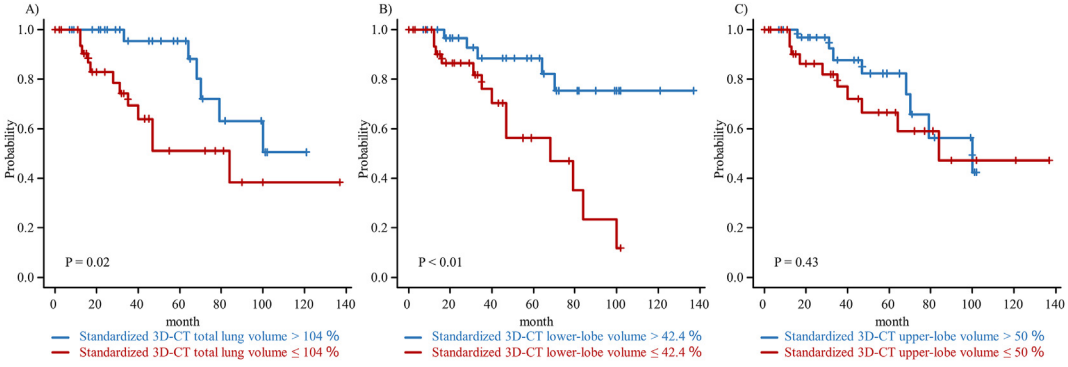

Fig. 2. Mortality risk in patients with fibrotic HP according to standardized three-dimensional computed tomography-derived LVs. The Kaplan–Meier curves of patients with fibrotic HP based on the median value of the **(A)** standardized total LV, **(B)** standardized lower-lobe LV, and **(C)** standardized upper-lobe LV. The cutoff value of each was the median. The P value was assessed using the log-rank test.
HP, hypersensitive pneumonitis; LV, lung volume.

Table 3
Cox proportion analyses for mortality in patients with fibrotic HP.

Predictor	HR	95% CI	P value		HR	95% CI	P value
Univariate analysis				Multivariate Analysis			
				Multivariate Analysis I			
Age, year	1.04	0.98–1.11	0.20	Age, year	1.10	1.01–1.21	0.02
Sex, male	1.37	0.49–3.86	0.55	Standardized total LV, <104%	3.05	1.13–9.17	0.03
BMI, kg/m^2	0.99	0.86–1.15	0.90	Ongoing exposure to inciting antigens	>5.00	5.15–inf	<0.01
Smoking history, yes	1.27	0.47–3.39	0.64				
FVC, percent predicted	0.98	0.95–1.01	0.23	**Multivariate analysis II**			
DLCO, %	1.00	0.97–1.04	0.78	Age, year	1.08	0.99–1.20	0.10
PPF criteria[†], yes	14.0	2.97–66.07	<0.01	Standardized lower-lobe volume, <42.4%	2.96	1.10–9.34	0.03
KL-6, U/mL	1.00	1.00–1.00	0.22	Ongoing exposure to inciting antigens	>5.00	5.51–inf	<0.01
SP-D, ng/mL	1.00	1.00–1.00	0.37				
Standardized total LV, %	0.97	0.95–1.00	0.02				
Standardized lower-lobe volume, %	0.98	0.95–1.02	0.34				
Standardized lower-lobe volume, %	0.95	0.91–0.99	0.01				
Standardized total LV, <104%	2.89	1.08–7.76	0.03				
Standardized lower-lobe volume<42.4%	4.24	1.5–12.0	<0.01				
Ongoing exposure to inciting antigens	>5.00	5.00–inf	<0.01				

HP, hypersensitivity pneumonitis; BMI, body mass index; FVC, forced vital capacity; DLCO, diffuse capacity of the lung for carbon monoxide; PPF, progressive pulmonary fibrosis; KL-6, Krebs von den Lunge-6; SP-D, surfactant protein-D; LV, lung volume; HR, hazard ratio; CI, confidence interval.
[†] Met both physiological criteria (absolute decline in FVC of ≥5% or a decline in DLCO of 10%) and radiological criteria for PPF within 1 year of follow-up from diagnosis.

peripheral (subpleural) or central (peribronchovascular) and basal in distribution.[1] However, none of the studies have evaluated LV loss in patients with fibrotic HP. The present study quantitatively measured standardized LV and found that both standardized upper and lower-lobe LVs reduced in patients with fibrotic HP, and the fibrosis predominantly involved the lower lobe. However, in patients with non-fibrotic HP, the standardized upper-lobe LV alone decreased. Collectively, our results are supported by the current guidelines and the differences in the LV reduction between fibrotic HP and non-fibrotic HP.

This study also demonstrated that standardized total LV reduction was associated with shorter survival in patients with fibrotic HP, particularly the reduction in the standardized lower-lobe LV. A previous study demonstrated that decreases in the standardized total LV, upper-lobe LV, and lower-lobe LV were associated with mortality in patients with IPF.[13] Meanwhile, compared with lower-lobe LV,

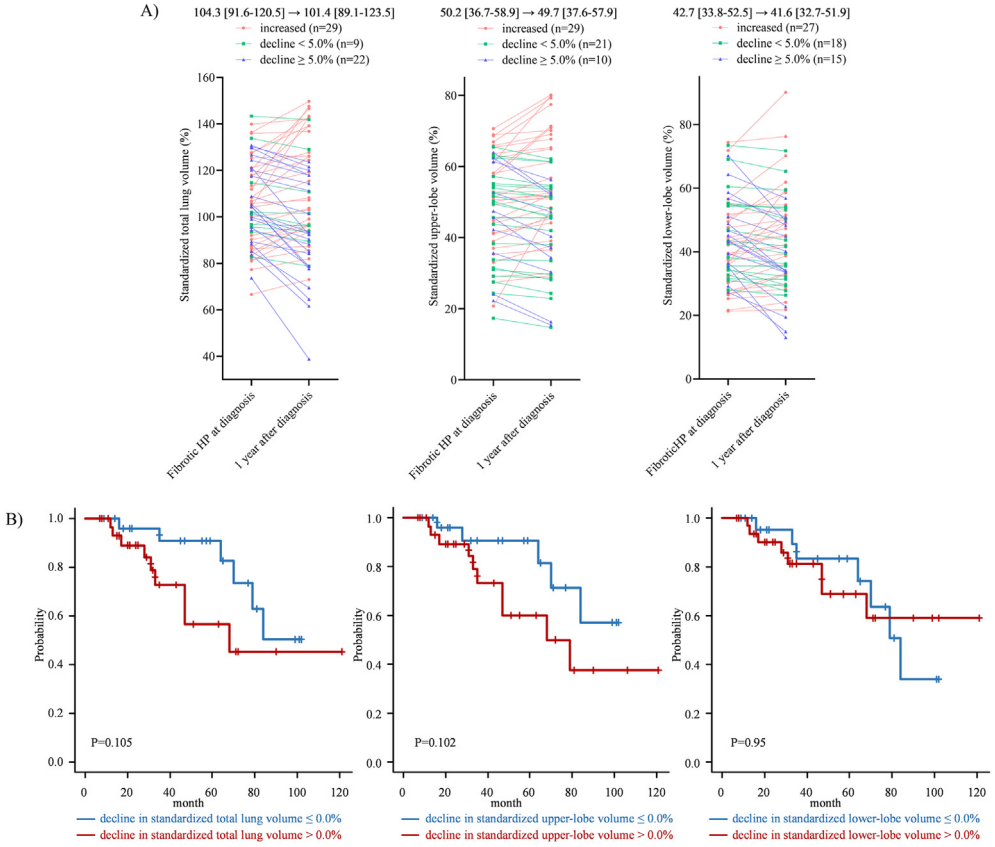

Fig. 3. Annual change in the standardized LV in patients with fibrotic HP. **(A)** Annual change in the LV. **(B)** Kaplan–Meier curves of patients with fibrotic HP according to the annual change in the standardized LV.
HP, hypersensitive pneumonitis; LV, lung volume.

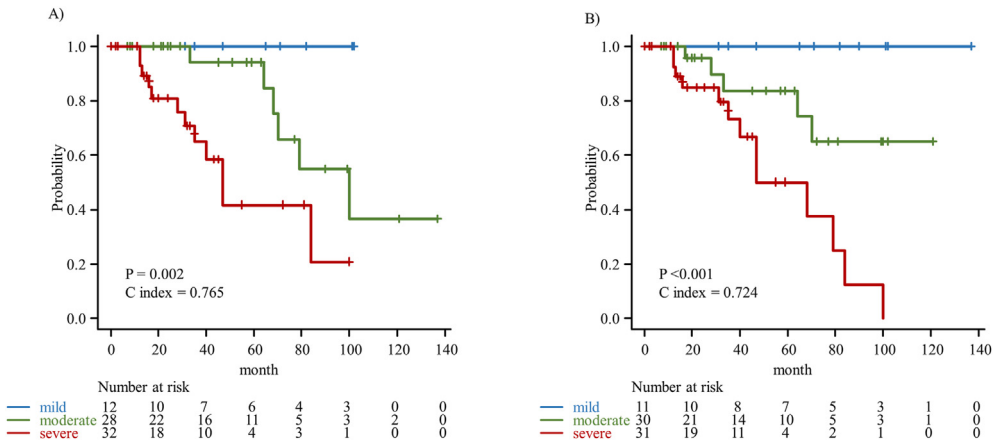

Fig. 4. Kaplan–Meier curves of patients with fibrotic HP with ongoing exposure to inciting antigen. Kaplan–Meier curves of patients with fibrotic HP based on ongoing exposure to the inciting antigen and standardized **(A)** total LV or **(B)** lower-lobe LV. The p-values were determined using the log-rank test. The number at risk is the number of subjects at risk immediately before the time point.
HP, hypersensitive pneumonitis; LV, lung volume.

upper-lobe LV had a prognostic value in patients with AE-IPF, AE-RA-ILD, and iPPFE.[13–15] These differences might indicate the distinct and heterogeneous disease progression in fibrotic HP and other etiologies of ILD.

Several risk factors for progression and mortality in patients with fibrotic HP have been identified, including the extent of fibrosis on HRCT, presence of the usual interstitial pneumonia (UIP) pattern on HRCT, bronchoalveolar lavage lymphocytosis, lower DLCO, and lower FVC.[1–3] Interestingly, lower FVC (%) was not associated with mortality in this study. However, the FVC demonstrated a significant correlation with the standardized total LV. This may be attributed to the fact that patients with fibrotic HP have airway-centered fibrosis (peribronchiolar metaplasia) and poorly formed granulomas in addition to alveolar fibrosis (namely UIP or non-specific fibrotic interstitial pneumonia). These pathological changes in the small airway might have affected the spirometry results as well as the small cohort size of this study.

The longitudinal analysis demonstrated that approximately 50% of the patients with fibrotic HP had a reduced standardized total LV, of which 30% demonstrated an annual reduction rate of >5%. The prevalence of PPF in patients with fibrotic HP is reportedly 1.5%–47.3% across various countries.[5] In our cohort, 54 patients were available for the evaluation of both the physiological and radiological criteria for PPF and 9 (16.7%) patients met the PPF criteria by fulfilling both the physiological and criteria within 1 year after diagnosis. Recently, a large cohort study reported that approximately 60% of patients with fibrotic HP met the criteria for progressive fibrosing ILD (PF-ILD),[21] suggesting not a few patients with fibrotic HP have a progressive disease. Therefore, 3D-CT analyses may be useful for monitoring disease progression.

Notably, ongoing exposure to the inciting antigen was mostly associated with mortality risk in our cohort. Similar to our study findings, the prognostic importance of identifying the inciting antigen and subsequent antigen avoidance has been previously reported.[16,22,23] In this study, although the inciting agent was identified in >70% of the patients with fibrotic HP, only 20% of them could avoid exposure to these inciting antigens. Furthermore, the frequency of avoidance of the inciting antigen was significantly lower in patients with fibrotic HP than in those with non-fibrotic HP. These results indicate the importance and difficulties of avoiding exposure to the inciting antigens in real life. A composite model consisting of the standardized LV and ongoing exposure to the inciting antigen was also developed during the study. Compared with the ILD gender-age-physiology (GAP) model, which combines age, sex, FVC, and DLCO,[24] our simple model comprised only two factors and successfully classified the patients into three groups based on the mortality risk.

This study has several limitations. First, this was a retrospective single cohort study, and only a small number of patients were analyzed. Second, CT images may not have been obtained properly in some patients, as they were required to be at full inspiration. Third, this study defined “avoidance of ongoing exposure” and “ongoing exposure” to the inciting antigen in accordance with a previous report.[16] However, it was potentially difficult to precisely judge the success or failure of antigen avoidance. Therefore, “failures” may be mixed in with “successful cases” to avoid exposure to the inciting antigen. Fourth, to characterize standardized LV in patients with HP, this study limited enrollment to patients diagnosed with a confidence level of moderate or higher. Thus, the utility of 3D-CT analyses and the composite model were confirmed only in these patients. Further studies are required to overcome these limitations and assess their utility in patients diagnosed with low confidence or other etiologies.

In conclusion, this study quantitatively measured the LV in patients with HP using standardized 3D-CT analyses. We found a significant reduction in the standardized total LV in patients with fibrotic HP, which was associated with an increase in mortality risk. Furthermore, a simple composite model for assessing ongoing exposure to inciting antigen and standardized LV yielded prognostic results according to mortality risk. Our study results indicate that LV assessment by 3D-CT analyses might be useful in the evaluation of disease progression, severity, and mortality risk in patients with fibrotic HP.

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The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2024.07.002.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

SY: Conception and design, data collection, data analysis and interpretation, and manuscript writing. YS: Conception and design, data collection, data analysis and interpretation, manuscript writing, and final approval of the manuscript. YT: Conception and design, data collection, and data analysis. AF: Conception and design, data collection, and data analysis. KY, MKo, DH, YI, HY, HH, MKa, KF, NE, TF, and NI: Data collection, data analysis, and supervision. TS: Supervise and administrative support.

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