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Antigen Avoidance and Outcome of Nonfibrotic and Fibrotic Hypersensitivity Pneumonitis

Takashi Nishida[1], MD; Eriko Kawate[1], MD; Takashi Ishiguro[1], MD, PhD; Tetsu Kanauchi[2], MD; Yoshihiko Shimizu[3], MD, PhD; Noboru Takayanagi[1], MD, PhD

[1]Department of Respiratory Medicine, [2]Department of Radiology, and [3]Department of Pathology, Saitama Cardiovascular and Respiratory Center

Corresponding author and requests for reprints: Takashi Nishida, MD

Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center,

1696 Itai, Kumagaya, Saitama 360-0105, Japan

Fax: +81-48-536-9920

E-mail: nishida.takashi@saitama-pho.jp

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Abstract

Background: Hypersensitivity pneumonitis (HP) is classified into nonfibrotic and fibrotic phenotypes. Patients with nonfibrotic HP often experience recurrence and develop fibrosis, whereas those with fibrotic HP have a poor prognosis. Although antigen avoidance has long been the first line of treatment for HP, its impact on prognosis has been poorly reported.

Methods: Medical records of 121 patients with HP diagnosed by new diagnostic criteria of ATS/JRS/ALAT guidelines and treated at our institution in Saitama, Japan, were retrospectively analysed. HP was classified into nonfibrotic and fibrotic phenotypes and 6 HP subtypes: summer-type, bird-related, home-related, and occupational HP, humidifier lung, and hot tub lung. Achievement of reduced exposure to inciting agents was divided into complete antigen avoidance (CAA) and incomplete antigen avoidance (IAA) by HP subtype.

Results: Of the 74 patients with nonfibrotic HP, 30 achieved CAA and experienced no recurrence or development of fibrosis. In the remaining 44 patients with IAA, 24 (54.5%) experienced recurrence and/or development of fibrosis. The all-cause 5-year mortality rate in the 47 patients with fibrotic HP was 47.8%. Negative prognostic factors of HP-related mortality in these patients were <50% lymphocytes in bronchoalveolar lavage (BAL) and honeycombing. Multivariate analysis showed a tendency for IAA to be related to poorer survival (hazard ratio: 3.452, 95% CI, 0.964-12.359, P=0.057).

Conclusions: In the patients with nonfibrotic HP, CAA resulted in no recurrence or development of fibrosis and longer survival. In the patients with fibrotic HP, <50% lymphocytes in BAL and honeycombing were negative prognostic factors for mortality.

KEY WORDS: antigen avoidance; hypersensitivity pneumonitis; nonfibrotic and fibrotic phenotype; prognosis; recurrence

ABBREVIATIONS: A-aDO_2: alveolar-arterial oxygen difference; ALAT: Asociación Latinoamericana del Tórax; ATS: American Thoracic Society; BAL: bronchoalveolar lavage; CAA: complete antigen avoidance; CI: confidence interval; CRP: C-reactive protein; DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; HP: hypersensitivity pneumonitis; HR: hazard ratio; HRCT: high-resolution computed tomography; IAA: incomplete antigen avoidance; JRS: Japanese Respiratory Society; KL-6: sialylated carbohydrate antigen Krebs von den Lungen-6; $PaCO_2$: partial pressure of arterial carbon dioxide; PaO_2: partial pressure of arterial oxygen; SP-D: pulmonary surfactant protein-D

Introduction

Hypersensitivity pneumonitis (HP) is an inflammatory and/or fibrotic disease affecting the lung parenchyma and small airways. It typically results from an immune-mediated reaction provoked by an overt or occult inhaled antigen in susceptible individuals [1]. Although various alternative definitions of HP have been proposed [2-5], clinical practice guidelines were developed by the American Thoracic Society (ATS), the Japanese Respiratory Society (JRS), and the Asociación Latinoamericana del Tórax (ALAT) [6], for the accurate diagnosis of HP. Accurate and timely diagnosis can help patients avoid culprit environmental factors known to induce HP and potentially change the disease course [7-9].

HP was historically categorised as acute, subacute, or chronic [5]. However, these categories are not easily demarcated, and their delineation has been variable and arbitrary in many studies [10-12]. Because the presence of radiographic or histopathological fibrosis is the primary determinant of prognosis [7-9, 13-19] the ATS/JRS/ALAT guideline categorises HP as either nonfibrotic or fibrotic. Patients with nonfibrotic HP often experience recurrence and develop fibrosis, whereas those with fibrotic HP have a poor prognosis. Whether complete antigen avoidance (CAA) improves the outcome of patients with nonfibrotic or fibrotic HP requires further study. We hypothesised that CAA would reduce the incidences of recurrence and fibrosis development in nonfibrotic HP patients and would prolong survival in patients with fibrotic HP.

Thus, the present study aimed to retrospectively review the medical records of 121 patients with HP diagnosed according to the new diagnostic criteria of ATS/JRS/ALAT guideline to assess both the relationship of CAA with recurrence or fibrosis development in patients with nonfibrotic HP and prognostic factors including CAA in patients with fibrotic HP.

Study Design and Methods

Study Design

We performed a retrospective cohort study in Saitama Cardiovascular and Respiratory Center in Saitama, Japan. We studied 121 HP patients aged >18 years old who fulfilled the 2020 ATS/JRS/ALAT diagnostic criteria of definite, high confidence, and moderate confidence, and were newly diagnosed from 1991 through 2016 (Table 1). Following publication of the ATS/JRS/ALAT clinical practice guideline in 2020, we reviewed all clinical, radiographic, bronchoalveolar lavage (BAL), and pathological data, treatments, CAA, and outcomes from medical records of all patients who had been diagnosed as having HP. Patients with a diagnosis of HP of low confidence or not excluded were not included. Standard high-resolution computed tomography (HRCT) protocols were used to obtain images for evaluation. The scans were reviewed independently in a blinded fashion by two observers (N.T., T.K.). Scans consistent with fibrotic HP contained irregular fine or coarse reticulation with architectural lung distortion and traction bronchiectasis and were divided into two

groups: those with and without honeycombing. In cases of disagreement, consensus was obtained following further review. All patients were classified as having fibrotic or nonfibrotic HP based on the presence or absence, respectively, of radiological fibrosis. HRCT scan features and histopathological criteria for the diagnosis of HP were classified according to the following 3 patterns: typical HP, compatible HP, or indeterminate HP and HP, probable HP, or indeterminate for HP, respectively (Table 1). Based on exposure history and/or serum antibody testing, HP was classified into 6 categories: summer-type HP, bird-related HP, home-related HP, occupational HP (including mushroom worker's lung, isocyanate alveolitis, farmer's lung, and workplace-associated HP due to *Aspergillus fumigatus*), humidifier lung, and hot tub lung (Table 2).

All patients are advised to reduce or avoid culprit environmental factors, and reduction in the intensity of exposure to inciting antigens was classified into the categories of CAA and incomplete antigen avoidance (IAA). In patients with summer-type, bird-related, and home-related HP, changing homes was considered to be CAA, whereas renovation, clean-up, or stopping breeding of birds but continuing to live in the same house was considered IAA. In patients with occupational HP, humidifier lung, and hot tub lung, job change or job relocation, not using the humidifier, and not using the hot tub, respectively, were considered CAA (Table 2). Patients were followed through December 2018 or until death before then. Survival status was obtained from medical records and/or telephone interviews. In patients with nonfibrotic

HP, we examined whether IAA was associated with recurrence (re-exacerbation of respiratory symptoms and ground-glass opacities on HRCT) and/or fibrosis development and searched for predictors of recurrence and/or fibrosis development in the patients with nonfibrotic HP who did not do CAA. In the patients with fibrotic HP, prognosis and prognostic markers were investigated.

Data Analysis

Categorical baseline characteristics are summarised by frequency and percent, and continuous characteristics are reported as the median (interquartile range [IQR]). We compared baseline characteristics and therapy for nonfibrotic and fibrotic HP by Fisher's exact test or Wilcoxon test in accordance with nominal and continuous variables, respectively. Recurrence and/or fibrosis development in each patient group with or without CAA was estimated by Kaplan-Meier analysis. Because recurrence and/or fibrosis development occurred only in the IAA group, we investigated potential risk factors of recurrence and/or developing fibrosis only in these patients. We chose the following variables for entry into univariate Cox regression analysis: sex, age, smoking history, HP subtype, presence of fever, BAL lymphocytes, BAL neutrophils, BAL CD4/CD8, forced vital capacity (FVC) % predicted, diffusing capacity for carbon monoxide (DLCO) % predicted, partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), alveolar-arterial oxygen difference ($A\text{-}aDO_2$),

erythrocyte sedimentation rate, C-reactive protein (CRP), sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6), pulmonary surfactant protein-D (SP-D), and steroid therapy. Survival times of patients with nonfibrotic and fibrotic HP were estimated by Kaplan-Meier analysis. All-cause mortality rates were compared with a log-rank test. To investigate potential risk factors of mortality of patients with fibrotic HP, we used the following variables for entry into univariate Cox regression analysis: sex, age, smoking history, type of disease onset, HP subtype, BAL lymphocytes, BAL neutrophils, BAL CD4/CD8, FVC % predicted, DLCO % predicted, PaO_2, $PaCO_2$, A-aDO_2, erythrocyte sedimentation rate, CRP, KL-6, SP-D, HRCT findings of honeycombing, traction bronchiectasis, and lung distortion, steroid therapy, and CAA. We then performed univariate and multivariate Cox regression analysis with backward variable selection. Fibrotic HP can be divided clinically into two types of onset: insidious type, which develops without a history of acute episodes but is a slowly progressive chronic respiratory disease, and recurrent type, which develops after recurrent acute episodes. A *P* value of <0.05 was considered to be statistically significant in all analyses. Missing data were categorised as ‘unknown‘ and were entered into each statistical analysis model. All data were analysed with SAS version 9.1.3 (SAS Institute, Cary, NC, USA). The Saitama Cardiovascular and Respiratory Center institutional review board approved this study (no. 2020034).

Results

Patient Characteristics

Of the 121 patients, 60 (49.6%) were female. Median patient age was 63.0 years. Phenotypes includes nonfibrotic (61.2%) and fibrotic (38.8%) HP. HP subtypes included summer-type (43.0%), bird-related (26.4%), home-related (14.0%), occupational (9.1%), humidifier (6.6%), and hot tub lung (0.8%) (Table 3).

Compared with patients with fibrotic HP, those with nonfibrotic HP were significantly more frequently to be female, non-smokers, have a shorter duration of symptoms, and have fever and summer-type HP. HRCT scan features of ill-defined centrilobular nodules, ground-glass opacities, and mosaic attenuation, BAL lymphocytosis, low CD4/CD8 of BAL lymphocytes, higher CRP, lower SP-D, lower PaO_2, lower $PaCO_2$, higher A-aDO_2, and higher FVC % predicted all occurred significantly more frequently in those with nonfibrotic HP. Steroid therapy was more frequently administered to patients with fibrotic versus nonfibrotic HP, but CAA was more frequently done by patients with nonfibrotic versus fibrotic HP.

HP Recurrence/Fibrosis in Nonfibrotic HP

Of the 74 patients with nonfibrotic HP, 30 did CAA and experienced no recurrence or fibrosis development, and complete resolution was maintained at the last follow-up regardless of whether short-course steroid therapy was administered (Figure 1A). In the remaining 44

patients not doing CAA, recurrence and/or fibrosis development occurred in 24 (54.5%) patients, and the median time to recurrence and/or developing fibrosis was 3.7 years. Of the 20 patients who did not experience a recurrence or develop fibrosis, all maintained complete resolution. The log-rank test showed a significant difference between event-free curves in the patients with CAA and IAA (P<0.001) (Figure 2). Among the 24 patients with recurrence and/or fibrosis development, recurrence occurred in 22 patients and fibrosis developed in 7 (Figure 1B). The first episode of recurrence or fibrosis development was recurrence only in 21 patients, fibrosis only in 2 patients, and both in 1 patient. Of the 21 patients with recurrence, 3 did CAA, and none experienced recurrence or developed fibrosis. Of the remaining 18 patients without CAA, 11 patients experienced a second recurrence, and 3 experienced recurrence and developed fibrosis. Of the 11 patients with a second recurrence, 2 patients did CAA, and neither experienced recurrence nor developed fibrosis. Of the remaining 9 patients without CAA, 2 patients experienced a third recurrence, and 1 patient experienced recurrence and developed fibrosis. Among the 74 patients in the nonfibrotic HP group, none of the 7 patients with fibrosis development died, but 6 patients had progressive lung fibrosis, for which 2 required home oxygen therapy.

In a univariate Cox proportional hazard model, no factor was found to be a risk factor for recurrence and/or fibrosis development among the patients with nonfibrotic HP who did not do CAA (Table 4).

Mortality and Causes of Death

Death from any cause occurred in 28 (23.1%) patients over a median follow-up period of 5.6 years (IQR, 2.7-9.2 years), and the overall cumulative 5- and 10-year mortality rates were 19.3% and 31.0%, respectively. The respective overall cumulative 5- and 10-year mortality rates were 0.0% and 2.9% in the nonfibrotic HP group and 47.8% and 79.6% in the fibrotic HP group. The log-rank test showed a significant difference between survival curves in patients with nonfibrotic versus fibrotic HP (P<0.001, Figure 3). Three patients with nonfibrotic HP died from non-pulmonary malignancy (2 patients), and unknown cause (1 patient), and 25 patients with fibrotic HP died from respiratory failure due to HP progression (13 patients), acute exacerbation of HP (11 patients), and pulmonary tuberculosis (1 patient).

Prognostic Factors of HP-specific Mortality

In a multivariate Cox proportional hazard model, <50% lymphocytes in BAL and HRCT features of honeycombing were found to be negative prognostic factors of HP-specific mortality in the patients with fibrotic HP. IAA showed a tendency to be related to poorer survival according to the multivariate analysis (hazard ratio: 3.452, 95% confidence interval, 0.964, 12.359, P=0.057).

Discussion

The present study patients with nonfibrotic HP who did CAA did not experience recurrence or develop fibrosis and sustained their clinical improvement, whereas those with fibrotic HP not doing CAA showed a trend toward poor prognosis. Although antigen avoidance has long been the first line of treatment for HP, its impact on prognosis has been poorly reported.

De Sadeleer et al reported that antigen avoidance improved the lung function trajectory (FVC % predicted, DLCO % predicted) in patients with nonfibrotic HP but did not improve mortality in patients with nonfibrotic or fibrotic HP [9]. Gimenez et al investigated the relationship of antigen avoidance and survival in patients with fibrotic HP. Among their 112 patients, 61 (54.4%) patients reported antigen avoidance and 25 (41%) reported sustained clinical improvement. Clinical improvement with antigen avoidance (not just antigen avoidance itself) was associated with reduced mortality [18]. Some patients with insidiously progressive fibrotic HP do not show significant improvement of symptoms even with antigen avoidance [20], and in the Gimenez et al study, survival was compared in patients who achieved sustained clinical improvement after avoiding exposure and in patients who did not achieve clinical improvement and those not avoiding exposure. Fernández Pérez et al found that identifying an antigen was associated with improved survival in patients with chronic HP [7]. In this report, antigens could be identified only in 67 (47%) of 142 patients with HP, and at least 27 patients (40%) had occupational HP or hot tub lung, for which the antigen could

easily be completely avoided, and had a good prognosis [21, 22]. In the present study, the inciting antigen was identified in nearly all patients other than 5 of the 17 patients with home-related HP.

Unfortunately, appropriate means of antigen avoidance are not well defined [23]. Craig et al [24] and Sema et al [25] reported that high levels of bird antigen can be detected for a prolonged period after bird removal and environmental clean-up in patients with bird-related HP. In fact, 2 of our 4 patients with bird-related nonfibrotic HP who continued to live in the same house after bird removal experienced a recurrence. Tsutsui et al [26] reported that the amount of avian antigen in household dust is related to disease progression and prognosis in chronic bird-related HP, indicating that fibrosis development and prognosis in patients with HP depend on the degree of antigen avoidance. Therefore, to clearly classify whether CAA was done, we defined CAA in each type of HP (Table 2). Especially for summer-type, bird-related, and home-related HP, we defined changing home to be the only complete change of environment satisfying CAA. CAA is straightforward for patients with occupational HP (job change or relocation), humidifier lung (no use), and hot tub lung (no use). When limited to the patients with these types of HP, only 15 of the 58 patients with nonfibrotic HP and 6 of the 45 patients with fibrotic HP actually changed homes.

Although the efficacy of antigen avoidance in patients with nonfibrotic HP is well established [9, 22, 27, 28], some reports suggest that their symptoms do not progress and their pulmonary

function does not always decline even without adequate antigen avoidance [29-31]. Of our 44 patients with nonfibrotic HP without CAA, 24 experienced recurrence and/or developed fibrosis, whereas the remaining 20 patients had no recurrence afterward and achieved sustained clinical improvement (Figure 1A). Five patients did CAA after one or two recurrences, and none of them had recurrence or fibrosis after CAA (Figure 1B). These results suggest that if a patient who could not do CAA at the time of diagnosis still has a recurrence after efforts to reduce the antigen level, CAA might be recommended again at the new recurrence. Sema et al found that the amounts of avian antigens in household dust were related to disease progression and poor prognosis in chronic bird-related HP [25], and even if changing homes is not possible for various reasons, efforts should be made to thoroughly reduce the amounts of antigen by clean-up and renovation.

Patients with nonfibrotic HP have a low mortality rate [9, 11, 18], and none of the present study patients died of HP-related causes. Among the 74 patients with nonfibrotic HP, some experienced repeated recurrences without developing fibrosis, but 7 patients also developed fibrosis. Recently, genomics has begun to have an important role in researching the mechanisms underlying the susceptibility to and progression of pulmonary fibrosis [32]. Ley et al found that among patients with chronic HP, the mucin 5B (MUC5B) minor allele and shorter telomere length measured in peripheral blood leukocytes were associated with the extent of radiographic fibrosis [33]. Future studies are needed to determine whether the

background genetics of patients with nonfibrotic HP may influence the onset of pulmonary fibrosis.

Fibrosis in HP is a poor prognostic factor, with median survival time ranging between 4.9-9.2 years [7-9, 11, 17-19]. The prognosis of honeycomb HP is even poorer, with Salisbury et al reporting a survival time of 2.8 years, similar to that for idiopathic pulmonary fibrosis with honeycombing [11]. Twenty-six of the 47 patients with fibrotic HP had honeycomb HP, and their median survival was 3.69 years, similar to that of Salisbury et al. Of the 8 patients with fibrotic HP with CAA, all 3 patients who died during the follow-up period had honeycombing. The median survival times of patients with honeycomb HP with CAA (N=4) and with IAA (N=22) were 4.54 years and 3.15 years, respectively, but the difference was not significant (P=0.508) because of the small number of patients. Additional study is needed to clarify whether CAA should be recommended for honeycomb HP.

An important strength of this study was that HP was diagnosed by the new diagnostic criteria of the ATS/JRS/ALAT guideline, all patients could be classified into 6 HP subtypes, and the decrease in exposure to inciting agents was divided into the grades of CAA or IAA by HP subtype. So, although this was a retrospective study performed in a single hospital, these results could have some generalisability.

Our study has some limitations. First, the distinction between CAA and IAA was strictly defined in this study. Although the definition of CAA in occupational HP, humidifier lung,

and hot tub lung was not so difficult, the distinction between CAA and IAA is not so easily defined for summer-type, bird-related, and home-related HP. Actually, in summer-type and home-related HP, after the colonising places in the patients' houses were intensively cleaned and the patients returned home, some experienced recurrence whereas others did not. Thus, in patients without recurrence, this type of intensive cleaning would be considered CAA. Similarly, in bird-related HP, some patients experienced recurrence after stopping the breeding of birds but others did not. However, at least, no one experienced a recurrence or developed fibrosis after CAA according to our definition. The accuracy of our distinction between CAA and IAA should be reevaluated. Second, because only 8 of the 47 patients with fibrotic HP did CAA, the conclusion from the multivariate analysis that IAA tended to be related to poorer survival could indicate bias due to the small sample size. Third, although 20-53% of patients included in previous reports had unknown inciting antigen [7-9], all patients in the present study had an inciting antigen or an identified site of exacerbation by inhalation provocation tests and specific antibodies. We carefully judged the indication for surgical lung biopsy in fibrotic diffuse lung diseases and performed it in only 10 of the 121 patients. Because most patients with unknown inciting antigen and no histopathological findings are considered 'low confidence' or 'not excluded' in the ATS/JRS/ALAT guidelines, this study did not include patients with unknown inciting antigen without histopathological findings of HP pattern and thus may not reflect the whole population of HP.

Conclusions

In this analysis, CAA done by patients with nonfibrotic HP was related to no recurrence and/or no fibrosis development. Moreover, CAA was useful after a second or third recurrence. However, nearly all of these patients with fibrosis development developed progressive lung fibrosis. In the patients with fibrotic HP, <50% lymphocytes in BAL and radiographic honeycombing were negative prognostic factors for HP-related mortality, and CAA was suggested to be related to longer survival. These findings may have important implications for the care of patients with HP in terms of the need for CAA.

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in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure 1 – (A) Patient flow diagram detailing the relationship between ‘complete antigen avoidance‘ and ‘recurrence and/or developing fibrosis’ in patients with nonfibrotic HP. Of the 74 patients with nonfibrotic HP, 30 patients did CAA, and these patients experienced no recurrence nor develop fibrosis. Of the nonfibrotic HP patients without CAA (N=44), 24 experienced recurrence and/or developed fibrosis. (B) Patient flow diagram detailing the clinical course of nonfibrotic HP patients with incomplete antigen avoidance who experienced an episode of recurrence and/or developed fibrosis. Of the 21 patients with recurrence at the 1st episode, 3 did CAA after the 1st episode and none had a recurrence thereafter. Of the 18 patients who did not do CAA after the 1st episode, 11 had a recurrence only and 3 had a recurrence and developed fibrosis (2nd episode). Of the 11 patients with a 2nd episode of recurrence, 2 patients did CAA, and neither experienced recurrence nor developed fibrosis thereafter. Of the 9 patients not doing CAA and who did not develop fibrosis at the 2nd episode, 2 had recurrence only and 1 had recurrence and subsequently developed fibrosis (3rd episode). In total, 7 patients developed fibrosis during the observation period: 6 developed progressive pulmonary fibrosis, and 2 required home oxygen therapy. A: humidifier lung; B: bird-related HP; CAA: complete antigen avoidance; H: home-related HP; HP: hypersensitivity pneumonitis; N: number; O: occupational HP; S: summer-type HP; T: hot tub lung.

Figure 2 – Kaplan-Meier curves of the probability of recurrence and/or development of fibrosis in patients with nonfibrotic HP with or without complete antigen avoidance. None of the 30 patients with complete antigen avoidance experienced recurrence and/or developed fibrosis, whereas 24 of the 44 patients without complete antigen avoidance experienced recurrence and/or developed fibrosis. A log-rank test showed a significant difference between event-free curves in the patients with or without complete antigen avoidance (hazard ratio >999.99, confidence interval 0.00, -, $P < 0.001$).

Figure 3 – Kaplan-Meier survival curves of all-cause mortality in all patients and those with nonfibrotic and fibrotic hypersensitivity pneumonitis. Overall cumulative 5- and 10-year mortality rates were 19.3% and 31.0%, respectively. Respective 5- and 10-year all-cause mortality rates in the nonfibrotic HP patients were 0% and 2.9% vs. 47.8% and 79.6% in the fibrotic HP patients. A log-rank test showed a significant difference between survival curves in the patients with nonfibrotic HP and fibrotic HP (hazard ratio 65.7, confidence interval [CI] 8.8, 490.1, $P<0.001$). Median survival time for fibrotic HP patients was 5.25 year (95% CI, 3.81-9.09).

TABLE 1 Hypersensitivity pneumonitis diagnosis based on incorporation of imaging, exposure assessment, BAL lymphocytosis, and histopathological findings according to the official ATS/JRS/ALAT Clinical Practice Guideline

Demographics	All patients	Nonfibrotic	Fibrotic
No. of patients	121 (100)	74 (100)	47 (100)
HRCT			
Typical	110 (90.9)	73 (98.6)	37 (78.7)
Compatible	11 (9.1)	1 (1.4)	10 (21.3)
Indeterminate	0 (0)	0 (0)	0 (0)
Exposure assessment			
Improved with antigen avoidance test	97 (78.5)	73 (98.6)	24 (51.1)
Challenge test positive	83 (68.6)	57 (77.0)	26 (55.3)
Specific antibodies positive	99 (81.8)	59 (79.7)	40 (85.1)
BAL lymphocytosis (>30%)	92 (76.0)	65 (87.8)	27 (57.4)
Histopathology			
SLB	10 (8.3%)	1 (1.4)	9 (19.1)
TBLB	97 (80.2)	68 (91.9)	29 (61.7)
Typical	31 (25.6)	24 (32.4)	7 (14.9)
Probable	7 (5.7)	2 (4.3)	5 (10.6)
Indeterminate	40 (54.1)	29 (39.2)	11 (23.4)
Diagnosis			
Definite	70 (57.9)	55 (74.3)	15 (31.9)
High confidence	19 (15.7)	12 (16.2)	7 (14.9)
Moderate confidence	32 (26.4)	7 (9.50)	25 (53.2)
Low confidence	0	0	0

ALAT: Asociación Latinoamericana del Tórax; ATS: American Thoracic Society; BAL: bronchoalveolar lavage; HRCT: high-resolution computed tomography; JRS: Japanese Respiratory Society; SLB, surgical lung biopsy; TBLB, transbronchial lung biopsy.

Data are given as the no. (%) of patients

TABLE 2 Diagnosis of hypersensitivity pneumonitis subtype according to exposure assessment and serum antibody and definition of antigen avoidance

Subtype of HP	Exposure assessment (No of positive patients/No of total patients)	Serum antibody: No. of positive patients/No. of total patients	Definition of complete antigen avoidance
Summer-type HP	Occurred in summer (52/52). Positive inhalation challenge at home or relapse in summer (47/52). The other 5 patients moved to another house and did not have a challenge test.	*Trichosporon*: 52/52	Changing homes
Bird-related HP	History of avian contact (32/32). Positive inhalation challenge at home with bird (19/32)	Avian antigens: 28/32	Changing homes and removal of birds
Home-related HP	Occurred in home (17/17). Positive inhalation challenge at home (12/17). The other 5 patients had relapse at home the following year.	Trichosporon: 0/17, Fungus*: 12/17	Changing homes
Occupational HP	Positive inhalation challenge with mushrooms (6/6), isocyanate (3/3), moldy hay (1/1), and at workplace (1/1).	Mushrooms: 2/6, isocyanate 1/3, *Aspergillus niger* 1/1 (Farmer's lung), *A. fumigatus* 1/1 (HP at workplace)	Job change, relocation
Humidifier lung	Used ultrasonic humidifier (8/8). Positive inhalation challenge using humidifier at hospital (8/8)	Fungus: 2/8	Do not use a humidifier
Hot tub lung	Positive inhalation challenge using hot tub at home and culture of *Mycobacterium avium* complex from both patient and hot tub (1/1).	Not done	Do not use hot tub

*Antibodies to fungi included *Cephalosporium acremonium* (n = 5), *Penicillium digitatum* (n = 5), *Candida albicans* (n = 5), *Aspergillus niger* (n = 4), *A. versicolor* (n = 4), *A. fumigatus* (n = 4), *A. flavus* (n = 3), *A. nidulans* (n = 3), *A. restrictus* (n = 2), and *Aureobasidium pullulans* (n = 1). Many patients had multiple antibodies.

TABLE 3 Baseline characteristics and treatment of the 121 study patients with hypersensitivity pneumonitis according to nonfibrotic and fibrotic phenotypes

Characteristics	Total	HP phenotypes		*P* value
		Nonfibrotic	Fibrotic	
No. of patients	121 (100)	74 (100)	47 (100)	
Female	60 (49.6)	44 (59.5)	16 (34.0)	0.009
Age, y	63.0 (52.0-71.0)	59.0 (49.0-66.0)	67.0 (60.0-73.0)	<0.001
Smoker	52 (43.0)	27 (36.5)	25 (53.2)	0.09
Symptom				
Duration of symptoms, d	68 (38-150)	58 (30-90)	210 (90-850)	<.001
Cough	101 (83.5)	67 (90.5)	34 (72.3)	0.012
Sputum	38 (31.4)	29 (39.2)	9 (19.1)	0.027
Dyspnoea	100 (82.6)	58 (78.4)	42 (89.4)	0.144
Fever	45 (37.2)	35 (47.2)	10 (21.3)	0.004
HP subtype				<0.001
Summer-type	52 (43.0)	43 (58.1)	9 (19.1)	
Bird-related	32 (26.4)	9 (12.2)	23 (48.9)	
Home-related	17 (14.0)	6 (8.1)	11 (23.4)	
Occupational*	11 (9.1)	9 (12.2)	2 (4.3)	
Humidifier	8 (6.6)	6 (8.1)	2 (4.3)	
Hot tub	1 (0.8)	1 (1.4)	0 (0.0%)	
HRCT scan features				
Ill-defined centrilobular nodules	90 (74.4)	69 (93.2)	21 (44.7)	<0.001
Ground-glass opacities	119 (98.3)	74 (100.0)	45 (95.7)	<0.001
Mosaic attenuation	72 (59.5)	58 (78.4)	14 (29.8)	<0.001
Honeycombing	26 (21.5)	0 (0.0)	26 (55.3)	<0.001
Traction bronchiectasis	45 (37.2)	0 (0.0)	45 (95.7)	<0.001
Lung distortion	45 (37.2)	0 (0.0)	45 (95.7)	<0.001
BALF				
Lymphocyte, %	64.9 (40.3-77.6)	69.0 (58.0-81.6)	45.0 (7.6-71.3g)	<0.001
Neutrophil, %	3.2 (1.4-8.3)	5.05 (1.6-12.0)	2.75 (1.1-6.4)	0.065
CD4/CD8 ratio	0.8 (0.3-2.1)	0.4 (0.2-0.8)	2.0 (1.2-4.0)	<0.001
Laboratory data				
WBC, /mm^3	7700 (6400-9100)	7700 (6300-10000)	7700 (6400-8900)	0.414
LDH, IU/L	258 (210-307)	246 (205-314)	264 (217-307)	0.555
ESR, mm/h	42 (22-59)	22 (42-58)	39 (22-60)	0.717
CRP, mg/dL	1.0 (0.2-2.6)	1.7 (0.4-2.9)	0.5 (0.1-1.4)	<0.001
KL-6, U/mL	1832 (934-2732)	1496 (898-2711)	2121 (1414-3552)	0.07

SP-D, ng/mL	243 (173-423)	197 (141-277)	354 (214-545)	<0.001
PaO_2, Torr (room air)	70.1 (62.5-78.5)	67.6 (60.1-75.5)	74.5 (66.5-84.0)	0.005
$PaCO_2$, Torr (room air)	38.6 (35.4-41.7)	37.0 (35.2-40.6)	39.2 (37.3-42.5)	0.042
A-a DO_2	33.9 (22.9-42.8)	37.4 (28.9-45.0)	28.0 (19.1-35.3)	<0.001
Pulmonary function				
FVC, % predicted	67.4 (50.9-79.0)	70.4 (56.9-81.9)	63.6 (49.4-71.5)	0.039
DLCO, % predicted	67.0 (55.1-80.7)	67.0 (56.3-81.5)	64.8 (52.0-80.7)	0.389
Treatment				
Steroid†	33 (27.3)	11 (14.9)	22 (46.8)	<0.001
Complete antigen avoidance	38 (31.4)	30 (40.5)	8 (17.0)	0.009

BALF: bronchoalveolar lavage fluid; CRP: C-reactive protein; DL_{CO}: diffusing capacity of lung for carbon monoxide; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; HP: hypersensitivity pneumonitis; HRCT: high-resolution computed tomography; KL-6: Krebs von den Lungen-6; LDH: lactate dehydrogenase; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; SP-D: surfactant protein D; WBC: white blood cell count.

Data are given as the median (interquartile range), mean ± SD, or no. (%) of patients, unless otherwise indicated.

*Occupational includes cases of mushroom worker's lung (n = 6), isocyanate alveolitis (n = 3), farmer's lung (n = 1), and workplace-associated HP due to *Aspergillus fumigatus*.

†Steroid was given in nonfibrotic HP patients who did not improve enough after admission to hospital, and in fibrotic HP patients who did not improve enough after admission to hospital and had diffuse ground-glass opacities. Patients who were treated with steroid at relapse or at acute exacerbation were not included.

TABLE 4 Univariate analysis of predictors of recurrence and/or developing fibrosis in 43 patients with nonfibrotic hypersensitivity pneumonitis who did not do complete antigen avoidance

Variables	Univariate analysis		
	HR	95% CI	P Value
Male sex	1.04	0.43, 2.50	0.937
Age ≥60 years	1.91	0.84, 4.34	0.122
Ever smoker	0.80	0.32, 2.01	0.631
HP subtype			
Summer-type	Reference		
Bird-related	0.60	0.20, 1.76	0.349
Household	0.32	0.043, 2.40	0.267
Occupational*	0.65	0.14, 3.03	0.991
Fever	0.64	0.27, 1.51	0.307
BALF			
Lymphocytes <50%	0.62	0.21, 1,81	0.381
Neutrophil ≥5%	0.58	0.26, 1.30	0.186
CD4/CD8 ≥2.0	1.68	0.66, 4.25	0.274
PFT			
%FVC <70%	0.62	0.26, 1.47	0.279
%DLCO <70%	0.87	0.36, 2.10	0.759
Arterial blood gas analysis			
PaO_2 <70	0.51	0.22, 1.17	0.112
$PaCO_2$ ≥35	0.42	0.13, 1.42	0.164
A-aDO_2 ≥40	0.696	0.31, 1.61	0.397
Laboratory findings			
ESR (1 h) ≥40	0.57	0.24, 1.33	0.190
CRP ≥1.0	0.59	0.26, 1.33	0.201
KL-6 ≥2000	0.90	0.37, 2.19	0.822
SP-D ≥250	0.65	0.23, 1.88	0.426
Treatment			
Steroid	1.55	0.62, 3.92	0.351

BALF: bronchoalveolar lavage fluid; CI: confidence interval; CRP: C-reactive protein; DL_{CO}: diffusing capacity of lung for carbon monoxide; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; HR: hazard ratio; HRCT: high-resolution computed tomography; KL-6: Krebs von den Lungen-6; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PFT: pulmonary function test; SP-D: surfactant protein D.

*Occupational includes 1 case of mushroom worker’s lung.

TABLE 5 Univariate and multivariate Cox regression models of the risk of HP-related mortality in 47 patients with fibrotic HP

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P Value	Adjusted HR	95% CI	P Value
Male sex	1.44	0.57, 3.7	0.442			
Age ≥60 years	1.13	0.47, 2.74	0.789			
Ever smoker	1.25	0.55, 2.86	0.599			
Insidious type* (vs recurrent)	2.1	0.93, 4.75	0.075			
HP subtype						
Summer-type	Reference					
Bird-related	0.97	0.28, 3.39	0.966			
Household	0.65	0.14, 3.03	0.586			
Occupational†	<0.01		0.991			
Humidifier	0.41	0.04, 4.28	0.459			
BALF						
Lymphocytes <50%	2.65	1.02, 6.84	0.044	3.128	1.15, 8.53	0.026
Neutrophil ≥5%	2.02	0.81, 5.02	0.130			
CD4/CD8 ≥2.0	0.77	0.31, 1.91	0.576			
PFT						
%FVC <70%	1.41	0.56, 3.59	0.468			
%DLCO <70%	1.92	0.66, 5.58	0.231			
Arterial blood gas analysis						
PaO_2 <70	1.51	0.64, 3.55	0.350			
$PaCO_2$ ≥35	0.58	0.13, 2.54	0.471			
A-aDO_2 ≥40	0.96	0.28, 3.29	0.953			
Laboratory findings						
ESR ≥40	1.45	0.59, 3.60	0.422			
CRP ≥1.0	0.65	0.24, 1.75	0.394			
KL-6 ≥2000	0.793	0.34, 1.87	0.597			
SP-D ≥250	0.93	0.36, 2.45	0.855			
HRCT findings						
Honeycombing	3.08	1.26, 7.54	0.014	3.081	1.26, 7.54	0.014
Treatment						
Steroid	0.778	0.35, 1.74	0.541			
No antigen avoidance	2.695	0.80, 9.10	0.110	3.452	0.96,12.36	0.057

BALF: bronchoalveolar lavage fluid; CI: confidence interval; CRP: C-reactive protein; $DL_{CO:}$ diffusing capacity of lung for carbon monoxide; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; HR: hazard ratio; HRCT: high-resolution computed tomography; KL-6: Krebs von den Lungen-6; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PFT: pulmonary function test; SP-D: surfactant protein D.

*Fibrotic HP can be divided clinically into two types: insidious type develops HP without a history of acute episodes but has a slowly progressive chronic respiratory disease, and recurrent type develops HP after recurrent acute episodes.

†Occupational includes cases of mushroom worker's lung (n = 1) and workplace-associated HP due to *Aspergillus fumigatus*.

Figure 1A.

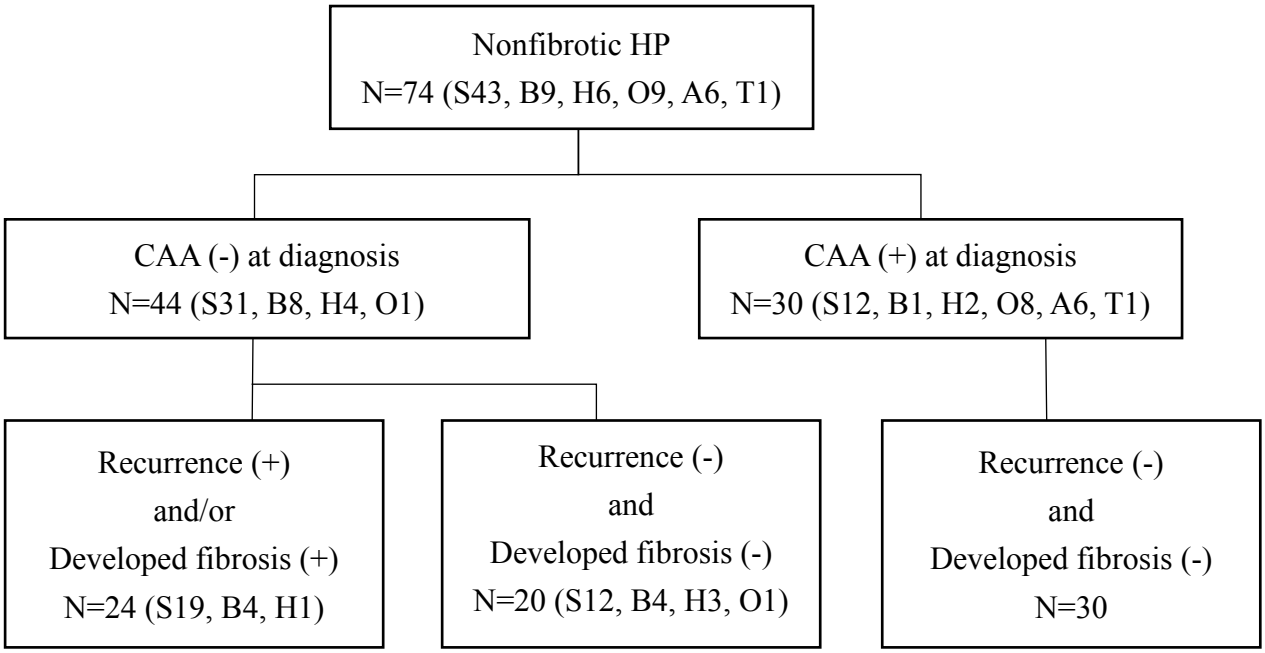

Nonfibrotic HP
N=74 (S43, B9, H6, O9, A6, T1)
CAA (-) at diagnosis
N=44 (S31, B8, H4, O1)
CAA (+) at diagnosis
N=30 (S12, B1, H2, O8, A6, T1)
Recurrence (+)
and/or
Developed fibrosis (+)
N=24 (S19, B4, H1)
Recurrence (-)
and
Developed fibrosis (-)
N=20 (S12, B4, H3, O1)
Recurrence (-)
and
Developed fibrosis (-)
N=30

Figure 1B.

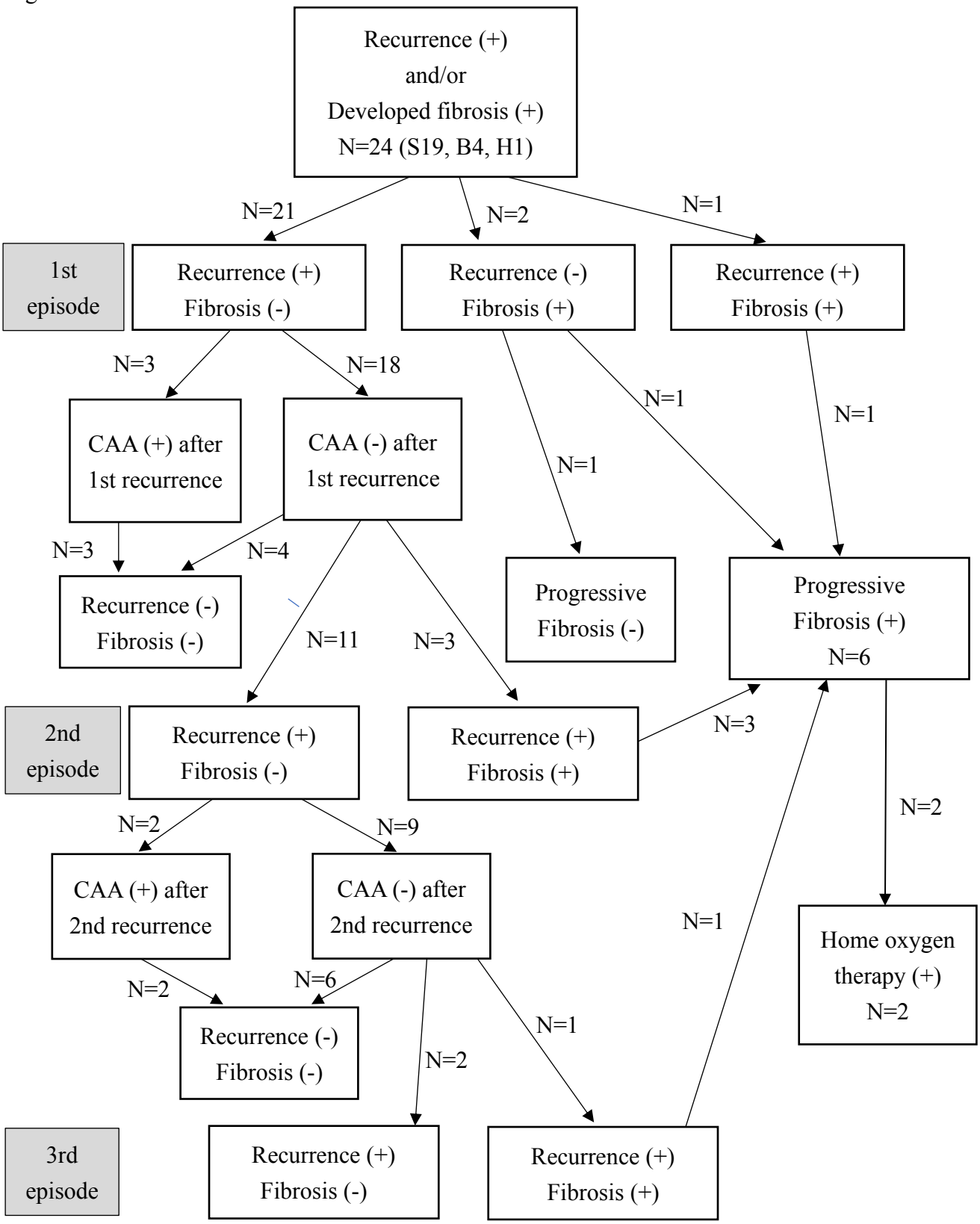

Recurrence (+)
and/or
Developed fibrosis (+)
N=24 (S19, B4, H1)
N=21
N=2
N=1
1st episode
Recurrence (+)
Fibrosis (-)
Recurrence (-)
Fibrosis (+)
Recurrence (+)
Fibrosis (+)
N=3
N=18
CAA (+) after
1st recurrence
CAA (-) after
1st recurrence
N=1
N=1
N=1
N=3
N=4
Recurrence (-)
Fibrosis (-)
Progressive
Fibrosis (-)
Progressive
Fibrosis (+)
N=6
N=11
N=3
2nd episode
Recurrence (+)
Fibrosis (-)
Recurrence (+)
Fibrosis (+)
N=3
N=2
N=2
N=9
CAA (+) after
2nd recurrence
CAA (-) after
2nd recurrence
N=1
Home oxygen
therapy (+)
N=2
N=2
N=6
N=1
Recurrence (-)
Fibrosis (-)
N=2
3rd episode
Recurrence (+)
Fibrosis (-)
Recurrence (+)
Fibrosis (+)

Figure 2.

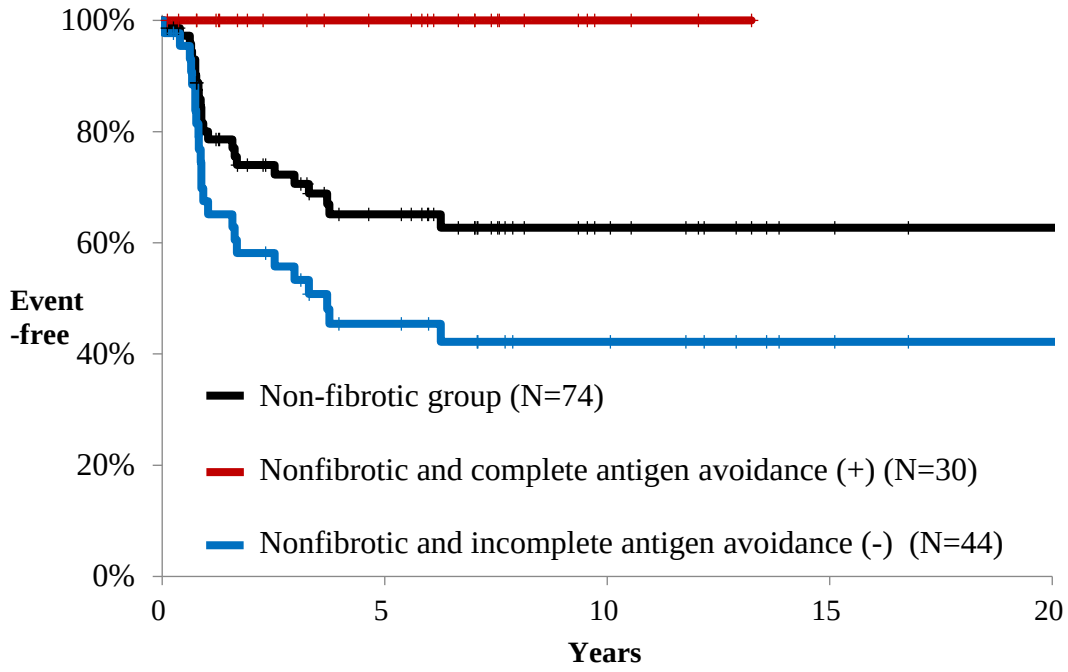
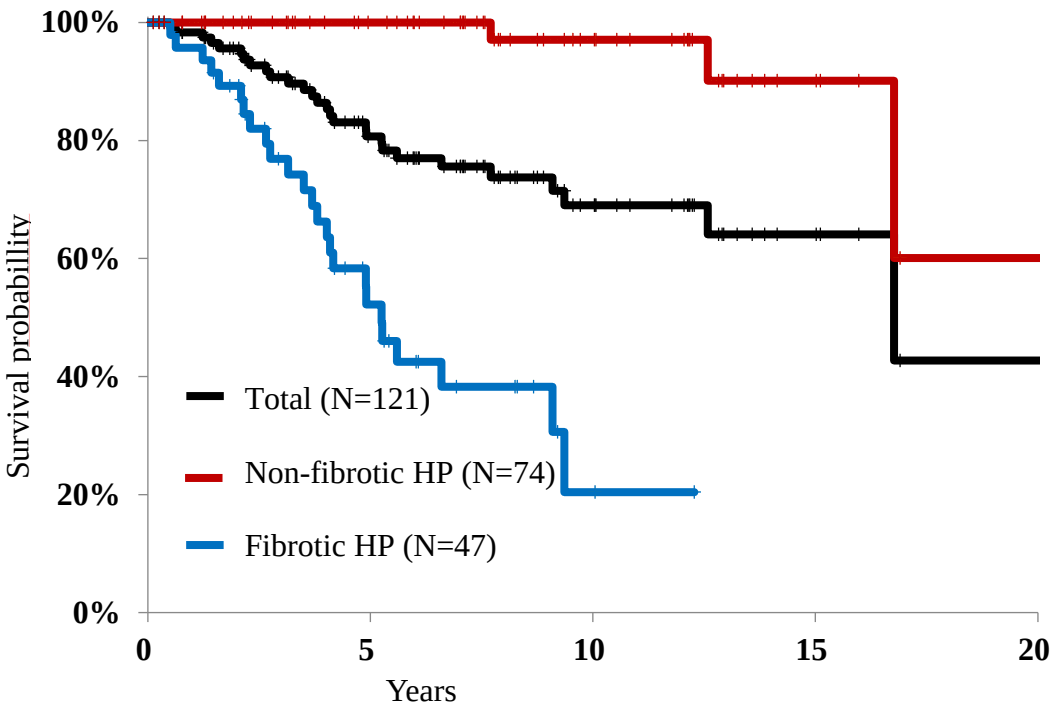

100%
80%
60%
40%
20%
0%
Event
-free
0
5
10
15
20
Years
Non-fibrotic group (N=74)
Nonfibrotic and complete antigen avoidance (+) (N=30)
Nonfibrotic and incomplete antigen avoidance (-) (N=44)

Figure 3.


100%
80%
60%
40%
20%
0%
Survival probability
0
5
10
15
20
Years
Total (N=121)
Non-fibrotic HP (N=74)
Fibrotic HP (N=47)