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Clinical characteristics and outcomes of hypersensitivity pneumonitis in South Korea

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Abstract

Background: Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) that results from an immune-mediated reaction involving various antigens in susceptible individuals. However, the clinical characteristics and outcomes of HP in South Korea are not well understood.

Objectives: This study was conducted to identify the clinical characteristics and outcomes of HP in South Korea.

Design: This is a retrospective observational study investigating patients with pathologically confirmed HP at our center, along with a comprehensive review of published HP cases in the Republic of Korea.

Methods: This retrospective study analyzed 43 patients with pathologically proven HP at a single tertiary hospital in Korea between 1996 and 2020. In addition, case reports of HP published in Korea were collected. The clinical characteristics, etiologies, treatment, and outcomes of patients from our center, as well as case reports, were reviewed. Patients from our hospital were divided into fibrotic and nonfibrotic subtypes according to the ATS/JRS/ALAT guidelines.

Results: Among 43 patients with biopsy-proven HP, 12 (27.9%) and 31 (72.1%) patients were classified into the fibrotic and nonfibrotic subtypes, respectively. The fibrotic HP group was older (64.6 ± 8.5 *versus* 55.2 ± 8.3, $p = 0.002$) with less frequent complaints of fever (0% *versus* 45.2%, $p = 0.013$) compared to the nonfibrotic HP group. The most common inciting antigen was household mold (21, 48.8%), followed by inorganic substances (6, 14.0%). Inciting antigens were not identified in eight (18.6%) patients. Treatment of corticosteroids was initiated in 34 (79.1%) patients. An analysis of 46 patients from Korea by literature review demonstrated that reported cases were relatively younger and drugs were the most common etiology compared to our cohort.

Conclusion: The analysis of reported cases, as well as our cohort, showed that exposure history and clinical manifestations are heterogeneous for patients with HP in South Korea.

Keywords: diagnosis, fibrotic, hypersensitivity pneumonitis, nonfibrotic

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Introduction

Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) characterized by immune-mediated reactions to various antigens in susceptible individuals, leading to granulomatous interstitial, bronchiolar, and alveolar inflammation.[1] Although the prevalence and incidence of HP may vary according to geographical heterogeneity, including environmental or occupational disparities, previous reports have demonstrated that HP is one of the most common ILDs.[2–4] The significance of HP lies not only in terms of commonness but also in its prognostic impact. Recent studies have repeatedly demonstrated that disease may progress

despite treatment in a substantial subset of HP patients, resembling the clinical course of idiopathic pulmonary fibrosis (IPF).[5,6]

Given its clinical importance, accurate diagnosis and appropriate treatment are necessary. However, the differential diagnosis of HP can be challenging for clinicians because of difficulties in identifying inciting antigens despite a thorough history[7] and heterogeneous clinical features of HP that share clinical, radiographic, and pathologic aspects with other pulmonary diseases, including IPF.[8] The current guidelines state that a high index of suspicion by clinicians followed by multidisciplinary assessment is required for the diagnosis of HP.[9] Thus, understanding the frequent inciting antigens as well as the clinical characteristics of HP, especially in relevant regions, is mandatory. However, only a few case reports of HP in the Republic of Korea are available for review. Therefore, we aimed to identify the clinical characteristics and outcomes of HP by investigating pathologically confirmed HP patients from our center, while applying the latest classification of nonfibrotic and fibrotic HP from recently published clinical practice guidelines.[9] Furthermore, we reviewed and analyzed published cases of HP in the Republic of Korea to investigate the clinical characteristics of HP in Korean patients.

Material and methods

Study population

A total of 43 patients diagnosed with pathologically proven HP at the Samsung Medical Center, a tertiary referral hospital in the Republic of Korea, between 1996 and 2020 were identified. All ILD diagnoses in our hospital were made through multidisciplinary discussions by pulmonologists, radiologists, and pathologists. We retrospectively reviewed the medical records, including exposure history, clinical characteristics, treatment, and mortality. Pulmonary function tests (PFTs) and bronchoalveolar lavage (BAL) were performed according to the guidelines.[10,11] Radiological findings from chest computed tomography (CT) and histopathological findings were also reviewed. The final diagnosis and inclusion in the analysis was based on clinical history including exposure, chest CT features, and pathologic findings. The Institutional Review Board of the Samsung Medical Center approved this study and permitted the review and publication of patient records (IRB No. 2022-08-088). The requirement for informed consent was waived owing to the retrospective nature of the study. In addition, the reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[12]

In addition, cases of HP reported in the Republic of Korea before 31 December 2021, were collected using PubMed as well as other representative paper search systems of KoreaMed, Dbpia, Riss, and Kiss in May 2022. The search term "hypersensitivity pneumonitis" was used in both English and Korean languages.

Definitions

Nonfibrotic and fibrotic HP were classified according to recently published guidelines.[9] The chest CT pattern of nonfibrotic HP was defined as the presence of ground-glass opacity or mosaic attenuation along with evidence of small airway disease. Chest CT patterns indicative of fibrotic HP included irregular linear opacities/coarse reticulation with lung distortion and small-airway disease. The histopathological pattern of nonfibrotic HP required evidence of both cellular interstitial pneumonia and cellular bronchiolitis with or without non-necrotizing granulomas. Pathologic features of fibrotic HP include chronic fibrosing interstitial pneumonia and airway-centered fibrosis with or without non-necrotizing granulomas.

Statistical analysis

All data are presented as numbers (percentages) for categorical variables and as medians [interquartile range (IQR)] for continuous variables. Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the χ^2 or Fisher's exact test. Wilcoxon signed-rank test was conducted to assess the changes of Forced vital capacity (FVC) and Forced expiratory volume in 1 second (FEV_1) between the initial and last CT pulmonary function test. All p-values were two-tailed, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the R software (version 4.1.0; R Development Core Team, Vienna, Austria).

Results

Baseline characteristics

The characteristics of 43 patients with biopsy-proven HP are shown in Table 1. The median age was 57.8 years, and 21 (48.8%) were male. The most common comorbidities were diverse respiratory diseases (5, 11.6%), including asthma and chronic obstructive pulmonary disease. The most common symptom was cough (8, 88.4%), followed by dyspnea (35, 81.4%), and excess sputum (28, 65.1%). Ground-glass opacity (95.3%) indicating parenchymal involvement was the most frequently observed chest CT finding in our

Table 1. Baseline characteristics of study cohort ($N = 43$).

Characteristics	Total ($n = 43$)	Fibrotic ($n = 12$)	Non-fibrotic ($n = 31$)	*p* Value
Age, years	57.8 ± 9.3	64.6 ± 8.5	55.2 ± 8.3	0.002
Male	21 (48.8)	7 (58.3)	14 (45.2)	0.664
Ever-smoker*	20 (46.5)	7 (58.3)	13 (41.9)	0.531
Body mass index, kg/m^2	23.1 ± 3.7	24.0 ± 4.4	22.8 ± 3.4	0.381
Comorbidities				
Respiratory disease	5 (11.6)	3 (9.7)	2 (16.7)	0.912
Cardiovascular disease	3 (7.0)	1 (8.3)	2 (6.5)	>0.999
Diabetes mellitus	4 (9.3)	1 (8.3)	3 (9.7)	>0.999
Malignancy	4 (9.3)	3 (25.0)	1 (3.2)	0.376
Symptoms				
Cough	38 (88.4)	9 (75.0)	29 (93.5)	0.241
Sputum	28 (65.1)	5 (41.7)	23 (74.2)	0.099
Dyspnea	35 (81.4)	8 (66.7)	27 (87.1)	0.268
Fever	14 (32.6)	0 (0.0)	14 (45.2)	0.013
Myalgia	7 (16.3)	0 (0.0)	7 (22.6)	0.181
Weight loss	7 (16.3)	1 (8.3)	6 (19.4)	0.676
Arthralgia	6 (14.0)	5 (41.7)	1 (3.2)	0.006
Pulmonary function, % predicted				
Initial FVC	78.7 ± 18.9	82.7 ± 23.6	77.1 ± 17.0	0.393
Initial FEV_1	81.4 ± 23.3	86.1 ± 28.2	79.1 ± 21.4	0.417
Last FVC ($n = 34$)	88.6 ± 17.2	82.5 ± 17.9	91.6 ± 16.5	0.150
Last FEV_1 ($n = 34$)	91.2 ± 18.3	85.0 ± 20.5	94.2 ± 16.8	0.175
Annual change of FVC ($n = 34$)	3.5 (−1.5 to 9.6)	−3.2 (−10.4 to 2.2)	7.1 (1.9 to 15.5)	0.002

(Continued)

Table 1. (Continued)

Characteristics	Total (*n* = 43)	Fibrotic (*n* = 12)	Non-fibrotic (*n* = 31)	*p* Value
Annual change of FE V1 (*n* = 34)	2.9 (−2.7 to 13.0)	−2.7 (−11.3 to 4.8)	7.1 (1.5 to 16.1)	0.008
Chest CT				
Small airway disease findings[$]	15 (34.9)	2 (16.7)	13 (41.9)	0.229
Parenchymal infiltration				
Ground-glass opacity	41 (95.3)	11 (91.7)	30 (96.8)	>0.999
Mosaic attenuation	7 (16.3)	1 (8.3)	6 (19.4)	0.676
Distribution				0.013
Diffuse	33 (76.7)	6 (50.0)	27 (87.1)	
Mid to upper lung predominant	5 (11.6)	2 (16.7)	3 (9.7)	
Lower predominant	5 (11.6)	4 (33.3)	1 (3.2)	
Fibrosis	15 (34.9)	12 (100.0)	3 (9.7)	<0.001
Bronchoalveolar lavage (*n* = 33)				
Lymphocyte (%)	44.0 ± 25.0	34.2 ± 31.2	42.7 ± 22.5	0.397
BAL lymphocytosis (⩾20%)	25/33 (75.8)	6/9 (66.7)	19/24 (79.2)	0.772
BAL lymphocytosis (⩾30%)	21/33 (63.6)	4/9 (44.4)	17/24 (70.8)	0.319
CD4/CD8	1.6 (0.9 to 2.9)	1.2 (0.7 to 2.6)	1.7 (1.0 to 3.7)	0.435
CD4/CD8 < 1	12/33 (29.3)	5/9 (45.5)	7/24 (23.3)	0.321
Biopsy				
Transbronchial biopsy	42 (97.7)	12 (100.0)	30 (96.8)	>0.999
Surgical lung biopsy	22 (51.2)	8 (66.7)	14 (45.2)	0.355
Presence of granuloma	23 (53.5)	7 (58.3)	16 (51.6)	0.956
Follow-up duration (months)	24.9 (8.0 to 58.5)	23.5 (7.9 to 62.9)	30.4 (8.2 to 50.8)	>0.999

Data are presented as number (%), mean value ± standard deviation, or median (interquartile range). The clinical characteristics of study patients were based on the time of diagnosis.
*Includes current and former smokers.
[$]Includes ill-defined, centrilobular nodules or air trapping findings.
BAL, bronchoalveolar lavage; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

study subjects, followed by features of small airway involvement (34.9%) including ill-defined nodules or air trapping. Distribution of the lesions was diffuse in most patients (76.7%).

Diagnostic modalities and etiologies

All patients underwent bronchoscopy, while 33 patients had records of BAL fluid analysis. The overall mean proportion of BAL lymphocytes

was 44.0 ± 25.0 (%). Although not statistically significant, the proportion of lymphocytes tended to be higher in the nonfibrotic group than in the fibrotic group (42.7 ± 22.5 *versus* 34.2 ± 31.2, $p = 0.397$). In the nonfibrotic group, 19 (79.2%) patients with BAL lymphocytosis over 20% were identified, showing higher proportion compared to 6 (66.7%) patients in the fibrotic group. A tendency of distinction between two groups was still observed when a threshold of 30% was applied (70.8% *versus* 44.4%, $p = 0.319$).

Transbronchial lung biopsy (TBLB) was performed in all except one patient. Approximately half (22, 51.2%) of the study patients underwent surgical lung biopsy. Pathological features of HP were observed in 21 (49%) patients who underwent TBLB. All the patients who underwent surgical lung biopsy had features consistent with those of HP. A review of lung biopsy specimens revealed granulomas in 23 (53%) patients in total. Granuloma was noted in 22 of 42 cases with TBLB and in 13 of 22 cases with surgical lung biopsy. In addition, cellular interstitial pneumonia and cellular bronchiolitis were observed in 29 (67.4%) and 20 (46.5%) of the cohort, respectively.

The most common etiology was household mold (21, 48.8%), followed by inorganic substances (6, 14.0%). Etiologic antigens were not identified despite thorough history taking in eight (18.6%) patients (Table 2).

Fibrotic or nonfibrotic HP

Of 43 patients, 12 (27.9%) were classified as fibrotic HP, while the remaining 31 (72.1%) were classified into nonfibrotic HP (Table 1). Overall median follow-up duration was 25 months. The baseline characteristics of the fibrotic and nonfibrotic groups were comparable. However, patients with fibrotic HP were older (64.6 ± 8.5 *versus* 55.2 ± 8.3, $p = 0.002$) and complained arthralgia more frequently (41.7% *versus* 3.2%, $p = 0.006$) compared to those with nonfibrotic HP. In contrast, about half of the patients with nonfibrotic HP suffered from fever, while no patients with fibrotic HP were febrile (45.2% *versus* 0.0%, $p = 0.013$). In addition, annual changes in pulmonary function, including FVC and FEV1, were more significant in non-fibrotic HP group, compared to fibrotic HP group ($p = 0.002$ and 0.008, respectively).

Treatment and clinical outcomes

During the median follow-up duration of 25 months, treatment of corticosteroids was initiated in 34 (79.1%) patients (Table 3). In the nonfibrotic group, the initial corticosteroid dosage was higher (30.0 *versus* 15.0 mg, $p = 0.022$) and the duration was longer (8.3 *versus* 3.3 months, $p = 0.060$) than in the fibrotic group. Eight patients (18.6%) recovered with only avoidance of the causative antigens without requiring pharmacological treatment. In addition, an antifibrotic agent

Table 2. Etiology of HP in study cohort ($N = 43$).

Etiology	Total ($n = 43$)	Fibrotic ($n = 12$)	Non-Fibrotic ($n = 31$)	*p* Value
				0.815
Household mold	21 (48.8)	7 (58.3)	14 (45.2)	
Drugs	1 (2.3)	0 (0.0)	1 (3.2)	
Inorganic metal or chemical	6 (14.0)	1 (8.3)	5 (16.1)	
Hot tub lung	2 (4.7)	0 (0.0)	2 (6.5)	
Plants	5 (11.6)	2 (16.7)	3 (9.7)	
Unknown	8 (18.6)	2 (16.7)	6 (19.4)	
Total	43 (100.0)	12 (100.0)	31 (100.0)	

Data are presented as number (%).
HP, hypersensitivity pneumonitis.

Table 3. Treatment of HP in study cohort ($N = 43$).

Treatment	Total ($n = 43$)	Fibrotic ($n = 12$)	Non-Fibrotic ($n = 31$)	*p* Value
				0.435
Avoidance, no other treatment	8 (18.6)	1 (8.3)	7 (22.6)	
Corticosteroid treatment	34 (79.1)	11 (91.7)	23 (74.2)	
Initial dose of corticosteroid (mg)	20.0 (15.0–50.0)	15.0 (7.5–25.0)	30.0 (17.5–60.0)	0.022
Duration (months)	4.4 (2.6–10.4)	3.3 (1.8–6.5)	8.3 (4.8–13.0)	0.060
Antifibrotic agent	1 (2.3)	0 (0.0)	1 (3.2)	
Death	2 (4.7)	1 (8.3)	1 (3.2)	>0.999

Data are presented as number (%).
HP, hypersensitivity pneumonitis.

was administered to one patient with fibrotic HP who experienced progressive fibrosis despite antigen avoidance and corticosteroid treatment.

The overall prognosis was favorable. While two (4.7%) patients died during the follow-up, the cause of death in both patients was lung cancer, which was not related to HP.

Literature review of cases in the Republic of Korea

A total of 46 patients were identified from a search for case reports in Korea (Supplemental Table 1). The median age was 44.6 years, and 45.7% of patients were male. Fourteen patients (30.4%) were diagnosed with HP based on exposure history, without biopsy confirmation. For treatment, 31 patients (67.4%) received corticosteroid treatment. The remaining 15 patients (32.6%) recovered from HP by avoiding causative antigen, without additional treatment.

Regarding etiology, drugs were most commonly reported (16, 34.8%), followed by bacterial or fungal organisms (9, 19.6%). In 3 (6.5%) patients, etiology was unidentified (Supplemental Table 2).

Discussion

In this study, we investigated biopsy-proven HP cases in our institution and published case reports from the Republic of Korea to identify the etiologies, clinical characteristics, and outcomes of HP. In addition, patients were further divided into the nonfibrotic and fibrotic HP groups according to the recently proposed classification and were compared accordingly. Our analysis of 43 study patients demonstrated that HP was induced by various antigens, commonly molds and inorganic metals or chemicals and that their treatment outcomes were favorable. While patients with fibrotic HP were older and received a lower dose of corticosteroids, there were no differences in inciting antigens, pulmonary function, or prognosis. The results of a literature review of 46 cases from the Republic of Korea were similar to those of our cohorts. However, these patients were slightly younger, and drugs and infectious organisms were the common inciting antigens.

Various inciting antigens of HP have been reported, ranging from bacterial and fungal organisms to chemicals and drugs.[9,13] Climatic and geographical characteristics, living conditions, occupational practices and environment, and recreational preferences vary, which influence the presence of certain antigens and intensity of exposure. The types and frequency of causative antigens of HP show demographic and geographic diversities.[7,14–16] Furthermore, most studies have focused on specific populations with definitive exposure, especially occupational ones, which precludes comprehending the distribution of inciting antigens in the general population.[17–19]

Recognizing possible inciting antigens and identifying them are crucial for diagnosing and improving the outcomes of HP.[7,9] In our study, the most common antigen was household mold, constituting almost half of the study patients (21, 48.8%), followed by inorganic metals or chemicals. Although avian antigens have been reported as the most common trigger in Western countries in several studies,[7,15] molds are also common, especially in Asian countries, probably because of the hot and humid climate shared among many Asian countries.[4,16,20] In particular, summer-type HP caused by the *Trichosporon* species that contaminates wooden houses during hot and humid summers after the rainy season is the most common type of HP in Japan, one of the countries closest to Korea.[13,21,22] However, drugs were the most common inciting antigens, according to 46 case series in Korea. This difference may be partially due to the nature of the case reports *per se* which focus on presenting unprecedented or unique cases. Of note, etiologic antigens were not identified in 20% of our study patients. Although the proportion is relatively small, this is consistent with previous studies that reported that the antigens and exposures were not identified in up to 60% of patients with HP, despite a thorough evaluation.[7,15] Although it is well known that confirmation of antigen is crucial in the diagnosis and treatment of HP, identification still relies largely on history-taking by clinicians as alternative methods of specific antibody or inhalation challenge tests are not validated. Thus, further research is necessary to develop effective means to verify antigens, such as tailored questionnaires based on the distribution of antigens in each region.

Out of 43 patients with biopsy-proven HP, fibrotic HP accounted for 27.9%. Patients with fibrosis were older and reported arthralgia symptoms more frequently than patients with nonfibrotic HP. In contrast, fever was more frequent in the nonfibrotic HP group. Recently updated guidelines of HP proposed a new classification of nonfibrotic and fibrotic HP based on accumulating evidence that the presence of fibrosis is related to prognosis as well as differences in patients' clinical features.[23–25] These results concur with those of previous studies and with speculations that acute presentations with constitutional symptoms are more consistent with nonfibrotic HP. Influenza-like symptoms, including fever, chills, cough, and acute dyspnea, are known to be more common in acute HP and share many traits with nonfibrotic HP. Symptoms usually present shortly after exposure and probably result from an immediate inflammatory response, suggesting a causal link between exposure and symptomatology. However, insidious presentations are consistent with chronic HP or fibrotic HP, probably reflecting the suspected pathogenetic mechanism of repetitive and low-dose antigen exposure that eventually leads to fibrosis.[1,26] In addition, although not statistically significant, the proportion of lymphocytes in the BAL of the nonfibrotic group tended to be higher than that of the fibrotic group in our study. Correlation with higher levels of lymphocytosis (30–40%) in BAL fluid in acute HP but only slightly increased lymphocytic count (>20%) or even a normal level in chronic HP, especially in patients with radiologic usual interstitial pneumonia (UIP), has been demonstrated in previous studies.[27,28] Similarly, a higher percentage of lymphocytes in BAL fluid in nonfibrotic HP than in fibrotic HP has been reported in a recent study,[29] reflecting lymphocytic inflammation in the early stage of HP, probably caused by an immune reaction after exposure to an antigen.[30] Interestingly, there were no differences in the types of antigens between the two groups. Low-intensity but repetitive exposure to inciting antigens is suspected to be one of the underlying mechanisms of chronic or fibrotic HP, whereas acute/subacute or nonfibrotic HP is usually induced by recognizable exposure to high concentrations of antigen.[31–33] Thus, the inciting antigens may differ according to clinical phenotypes. Although the data are limited, it has been reported that most cases of acute HP are caused by fungi, whereas avian antigens are the most common cause of chronic HP.[34] The fact that chronic HP does not always correlate with fibrotic HP may explain this difference.[33] Furthermore, genetic susceptibility, distinct pathogenesis, and exposure play a role in the development of fibrosis.[35] However, additional studies are necessary to understand the epidemiological differences between nonfibrotic and fibrotic HP.

One of the most important reasons for classifying patients with HP based on the presence of fibrosis is its impact on outcome[6,27]; however, no difference in mortality was observed in our study. One possible explanation for this is the inclusion criteria. As we analyzed patients with biopsy-proven HP, this may have resulted in the inclusion of relatively mild cases, leading to favorable

outcomes. In addition, although not statistically significant, pulmonary function showed a slightly higher tendency in the fibrotic HP group than in the nonfibrotic group. Patients with newly detected ILD with severe fibrosis who are at risk of attempting histologic confirmation may have been excluded. Moreover, among patients with fibrotic HP, only one (8%) patient demonstrated UIP pattern. Although fibrosis is an important prognostic factor, the UIP pattern has the most significant impact on prognosis.[36] Thus, the similar outcomes between nonfibrotic and fibrotic HP in our study should not lead to the conclusion that fibrosis is not associated with prognosis.

This study had several limitations. First, it was a retrospective study conducted at a single tertiary hospital. Although we included a relatively large number of patients, our institution is one of the largest referral hospitals with ILD clinic in the capital city of the Republic of Korea, which may limit the generalizability of the data, including the distribution of inciting antigens. Second, as mentioned above, since this study only included biopsy-proven HP cases, patients with severe fibrosis who are at a high risk of complications to undergo lung biopsy may have been excluded. This exclusion may have caused unintentional selection bias that eventually resulted in a relatively favorable prognosis in our study and comparable prognosis between the nonfibrotic and fibrotic groups. Moreover, considering the inherent limitations of TBLB attributable to small sample size and specimen quality, it is possible that patients with HP in whom TBLB failed to capture the characteristic patterns may have been excluded from the study, especially ones with fibrotic HP whose architectural distortion is relatively more difficult to detect by TBLB. Although diagnostic confidence may be lower without pathological evidence, recently published international guidelines do not always require pathology in diagnosis of HP.[9,37,38] Thus, it should be noted patients of our study may be different from ones identified by the new guidelines. Future studies of multicenter registries or prospective cohorts using new international guidelines are necessary for better understanding of HP in South Korea. Third, sample size calculation was not performed due to the retrospective nature of the study. Thus, interpretation of the results as well as statistical significance requires caution given the relatively small number of patients included in the study. Lastly, inciting antigens were identified by method of history-taking. All patients in our study were thoroughly interviewed under our institute's guidelines requiring detailed checks on residential and occupational environments. However, although not validated, additional methods for antigen identification such as serum IgG antibody tests or challenge tests were not used since they are not available in South Korea. Interestingly, there were no cases of bird-related HP in our study, despite bird proteins being one of the most common antigens worldwide. This may be due to the fact that poultry farms or bird-keeping hobbies are relatively uncommon in South Korea. However, unavailability of antibody tests to bird proteins may have influenced the results. Nonetheless, this reflects real-world clinical practice. Due to the limited number of IgG antibody types and unclear diagnostic yield of such tests, current guidelines as well as clinical practice rely on thorough history taking for the identification of inciting antigens.

Conclusion

In conclusion, inciting antigens and clinical characteristics of HP patients in South Korea were heterogeneous. There were no differences in the clinical characteristics and outcomes except for age and fever between nonfibrotic and fibrotic HP.

Summary at a glance

Hypersensitivity pneumonitis (HP) results from an immune-mediated reaction involving various antigens in susceptible individuals, in which understanding of the characteristics of the region is essential for diagnosis. This is the first article that described the clinical characteristics and outcomes of HP in South Korea.

Declarations

Ethics approval and consent to participate

The Institution Review Board of the Samsung Medical Center approved this study and permitted the review and publication of patient records (IRB No. 2022-08-088). The requirement for informed consent was waived owing to the retrospective nature of the study.

Consent for publication

Not applicable.

Author contributions

Sungmin Zo: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Man Pyo Chung: Conceptualization; Project administration; Supervision.

Hak Young Yoo: Data curation; Investigation.

Kyung Soo Lee: Conceptualization; Supervision.

Joungho Han: Data curation; Investigation; Supervision.

Myung Jin Chung: Data curation; Supervision.

Hongseok Yoo: Conceptualization; Data curation; Supervision; Validation; Writing – original draft.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

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

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Supplemental material

Supplemental material for this article is available online.

References

1. Vasakova M, Morell F, Walsh S, *et al.* Hypersensitivity pneumonitis: perspectives in diagnosis and management. *Am J Respir Crit Care Med* 2017; 196: 680–689.
2. Fernandez Perez ER, Kong AM and Raimundo K , *et al.* Epidemiology of hypersensitivity pneumonitis among an insured population in the United States: a claims-based cohort analysis. *Ann Am Thorac Soc* 2018; 15: 460–469.
3. Kreuter M, Herth FJ, Wacker M, *et al.* Exploring clinical and epidemiological characteristics of interstitial lung diseases: rationale, aims, and design of a nationwide prospective registry – the EXCITING-ILD registry. *Biomed Res Int* 2015; 2015: 123876.
4. Singh S, Collins BF, Sharma BB, *et al.* Interstitial lung disease in India. Results of a prospective registry. *Am J Respir Crit Care Med* 2017; 195: 801–813.
5. Hamblin M, Prosch H and Vašáková M. Diagnosis, course and management of hypersensitivity pneumonitis. *Eur Respir Rev* 2022; 31: 210169.
6. Wang P, Jones KD, Urisman A, *et al.* Pathologic findings and prognosis in a large prospective cohort of chronic hypersensitivity pneumonitis. *Chest* 2017; 152: 502–509.
7. Fernández Pérez ER, Swigris JJ, Forssén AV, *et al.* Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. *Chest* 2013; 144: 1644–1651.
8. Morell F, Villar A, Montero M, *et al.* Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med* 2013; 1: 685–694.
9. Raghu G, Remy-Jardin M, Ryerson CJ, *et al.* Diagnosis of hypersensitivity pneumonitis in adults. an official ATS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2020; 202: e36–e69.
10. Meyer KC, Raghu G, Baughman RP, *et al.* An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med* 2012; 185: 1004–1014.
11. Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
12. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453–1457.
13. Nogueira R, Melo N, Novais EBH, *et al.* Hypersensitivity pneumonitis: antigen diversity and disease implications. *Pulmonology* 2019; 25: 97–108.

14. Asai N, Kaneko N, Ohkuni Y, *et al.* Familial Summer-type Hypersensitivity Pneumonitis: a review of 25 families and 50 cases in Japan. *Intern Med* 2016; 55: 279–283.

15. Hanak V, Golbin JM and Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. *Mayo Clin Proc* 2007; 82: 812–816.

16. Nishida T, Kawate E, Ishiguro T, *et al.* Antigen avoidance and outcome of nonfibrotic and fibrotic hypersensitivity pneumonitis. *ERJ Open Res* 2022; 8.

17. Depierre A, Dalphin JC, Pernet D, *et al.* Epidemiological study of farmer's lung in five districts of the French Doubs province. *Thorax* 1988; 43: 429–435.

18. Banham SW, McSharry C, Lynch PP, *et al.* Relationships between avian exposure, humoral immune response, and pigeon breeders' disease among Scottish pigeon fanciers. *Thorax* 1986; 41: 274–278.

19. Bernstein DI, Lummus ZL, Santilli G, *et al.* Machine operator's lung. A hypersensitivity pneumonitis disorder associated with exposure to metalworking fluid aerosols. *Chest* 1995; 108: 636–641.

20. Kang J, Kim YJ, Choe J, *et al.* Prognostic implication of diagnostic confidence level in patients with fibrotic hypersensitivity pneumonitis. *Respiration* 2021; 100(10): 940-948.

21. Ando M, Arima K, Yoneda R, *et al.* Japanese summer-type hypersensitivity pneumonitis. Geographic distribution, home environment, and clinical characteristics of 621 cases. *Am Rev Respir Dis* 1991; 144: 765–769.

22. Yoshizawa Y, Ohtani Y, Hayakawa H, *et al.* Chronic hypersensitivity pneumonitis in Japan: a nationwide epidemiologic survey. *J Allergy Clin Immunol* 1999; 103(Pt 1): 315–320.

23. Mooney JJ, Elicker BM, Urbania TH, *et al.* Radiographic fibrosis score predicts survival in hypersensitivity pneumonitis. *Chest* 2013; 144: 586-592.

24. Chiba S, Tsuchiya K, Akashi T, *et al.* Chronic hypersensitivity pneumonitis with a usual interstitial pneumonia-like pattern: correlation between histopathologic and clinical findings. *Chest* 2016; 149: 1473–1481.

25. Hanak V, Golbin JM, Hartman TE, *et al.* High-resolution CT findings of parenchymal fibrosis correlate with prognosis in hypersensitivity pneumonitis. *Chest* 2008; 134: 133–138.

26. Cottin V, Hirani NA, Hotchkin DL, *et al.* Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018; 27: 180076.

27. Vourlekis JS, Schwarz MI, Cherniack RM, *et al.* The effect of pulmonary fibrosis on survival in patients with hypersensitivity pneumonitis. *Am J Med* 2004; 116: 662–668.

28. Leone PM and Richeldi L. Current diagnosis and management of hypersensitivity pneumonitis. *Tuberc Respir Dis (Seoul)* 2020; 83: 122–131.

29. De Sadeleer LJ, Hermans F, De Dycker E, *et al.* Effects of corticosteroid treatment and antigen avoidance in a large hypersensitivity pneumonitis cohort: a single-centre cohort study. *J Clin Med* 2018; 8: 14.

30. Vasakova M, Selman M, Morell F, *et al.* Hypersensitivity pneumonitis: current concepts of pathogenesis and potential targets for treatment. *Am J Respir Crit Care Med* 2019; 200: 301-308.

31. Varone F, Iovene B, Sgalla G, *et al.* Fibrotic Hypersensitivity pneumonitis: diagnosis and management. *Lung* 2020; 198: 429–440.

32. Broaddus VC, Ernst JD, King TE Jr., *et al.* *Murray & Nadel's textbook of respiratory medicine*. 7th ed. Philadelphia, PA: Elsevier, 2022.

33. Costabel U, Miyazaki Y, Pardo A, *et al.* Hypersensitivity pneumonitis. *Nat Rev Dis Primers* 2020; 6: 65.

34. Selman M, Lacasse Y, Pardo A, *et al.* Hypersensitivity pneumonitis caused by fungi. *Proc Am Thorac Soc* 2010; 7: 229–236.

35. Furusawa H, Cardwell JH, Okamoto T, *et al.* Chronic hypersensitivity pneumonitis, an interstitial lung disease with distinct molecular signatures. *Am J Respir Crit Care Med* 2020; 202: 1430–1444.

36. Salisbury ML, Gu T, Murray S, *et al.* Hypersensitivity pneumonitis: radiologic phenotypes are associated with distinct survival time and pulmonary function trajectory. *Chest* 2019; 155: 699–711.

37. Buendia-Roldan I, Aguilar-Duran H, Johannson KA, *et al.* Comparing the performance of two recommended criteria for establishing a diagnosis for hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2021; 204: 865–868.

38. Fernández Pérez ER, Travis WD, Lynch DA, *et al.* Diagnosis and evaluation of hypersensitivity pneumonitis: CHEST guideline and expert panel report. *Chest* 2021; 160: e97–e156.