Evaluation of high-resolution computed tomography findings and associated factors in hypersensitivity pneumonitis

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Abstract

Background/Aim: Hypersensitivity pneumonitis (HP) is a lung disease from inhaling diverse environmental and occupational organic substances, such as fungi, bacteria, birds, and occasionally nonorganic materials. An immune response triggers this condition. A high-resolution chest computed tomography (HRCT) scan is typically performed as part of the initial diagnostic assessment. This study assesses HRCT findings in HP patients and examines associated factors between fibrotic and non-fibrotic patient groups.

Methods: This retrospective cross-sectional study encompassed all HP patients monitored between 2010 and 2022. The analysis included data from 117 patients. HRCT findings from the patients were categorized based on fibrosis presence, leading to the division of patients into fibrotic and non-fibrotic groups. Comparative analyses were conducted between these groups.

Results: Among the 117 subjects analyzed, 59 (50.4%) were male, and 58 (49.6%) were female. The mean age at diagnosis was 52.1 (13.6) years, ranging from 20 to 81. The non-fibrotic HP group comprised 70 (59.8%) patients, while the fibrotic HP group comprised 47 (40.2%). The most prevalent HRCT findings were ground-glass opacity (90.6%), mosaic attenuation (87.2%), and traction bronchiectasis (50.4%). Statistically significant disparities were observed between non-fibrotic and fibrotic HP groups in terms of HRCT findings: ground-glass opacity, irregular linear opacities, reticulation, traction bronchiectasis, honeycombing, and fibrosis (P<0.001). In contrast, the lymphocyte ratio in bronchoalveolar lavage fluid was 28.78 (16.2) in the non-fibrotic HP group and 14.66 (10.3) in the fibrotic HP group. The fibrotic HP group exhibited a statistically significant lower lymphocyte ratio in bronchoalveolar lavage fluid (P<0.001).

Conclusion: HRCT findings are pivotal in HP diagnosis and classification. Computed tomography also assists in delineating the HP classification. This study identified ground-glass opacity and mosaic attenuation as the most prevalent HRCT findings in HP patients. Investigating the connection between fibrosis and prognosis is vital for determining patient outcomes, as fibrosis appears to be the principal determinant.

Keywords: hypersensitivity pneumonitis, non-fibrotic hypersensitivity pneumonitis, fibrotic hypersensitivity pneumonitis, high-resolution computed tomography
Introduction

Hypersensitivity pneumonitis (HP) is an immune-mediated lung disorder triggered by inhaling various environmental and occupational organic substances, primarily encompassing fungi, bacteria, avian sources, and, less commonly, nonorganic irritants [1]. This condition’s historical identification dates back to 1700 and has been associated with many inciting agents. More than 300 etiological agents have been pinpointed as contributors to the ailment. Understanding the historical evolution of HP is crucial not only for discerning its antigenic triggers but also for comprehending how changes in risk factors over time have impacted its development [2]. In the United Kingdom, the reported incidence stands at 0.9 cases per 100,000 person-years, while the overall age-adjusted mortality rate in the United States is 0.19 per million individuals [3].

HP is conventionally classified as acute, subacute, or chronic, delineated by its clinical attributes and the duration of the ailment [4]. Nevertheless, these categories often prove difficult to confine due to their variable and arbitrary definitions across numerous studies. The ATS/JRS/ALAT guideline committee has opted for an alternative classification, sorting HP into fibrotic (including mixed inflammatory and fibrotic patterns or exclusively fibrotic presentations) and non-fibrotic (purely inflammatory) categories. This classification hinges on the pivotal role of radiographic fibrosis in prognostic determination, offering enhanced clinical applicability [5]. In HP cases, histological identification or detection via chest computed tomography of fibrosis is correlated with reduced survival rates [6].

A chest high-resolution computed tomography (HRCT) scan is often conducted as an integral component of the initial diagnostic assessment. Specific HRCT patterns may indicate the likelihood of HP in a relevant clinical context. Patients diagnosed with HP are categorized into fibrotic or non-fibrotic classifications based on the presence or absence of fibrosis in their HRCT results. HRCT indications of pulmonary fibrosis encompass irregular linear opacities, reticulation, traction bronchiectasis, and honeycomb formations [1]. This study assesses the HRCT findings in HP patients and scrutinizes the factors associated with the division between fibrotic and non-fibrotic patient groups.

Materials and methods

The population of this retrospective cross-sectional study comprises all patients diagnosed with hypersensitivity pneumonia at the outpatient clinic and service of Ankara Ataturk Sanatorium Training and Research Hospital between January 1, 2010, and December 31, 2022. HP is a rare disease. Due to its rarity, the study aims to encompass the entire patient population rather than opting for a sample selection. The hospital management information system identified patients diagnosed with J67 HP. Over the designated research period, 132 patients with HP were identified in the hospital’s management information system. However, fifteen patients were excluded from the study due to the unavailability of their HRCT images and information.

For the study, the hospital employed data from their records on cases of HP. This encompassed laboratory test results, evaluations of pulmonary function, and radiological images stored within their information management system. The HRCT findings were subjected to analysis for a range of observations, including centrilobular nodules, ground-glass opacity, mosaic attenuation, irregular linear opacities, reticulation, traction bronchiectasis, honeycomb formations, fibrosis, and prevalence of distribution of fibrotic opacities. A Radiology Specialist within the research team meticulously reviewed the HRCT scans of the enrolled patients to ascertain the presence of either fibrotic or non-fibrotic findings, aligning with the guidelines stipulated by ATS/JRS/ALAT. The identification of fibrosis hinged on the concurrent presence of a reticular pattern alongside traction bronchiectasis and/or honeycomb formations.

The study’s primary dependent variable categorizes HP cases based on their fibrosis status in HRCT scans, distinguishing between fibrotic and non-fibrotic instances. Meanwhile, the independent variables encompass a spectrum of socio-demographic factors such as age, gender, smoking status, and attributes linked to occupational history. Additionally, the independent variables include functional assessment outcomes (FEV1, FVC, FEV1/FVC, DLCO), laboratory findings (hemogram, biochemistry), and exposure-related characteristics. The accumulation of data was facilitated by using a dedicated patient follow-up form.

The study received ethical clearance via decision number 2012-KAEK-15/2727, granted by the Ankara Atatürk Sanatorium Education and Research Hospital Ethics Committee. After obtaining the committee’s ethical endorsement, the study was initiated.

Statistical analysis

The statistical analysis was performed utilizing the SPSS Windows version 22.0, a commonly employed software package. Descriptive statistics, specifically mean (standard deviation) (SD), were employed to depict numerical data. The independent groups t-test assessed the distinctions between continuous variables within two groups. In contrast, the chi-square test was employed to compare categorical variables. Outcomes with a P-value of <0.05 were considered statistically significant.

Results

Between January 1, 2010, and December 31, 2022, a total of 117 cases of HP were diagnosed at the Ankara Ataturk Sanatorium Training and Research Hospital, constituting the research cohort. Among the 117 subjects encompassed in this study, 59 (50.4%) were male, while 58 (49.6%) were female. The mean age of patients at the time of diagnosis was 52.1 (13.6) years, ranging from 20 to 81 years. The cases were stratified into two groups based on their fibrosis status observed in HRCT scans. The non-fibrotic HP group accounted for 70 (59.8%) patients, while the fibrotic HP group comprised 47 (40.2%). Among patients subjected to HRCT evaluation, the most prevalent findings included ground-glass opacity (90.6%), mosaic attenuation (87.2%), traction bronchiectasis (50.4%), centrilobular nodules (45.3%), reticulation (44.4%), and irregular linear opacities (41.0%). Comparatively less common
observations were fibrosis (40.2%), three-density findings (28.2%), and honeycomb formations (13.7%) (Table 1).

No statistically significant differences were observed in centrilobular nodules, mosaic attenuation, and three-density patterns between non-fibrotic HP and fibrotic HP HRCT findings. However, a statistically significant distinction emerged between the two groups concerning ground-glass opacity, irregular linear opacities, reticulation, traction bronchiectasis, honeycombing, and fibrosis (Table 1).

Table 1: HRCT findings of the 117 patients with non-fibrotic HP and fibrotic HP cases.

| Characteristics                  | Total (n=117) | Non-Fibrotic HP (n%) | Fibrotic HP (n%) | P-value *
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Centrallobular nodules</td>
<td>53 (45.3)</td>
<td>19 (36.0)</td>
<td>34 (64.0)</td>
<td>0.257</td>
</tr>
<tr>
<td>Ground-glass opacity</td>
<td>106 (90.6)</td>
<td>77 (69.7)</td>
<td>29 (54.7)</td>
<td>0.024</td>
</tr>
<tr>
<td>Mosaic attenuation</td>
<td>102 (87.2)</td>
<td>82 (76.1)</td>
<td>20 (38.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Three-density pattern</td>
<td>33 (28.2)</td>
<td>10 (30.3)</td>
<td>23 (46.8)</td>
<td>0.543</td>
</tr>
<tr>
<td>Irregular linear opacities</td>
<td>48 (41.0)</td>
<td>30 (62.5)</td>
<td>18 (37.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Reticulation</td>
<td>52 (44.4)</td>
<td>32 (61.5)</td>
<td>20 (38.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Traction bronchiectasis</td>
<td>59 (50.4)</td>
<td>40 (67.8)</td>
<td>19 (32.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>16 (13.7)</td>
<td>13 (81.3)</td>
<td>3 (18.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>47 (40.2)</td>
<td>24 (51.1)</td>
<td>23 (48.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Chi-square test, HRCT: High-Resolution Computed Tomography, HP: Hypersensitivity pneumonitis.

No statistically significant differences were identified in terms of gender, recognized environmental risk factors, presence of cough, shortness of breath, and smoking status, whether considering fibrotic HP or non-fibrotic HP. However, notable statistical significance emerged regarding fibrotic HP and non-fibrotic HP cases concerning the presence of a known occupational risk factor and the detection of crackles during physical examination (P=0.022, P<0.001) (Table 2).

Application of the HRCT findings to determine the extent of diffuse parenchymal infiltration and signs of small airway disease. Parenchymal infiltration might manifest as ground-glass opacity or mosaicism, while signs of small airway disease could exhibit signs of air trapping and vaguely defined centrilobular nodules up to 5 mm in size. In cases where fibrotic patterns are observed on HRCT scans, compatible with HP, it suggests a combination of fibrosis and small airway disease in specific areas [5].

The study encompassed the assessment of HRCT findings from 117 cases that had been diagnosed with HP. The HRCT outcomes revealed that ground-glass opacities (90.6%) and mosaic attenuation (87.2%) were the most frequently observed features. Similar evaluations were carried out in a separate study conducted by Shobeiri et al. [8] involving 45 HP patients. Additionally, in a study focused on 92 patients with fibrotic HP, Walsh et al. [9] identified ground-glass opacification (93.3%) and reticulation (93.3%) as the predominant HRCT findings.

Mosaic attenuation and three-density findings are radiological terms associated with heterogeneous lung attenuation. “Mosaic attenuation” pertains specifically to computed tomography during the inspiratory phase. It is defined as distinctly demarcated areas of both low and high attenuation. This phenomenon can be observed in vascular, airway, or infiltrative diseases [5]. Recognizing that the “headcheese” sign might not resonate with most individuals, the term “three-density pattern” has become the preferred nomenclature [10]. This term is utilized to depict a scenario where obstructions and infiltrations coexist with regions of healthy lung tissue, resulting in well-defined zones exhibiting three distinct levels of
attenuation [11]. Within the domain of fibrotic HP, three-density findings have been identified [10].

Our study revealed no significant distinction between fibrotic and non-fibrotic HP patients concerning mosaic attenuation and three-density findings. However, our research exhibited statistically notable elevations in irregular linear opacities, reticulation, Traction Bronchiectasis, honeycombing, and fibrosis within the fibrotic patient group. This aligns with the findings of Nishida et al. [12], who, in their investigation involving 121 HP patients, identified higher statistical significance in honeycombing, traction bronchiectasis, and lung distortion findings within the fibrotic patient group, akin to our study.

When dealing with individuals suspected of having HP, it is recommended to amalgamate HP-specific HRCT findings with clinical information to bolster the diagnosis of HP. However, relying solely on CT findings for a definitive diagnosis is cautioned against [11]. Numerous studies have underscored the pivotal role of lung fibrosis in prognostic determination [13-17]. In their examination of 69 HP patients, Hanak et al. [16] categorized 37.6% as having fibrotic HP. Similarly, Nishida et al. [12] reported a fibrotic patient rate of 38.8% among 121 patients. In concurrence with this literature, our study found 40.2% of patients fall into the fibrotic HP category.

While the mean age of all diagnosed patients was 52.1 (13.6) years, the non-fibrotic HP group exhibited a mean age at diagnosis of 47.79 (13.1) years, while the fibrotic HP group skewed older, with a mean age of 58.68 (11.6) years. In the study conducted by Nishida et al. [12], the mean age of HP patients was 63.0, with the non-fibrotic patient group averaging 59 years and the fibrotic patient group averaging 67 years. In a separate investigation, Wang et al. [18] identified the mean age across all patients as 53.6, with the acute hypersensitivity group averaging 51.9 and the chronic hypersensitivity group averaging 57.8. Corresponding with our findings, the literature also indicates that fibrotic HP patients tend to receive their diagnosis at an older age.

Despite thoroughly evaluating exposure histories, laboratory results, and radiological findings in HP cases, the causative agent may remain undetectable in 49-60% of instances [1,19]. The responsible agent can be identified in approximately half of HP cases by meticulously exploring environmental and occupational backgrounds. A notable observation emerged in our study: while there was a statistically significant increase in non-fibrotic HP cases within the group exposed to occupational risk factors, no statistically significant distinction was noted for either group in patients with environmental risk factors.

A parallel discovery was made in the study conducted by Walters et al., where, akin to our results, no disparity surfaced within the group harboring environmental risk factors. However, they did find a statistically significant reduction in fibrosis among individuals with occupational risk factors. By delving into a comprehensive occupational history, detecting non-fibrotic HP cases early becomes feasible, facilitating their treatment by removing the causative agent [19].

Frequently observed symptoms and indications in non-fibrotic and fibrotic HP encompass breathlessness, cough, and mid-inspiratory squat. Our investigation unveiled no noteworthy contrast between patient groups with fibrotic and non-fibrotic HP concerning symptoms like cough and shortness of breath. However, a significant elevation was identified in the occurrence of crackles during physical examinations within the fibrotic patient group.

Consistent with our findings, Walters et al. reported no discernible differences in cough, fever, weight loss, or dyspnea. Nevertheless, they did establish a statistically significant increase in crackles detected through physical examination within the fibrotic patient cohort [19].

Recently published reports have ignited a discourse regarding the influence of smoking on individuals with HP. Warren [20] and Terho et al. [21] proposed a notable association between HP and non-smoking, asserting that acute hypersensitivity pneumonitis is less prevalent among current smokers than non-smokers with similar exposure risks. A study by Furuiye et al. [22] demonstrated that cigarette smoke could dampen inflammation and lymphocyte proliferation in cases of acute hypersensitivity pneumonitis. However, an intriguing counterpoint emerges: if an individual who smokes develops HP, the condition may progress into a chronic state, accompanied by poorer survival rates than their non-smoking counterparts. This divergence stems from prolonged exposure to cigarette smoke can exacerbate both lung inflammation and fibrosis [23].

In line with the existing literature, our research found a parallel pattern; specifically, the duration of smoking within the fibrotic group significantly exceeded that of the non-fibrotic group.

Pulmonary function tests are a valuable tool for assessing the pattern and extent of respiratory impairment, although neither model stands alone as diagnostic. Distinguishing between non-fibrotic HP and fibrotic HP is beyond the capabilities of pulmonary function tests. Within our study, despite lacking a statistically significant differentiation in the pulmonary function tests (FEV1, FVC, FEV1/FVC, DLCO) of the fibrotic and non-fibrotic patient groups, it was observed that the FEV1, FVC, and DLCO values were notably lower within the fibrotic patient cohort. Consistent with our findings, Nishida et al.’s study reported similar results: while no discernible disparity existed in diffusion between the fibrotic and non-fibrotic patient groups, the FVC value was reduced in the fibrotic patient group [12].

Bronchoscopy plays a pivotal role in diagnosing HP, with bronchoalveolar lavage (BAL) fluid collection and analysis and lung biopsy serving as the principal procedures conducted through this method. BAL testing emerges as a highly effective means of identifying alveolitis in individuals suspected of having HP. Typically, patients afflicted with HP exhibit alveolitis characterized by a notable abundance of lymphocytes. However, it’s noteworthy that individuals with fibrotic HP tend to display lower levels of lymphocytes in their BAL fluids when contrasted with those suffering from non-fibrotic HP [5].

Within our investigation, the lymphocyte ratio in the BAL samples of fibrotic HP cases was measured at 14.66 (10.3), while non-fibrotic HP cases exhibited a lymphocyte ratio of 28.78 (16.2), resulting in a statistically significant discrepancy. In alignment with our study, Nishida et al. [12] also identified a
significantly lower lymphocyte ratio in the BAL samples of the fibrotic HP patient group compared to the non-fibrotic HP patient group. Notably, a diminished lymphocyte ratio in BAL has been linked to an unfavorable prognosis in patients diagnosed with HP [5].

Limitations
Our study possesses certain limitations. The primary limitations of our research stem from the small sample size and retrospective design employed in the study. Due to the retrospective design of the study, we were unable to access the prognosis of the patients. Consequently, there is a need for future studies to examine the correlation between fibrosis and prognosis.

Conclusion
The outcomes of an HRCT scan hold substantial significance in identifying HP. Computer tomography aids in categorizing HP. Following this study, ground-glass opacity and mosaic attenuation were frequently noted in HRCT scans of individuals with HP. Irregular linear opacities, reticulation, traction bronchiectasis, honeycombing, and fibrosis exhibit a statistically higher prevalence in fibrotic HP cases than in non-fibrotic HP cases. Our investigation revealed that the non-fibrotic patient group skewed younger, and the lymphocyte ratio was statistically higher prevalence in fibrotic HP cases than in non-fibrotic HP patients. Irregular linear opacities, reticulation, traction bronchiectasis, honeycombing, and fibrosis exhibit a statistically higher prevalence in fibrotic HP cases than in non-fibrotic HP cases. Since fibrosis is the principal determinant of prognosis, investigations exploring the relationship between fibrosis and prognosis are imperative.

References


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