Radiological Diagnosis Model for Clinically Diagnosed Hypersensitivity Pneumonitis

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Abstract

Introduction: Hypersensitivity Pneumonitis is an immune-mediated interstitial lung disease that manifests in susceptible patients following exposure to an inciting agent(s)**.** It is classified based on symptoms behavior and disease course into three categories acute, subacute and chronic. Diagnosis of Hypersensitivity Pneumonitis is challenging because of the lack of any unique radiological finding distinguishing it from other interstitial lung disease. Hypersensitivity Pneumonitis diagnosis depends on a high level of clinical suspicion, the recognition of antigen exposure, and a constellation of, radiologic, laboratory, and pathologic findings. Creating a diagnostic model including patient age, history of antigen exposure and radiological findings can increase specificity for diagnosis of hypersensitivity pneumonitis. **Results:** Females represented the vast majority of the included patients accounting for 90% of them. All (100%) of the included patients presented with cough and dyspnea predominantly of grade II (36.7%). Also, all (100%) of included patients reported current status of raising birds. There was a statistically positive and moderate correlation between the patient's dyspnea score and their global CT score with p value 0.005. **Conclusion:** Radiological diagnostic model with clinical correlation are highly specific diagnostic parameters for hypersensitivity pneumonitis, it offers a high level of inter-observer agreement and internal consistency.

Keywords: HRCT – CT scoring – Interstitial lung disease

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Kasr Al Ainy Medical Journal
2023, 29:21–28

INTRODUCTION

Hypersensitivity Pneumonitis (HP) is an immune-mediated interstitial lung disease (ILD) disease that manifests in susceptible patients following exposure to an inciting agent(s) [1]. Its pathogenesis is still unclear, exhibiting features of type III and type IV hypersensitivity responses [2].

HP is classified based on symptoms behavior and disease course into three categories acute, subacute and chronic [3, 4].

Acute HP results from high-intensity exposure to antigen with symptoms ranging from myalgia, cough and dyspnea to pulmonary edema [5, 6, 7, 8].

Subacute HP results from low-intensity exposure to antigen or as a sequel of long-standing undiagnosed acute HP with symptoms usually milder, although cyanosis, fatigue, anorexia and weight loss may occur [9, 10].

Chronic HP is a result of progression of acute or subacute HP, or may result from ongoing low-level antigen exposure with symptoms including progressive dyspnea on exertion, fatigue and malaise, cough and weight loss [10]

High resolution computed tomography (HRCT) is recognized nowadays as the tool with the highest sensitivity in identifying HP findings [11].

HRCT in acute HP may be normal or may show diffuse ground glass or ground glass centrilobular nodules (Fig. 1 & 2) [12]. Subacute HP shows ground glass opacities, ill-defined ground glass centrilobular nodules, and areas of air trapping with mid- and upper-lung zones predominance giving mosaic attenuation pattern (Fig. 3) [13]. While chronic HP shows fibrotic changes with septal thickening, traction bronchiectasis and honeycombing, in a peribronchovascular distribution with a mid- and upper-lung zone predominance (Fig. 4 & 5) [14]. The extent of

 DOI: 10.21608/kamj.2024.336320.1016

pulmonary fibrosis correlates positively with increased mortality in HP patients [13].

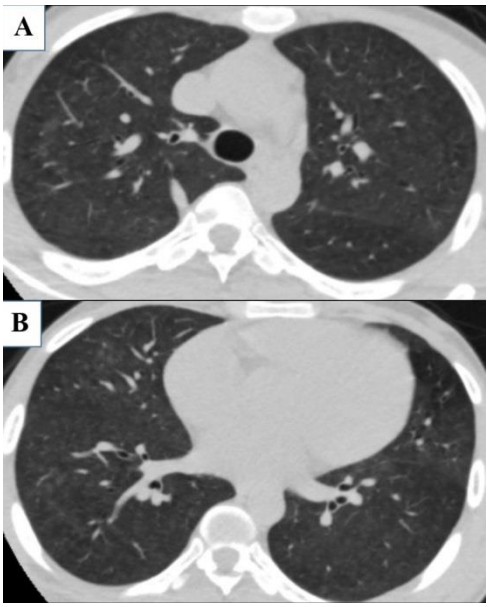

Fig. (1): 40-year-old male presented by cough and dyspnea grade III with history of bird raising. (A, B) Axial HRCT images (lung window) showing diffusely scattered subcentimetric ground-glass centri-lobular nodules. **Radiological score** = 21/25

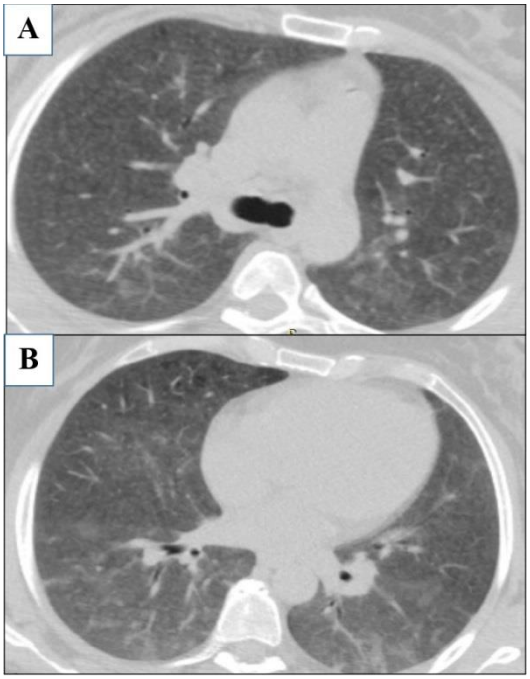

Fig. (2): 38-year-old male presented by cough, and dyspnea grade IV with history of bird raising. (A, B) Axial HRCT images (lung window) showing diffuse centri-lobular ground glass nodules, right and middle lobes air trapping and bilateral lower lobes reticulations. **Radiological score** = 22/25

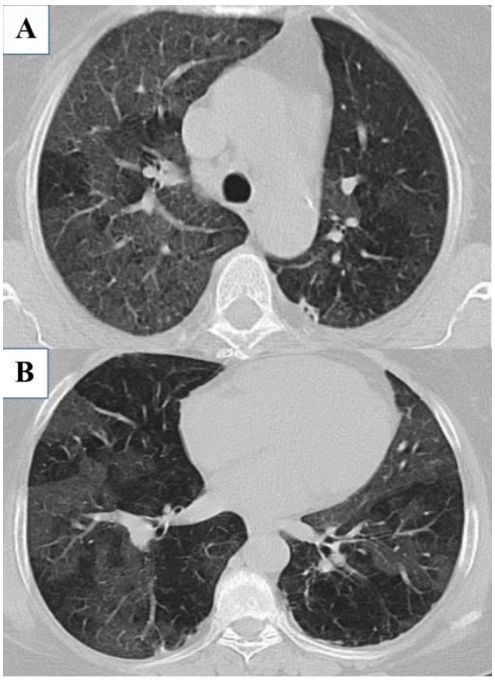

Fig. (3): 60-year-old female presented by dyspnea grade III with history of bird raising. (A, B) Axial HRCT images (lung window) showing ground glass opacities intermingled with air trapping giving mosaic attenuation pattern with bilateral lower lobes subpleural reticulations. **Radiological score** = 21/25

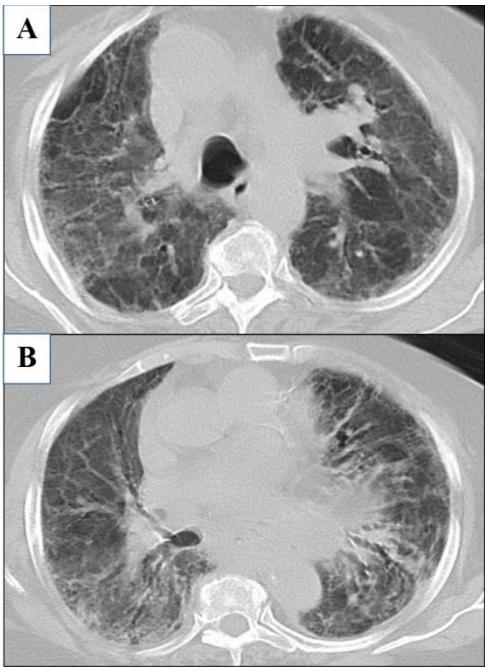

Fig. (4): 77-year-old female presented by cough and dyspnea grade IV with history of bird raising. (A, B) Axial HRCT images (lung window) showing reticulations, traction bronchiolectasis, ground-glass opacities, and mosaic attenuation with right upper lobe air trapping. **Radiological score** = 14/25

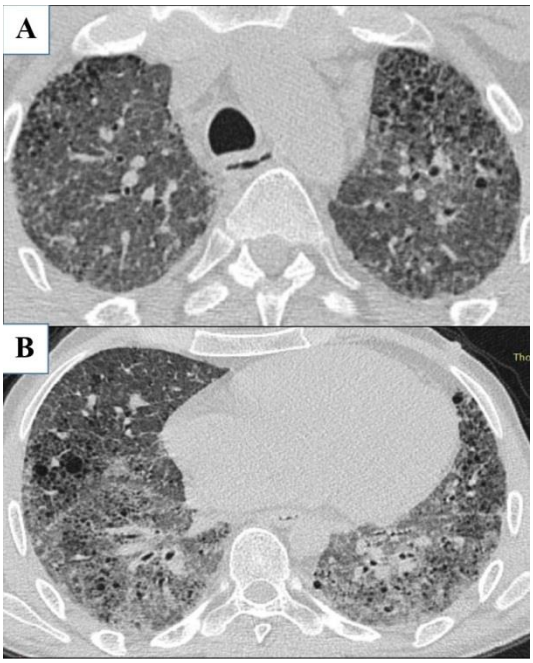

Fig. (5): 38-year-old male presented by cough and dyspnea grade IV with history of bird raising. (A, B): Axial HRCT images (lung window) showing bilateral scattered ground glass attenuation, reticulations, traction bronchiolectasis and honeycombing. **Radiological score =** 21/25

Diagnosis of HP is challenging because of the lack of any unique radiological finding distinguishing it from other ILDs. HP diagnosis depends on a high level of clinical suspicion, the recognition of antigen exposure, and a constellation of, radiologic, laboratory, and pathologic findings [10].

Creating a diagnostic model including patient age, history of antigen exposure and radiological findings can increase specificity for diagnosis of HP [15].

This study aims to assess the role of HRCT in the diagnosis of HP and creating radiological scoring model for clinically diagnosed patients with hypersensitivity pneumonitis as well as correlating between the clinical symptoms and extent of lung affection on HRCT.

MATERIALS AND METHODS

Study population:

This cross sectional study involved 30 patients (27 females and 3 males), age range was 34 to 70 years (mean age = 52.8 ± 11.6 years old). All patients were clinically diagnosed as hypersensitivity pneumonitis. They were referred from the outpatient clinic of pulmonology department to perform HRCT of lungs in the radiology department. The study was conducted in the period from (Feb-Dec 2022). Ethical committee approval and patient's consent were obtained.

Inclusion Criteria:

- Patients clinically diagnosed as hypersensitivity pneumonitis in pulmonology department.

Exclusion Criteria:

- Patients who were histopathologically proven not to be hypersensitivity pneumonitis.
- No thin-section inspiratory chest CT available for reviewing.
- Pregnant female patients.
- Un-cooperative patients.

All patients were subjected to:

- Clinical assessment including demographic data, age, gender, symptoms (including cough, & dyspnea score), history of smoking, bird raising or other antigen exposure and history of steroid/methotrexate treatment.
- Radiological assessment

Methods

I) Patient Preparation

The aim and process of the HRCT scan is explained to the patient. There is no need for the patient to be fasting as no contrast is administered during the scan. Breath holding technique in the form of taking a deep breath and holding it in for the duration of the scan is explained to the patient and demonstrated by the radiologist or technician in charge of the scan to ensure good quality of the HRCT images.

II) Technique of Examination:

HRCT of the chest was done to all patients using Siemens SOMATOM Scope, Germany (CTAWP92544) 16 channel Multi-detected CT.

Scans were performed from lung apex to base during single breath hold at full inspiration with the patient lying in supine position, and arms positioned comfortably above the head.

Reconstructed axial, coronal and sagittal images were done to all patients; also complementary mediastinal images were taken. Maximum Intensity Projection (MIP) images were reconstructed mostly in the axial plane (Table 1).

Table (1): HRCT techniques used in this study

Conventional HRCT	
Scout	Kv 130 mA 25 Holding breath
Scan type Helical Detector Row 16 Pitch 1.25mm Detector configuration 16x0.6 Beam collimation 5.0mm Gantry tilt 0.0 FOV Depends on the Patient size	
Kv 130 mA 78 Total exposure time 8-10 secs	
Reconstructed images Axial, sagittal and coronal HRCT images WW 1000 WL -700 Axial MIP images. Coronal MINP images Axial mediastinal window images.	

III) Interpretation:

HRCT was assessed by three observers (two radiologist experienced in thoracic radiology and a radiology resident with 3 years of experience) blinded to the clinical data of the patients. Results were based on consensus agreement. The CT scans were evaluated for the presence, distribution and extent of airway and parenchymal abnormalities. Standard CT criteria were used to establish a diagnosis of interstitial lung disease (ILD), bronchiectasis and mosaic attenuation. HP was defined by the presence of characteristic abnormalities (e.g. ground glass opacities, reticulations, bronchiectatic changes, air trapping, honeycomb lung) if they were multifocal or diffuse, bilateral and present at multiple levels

Statistical Analysis:

Data was entered on the computer using Microsoft Office Excel Software Program 2019. Data was then transferred and entered into the Statistical Package of Social Science Software program, version 26 (SPSS) to be statistically analyzed. Quantitative variables were summarized as mean, standard deviation, median, and IQR, compared using Mann Whitney U test, where p value<0.05 was considered significant. Qualitative variables were summarized as frequency and percentage. ROC curve was constructed with area under curve analysis performed to detect. P-values less than 0.05 were considered as statistically significant.

RESULTS

The current study included 30 patients diagnosed with hypersensitivity pneumonitis; the enrolled patients ranged in age between 35-77 years with mean age of 52.8 ± 11.6 years old. Females represented the vast majority of the included patients accounting for 90% (n=27) of them. All (100%) of the included patients presented with cough and dyspnea predominantly of grade II (36.7%) as shown in (Fig. 6).

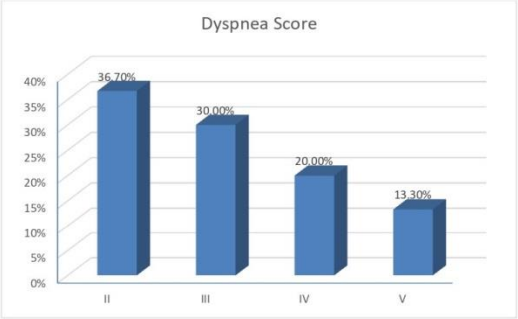

Fig. (6): Bar chart showing dyspnea score of the included patients

Twelve (40%) patients were active smokers, 15 (50%) patients were living in urban areas and 15 (50%) patients were living in rural areas, and the majority (80%) of the included patients were housewives. Also, all (100%) of included patients reported current status of raising birds. The exposure characteristics of the included patients are presented in table (2)

Table (2): Exposure characteristics of the included patients.

		Count	%
Smoking	**No**	18	60.0%
	Yes	12	40.0%
Occupation	**Employee**	1	3.3%
	Housewife	24	80.0%
	Porters	2	6.7%
	Bird Raisers	3	10.0%
Residence	**Urban**	15	50.0%
	Rural	15	50.0%
Bird raising	**Yes**	30	100.0%
Other exposures (Biomass exposure)	**Yes**	19	63.3%
	No	11	36.7%
Co-Morbidities	**Yes**	11	36.7%
	No	19	63.3%

Regarding management, all (100%) of the included patients were receiving steroids, yet, none was receiving methotrexate therapy.

According to lobar distribution of the radiological findings, the right upper lobe (50%) was the most commonly affected lobe with honeycombing followed by left upper lobe (46.7%), middle lobe (40%), right and left lower lobes (36.7%). The left lower lobe (83.3%), was the most common site of reticulations followed by right upper lobe (80%), left upper lobe (76.7%), middle lobe (73.3%) and right lower lobe (73.3%). The right lower lobe and the left upper lobe were the most commonly affected sites with ground glass appearance (83.3%) followed by right upper and middle lobes (80%) then the left lower lobe (73.3%). Mosaic attenuation was most prevalent in the middle lobe (80%) followed by right lower lobe (73.3%), left upper lobe (70%), left lower lobe (66.7%) and right upper lobe (63.3%). Air trapping was mainly present in the right middle lobe (76.7%) followed by the left lower and left

upper lobes (73.3%), right lower lobe (70%) and right upper lobe (46.7%).

Centrilobular nodules were less common findings in the HRCT images of the included patients, however it was mainly present in the right upper lobe, and left lower and upper lobes accounting for 26.7% each, followed by middle lobe (23.3%) and right lower lobe (20%). Bronchiectatic changes were moderately prevalent among the included patients and it was mainly present in the left upper lobe (50%), followed by middle lobe (36.7%), right upper lobe (33.3%), left lower lobe (30%) and right lower lobe (20%).

In the current study, three radiologists assessed the HRCT scans to identify the radiological score, summary statistics showed a mean score of 17.67 ±3.61, 15.5 ±4, and 18.9 ±3.9 for observer 1, 2 and 3 respectively, as shown in table (3).

Table (3): Radiological score of three different observers.

	Mean	Standard Deviation	Minimum	Maximum
Dr 1 (Global score)	17.67	3.61	10.00	23.00
Dr 2 (Global score)	15.50	4.02	6.00	22.00
Dr 3 (Global score)	18.90	3.95	10.00	25.00

Interclass correlation analysis showed statistically significant agreement between the three observers with correlation coefficient 70.6% and Cronbach's Alpha showed good internal consistency between the three readers (Cronbach's Alpha 0.878)

Interclass correlation analysis showed statistically significant agreement between observer 1 and 2 with correlation coefficient 70.4% and Cronbach's Alpha showed good internal consistency between the two readers (Cronbach's Alpha 0.827). Interclass correlation analysis showed statistically significant agreement between observer 1 and 3 with correlation coefficient 69.3% and Cronbach's Alpha showed good internal consistency between the two readers (Cronbach's Alpha 0.819). Interclass correlation analysis showed statistically significant agreement between observer 2 and 3 with correlation coefficient 71.8% and Cronbach's Alpha showed good internal consistency between the two readers (Cronbach's Alpha 0.836).

There was a statistically positive and moderate correlation between the patient's dyspnea score and their global CT score with p value 0.005, as shown in (Fig. 7).

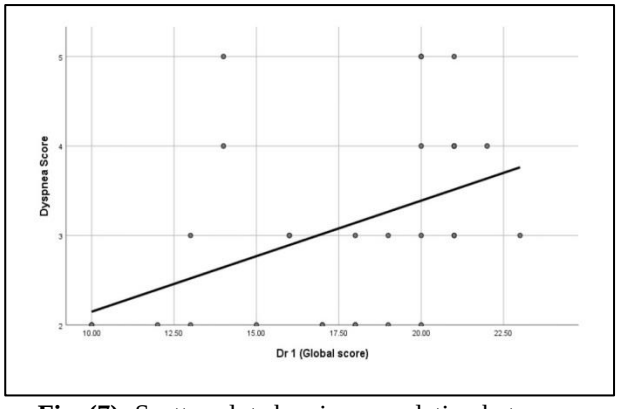

Fig. (7): Scatter plot showing correlation between dyspnea score and global prediction score

DISCUSSION

HP is classified as an ILD and it represents a complex immunological reaction of the lung parenchyma in response to allergen inhalation [16].

Several antigens can induce this immune reaction. One of the commonest types in the middle east region is Bird or Pigeon fancier's lung caused by exposure to organic antigens in bird (particularly pigeon) excreta [17, 18].

HRCT is a sensitive and effective tool used in the diagnosis of ILDs [19]. Multiple studies have evaluated the HRCT findings associated with HP and found that a radiologist's confident diagnosis of HP is correct in 87%–92% of the time [3, 14, 20].

We conducted this cross section study on 30 patients to assess the role of HRCT in diagnosis of clinically diagnosed patients with HP. Most of the enrolled patients were females, while, all of them reported current status of birds raising.

This was consistent with the evidence in literature that indicates higher affection of females by HP with common history of exposure to birds and feathers or other allergen exposure [21, 22], however, Abdel Kareem et al., stated that in their cohort of 43 patents diagnosed with HP, 64% didn't give history of any kind of antigen exposure [17].

Chills, fever, sweating, myalgia, lassitude, headache, and nausea are common in acute HP. While, cough and dyspnea are frequent but not prevalent in the acute phase [8]. Subacute HP is characterized by cough and dyspnea, which may progress to severe dyspnea and cyanosis, requiring hospitalization [23]. Chronic HP presents with increased cough and exertional dyspnea [24].

In the current study, patients who presented with dyspnea were classified as grade II dyspnea in 36.7%, followed by grade III in 30.0%, grade IV in 20.0% and grade V in 13.3%. Most of the included patients were subacute and chronic subtype of HP which explained the higher prevalence of grade II and III dyspnea.

Similar to our study, Ohtani et al., reported that patients with chronic HP usually present with gradually increasing dyspnea on exertion (grade II), fatigue, anorexia, cough, and weight loss [25].

We found in our study that the grade of dyspnea can be considered as an indicator for disease progression and diagnosis of HP class, however, this point should be thoroughly investigated in future research.

The presence of centrilobular nodules, ground-glass opacities, mosaic attenuation, and air trapping, are key radiological findings for HP diagnosis. The "three-density pattern," a type of mosaic attenuation that encompass areas of ground-glass opacification, areas of low attenuation, and areas of normal lung, has a diagnostic specificity of 93% for HP [26].

Our findings have shown that the right lower lobe and left upper lobe were the most affected sites with ground-glass appearance accounting for 83.3% each followed by right upper and middle lobes accounting for 80% and finally left lower lobe in 73.3% of the included patients.

These findings highlight the severity of HP among the included patients as ground-glass appearance was affecting almost all lung lobes in 73.3-83.3% of the included patients.

Our findings showed that mosaic attenuation and air trapping were mainly present in the middle and lower lobes in 80% of the included patients, these findings are confirmed by many studies which stated that air-trapping affects up to 75% of HP patients [27].

Our data showed that upper lobes are the most affected lobes with honeycombing (46.7%-50%), then middle lobe (40%) and lower lobes (36.7%).

These findings are consistent with many studies in literature which highlighted that upper lobar honeycombing is pathognomonic for HP diagnosis [17, 28], while other studies have added that in addition to upper lobes affection, lower lobes are the second common affected site in HP patients especially those with chronic HP subtype [14].

Our results showed that the left lower lobe was the commonest site of reticulation accounting for 83.3%, followed by upper lobes in 76.7%-80% of the included patients.

These rates are slightly higher than that reported in literature, as Castonguay et al., reported that 65% of the included patients had reticular opacities in HRCT [21].

Ground glass centrilobular nodules may be the dominant or only HRCT abnormality in patients with subacute HP [29].

We found that centrilobular nodules affected 26.7% of the included patients and were present mainly in upper lobes. While, bronchiectatic changes were moderately prevalent among the included patients and it was mainly present in the left upper lobe, followed by the middle lobe in 50% and 37.3% respectively.

In a large study conducted by Hill et al., HRCT showed that 17% of HP patients had centrilobular nodules [30]. Abdel Kareem el al., stated that among a cohort of 43 patients, they found centrilobular nodules in 20.6% of the included patients, this rate was comparable to the one reported in our study [17].

We found that the largest proportion of the included patients in our study were in the chronic stage of HP due to predominance of honeycombing, bronchiectatic changes, and reticulations while the lower proportion was in the subacute stage with predominace of centrilobular nodules, ground glass opacities, mosaic attenuation and air trapping.

Johansson et al. created a clinical prediction model including patient age, history of antigen exposure and radiological findings of ground-glass centrilobular nodules and mosaic attenuation pattern. This model-based score is proved to increase the specificity of HP diagnosis [15].

Our model was composed of clinical data and radiological findings. For clinical parameter, we included age, gender, history of raising birds, history of steroid intake and severity of symptoms including cough and dyspnea grade from 1-5 (according to Modified Medical Research Council dyspnea score). Radiological parameters included honeycombing, centrilobular nodules, mosaic attenuation, reticulations, ground-glass opacities, air trapping, and bronchiectasis changes. We assessed these findings in each lobe separately and each finding was recorded as 1 if present and 0 if absent, then each lobe was given a score according to extent of affection with all or some of previously mentioned findings collectively from 1-5 points, score 1 indicating less than 5% of the lobe affected, score 2 indicting from 5-25% of the lobe affected, score 3 from 25-50% of the lobe affected, score 4 from 50-75 of the lobe affected and score 5 indicating more than 75 % of the lobe affected. Global score was assessed by the sum of each lobe score (total scoring from 25).

Our study showed that there was a statistically positive and moderate correlation between the patient's dyspnea score and their global CT score with p value 0.005. To our knowledge this is the first study to assess the correlation between grade of dyspnea and global CT score.

These findings are consistent with recent studies that showed that there is correlation between dyspnea and CT findings as indicators for occurrence of pulmonary hypertension on top of HP [31].

In the present study interclass correlation analysis showed statistically significant agreement between the three observers with correlation coefficient 70.6% and Cronbach's Alpha showed good internal consistency between the three readers. Same levels of agreement and internal consistency were reported in the paired wise correlation. As well, there was a statistically positive and moderate correlation between dyspnea score and global score of clinical prediction model with p value 0.005 and r= 0.498.

These findings support the study conducted by Johansson et al. and offers new evidence on the inter radiologists reliability of the model as well as the good internal consistency of the proposed prediction model. We also found the moderate correlation between radiological diagnostic score and severity of symptoms (dyspnea score) which can be open new horizons for its

application on the prognosis and early detection of patients with HP.

The practical application of this type of score requires consideration of the sensitivity and specificity of the test, as well as the post-test probability of disease, which is based on disease prevalence.

In the current study we faced some limitations which includes the small sample size and lack of histopathology diagnosis.

We do recommend the following:

- Conduction of a larger study to assess the diagnostic ability of clinical and radiological models in HP diagnosis.
- Comparison of diagnostic model between HP patients and healthy controls.
- Conduction of multicenter studies to support the generalizability of our findings.
- Assess the correlation of radiological diagnostic model along with disease severity and prognosis.

It was concluded that radiological diagnostic model with clinical correlation are highly specific diagnostic parameters for hypersensitivity pneumonitis, it offers a high level of inter-observer agreement and internal consistency.

List of Abbreviations

HRCT: High resolution computed tomography
HP: Hypersensitivity pneumonitis
ILD: Interstitial lung disease

Declarations:

Ethics approval and consent to participate:

- Approval of the ethical committee of the 'Radiology department, Faculty of
Medicine, Cairo University' was granted before conducting this prospective study; Reference number: MS-158-2022
- Local institutional review board approval was granted before conducting this cross sectional study, and written informed consent was obtained from all patients.

Consent for publication:

All patients included in this research gave written informed consent to publish the data contained within this study. If the patients were less than 16-year-old, deceased, or unconscious when consent for publication was requested, written informed consent for the publication of this data was given by their parents or legal guardians.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions:

YAA, SFT and IHI formulated the concept and design of the study.
SFT, YAA, RAZ, IHI, and RIE searched the literature and analyzed the patient data.
RAZ did the statistical analysis
SFT prepared the manuscript and IHI reviewed it.

Competing interests:

The authors declare that they have no competing interests.

Funding:

The authors state that this work has not received any funding.

All authors have read and approved the manuscript.

Acknowledgements:

Not applicable.

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