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IDIOPATHIC INTERSTITIAL PNEUMONIA PATTERNS AND CORRELATION WITH SPIROMETRY STUDIES IN TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

A thesis for qualifying in Radiology as a partial fulfillment for graduation.

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IDIOPATHIC INTERSTITIAL PNEUMONIA PATTERNS AND CORRELATION WITH SPIROMETRY STUDIES IN TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

By

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ABBREVIATIONS

AAU	Addis Ababa University
TASH	Tikur Anbessa Specialized Hospital
IIPs	Idiopathic Interstitial Pneumonias
ATS	American Thoracic Society
ERS	European Respiratory Society
HRCT	High-resolution computed tomography
PFT	Pulmonary Function Test
IPF	Idiopathic Pulmonary Fibrosis
UIP	Usual intestinal pneumonia
NSIP	Nonspecific Interstitial Pneumonia
COP	Cryptogenic Organizing Pneumonia
AIP	Acute Interstitial Pneumonia)
RB-ILD	Respiratory bronchiolitis-associated interstitial lung disease
DIP	Desquamative Interstitial Pneumonia
LIP	Lymphoid interstitial pneumonia
DLco	Diffusing capacity for carbon monoxide
FVC	Forced vital capacity

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Abstract

Background: Idiopathic interstitial pneumonias are widespread interstitial lung diseases with no known cause. The diseases are characterized by a steady decline in dyspnea and lung function.

Objective: To assess the patterns of interstitial idiopathic pneumonias and investigate the correlation between the extent of lung involvement on High-Resolution Computed Tomography (HRCT) with spirometric findings in Tikur Anbessa Specialized Hospital(TASH) chest clinic, covering the period from February 2020 to February 2023.

Methods: An institutional-based retrospective, descriptive cross-sectional study design was used. All cases with a diagnosis of IIPs who have HRCT and spirometry within a 3-month window were included in this study. Finally, Pearson correlation test was used with less than 0.05 significance 2-tailed value taken as a cut-off. Then the information is presented using simple frequencies, summary measures, tables and figures.

Result: There were 54 patients diagnosed with IIPs. The overall median age of the patients was 53.9 ± 15.4. NSIP was the commonest interstitial lung disease diagnosed. Ground glass opacity was the most dominant HRCT feature identified. Pearson correlation tests ($p < 0.05$) to examine the correlation between lung involvement and spirometry parameters, as well as pulse oximetry-measured oxygen saturation. All spirometry parameters (FVC, FEV1, PEF, FEF 25-75%) and oxygen saturation demonstrated a significant negative correlation with lung involvement. The strongest correlations were observed with FVC ($r = -0.827$) and FEV1 ($r = -0.789$), both with $p < 0.001$. Oxygen saturation showed a moderate correlation ($r = -0.49$, $p < 0.001$), while PEF and FEF 25-75% exhibited weak correlations ($r = -0.39$, $p = 0.003$, and $r = -0.38$, $p = 0.005$, respectively).

Conclusion and recommendations: There was a significant negative correlation between FVC and FEV1 and extent of lung involvement identified by HRCT in idiopathic interstitial pneumonias(IIPs). Suggesting a pivotal role of pulmonary function tests (PFTs), specifically FVC, in monitoring IIP progression, supported by HRCT for diagnostic clarity. To enhance IIPs patient care, routine PFTs, particularly FVC, are recommended for monitoring.

1. INTRODUCTION

2.1 **Background**

Idiopathic interstitial pneumonia is a diverse category of chronic, progressive fibrosing interstitial non-neoplastic disorders caused by various inflammation patterns and fibrosis in the lung parenchyma (2,3). There have been several modalities used to follow patients with this condition, but HRCT has been employed in the assessment of these patients to establish safe, cost-effective parameters to evaluate disease progression (2). High-resolution CT, by describing the pattern and distribution of features that closely correlate with histological findings, has had a pivotal role in determining the diagnosis.

In a histopathologic examination, reticular abnormality on CT correlates with fibrosis. The presence of honeycombing on CT corresponds to the presence of honeycombing on biopsy (4,5) Ground glass attenuation represents evidence of interstitial inflammation, macrophage airspace filling, patchy fibrosis, or a combination of these conditions (6). Thus HRCT can be a non-invasive tool to predict histologic patterns observed in samples obtained by open lung biopsy. However, Its recurrent repetition is challenging because of the radiation load and the considerable economic cost.

Because it is easy, non-invasive, rapid, does not require any specific preparation, and has no influence on the patient, pulmonary function testing (PFT) is used in patients with IIPs to evaluate the clinical course and severity. However, the correlation between the pulmonary function test and

a well-known modality for predicting the clinical course and fate of IIPs, HRCT, has not been thoroughly explored. The primary goal of this study is to discover the pulmonary function parameters that have an association with the severity and progression of disease in IIPs, using HRCT as the gold standard.

2.2 **Statement of problem**

Interstitial Idiopathic Pneumonia (IIP) diagnosis and management have been challenging due to their diverse clinical, radiological, and histopathological features. Computed tomography (CT) has been the central component and reliable tool for the diagnosis and monitoring of IIPs(6,7), but the recurrent radiation and cost associated with the imaging make it difficult to use as a routine diagnostic tool, particularly in low-resource countries like Ethiopia. The aim of this research proposal is to investigate the correlation between CT patterns of IIPs and spirometry and to evaluate whether spirometry could be a reliable investigation for predicting the prognosis and outcome of patients with IIPs. The research was be conducted in Ethiopia, where the resources for diagnostic imaging are limited.

Spirometry is a non-invasive and affordable investigation, as per my literature review there is an absence of data regarding its role in predicting the outcome of patients and remains unclear of its usage in predicting the prognosis in patients with IIPs. The proposed study utilized spirometry to evaluate the pulmonary function of patients and correlate the results with the CT patterns of IIPs.

2. Literature review

Idiopathic interstitial pneumonias are divided into seven clinicopathologic entities in the American Thoracic Society/European Respiratory Society consensus (ATS/ERS) classification, in order of relative frequency: IPF, NSIP, COP, AIP, RB-ILD, DIP, and LIP. The classification is mostly based on histopathology, but it is also dependent on the clinician's, radiologist's, and pathologist's close collaboration(3). This is mainly because the histologic patterns seen by pathologists allow for better separation of these entities than the imaging patterns seen by radiologists, these histologic patterns provide the primary basis for the various categories of IIP and serve as the foundation for the classification. Yet only after careful correlation with clinical and radiologic aspects, including the issue of whether the condition is idiopathic, can the definitive clinicopathologic diagnosis be determined.

ATS/ERS consensus classified IIPs more clearly with a goal to emphasize the importance of dynamic interactions among clinicians, radiologists, and pathologists to arrive at a final clinical-radiologic-pathologic diagnosis in contrast to using histopathology pattern as the gold standard. Following this development, HRCT has become an integral part of the diagnosis and classification of IIPs(1).

With a median survival period ranging from 2 to 4 years, Idiopathic pulmonary fibrosis (IPF) is the most frequent interstitial lung disease of unclear aetiology.(8) IPF has a significantly worse prognosis than the other IIPs (NSIP, COP, RB-ILD, DIP, and LIP)(3,9). The updated definition of IPF is chronic fibrosing interstitial pneumonia limited to the lungs and associated with a histologic pattern of usual interstitial pneumonia (UIP) on surgical lung biopsy(3). The diagnosis

of IPF requires the exclusion of other known causes of interstitial lung disease, characteristic abnormalities on conventional chest radiographs or high-resolution computed tomography (HRCT) scans, and abnormal pulmonary function studies.

A definitive histologic diagnosis of IPF requires a surgical lung biopsy, but the diagnosis can be likely in the absence of a biopsy based on clinical and radiological features. The CT features of UIP include reticular opacities, traction bronchiectasis, honeycombing, ground glass attenuation, and architectural distortion(7). On high-resolution CT images, parenchymal involvement that increases in the apicobasal direction (apicobasal gradient) along with traction bronchiectasis, macrocystic honeycombing, and sub-pleural reticular opacities strongly suggests UIP(10,11). When evaluating an HRCT scan of a patient with diffuse lung illness, the radiologist must first evaluate whether or not a pattern characteristic of UIP is present. The need for surgical lung biopsy can be eliminated in more than 50% of the cases with suspected IPF/UIP having the presence of typical clinical and HRCT features of the disease when evaluated by experienced clinicians and radiologists(12).

Clues to non-IIP disorders such as hypersensitivity pneumonitis(7), lymphangioleiomyomatosis and Langerhans' cell histiocytosis(13), and pulmonary alveolar proteinosis(14) may also be provided by HRCT patterns which prompt the selection of bronchoscopy (usually with both bronchoalveolar lavage and transbronchial biopsy) in preference to proceeding to a surgical lung biopsy. As a result, the primary role of HRCT is to distinguish between individuals with UIP and those with non-UIP lesions or less specific abnormalities associated with other idiopathic interstitial pneumonia (NSIP, RB-ILD, DIP, and AIP).

David A. Lynch and his colleagues addressed the use of HRCT in the diagnostic assessment of patients with suspected IPF and suggested that HRCT have excellent accuracy for the diagnosis of UIP pattern. Expert thoracic radiologists are frequently indicated for interpretation according to prior criteria for HRCT examination. However, this study demonstrates that in 90% of the 315 baseline scans, core radiologists corroborated the study site radiologists' interpretation of IPF using HRCT using specified criteria, and agreement on the presence or absence of honeycombing was identified in 85% of the images. This shows that radiologists at the study sites have a strong understanding of IPF and can diagnose it with HRCT, which is better than what was predicted based on prior research.

Although nonspecific interstitial pneumonia (NSIP) is less frequent than UIP, it is one of the most common patterns of IIPs(15). The diagnosis of NSIP is extremely challenging and is accompanied by a wide range of imaging and histologic findings. Yet, considering the more significant response to corticosteroids shown in patients with NSIP, differentiating NSIP and UIP is highly crucial(16). Patchy ground-glass opacities mixed with irregular linear or reticular opacities with symmetric subpleural distribution make up the most typical HRCT manifestation(17). The main CT differential diagnosis for NSIP is UIP due to the significant overlap of high-resolution CT patterns. Micronodules, extensive ground-glass abnormalities, a finer reticular pattern, and homogeneous lung involvement without a clear apicobasal gradient are the main CT findings that favour the diagnosis of NSIP over UIP(9).

Other common IIPs are smoking-related. There is a significant overlap between smoking-related IIPs(DIP, RB-ILD) in clinical, imaging, and histologic features. And considered as a continuation of pathomorphological continuum with DIP being the end of the spectrum(9). RB-ILD has centrilobular nodules in combination with ground-glass opacities and bronchial wall thickening

features high-resolution CT(18). DIP is characterized by diffuse ground-glass opacities with lower lobe and peripheral predominance on high-resolution CT scans. Small cystic areas and spatially constrained irregular linear opacities are two additional typical CT findings. Despite RB-ILD and DIP having different CT appearances, imaging findings may overlap and be difficult to identify from one another. In all cases of suspected RB-ILD or DIP, a lung biopsy is necessary to increase diagnostic precision(3).

Cryptogenic organizing pneumonia (COP) has a pattern identified by organization within alveolar ducts and alveoli ("organizing pneumonia") with or without organization within bronchioles. CT characteristics include areas of airspace consolidation in 90% of patients with COP, and in up to 50% of cases, CT shows a subpleural or peribronchial distribution. More frequently, the lower lung zones are affected with consistent features of air bronchogram (3). The Idiopathic form of lymphoid interstitial pneumonia(LIP) is extremely rare rather the secondary form commonly associated with conditions such as Sjogren syndrome, human immunodeficiency virus infection, and variable immunodeficiency syndromes are more common(19). Ground-glass attenuation and thin-walled perivascular cysts are the most prominent HRCT features. The cysts of LIP are often located inside the lung parenchyma across the mid-lung zones and are thought to be caused by air entrapment brought on by peribronchiolar cellular infiltration, in contrast to the subpleural, lower lung cystic changes in UIP (9).

Pulmonary function testing (PFT) is a non-invasive procedure that measures lung function, including the amount of air that can be exhaled forcefully and the volume of air that can be held in the lungs. PFT is often used and recommended in the assessment and diagnosis of IIPs and

physiologic testing has the potential to aid in the diagnosis, though its utility in the differential diagnosis is limited(20). The majority of IIPs share a common physiologic abnormality pattern. Lung recoil increases over the inspiratory capacity range, resulting in a decrease in total lung capacity (TLC) and vital capacity (VC). The VC is reduced, but the FRC is usually reduced to a lesser extent.(21,22). In IIPs, Diffuse capacity of carbon monoxide (DLco) is typically reduced to a greater extent than lung volume. DLCO values appear to be more affected by IPF than for other IIPs(20).

Several studies have examined the use of PFT in the diagnosis, monitoring, assessment of treatment response, and prediction prognosis of IIPs. PFTs can be used as early diagnostic tools for IIPs. DLCO was found to be lower than normal in 73% of patients who had shortness of breath and biopsy-proven IPF but no chest radiograph findings. Furthermore, 57% of the study population had low VC, and 16% had low TLC(23). Unfortunately, in the presence of histologic and radiographic evidence of IPF, PFTs may be normal. Risk and colleagues, for example, identified two patients with biopsy-proven IPF who had a DlCO 70% predicted despite having abnormal rest and exercise P(a-a)O2. As a result, normal PFTs, while unusual, cannot be assumed to rule out IPF in the presence of suggestive clinical or radiographic abnormalities (24).

Many researchers have attempted to use PFTs to differentiate between IIPs. The study discovered that patients with UIP had higher P(a-a)O2 levels than those with desquamative interstitial pneumonia and a lower DLco predicted (24). Keogh and colleagues also reported similar results(25). When compared to IPF, hypersensitivity pneumonitis has a relatively higher residual volume, which is thought to be a result of small airway involvement(26). Despite numerous

studies, such as those mentioned above, there is significant overlap in these findings, limiting the practical clinical utility of these differences.

There have been attempts to correlate HRCT with PFT to assess the severity of IIps. A prospective study comparing HRCT results with PFT results in 53 rheumatoid arthritis patients with suspected IPF diagnoses indicated that HRCT is a useful technique for identifying and quantifying interstitial lung disease (ILD) lesions that involve less than 10% of the lung parenchyma and are discovered among the PFT parameters. The highest correlation among all the variables is for DLco, which demonstrates a moderately negative correlation between the proportion of lung parenchyma involved in HRCT scans and lung diffusion capacity ($r=-0.50$, $p<0.001$). Moreover, there was a weak but statistically significant negative correlation between lesion profusion and forced expiratory volume in one second (FEV1; $r=-0.31$, p0.05) and lesion profusion and vital capacity ($r=-0.27$, p0.05). Patients' DLco, vital lung capacity, and FEV1 are often reduced in those with at least a 10–20% estimated involvement of lung parenchyma on HRCT. However, other parameters such as forced expiratory flow and FEV1/FVC did not correlate with lesion extent. Concluding that FEV1/FVC ratio was not a reliable tool for the follow-up of patients with IIPs, DLco could be an effective parameter to monitor disease development in patients with IIPs (20).

In a study of 39 untreated patients with confirmed diagnoses of IPF (17 patients with open lung biopsy, 22 patients with HRCT findings compatible with IPF findings with HRCT), 23 of whom were followed for 7.5 ± 0.3 months and none of whom had collagen vascular disease, pulmonary function parameters were correlated with the severity and progression of IPF using HRCT as the gold standard. The study suggested the overall disease extent in the HRCT was significantly

correlated with both FVC (r = 0.46, p = 0.003) and DLco (r = 0.40, p = 0.03). A strong association between changes in HRCT total lung involvement and changes in both DLco and VC was discovered in the follow-up investigations (r = -0.57, p = 0.01, and r = -0.51, p=0.01, respectively). The study suggested valuable information on both baseline and disease progression can be provided using PFT parameters of FVC and DLco. the authors explained their result disparity with other papers published on this topic having an inconclusive correlation between HRCT and PFT(27–29) by the study population of the research was representative of all stages of the disease as they used typical HRCT patterns of IIPs as an inclusion criterion in contrast to the prior research using only histologic diagnosis, allowing patients that are too compromised for open lung biopsy to be included in the research.

3. Objective

3.1 General Objective

- Examine the patterns of interstitial idiopathic pneumonias and the correlation between the extent of lung involvement on High-Resolution Computed Tomography (HRCT) with spirometry results. The study focused on patients at Tikur Anbessa Specialized Hospital's (TASH) chest clinic from February 2020 to February 2023.

3.2 Specific objectives

I. To investigate the common HRCT patterns in patients with the diagnosis of IIPs.

II. Determine the correlation between HRCT and spirometry in extent of lung parenchymal involvement in individuals with idiopathic interstitial pneumonias.

III. To identify specific spirometry parameters that are most predictive of lung function impairment and the pattern of parenchymal involvement in idiopathic interstitial pneumonias.

4. Materials and methods

4.1 Study Area and Period

The research took place at Tikur Anbessa Specialty Hospital (TASH), part of the Addis Ababa University Faculty of Health Science. The largest hospital in the nation's capital, Addis Ababa. It serves as both the primary teaching hospital and the biggest referral center in the nation. With approximately 900 beds and 24-hour emergency service, the hospital offers tertiary referral care.

4.2 Study Design

Institutional-based retrospective, descriptive cross-sectional study design was used.

4.3 Source Population

All patients with an established diagnosis of Idiopathic interstitial pneumonia (IIP) visited the chest clinic at TASH.

4.4 Study population

All patients admitted or visited the chest clinic at TASH who have a IIPs diagnosis and undergo HRCT and spirometry.

4.5 Inclusion and Exclusion Criteria

4.5.1 Inclusion Criteria

All patients with a diagnosis of IIPs and who had HRCT and have spirometry within 3 months of HRCT acquisition at TASH in the last 3 years.

4.5.2 **Exclusion criteria**

- Poor quality HRCT
- Inconclusive diagnosis
- Significant associated emphysematous changes
- lack of patient record data

4.5.3 **Sampling technique and sample size**

All patients seen at the chest clinic at TASH in the past three years diagnosed with IIPs who fulfil the eligibility criteria.

4.6 **Data collection tool**

The research involved a review of medical records, HRCT images, and spirometry records to collect data on patient demographic, medical history, CT features, and PFT results, on a google form structured questionnaire. The questionnaire is adopted from the literature. The questionnaire is prepared in English language and close-ended.

4.7 **Data collection procedure**

A registry book from the chest clinic was used to Identify 54 patients with the diagnosis of IIPs from February 2020-Feburary 2023. The history was collected using the Icare system and the image is retrieved from the hospital's Picture archiving and communication system (PACS). 9 patients had imaging done outside the institution; in those cases, the images were obtained by

collecting the CD from the patients. Then the HRCT report diagnosis was taken. Axial CT images were taken at six specific levels at the great vessels, aortic arch, tracheal carina, pulmonary hilum, and pulmonary venous confluence, and 1 cm above the right diaphragm at window levels that were suitable for pulmonary parenchyma, with a mean of 2500 to 2600 Hounsfield units and a width of 1,400 to 1,600 Hounsfield units. Using a similar method to previous research on the same topic(2,27,30), the images were evaluated in a standardized manner for the extent of the overall parenchymal abnormalities, and each extent of consolidation, ground glass opacity, reticulation, and honeycombing. Consolidation was considered present when the opacity hides the underlying vessels, ground glass opacity was characterized as an area of haziness with increased attenuation, reticulation was defined as lesions with innumerable interlacing lines, and honeycombing was regarded as clustered cystic airspaces 3 to 10 mm in diameter with layering in the subpleural lungs. The extent of involvement was scored to the nearest 5%, except when less than 10% of the lung is involved, in those cases, estimation was scored to the nearest 1%. The scores of the six lung zones were averaged out to obtain a mean score. On each level the dominant parenchymal abnormality was categorized in to the four aforementioned abnormality and finally, The average dominant parenchymal abnormality was taken as the predominant finding for the specific diagnosis. All patients who underwent pulmonary function testing were included. The results of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), Peak expiratory flow(PEF), and Forced Expiratory Flow (FEF) of individual patients were collected from the database in the chest clinic computer. Reference values from our laboratory (TASH) were used.

4.8 **Study variable**

4.8.1 Dependent variable

- Spirometry findings

4.8.2 **Independent variable**

- Imaging patterns and extent of parenchyma abnormalities
- Sociodemographic factors (Age, sex, place)
- Smoking
- Pathologic diagnosis

4.9 **Operational definitions**

- **Diagnosis**: - was derived from the structured radiology report that accompanied the High-Resolution Computed Tomography (HRCT) scans.
- **Percentage of parenchymal abnormalities**: - When less than 10% of the lung is affected, the estimation was scored to the nearest 1%, otherwise the extent of involvement was scored to the nearest 5%. Six predeterminate levels were be taken at the great vessels, aortic arch, tracheal carina, pulmonary hilum, and pulmonary venous confluence, and 1 cm above the right diaphragm. A mean score was calculated by averaging the scores of the six lung zones.
- **Dominant feature**: - The dominant feature on each level was categorized into the four parenchymal abnormalities below then the average dominant feature was taken the predominant feature of the HRCT.
    - **Consolidation**: -When the underlying vessels are hidden by the opacity
    - **Ground glass opacity**: - Region of increased attenuation and haziness without obscuring the underlying vessels.

- **Reticulation**: - Thickening of the interlobular or intralobular septa and appears as several linear opacities that resemble a mesh
- **Honeycombing**: - Between 3 and 10 mm in diameter, clustered cystic air pockets that are typically subpleural and peripheral.
- **Pulmonary cysts: -** Round, thin-walled, low attenuation spaces/lucencies in the lung.

4.10 Data Processing and Analysis

To reduce logical errors and design skipping patterns, the collected data was verified for completeness, cleaned, edited, coded, and entered Epi data version 3.1. Data was then exported for analysis into SPSS Windows version 27. Descriptive analysis was done by computing proportions and summary statistics. Then the information is presented by using simple frequencies, summary measures, tables, and figures.

4.11 Ethical Consideration

Written ethical clearance were obtained from the department's research and ethics committee. Any piece of information was kept confidential by keeping the anonymity of the study subjects. A formal letter of permission and support was written to the internal medicine department, pulmonology unit. Then informed, voluntary, written and signed consent was obtained from the radiology department head.

5 Result

5.1 sociodemographic characteristics

A total of 54 patients diagnosed with Interstitial Idiopathic Pneumonias (IIPs) and who underwent spirometry were identified from February 2020 to February 2023. The demographic, clinical, and physiologic characteristics of these patients are summarized in Table 1. The median age of patients was 53.9 ± 15.4 years; the age ranges between 27 to 91 and most of the patients was female (64.8%, 35). 8 patients were smokers (14.8%) mean pack years among the smokers was 7± 4.2. Restrictive was the most common PFT diagnosis seen among 64.8% of the patients (35),13 patients had normal spirometry.

Table 1 Describing the sociodemographic, clinical and physiologic characteristics of IIPs patients visiting chest clinic in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia 2020-2023.

Characteristics		Frequency (n=54)
Age, mean (years) ±SD		53.9 ± 15.4
Sex Male/Female	Male	19
	Female	35
Smoking history	yes	8

	No	46
Pack year mean ± SD		7± 4.2
PFT	FVC% predicted (%) mean±SD	65.1 ± 19.4
	FEV1 % predicted (%) mean±SD	65.46 ±18.4
	FEV1/FVC % mean±SD	97.28 ± 11.5
	FEF 25-75% mean±SD	82.9 ±23.5
	PEF mean±SD	82.87 ±18.27
PFT diagnosis Normal/ restrictive/ mixed/ obstructive		13/35/2/3
Pulmonary hypertension (>2.9cm cut off)		19
Mean pulmonary diameter, mean ± SD±		2.8±0.5
Severity on	Mild	6

(echocardiography)	Moderate	10
	Severe	3

5.2 HRCT and spirometry correlation

Pearson correlation test was used with less than 0.05 significance 2-tailed value taken as a cut-off. All of the spirometry parameters (FVC, FEV1, PEF, FEF 25-75%) and oxygen saturation levels measured on pulse oximetry showed a negative and significant correlation with the extent of lung involvement. The strongest correlation from the parameters seen with FCV and FEV1 r= -0.827 and r= -0.789 respectively with a P-value of <0.001 for both. While moderate correlation r= -0.49 P-value <0.001 was seen with oxygen saturation. A weak correlation of r= -0.39 and r= -0.38 P values = 0.003 and 0.005 was identified with PEF and FEF 25-75% respectively.

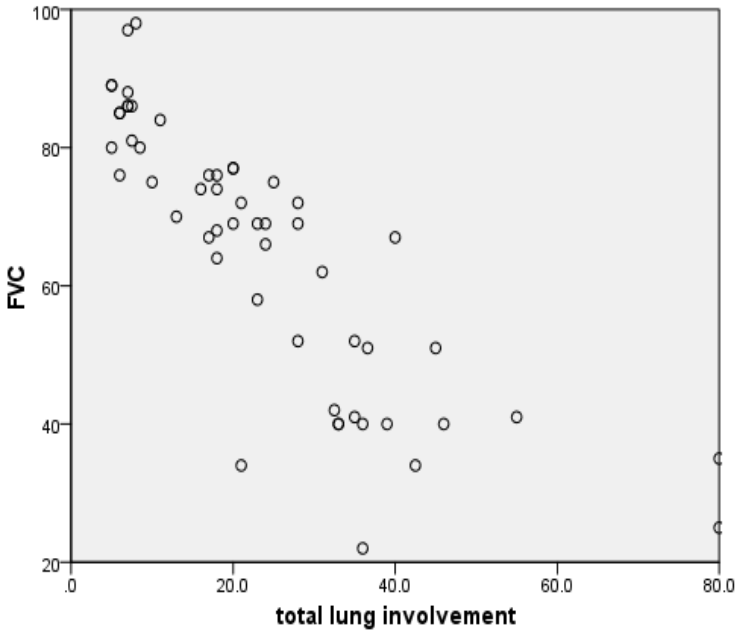

Figure 1) Correlation between to the extent total lung involvement in HRCT and functional vital capacity (FVC) in IIPs patients visiting clinic, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia 2020-2023

13 patients had a normal spirometer finding among this patient the average extent of lung involvement was 6.9± 1.3. 76% of the patients had a dominant finding of ground glass opacity. The commonest radiological diagnosis was NSIP (76%) and the next common diagnosis was LIP (15.4%)

5.3 Idiopathic interstitial pneumonia patterns and HRCT features

The comments IIPs is NSIP 57.4%(31) followed by UIP 20.4%(11) (table 2) .38 patients received immunosuppressive therapy (table 3) 33 of 38 were treated with prednisolone (15 of the 33 received prednisolone alone, and 13 of 33 received CPT three times per week), Azathioprine was the next immunosuppressive therapy commonly used 5 of 38 (2 times with a combination of prednisolone).

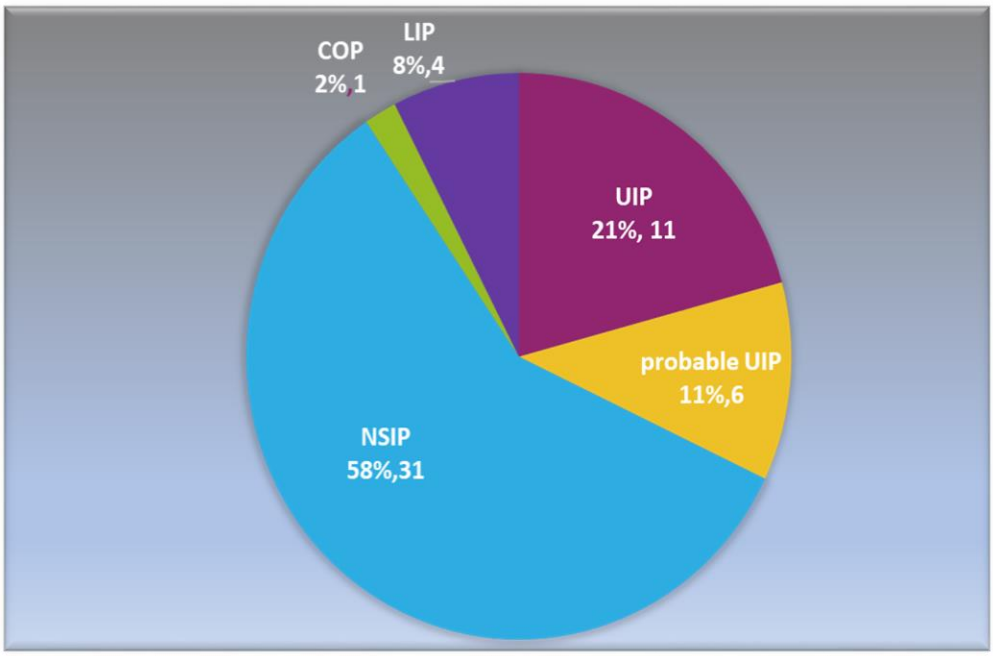

Figure 2 **Distribution of IIPs patterns in patients visiting chest clinic, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia 2020-2023**

Table 3 Medication intake by IIPs patients visiting chest clinic in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia 2020-2023

Medication	%(n=54)
Antiretroviral	1.9
Azathioprine, cardiovascular drugs, combined prednisolone and CPT 3x per week	3.7
Azathioprine, combined prednisolone and CPT 3x per week	1.9
Cardiovascular drugs	7.4
Cardiovascular drugs, anti-diabetic	3.7
Cardiovascular drugs, Mycophenolate mofetil	1.9
Combined prednisolone and CPT 3x per week	16.7
Methotrexate	1.9
methotrexate, combined prednisolone and CPT 3x per week	1.9
Mycophenolate mofetil	1.9
None	16.7
Pirfenidone	1.9
Prednisolone	24.1
Prednisolone, Azathioprine	3.7
Prednisolone, cardiovascular drugs	3.7

Prednisolone, imatinib(drug-induced)	1.9
Prednisolone, methotrexate, Azathioprine	1.9
Prednisolone, Mycophenolate mofetil	1.9
Prifenidone with CPT, Mycophenolate mofetil	1.9

The dominant HRCT findings are summarized on (table 4) for ground glass opacity was the most common HRCT feature followed by reticulation and honeycombing.

Table 4 Common HRCT features in IIPs patients visiting chest clinic in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia 2020-2023

HRCT features	%(n=54)
Honeycombing	16.7%
Reticulation	20.4%
Ground Glass Opacity	57.4%
Consolidation	1.9%
Cystic	3.7%

The majority of the patients diagnosed with NSIP were females 67.7%(21/31) with the dominant feature being GGO at 93 % (29/31) The lung involvement shows an apicobasal gradient with the most involved level being the basal level 6 (1 cm above the diaphragm) with a mean value of 38.7% ±27.1. The mean age for NSIP is 51.6± 14

The predominant PFT finding was restrictive with the mean FVC and FCV1 values being 66.7% and 67.4 % respectively from the predicted. Scleroderma/systemic sclerosis were the most prevalent comorbidity for NSIP, present in 9 individuals (17%). All the patients with scleroderma were female with a relatively younger mean age of 43.7± 10.7. Mean Global extent of involvement on HRCT was 17.8±8.9 which is 45% less than the rest of patients with NSIP. Mean FVC is also higher (70.3± 12)

UIP shows female predominance with 64 %(7) The mean age is relatively older compared to NSIP with a mean age of 56.7+/15. Shows apicobasal gradient with basal lung with level 6 involvement at 55% and total lung involvement the mean FVC and FCV1 values were 61.8% and 62.2% respectively. The most common comorbidity was RA (3/54). The dominant feature was Honeycombing at 64% (7/54) and 36% reticulation (4/54). 90% of the patients have a restrictive PFT. In patients without honeycombing and diagnosed with UIP the features were CT findings of apicobasal gradient of reticular changes with the least involved segment being level one with 7.5% and level 6 being the most involved with 45%.

All of the four LIP-diagnosed patients have associated HIV infection but No sex predominance was seen on LIP. patients have an age range of 47-68 and a mean age of 55±9.2. Ground glass opacity and cystic lesions were the two dominant features seen on HRCT. Half of the patients had restrictive patterns on spirometry while the other half had normal spirometry. The mean total lung involvement was 13%±6 which is significantly less compared to the NSIP and UIP patterns. LIP also showed basal lung predominance with 23.7% of Level 6 and 18.7% of Level 5 involvement contrary to the 12% combined involvement of Level 1 and 2. And mean FVC and FEV1 are in the normal range (82 ±12 and 82.5 ±14). All the patients have normal CD4 count with a mean of 627.

6. Discussion

This study suggests that FVC1 and FEV1 have a strong negative correlation with the HRCT global extent of involvement. Considering that HRCT is known to be an accurate method for describing the histopathologic progression in IIPs patients (3). It has been shown in multiple studies (4–6) that the results of HRCT can be used to predict the histologic patterns and prognosis. Therefore, PFT can also offer crucial information about the extent of lung involvement by IIPs. As a result, it can be performed as a routine test to monitor disease progress, and HRCT can be utilized if there is uncertainty or a difference between the disease's clinical history and PFT. FVC is the more reliable PFT parameter. Restrictive lung disease is defined as decreased FCV with a normal FEV1/FVC ratio (31). Previous studies have explained why FCV is the most affected parameter in IIPs, because Idiopathic interstitial pneumonias increase the load on the inspiratory pump and decrease the ability of the lungs to expand thereby decreasing its ability to stretch and decreasing the amount of air exhaled forcefully after deep breath (FVC) (32–35). A similar finding was

identified in this study too. Xaubet and coworkers also described a similar negative statically significant moderate correlation between the extent of lung involvement graded by HRCT and FVC(r =-0.51, p= 0.01) in 39 untreated patients with IPF.

However, there are some studies showing diffuse lung disease and spirometry do not correlate. Fulmer and colleagues evaluated 23 patients with the diagnosis of IPF. All of the evaluated spirometry values do not correlate with the extent of lung involvement by fibrosis or cellularity (36) Cherniack and coworkers found similar findings among 96 IPF patients using a semiquantitative histologic scoring system.(37) however these studies did a correlation studies between spirometry and histologic extent of diffuse lung disease and the disease extent was not evaluated by HRCT and it's difficult to predict the global extent on involvement solely with histology.

The mean age for idiopathic interstitial pneumonia in our study was 53.9 years similar studies in Ethiopia in Tikur Anbessa Hospital, Addis Ababa and Ayder Hospital, Mekelle, Ethiopia revealed comparable mean age of 50 and 55 respectively.(38,39) studies done in Paris also has a mean age of 55.7 (40). 70 % of the patients were above the age of 40. The mean age between different types of IIPs ranged from 49-62 in studies done on this topic. (41) female predominance was seen which similar to studies done in Ethiopia and worldwide.(38,42,43)

NSIP was the commonest IIPs diagnosed with 57.4% followed by UIP 31.5 %, LIP 7.4% and COP 1.9%. Studies done in the same hospital and country suggest similar findings (38,39). These findings, however, disagree with those of other investigations. Collard and colleagues examined

literature on the prevalence and diagnosis of IIPs that was published between 1966 and 2001. The sample sizes of the research they analyzed ranged from 129 to 78, and each study discovered that the UIP was the commonest pattern.(44) . Recent studies in Cairo, Egypt ,Denver Colorado, USA and Paris, France suggest UIP to be the frequently encountered diffuse lung disease pattern.(40,45). The findings could be explained: the findings could be explained: all of the mentioned studies have a lung biopsy, and a confirmatory Histopathology test was done for the patients. (1,46,47) This is also supported by Flaherty et al in their study evaluating the importance of multidisciplinary discussion to reach a diagnosis for IIPs. The study revealed that radiologists initially diagnosing NSIP changed their diagnosis to UIP after histologic input from a pathologist. In an independent review of HRCT scans, 27 out of 58 cases were diagnosed as NSIP, while only 15 were diagnosed with UIP by cardiothoracic radiologists. However, in a multidisciplinary team setting involving clinicians and pathologists, UIP emerged as the most common IIPs —32 out of 58 cases by radiologist A and 30 by radiologist B—while NSIP diagnoses dropped to 14 and 15 patients, respectively. The absence of a multiciliary approach in all Ethiopian studies may contribute to NSIP emerging as a predominant feature. . Furthermore, considering that Melesse and his colleagues explained the NSIP predominance in similar research done on Mekelle, Ethiopia by age variation and difference in genetics. Given that this is the third study suggesting NSIP predominance in Ethiopia further multicentric study with larger study population encompassing a multidisciplinary team diagnosis is recommended to ascertain the distribution of the IIPs.

Examining individual IIPs distribution, 72% of those diagnosed with UIP were aged 50 and above, aligning with findings in other studies (1). The CT patterns observed in this study, such as

apicobasal gradient, predominant basal lung involvement, and honeycombing, are consistent with characteristics noted in previous research (1,5,45,47). In our study, two-thirds of the patients exhibited honeycombing changes, consistent with multiple studies on the topic. Notably, various studies suggest honeycombing as a determinant factor for suggesting UIP pattern with high confidence, demonstrating sensitivity of 90% and specificity of 86% (5,45,48).

demonstrated that honeycombing alone on HRCT indicated the presence of UIP with a sensitivity of 90% and specificity of 86%, the overall UIP pattern of fibrosis needs to be assessed to yield a confident diagnosis. The comments pattern next to honeycombing was peripheral reticulation with apicobasal gradient. The most common associated comorbidity with UIP pattern in our study was RA. This is in line with most studies on this topic considering UIP to be the most prevalent and possibly most dangerous extra-articular manifestation of RA.(50,51)In this study, the mean FVC for patients with UIP pattern was 61.8%. Similar findings from a study conducted at the Mayo Clinic in Rochester, Minnesota, the United States, were published. The FVC was 64% on average. They also found a correlation between the global extent of involvement and decline in FCV in UIP pattern.

The mean age of the patients with NSIP pattern in our study was 51.6, which is lower than the mean age of UIP patients (56.7). Ebner and his colleagues also found NSIP patients were significantly younger compared to UIP in a meta-analysis reviewing twelve studies involving 785 patients (338 NSIP and 447 UIP) .NSIP: median age 54.8 years, UIP: 59.7 years(52). Other series

also found NSIP patients to be decades younger than UIP with median age of between 40 and 50. (53,54) Female predominance was also seen in our study; this was also seen in most studies (52,55).

The dominant feature on HRCT for patients with NSIP was GGO which is also described in previous studies related to this topic. In previous series also its suggested that having ground-glass opacity as a predominant pattern of NSIP and was used as a distinguishing factor from UIP (52,53,56) and it was the only HRCT feature in about one-third of cases. Histologically, this can be explained by either fibrosis, inflammation, or both causing the alveolar walls to expand uniformly. The alveolar septa in cellular NSIP are thickened by lymphocyte and plasma cell infiltrates, while in fibrotic NSIP, collagen buildup is the primary cause of the thickening. These pathological changes can lead to the appearance of GGO on imaging studies.(57) Although apicobasal gradient is described with UIP, our study also revealed that NSIP has basal predominance. however, multiple study also suggested that NSIP can have basal predominance(3,47,58)

The most frequently occurring comorbidities for NSIP were scleroderma/systemic sclerosis (17%) in this study. Several recent reports also found that the commonest rheumatological disease among these patients is scleroderma/systemic sclerosis(58–61). Although the exact pathology in the lung is not fully understood, systemic sclerosis is an autoimmune rheumatic condition characterized by excessive production and accumulation of collagen in the skin and internal organs. (62) Therefore it can be explained as fibroblast recruitment/activation of lung interstitium, which then results in accumulation of extracellular matrix and scarring. The mean FVC for NSIP was 66.7% which is

5% higher than UIP this can be explained by the fact that the latter have more fibrotic interstitial changes impairing the normal expansion of the lungs. (61)

All of the patients with the diagnosis of Lymphoid interstitial pneumonia (LIP) in studies have concomitant HIV infection this is supported by idiopathic LIP is rare and it is highly doubted that it occurs without any systemic autoimmune illness or retroviral infection. (3). Our study's mean age(55) for LIP correlates with other research on the subject, where the mean age varies between 50 and 57. (1,63–66) However there are studies suggesting the age range could be younger ranging from 30-50, especially in HIV-infected patients. (67) This difference can be explained by the small sample sizes used in all of the studies on the subject, including this one. More research with a bigger sample size is advised. On HRCT, cysts with Ground-glass opacity were the most frequently observed features. These findings are also frequently observed in earlier literature. (3,67). In line with earlier research, the areas of the lung most involved were the basal lungs. (66,68) unlike UIP and NSIP where the commonest spirometry finding was restrictive. The predominant PFT abnormality in LIP was obstructive which does not also relate with previous studies. (67) Therefore we recommend further study on the topic with a bigger sample.

7. Conclusion

In conclusion, this study highlights a strong negative correlation between FVC1 and FEV1 with the HRCT global extent of involvement in idiopathic interstitial pneumonias (IIPs). The findings support the utility of pulmonary function tests (PFTs), particularly FVC, as valuable tools for monitoring the progression of IIPs, with HRCT serving as a complementary diagnostic method in cases of uncertainty. Non-specific Interstitial Pneumonia (NSIP) is the most common pattern observed, followed by Usual Interstitial Pneumonia (UIP), contradicting previous research that suggested usual interstitial pneumonia (UIP) was the most common pattern. The study explains the disparity with previous studies, which used a multidisciplinary approach and were better able to diagnose atypical UIP cases.

8. Recommendation

Considering the compelling negative correlation discovered between FVC1 and FEV1 concerning the HRCT global extent of involvement, this study emphatically suggests prioritizing particular pulmonary function test parameters, especially forced vital capacity (FVC), in the monitoring of patients with idiopathic interstitial pneumonias (IIPs). Additionally, we advocate for a multidisciplinary team approach rather than the routine radiological reporting when evaluating IIPs, highlighting incorporating clinicians and histologic confirmation is crucial in atypical UIP and NSIP cases.

9. Limitation

One notable limitation of this study is the relatively low sample size, reflecting the inherent challenge of conducting research on a rare disease with low prevalence, such as idiopathic interstitial pneumonias (IIPs). The scarcity of cases may affect the generalizability of the findings to a broader population. Moreover, not having information from biopsies, which is crucial for diagnosing IIPs, is a limitation. This absence could affect how well we understand the disease patterns and might result in misclassifying some cases. Additionally, the exclusion of DLco spirometry parameter, utilized in previous research, is due to resource limitations, as this specific test was not conducted in Ethiopia. Future research with larger, multicenter cohorts and the inclusion of biopsy data could address these limitations and provide a more robust foundation for studying IIPs.

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Assurance of Principal Investigator

The undersigned agrees to accept responsibility for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per the terms and conditions of the GRANT AGREEMENT to be signed between the researcher(s) and the Office of the Director for Research of AAU, if the grant is awarded as the result of this application.

Submitted by __Dr. Natnael Alemu Signature:_____
Date __05/01/2024__

12. Annex

12.1 Questionnaire

Chest CT and spirometry correlation in idiopathic interstitial pneumonia patients in TASH AA Ethiopia

This study examines the relationship between spirometric results and the patterns of lung parenchymal involvement and the extent on HRCT of interstitial idiopathic pneumonias seen at the TASH Chest Clinic over the previous three years.

1) Medical registration number _____
2) Age _____
3) Sex A) Male B) Female
4) Occupation A) Factory worker B) Office worker C) farmer D) unemployed E) Merchant F) Other_____
5) Smoking history A) yes B) NO
6) IF yes to Q.5 pack years _____
7) Symptoms
   A) shortness of breath
   B) cough
   C) easy fatigability
   D) Joint pain
   E) Fever
   F) combined symptoms of cough, SOB, easy fatiguility combined symptoms of cough and SOB
   G) combined symptoms of cough and fever
8) Duration of symptoms_____
9) Comorbidity
   A) Hypertension
   B) Diabetes
   C) Asthma
   D) SLE
   E) RA
   F) HIV
   G) previous TB treatment
   H) Post COVID
   I) Scleroderma/systemic sclerosis psoriasis
   J) IBD

K) Combined Hypertensive and DM RA and DM
L) Polymyositis/ dermatomyositis
M) Leukemia

10) Medication
A) prednisolone
B) CPT 3x per week
C) Pirfenidone
D) Methotrexate
E) Azathioprine
F) Cardiovascular drugs anti diabetic
G) Combined prednisolone and CPT 3x per week prifenidone with CPT
H) Mycophenolate mofetil
I) Imatinib

11) HRCT diagnosis
A) UIP
B) probable UIP
C) NSIP
D) COP
E) DIP
F) RB-ILD
G) LIP
H) ILD indeterminate

12) Oxygen saturation level _____

13) Presence of Pulmonary hypertension(2.9cm cutoff) A) yes B)No

14) Percentage of lung involvement
A) Level 1_____
B) Level 2_____
C) Level 3_____
D) Level 4_____
E) Level 5_____
F) Level 6_____
G) Total _____

15) Dominant feature

A) Level 1_ 1) honeycombing 2) reticulation 3) ground glass opacity 4) consolidation 5) cystic ___
B) Level 2___ 1) honeycombing 2) reticulation 3) ground glass opacity 4) consolidation 5) cystic ___ _____
C) Level 3__ 1) honeycombing 2) reticulation 3) ground glass opacity 4) consolidation 5) cystic ___ _____
D) Level 4__ 1) honeycombing 2) reticulation 3) ground glass opacity 4) consolidation 5) cystic ___ _____
E) Level 5___ 1) honeycombing 2) reticulation 3) ground glass opacity 4) consolidation 5) cystic ___ _____

F) Level 6___ 1) honeycombing 2) reticulation 3) ground glass opacity 4) consolidation 5) cystic ___ _____

G) Total _ 1)honeycombing 2) reticulation 3) ground glass opacity 4) consolidation 5) cystic

16) PFT
    A) Diagnosis 1) Normal 2) Restrictive 3) Mixed 4) Obstructive
    B) FVC_____
    C) FEV1_____
    D) FEV1/FVC_____
    E) PEF_____
    F) FEF25-75%_____

17) Echocardiography
    A) Pulmonary hypertension 1) Mild 2) Moderate 3) Severe
    B) Tricuspid regurgitation 1) yest 2) NO