Allergol Immunopathol (Madr). 2025;53(3):41-50 eISSN:1578-1267, pISSN:0301-0546

Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
www.all-imm.com

SEICAP

CODON PUBLICATIONS

ORIGINAL ARTICLE

OPEN ACCESS

Exploring noninfectious radiological lung findings in adult patients with primary immunodeficiency diseases

Filiz Sadi Aykan[a*], Fatih Çölkesen[b], Recep Evcen[c], Mehmet Kılınç[d], Eray Yıldız[e], Ümmügülsüm Yılmaz Ergün[b], Tuğba Önalan[b], Fatma Arzu Akkuş[b], Selim Kahraman[b], Mehmet Emin Gerek[b], Şevket Arslan[b]

[a]*Division of Clinical Immunology and Allergy, Department of Internal Medicine, Ankara Health Sciences University Gülhane Training and Research Hospital, Ankara, Türkiye*
[b]*Division of Clinical Immunology and Allergy, Department of Internal Medicine, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye*
[c]*Division of Clinical Immunology and Allergy, Department of Internal Medicine, Recep Tayyip Erdoğan University Training and Research Hospital, Rize, Türkiye*
[d]*Division of Clinical Immunology and Allergy, Department of Internal Medicine, Batman Training and Research Hospital, Batman, Türkiye*
[e]*Division of Clinical Immunology and Allergy, Department of Internal Medicine, Necip Fazıl City Hospital, Kahramanmaraş, Türkiye*

Received 8 January 2025; Accepted 20 March 2025
Available online 1 May 2025

KEYWORDS
class-switched memory B cell;
high-resolution computed tomography;
lung;
pulmonary function test;
primary immunodeficiency

Abstract
Primary immunodeficiency diseases (PIDs) show different patterns of airway involvement, particularly bronchiectasis; however, comparative studies of radiologic manifestations in patients with PIDs are scarce. Hence, the aim of this study to investigate radiologic lung findings in adult patients with PIDs and evaluate the possible relationship between clinical and immunologic features and respiratory function in these patients. In this study, the demographic and clinical characteristics, serum immunoglobulins (Ig), lymphocyte subgroups, high-resolution computed tomography (HRCT), and pulmonary function tests (PFTs) of 116 adult patients with PID were evaluated and those with and without abnormal HRCT were compared. The median age was 40 (28–48) years, and there were 51 (44%) females. Abnormal findings were detected in 55.2% of the HRCTs, but the most common findings were bronchiectasis (30.2%), bilateral involvement (73.5%), and lower lobe predominance. The median age and age of diagnosis were higher in those with HRCT findings. The obstructive pattern was the most common found in the PFTs. Forced vital capacity, maximal mid-expiratory flow at 25–75%, immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), cluster of differentiation (CD)4^{+} T cell, CD4^{+}/CD8^{+} ratio, and class-switched memory B (cSMB) cell levels were significantly lower, whereas mortality was higher. Noninfectious pulmonary complications are among the important causes of morbidity and mortality in PID that could result

***Corresponding author**: Filiz Sadi Aykan, Division of Clinical Immunology and Allergy, Department of Internal Medicine, Ankara Health Sciences University Gülhane Training and Research Hospital, Ankara, Türkiye. *Email address*: drfilizsadi@gmail.com

https://doi.org/10.15586/aei.v53i3.1302

in chronic lung disease despite adequate Ig therapy. Considering the extra radiation dose of HRCT, clinical findings and immunological and PFT parameters accompanying radiological features may be helpful in predicting the diagnosis; it may also be useful in determining additional treatment modalities and reducing mortality.

Introduction

Primary immunodeficiency diseases (PIDs) are a heterogeneous group of disorders caused by genetic defects affecting the innate and/or adaptive immune system. PID, also known as inborn errors of immunity, manifests as increased susceptibility to infectious diseases, autoimmunity, autoinflammatory diseases, allergy, and malignancy.[1]

The respiratory system is one of the most prominent organs causing morbidity and mortality in PIDs. Early diagnosis and treatment of pulmonary complications in PIDs can prevent or slow the development of respiratory complications.[2]

Comparative studies on the clinical and radiological features of pulmonary complications in adult patients with PID are limited, and so increasing knowledge and providing optimum patient management are critical for extending life expectancy in these patients. Hence, investigating radiological lung findings was the aim of this study for better understanding and early identification of pulmonary complications in adult patients with PID and evaluate the possible relationship between clinical and immunological features and pulmonary function.

Materials and Methods

Study design

This retrospective study was conducted at the Necmettin Erbakan University Faculty of Medicine, Adult Immunology and Allergy Clinic; approved by the local Ethics Committee (Decision No.: 2023/4355); and adhered to all relevant tenets of the Declaration of Helsinki (1975). About 137 adult patients with PID were retrospectively reviewed and followed-up at our institution between 2012 and 2022. When a genetic diagnosis was not available, it was defined according to the criteria of the European Society for Immunodeficiencies (ESID) Registry Working Group.[3] When the review was complete, 116 patients with common variable immunodeficiency (CVID), X-linked agammaglobulinemia, selective immunoglobulin A (IgA) deficiency, natural killer (NK) deficiency, hyper-IgE (immunoglobulin E) syndrome, ataxia-telangiectasia syndrome, and severe combined immunodeficiency were included in the study (Figure 1). Their clinical characteristics, laboratory data, high-resolution computed

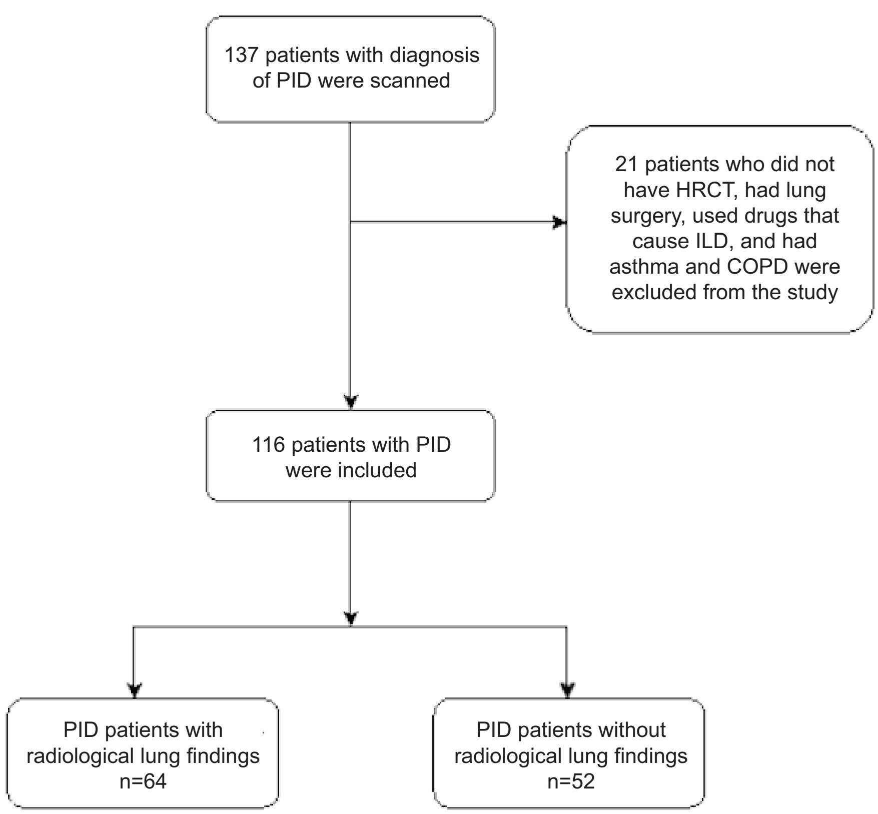

Figure 1 Flow chart of the patients included in the study.

tomography (HRCT), and pulmonary function tests (PFT) were evaluated.

Data collection

Data on the age, sex, age at the time of diagnosis, delay in diagnosis, follow-up time, complaints at admission, smoking status, concomitant autoimmune disease, malignancy, and mortality of the 116 adult PID patients were collected from the hospital's electronic medical record and archive system. In the initial diagnosis stage, serum immunoglobulin G (IgG), IgA, immunoglobulin M (IgM), IgE, total T cell (cluster of differentiation [CD]3$^+$), helper T cell (CD3$^+$CD4$^+$), cytotoxic T cell (CD3$^+$CD8$^+$), CD4$^+$/CD8$^+$ ratio, total B cell (CD19$^+$), class-switched memory B (cSMB) cell (CD19$^+$CD27$^+$IgD$^-$), NK (CD3$^-$CD16$^+$CD56$^+$) cell levels, antibody responses specific to protein and polysaccharide vaccines (tetanus and pneumococci), and isohemagglutinin titers (Anti-A, Anti-B) were recorded. Patients with HRCT in the stable period of the diagnostic process were screened. It was observed that a group of patients underwent PFT during the symptom-free period due to differences in clinicians' approaches to the follow-up process. Sixty-seven patients who underwent PFT with the appropriate technique were identified and evaluated; those with both solitary fibrous tumor (SFT) and HRCT were evaluated separately.

Serum immunoglobulin measurements

Serum immunoglobulin (Ig) levels were determined using a nephelometric analyzer (Siemens BNII System, Erlangen, Germany).

Specific antibody responses

Pneumococcal polysaccharide antibody titers were measured using a multiplex immunoassay (Elizen, Angleur, Belgium). An impaired response to the Pneumovax-23 vaccine was considered if the postvaccination titer was < 250 mU/mL or less than a twofold increase from the prevaccination titer. Tetanus antitoxin IgG Enzyme-Linked Immunosorbent Assay (ELISA) kits (Novalisa, Vienna, Austria) were used to detect tetanus antibodies. Tetanus antitoxin IgG was recognized as an antibody at a protective level of ≥ 0.1 IU/mL.

Isohemagglutinin titer

To measure the isohemagglutinin titer, blood samples in ethylenediaminetetraacetic acid (EDTA) tubes were centrifuged at 5000 rpm for 1 minute, and then the separated plasma was diluted with saline for titration. Titers ≥ 1:8 were considered normal.

Flow cytometric analysis

Peripheral blood samples (2 mL) were collected in tubes anticoagulated with EDTA and tested within 6 hours. Lymphocyte subsets were measured by multicolor flow cytometry using a key panel. The cells were analyzed on a Becton, Dickinson and Company fluorescence-activated cell sorting (BD FACS) Canto II Flow Cytometry System (BD Biosciences, San Jose, CA, USA).

Spirometric analysis

Spirometric measurements were obtained with an nSpire ZAN 100 spirometer (Health Inc., Oberthulba, Germany). The forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, and maximal mid-expiratory flow at 25–75% (MMEF25–75) were recorded for each patient. Abnormal lung function was defined as FEV1, FVC, or FEV1/FVC ratio less than 80% or less than 70% predicted for MMEF 25–75. Obstructive, restrictive, and mixed respiratory dysfunction patterns were determined using the American Thoracic Society recommendations.[4]

High-resolution computed tomography scans

Infection-free state and stable period HRCT scans taken during the diagnostic process were obtained. Parenchymal and interstitial findings in the upper, middle, and lower lobes of the lungs and mediastinal lymph nodes were evaluated and divided into two groups: those with and those without radiological lung findings.

Statistical analysis

IBM SPSS (Statistical Package for the Social Sciences) Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Continuous variables were expressed as medians with interquartile ranges (IQR: 25th to 75th percentiles) and categorical variables were expressed as numbers and percentages for each category. According to the presence of radiological lung findings, the Mann–Whitney U test was used to evaluate continuous data. Categorical variables were assessed using the Pearson's chi-squared or Fisher's exact tests where $P \leq 0.05$ was considered as statistically significant.

Results

Clinical and laboratory characteristics of the patients

This study included 116 adult patients with PID. The median age was 40 (range: 28–48) years and there were 51 (44%) females. Moreover, 78.4% presented with infectious causes. The most common type of PID was CVID (72.4%). Subcutaneous or intravenous Ig replacement therapy (IgRT) was given to 86.2% (100/116) of the patients and both IgRT and antibiotic prophylaxis were given to 68.1% (78/116). General characteristics of the patients and immunological parameters at the time of diagnosis are shown in Tables 1 and 2.

Table 1 General characteristics of the diagnosis and follow-up processes of adult patients with primary immunodeficiency.

Total PID patients, n (%)	**116 (100)**
Age, year, median (IQR)	40 (28-48)
Age of diagnosis, year, median (IQR)	30.6 (18-42)
Delay in diagnosis, months, median (IQR)	36 (12-96)
Sex, n (%)	
Male	65 (56)
Female	51 (44)
Application complaint, n (%)	
Infectious conditions	91 (78.4)
Noninfectious conditions	25 (21.6)
PID type, n (%)	
CVID	84 (72.4)
Selective IgA deficiency	16 (13.8)
NK deficiency	6 (5.2)
HIES	3 (2.6)
X-LA	3 (2.6)
Ataxia telangiectasia syndrome	2 (1.7)
SCID	2 (1.7)
Follow-up period, year, median (IQR)	7 (2-10)
Smoking, n (%)	10 (8.6)
Autoimmunity, n (%)	37 (31.9)
Malignancy, n (%)	9 (7.8)
Mortality, n (%)	18 (15.5)

PID, primary immunodeficiency diseases; IQR, interquartile range; CVID, common variable immunodeficiency; NK, natural killer; HIES, hyper-IgE syndromes; X-LA, X-linked agammaglobulinemia; SCID, severe combined immunodeficiency.

Evaluation of the radiological findings

When the HRCTs were evaluated, 64 (55.2%) patients had radiological lung findings where bronchiectasis was the most common (30.2%) and where they were commonly bilateral (73.5%). Unilateral involvement was commonly observed in the right lung (15.6%). The most commonly affected lobe was the lower lobe at a rate of 31.3%, whereas two to three lobes were involved together in 42.2% of the patients. There were two (1.9%) patients who were histopathologically diagnosed with granulomatous lymphocytic interstitial lung disease (GLILD) (Table 3).

Relationship between the pulmonary radiographic findings and pulmonary function tests

PFT was performed on 67 patients using appropriate techniques and compliance. Of these, 24 (35.8%) had normal PFT findings, 23 (34.3%) had obstructive findings, 13 (19.4%) had restrictive findings, and 7 (10.4%) had mixed pattern respiratory dysfunction. The MMEF 25-75 was low in 35 (52.2%) patients. The group with HRCT findings had abnormal PFT findings but no statistically significant difference was observed ($P = 0.28$). However, when the PFT parameters were compared individually between the two groups, the FVC and MMEF 25-75 values were significantly lower ($P = 0.039$ and $P = 0.048$, respectively) (Table 4).

Relationship between the pulmonary radiographic findings and clinical and laboratory findings

The median age and age at the time of diagnosis were significantly older in the group with HRCT findings (P = 0.02

Table 2 Immunological parameters of adult patients with primary immunodeficiency at the time of diagnosis.

Parameter	Normal range	Value
Lymphocyte count, 103/μL, median (IQR)	≥ 1.5	1.7 (1.1-2.2)
Immunoglobulins, g/L, median (IQR)		
IgA	0.7-4	0.26 (0.2-0.9)
IgM	0.46-3.04	0.41 (0.18-0.9)
IgG	7-16	5.5 (2.1-8.6)
IgE	0-100	18 (17-21)
Lymphocyte subgroups, %, median (IQR)		
CD3+ T cells	57-85	77 (70-84)
CD3+CD4+ T cells	30-61	36 (27-45)
CD3+CD8+ T cells	12 42	37 (30-49)
CD4+/CD8+ ratio	> 0.9	0.95 (0.55-1.51)
CD19+B cells	6-29	7 (2-13.7)
CD19+27+IgD-	9.2-18.9	5 (0.9-12.5)
CD16+56+ NK cells	4-25	7 (4-11)
Isohemagglutinins[a]		
Anti-A antibody, insufficient, n (%)	≥ 1:8	48 (41.4)
Anti-B antibody, insufficient, n (%)	≥ 1:8	48 (41.4)

[a]Six patients had AB blood type.
PID, primary immunodeficiency diseases; IQR, interquartile range; Ig, immunoglobulin; CD, cluster of differentiation; NK, natural killer.

and P = 0.04, respectively). Also significantly lower were serum IgG, IgA, IgM, $CD4^+$ T cell, $CD4^+/CD8^+$ ratio, and cSMB cell levels; the mortality rate was higher (P = 0.01). No significant correlation was found between the two groups in terms of the smoking status, PID type, concomitant autoimmune disease, and malignancy (Table 5).

Table 3 Radiological lung findings in adult patients with primary immunodeficiency.

Radiological lung finding, n (%)	**64 (55.2)**
Bronchiectasis, n (%)	35 (30.2)
Sequela fibrotic change, n (%)	33 (28.4)
Bronchial wall thickening, n (%)	20 (17.2)
Air trapping, bronchiolitis, n (%)	10 (8.6)
Ground glass opacity, n (%)	11 (9.5)
Mediastinal LAP, n (%)	15 (12.9)
< 1 cm	10 (8.6)
> 1 cm	5 (4.3)
Milimetric pulmonary nodule, n (%)	11 (9.4)
< 5 mm	4 (3.4)
5-10 mm	7 (6)
GLILD, n (%)	2 (1.9)
Lung involvement site, n (%)	
Bilateral	47 (73.5)
Unilateral	17 (26.5)
Right	10 (15.6)
Left	7 (10.9)
Involved lobe, n (%)	
Top	4 (6.3)
Middle	6 (9.4)
Lower	20 (31.3)
Middle + bottom	16 (25)
Top + middle	3 (4.6)
Top + middle + bottom	15 (23.4)
Number of involved lobes, n (%)	
Single lobe	14 (21.9)
Two to three lobes	27 (42.2)
Four to five lobes	23 (35.9)

PID, primary immunodeficiency diseases; LAP, lymphadenopathy; GLILD, granulomatous lymphocytic interstitial lung disease.

Discussion

Radiological lung findings in adult PID patients were investigated herein, and the relationship between their HRCT findings and clinical features, delay in diagnosis, immunological parameters, PFT, and mortality were evaluated. The most common radiological finding was bronchiectasis, where the bilateral and lower lobe involvement was more predominant. The obstructive pattern was the most common among those who underwent PFT, and those with HRCT findings, the obstructive pattern was also the most common; the decrease in the FVC and MEF 25-75 was significant. It was also observed that the mean age and age at the time of diagnosis were older, serum Ig, CD4+ T cell, CD4+/CD8+ ratio; cSMB cell levels were significantly lower; and mortality was higher in the PID patient group with HRCT.

PID has a reported prevalence of between 1:16,000 and 1:50,000. The International Union of Immunological Societies updated the number of PIDs to 485 in 2022, but it suspects that 70–90% of patients are undiagnosed.[5] Delayed diagnosis remains a problem in adult patients with PID, often due to lack of awareness. The delay in diagnosis has been reported to be 5.5 years for primary antibody deficiencies (PADs),[6] 4 years for CVID,[7] and in this study, the mean delay in diagnosis was 3 years. Our lower diagnostic delay time was attributed to the fact that our study included PID patients other than CVID and that these patients presented in childhood and were diagnosed early.

PID awareness studies have reported that patients with PID may present with symptoms of immune dysregulation. In a study of 16,486 PID patients compiled from the ESID registry data, 77% presented with infection and 18% with immune dysregulation.[8] In this study, infectious causes were observed in 78.4% of the initial presentations and noninfectious causes in 21.6%. Autoimmune conditions were found to accompany 31.9% of the patients, supporting the consideration of autoinflammatory events in terms of PID.

Table 4 Evaluation of the relationship between radiological lung involvement and pulmonary function test findings in adult patients with primary immunodeficiency.

Pulmonary function test findings	Radiological lung findings		*P-value*
	No (n: 24)	Yes (n: 43)	
Abnormal PFT finding, n (%)	13 (54.2)	30 (69.8)	0.28
Obstructive pattern, n (%)	9 (37.5)	14 (32.6)	0.79
Restrictive pattern, n (%)	3 (12.5)	10 (23.3)	0.35
Mixed pattern, n (%)	1 (4.2)	6 (14)	0.40
Low MMEF 25-75, n (%)	10 (41.7)	25 (58.1)	0.21
FEV1, %, median (IQR)	85 (74-97.5)	78 (66-87)	0.058
FVC, %, median (IQR)	89 (76.5-99)	78 (68-93)	**0.039**
FEV1/FVC	83 (76-87.7)	80 (74-84)	0.12
MMEF 25-75, %, median (IQR)	77 (61-99.2)	61 (48-85)	**0.048**

PID, primary immunodeficiency diseases; PFT, pulmonary function test; MMEF 25-75, maximal midexpiratory flow at 25-75%; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range.

Table 5 Comparison of radiological lung findings with demographic, clinical, and laboratory characteristics in adult patients with primary immunodeficiency.

	Radiological lung findings		*P-value*
	No (n: 52)	Yes (n: 64)	
Mortality, n (%)	2 (3.8)	16 (25)	0.01
Sex, n (%)			0.45
Male	27 (51.9)	38 (59.4)	
Female	25 (48.1)	26 (40.6)	
Smoking status, n (%)	5 (9.6)	5 (7.8)	0.75
Age, median in years (IQR)	31.5 (27-44)	40.5 (32-56)	**0.02**
Age at diagnosis, mean years ± ss	27.3 ± 14	33.3 ± 16	**0.04**
Delay in diagnosis, months, median (IQR)	34.5 (12-84)	44 (13-106)	0.26
Admission with infectious clinic, n (%)	40 (76.9)	51 (79.7)	0.44
Autoimmunity, n (%)	17 (32.7)	20 (31.3)	0.51
Malignancy, n (%)	2 (3.8)	7 (10.9)	0.14
PFT abnormality, n (%)	13 (54.2)	30 (69.8)	0.28
Lymphocyte count, 103/μL, median (IQR)	1.7 (1.1-2.5)	1.6 (1.0-2.2)	0.16
Immunoglobulins, g/L, median (IQR)			
IgA	0.35 (0.23-1)	0.25 (0.06-0.73)	**0.04**
IgM	0.55 (0.29-1.1)	0.29 (0.18-0.63)	**0.02**
IgG	6.3 (4.5-11.8)	4 (1.4-6.7)	**0.001**
IgE	18 (17-20)	18 (15-24)	0.68
Lymphocyte subgroups, %, median (IQR)			
CD3+ T cells	78 ± 9.7	74.8 ± 13.3	0.15
CD3+CD4+ T cells (T helper)	39.2 ± 12.4	32.7 ± 13.7	**0.009**
CD3+ CD8+ T cells (T cytotoxic)	33 (27-44)	38 (32-52)	0.75
CD4+/CD8+ ratio	(0.76-1.7)	0.86 (0.5-1.1)	**0.01**
CD19+ B cells	7.1 (2.4-13)	6.9 (2-14)	0.97
CD19+27+IgD– (cSMB)	7.9 (2.2-15.8)	2.7 (0.3-9.8)	**0.02**
CD16+56+ NK cells	7 (4-9.3)	7 (4-14)	0.33

[a]Common variable immunodeficiency, X-linked agammaglobulinemia.
[b]Artemis deficiency, ataxia telangiectasia syndrome, hyper-IgE syndromes.
PID, primary immunodeficiency diseases; IQR, interquartile range; PFT, pulmonary function test; SCID, severe combine immunodeficiency; CID, combine immunodeficiency; Ig, immunoglobulin; [c]SMB, class switched memory B; NK, natural killer; CD, cluster of differentiation.

The lower frequency of PIDs presenting with autoimmunity is due to the lack of awareness of clinicians and limited diagnostic possibilities for autoinflammatory events. However, thanks to recent developments, the relationship between immune dysregulation and immunodeficiencies is increasingly being elucidated, suggesting that the number of PIDs presenting with autoimmunity will increase.[9]

Antibody deficiencies are the most common among PIDs, and the most common symptomatic antibody deficiency is CVID, which is seen in approximately 75% of cases.[10] Although PIDs are generally considered to be pediatric diseases, CVID is mostly diagnosed in adults.[11] In this study, the prevalence of CVID was 72.4%, which was similar to that reported in literature.

It has been proven that there is an increased prevalence of lung disease in adult patients with PID compared to pediatric patients,[12] with radiological lung findings accompanying in approximately 60% of cases.[13] In this study, abnormal findings on HRCT were detected in 55.2% of patients. Similar to the literature, no significant difference was found between the patients with HRCT findings and the delay in diagnosis;[14,15] however, the median age and age at the time of diagnosis were significantly older. This supports the hypothesis that longer exposure of adult patients to infections and subclinical ongoing autoinflammatory processes may cause chronic damage to the lung.[16] The risk of chronic lung disease increases with the duration of the disease, independent of IgRT; however, it has not been reported to depend on age at the time of diagnosis.[16] Additionally, in this study, 63.2% of the patients had HRCT findings despite receiving antibiotic prophylaxis with IgRT. Despite IgRT and prophylactic antibiotics, the development of structural airway disease appears to progress.[16] Additional factors such as underlying subclinical infection, immune dysregulation, and comorbidities contribute to this.[13,16] Subclinical infections have been detected in patients with PAD and a number of bacteria and viruses have been identified even when patients were not actively infected.[17] Although early intervention with prophylactic antibiotics and/or IgRT can prevent respiratory infections and pulmonary disease morbidity and mortality, chronic lung disease advances in many patients.[18] Conventional chest X-ray imaging detects only one-third of bronchiectasis lesions, even the most common lung finding.[7] Even in PADs without respiratory symptoms, chest CT and PFT are recommended to look for evidence of chronic lung disease.[10] This will enable radiologists to better assess the spectrum of initial and progressive CT manifestations of pulmonary complications of PIDs.[19] With advances in diagnosis and treatment, an increasing proportion of PID patients now survive into adulthood. Earlier diagnosis may lead to better management of the disease.[19] Therefore, active and accurate screening is mandatory even in well-controlled patients, but the lack of standardized protocols for follow-up is a major challenge to the identification and treatment of pulmonary complications.[10] As chest screening with HRCT has shown that patients with PAD have a much higher proportion of interstitial lung disease (ILD) and bronchiectasis than previously estimated, accurate diagnosis is crucial, especially for the treatment of ILD.[20]

Pulmonary complications such as bronchiectasis, peribronchial thickening, air trapping, bronchiolitis, atelectasis, and parenchymal nodules have been demonstrated in PID.[21] In a cohort study of 117 patients with PID, bronchiectasis was the most common HRCT finding (58.3%), followed by bronchial wall thickening (22.9%) and consolidation (18.8%). It was proven that 64.3% of HRCT findings were bilateral and the right middle lobe was the most commonly affected.[22] Other previous studies have shown that bronchiectasis and bronchial wall thickening were the most common findings (14–60%) and the middle or lower lobe was the most commonly affected.[21,23] (21, 23). In this study, the most common radiological finding in all of the PIDs was bronchiectasis (30.2%), followed by sequel fibrotic changes (28.4%) and bronchial wall thickening (17.2%). Unlike previous studies, bilateral involvement was observed more frequently (73.1%). In unilateral involvement, the right lung (15.6%) was dominant. Regarding lobe dominance, lower lobe involvement (31.3%) was predominant, followed by middle-lower lobe (25%). There are not enough studies on the dominant lobe in adult PIDs in literature. However, the fact that bronchiectasis is most commonly seen in the lower lobes supports this.[24] It has also been shown that the course of bronchiectasis associated with PAD is similar to bronchiectasis caused by other causes.[25] Standardized HCRT scoring methods are needed for effective screening and follow-up of pulmonary complications associated with CVID, especially since CVID is common in adults.[26,27] To help assess lung disease progression in these patients, the scoring system should be based on abnormalities specific to PADs rather than adapted from other diseases such as cystic fibrosis. A scoring method was developed in a study of pediatric patients with stable CVID or CVID-like disorders.[27] However, more studies are needed in this regard in adult PID.

Bronchiectasis is less common in selective IgA deficiency than in XLA (an inherited immune disorder caused by an inability to produce B cells or the immunoglobulins [antibodies] that the B cells make) and CVID.[28] In this study, the HRCT finding was 60.9% in the antibody deficiency group and lower (37.5%) in the selective IgA deficiency group. This supports the opinion that selective IgA deficiency patients can produce IgG antibodies and are less prone to pulmonary infections.[28] The respiratory surface in the upper and lower airways is predominantly covered with secretory IgA (sIgA) and IgM, while IgG is the predominant isotype in the alveolar space.[29] Both sIgA and IgM on the bronchial surface originate mostly from mucosa-associated lymph tissue rather than from the systemic circulation.[30] Alveolar IgG originates from the systemic circulation by passive diffusion and effectively prevents bacterial infections such as pneumonia.[31] Since individuals with selective IgA deficiency are generally healthy, sIgA appears to play a negligible role in airway defense. However, the observation that patients with CVID suffer more severely from airway infections than those with very low IgA levels compared to those with higher IgA levels suggests that IgA may at least partially compensate for IgG deficiency in airway defense.[32]

GLILD, which is usually specific to CVID, develops in approximately 10% of patients.[33] Impaired T cell function in CVID is a factor in granuloma formation and increased incidence of lymphoproliferative disease, supported by the fact that GLILD is not seen in XLA.[34] In this study, GLILD was detected only in CVID. This rate was lower than those reported in the literature and was probably due to the limited possibilities of histopathological diagnosis. The presence of GLILD decreases survival.[20] The fact that one of the two GLILD patients in this study died at a young age supports this. As ILD appears asymptomatic in its initial phase, screening all patients with CVID may facilitate early disease detection and enable early treatment that may be less aggressive.[26]

In a study evaluating the PFTs of CVIDs, 60% abnormality was found (38.8% obstructive, 44.4% restrictive, and 16.7% mixed pattern);[35] however, another study found 34.5% obstructive, 17.2% restrictive, and 7.4% mixed patterns, similar to the results herein.[22] Additionally, studies comparing the PFTs of patients with and without HRCT findings generally showed a weak correlation.[15,35] In this study, PFT abnormalities were more common in the group with HRCT findings and the rate was higher than that reported in literature. Furthermore, a significant decrease in the FVC and MMEF 25–75 parameters were observed. In contrast to our study, in patients with PAD, the decline in FEV1 has been shown to be a more sensitive indicator of pulmonary function than FVC, as expected due to the obstructive nature of bronchiectasis. As in bronchiectasis of all causes, a reduction in the MMEF 25–75 in PID indicates early airway disease in the small airways or bronchioles and may precede other changes in lung function.[36] A decrease in MMEF-25-75 may be a harbinger of low FEV1 that may develop later in the disease. Alongside general clinical assessment and physical examination, lung function tests provide useful information about lung performance and the extent and progression of chronic lung disease in patients with PAD. The rate of decline in lung function in PAD is much faster than predicted in both healthy individuals and smokers.[37] Therefore, at least annual PFT follow-up (including DLCO [diffusing capacity of the lungs for carbon monoxide] if possible) is recommended.[38]

In adults with CVID, low IgM, IgG, and cSMB levels were associated with recurrent lower respiratory tract infections, chronic lung diseases, and HRCT abnormalities.[39,40] It has been shown that the absolute numbers of $CD4^+$ T cells, naive $CD4^+$ T cells, naive $CD8^+$ T cells, and cSMB cells are significantly reduced in patients with severe HRCT findings.

The absolute number of $CD4^+$ T cells and naive $CD4^+$ T cells were found to have the highest sensitivity and positive predictive value in identifying patients at risk of ILD.[15] Similarly, in this study, the serum IgG, IgA, IgM, $CD4^+$ T cell levels, $CD4^+/CD8^+$ ratio, and cSMB cell levels at diagnosis were significantly lower in the patients with HRCT findings. The low level of these parameters supports the literature and suggests that they may predict the risk of ILD; however, more prospective studies are needed.

Noninfectious pulmonary complications in PAD are common and contribute significantly to morbidity. In CVID in particular, two independent studies have shown that patients with disease-related noninfectious complications have a significantly worse survival prognosis than those without complications. The risk of death was estimated to be 11 times higher than in patients with infection alone.[41,42] The US Immunodeficiency Network database reported the overall mortality in PIDs as 8.7%[43] and the ESID Registry Network database reported it as 9.2%.[44] In more than one-third of these patients, mortality was due to respiratory causes.[11,13] In a study conducted in the Middle East and North Africa (MENA), the general mortality rate was 15.8%, where 27.6% was due to respiratory failure.[45] In this study, overall mortality was 15.5% and mortality due to respiratory causes was 32.2%, similar to that in MENA. The high mortality rate was thought to be due to the lack of funding for newborn screening, availability of genetic testing, and difficulties in accessing advanced treatment modalities.

This study had limitations. First, it was a retrospective and cross-sectional study. Second, clinical and laboratory diagnostic criteria were used in those without a definitive genetic diagnosis. Third, it was not possible to determine at what point HRCT abnormalities develop and assess progression. Adequate and equal periods of time were not available to follow the development of radiologic findings, the exact number of previous lower respiratory tract infections could not be determined, and SFTs could not be performed in all patients. Therefore, further follow-up studies are needed to evaluate the progression of preclinical pulmonary abnormalities and the development of clinical disease and its association with risk factors.

In conclusion, despite these limitations, very few studies have investigated the relationship between radiological lung findings and clinical features, respiratory functions, and immunological parameters in adult patients with PID. Therefore, the results of this study could shed light on future studies, taking into account the aforementioned limitations. Thus, the development of irreversible noninfectious pulmonary complications may be limited and early deaths due to lung disease could be prevented.

Acknowledgment

None.

Authors Contributions

FSA was involved in conceptualization, data collection, methodology, investigation, resources, validation, review & editing, writing the original draft, visualization, and project management. FÇ, RE, MK, and EY were responsible for conceptualization, data collection, formal analysis, methodology, validation, review and editing. ÜYE, TÖ, FAA, SK, and MEG were involved in formal analysis, investigation, resources, and review & editing. ŞA was responsible for formal analysis, methodology, validation, project management, supervision, and review & editing. All authors discussed the results and contributed to the final manuscript.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

Funding

The authors received no funding for this article.

References

1. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 Primary immunodeficiency diseases committee report on inborn errors of immunity. J Clin Immunol. 2018;38(1):96–128. https://doi.org/10.1007/s10875-017-0464-9
2. Jesenak M, Banovcin P, Jesenakova B, Babusikova E. Pulmonary manifestations of primary immunodeficiency disorders in children. Front Pediatr. 2014;2:77. https://doi.org/10.3389/fped.2014.00077
3. Grimbacher B, Party ERW. The European Society for Immunodeficiencies (ESID) registry 2014. Clin Exp Immunol. 2014;178(Suppl 1):18–20. https://doi.org/10.1111/cei.12496
4. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med. 2019;200(8):e70–88. https://doi.org/10.1164/rccm.201908-1590ST
5. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human inborn errors of immunity: 2022 Update on the classification from the international union of immunological societies expert committee. J Clin Immunol. 2022;42(7):1473–507. https://doi.org/10.1007/s10875-022-01289-3
6. Blore J, Haeney MR. Primary antibody deficiency and diagnostic delay. BMJ. 1989;298(6672):516–7. https://doi.org/10.1136/bmj.298.6672.516
7. Thickett KM, Kumararatne DS, Banerjee AK, Dudley R, Stableforth DE. Common variable immune deficiency: Respiratory manifestations, pulmonary function and high-resolution CT scan findings. QJM. 2002;95(10):655–62. https://doi.org/10.1093/qjmed/95.10.655
8. Thalhammer J, Kindle G, Nieters A, Rusch S, Seppanen MRJ, Fischer A, et al. Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations. J Allergy Clin Immunol. 2021;148(5):1332-41 e5.
9. Long A, Kleiner A, Looney RJ. Immune dysregulation. J Allergy Clin Immunol. 2023;151(1):70–80. https://doi.org/10.1016/j.jaci.2022.11.001

10. Jolles S, Sanchez-Ramon S, Quinti I, Soler-Palacin P, Agostini C, Florkin B, et al. Screening protocols to monitor respiratory status in primary immunodeficiency disease: Findings from a European survey and subclinical infection working group. Clin Exp Immunol. 2017;190(2):226-34. https://doi.org/10.1111/cei.13012
11. Cunningham-Rundles C. Clinical and immunologic analyses of 103 patients with common variable immunodeficiency. J Clin Immunol. 1989;9(1):22-33. https://doi.org/10.1007/BF00917124
12. Cunningham-Rundles C. How I treat common variable immune deficiency. Blood. 2010;116(1):7-15. https://doi.org/10.1182/blood-2010-01-254417
13. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol. 1999;92(1):34-48. https://doi.org/10.1006/clim.1999.4725
14. Turner PJ, Mehr S, Kemp AS. Detection of pulmonary complications in common variable immunodeficiency. Pediatr Allergy Immunol. 2011;22(4):449-50; author reply 51-2. https://doi.org/10.1111/j.1399-3038.2010.01118.x
15. Maarschalk-Ellerbroek LJ, de Jong PA, van Montfrans JM, Lammers JW, Bloem AC, Hoepelman AI, et al. CT screening for pulmonary pathology in common variable immunodeficiency disorders and the correlation with clinical and immunological parameters. J Clin Immunol. 2014;34(6):642-54. https://doi.org/10.1007/s10875-014-0068-6
16. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol. 2007;27(3):308-16. https://doi.org/10.1007/s10875-007-9075-1
17. Baumann U, Routes JM, Soler-Palacin P, Jolles S. The lung in primary immunodeficiencies: New concepts in infection and inflammation. Front Immunol. 2018;9:1837. https://doi.org/10.3389/fimmu.2018.01837
18. Gupta S, Pattanaik D, Krishnaswamy G. Common variable immune deficiency and associated complications. Chest. 2019;156(3):579-93. https://doi.org/10.1016/j.chest.2019.05.009
19. Grenier PA, Brun AL, Longchampt E, Lipski M, Mellot F, Catherinot E. Primary immunodeficiency diseases of adults: A review of pulmonary complication imaging findings. Eur Radiol. 2024;34(6):4142-54. https://doi.org/10.1007/s00330-023-10334-7
20. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol. 2004;114(2):415-21. https://doi.org/10.1016/j.jaci.2004.05.057
21. Costa-Carvalho BT, Wandalsen GF, Pulici G, Aranda CS, Sole D. Pulmonary complications in patients with antibody deficiency. Allergol Immunopathol (Madr). 2011;39(3):128-32. https://doi.org/10.1016/j.aller.2010.12.003
22. Movahedi M, Jamee M, Ghaffaripour H, Noori F, Ghaini M, Eskandarzadeh S, et al. Pulmonary manifestations in a cohort of patients with inborn errors of immunity: An 8-year follow-up study. Allergol Immunopathol (Madr). 2022;50(1):80-4. https://doi.org/10.15586/aei.v50i1.388
23. Bierry G, Boileau J, Barnig C, Gasser B, Korganow AS, Buy X, et al. Thoracic manifestations of primary humoral immunodeficiency: A comprehensive review. Radiographics. 2009;29(7):1909-20.
24. Barbosa M, Chalmers JD. Bronchiectasis. Presse Med. 2023;52(3):104174. https://doi.org/10.1016/j.lpm.2023.104174
25. Goussault H, Salvator H, Catherinot E, Chabi ML, Tcherakian C, Chabrol A, et al. Primary immunodeficiency-related bronchiectasis in adults: Comparison with bronchiectasis of other etiologies in a French reference center. Respir Res. 2019;20(1):275. https://doi.org/10.1186/s12931-019-1242-4
26. van de Ven AA, de Jong PA, Hoytema van Konijnenburg DP, Kessels OA, Boes M, Sanders EA, et al. Airway and interstitial lung disease are distinct entities in paediatric common variable immunodeficiency. Clin Exp Immunol. 2011;165(2):235-42. https://doi.org/10.1111/j.1365-2249.2011.04425.x
27. van de Ven AA, van Montfrans JM, Terheggen-Lagro SW, Beek FJ, Hoytema van Konijnenburg DP, Kessels OA, et al. A CT scan score for the assessment of lung disease in children with common variable immunodeficiency disorders. Chest. 2010;138(2):371-9. https://doi.org/10.1378/chest.09-2398
28. Buckley RH. Pulmonary complications of primary immunodeficiencies. Paediatr Respir Rev. 2004;5(Suppl A):S225-33. https://doi.org/10.1016/S1526-0542(04)90043-7
29. Baumann U, Gocke K, Gewecke B, Freihorst J, von Specht BU. Assessment of pulmonary antibodies with induced sputum and bronchoalveolar lavage induced by nasal vaccination against Pseudomonas aeruginosa: A clinical phase I/II study. Respir Res. 2007;8(1):57. https://doi.org/10.1186/1465-9921-8-57
30. Cerutti A, Chen K, Chorny A. Immunoglobulin responses at the mucosal interface. Annu Rev Immunol. 2011;29:273-93. https://doi.org/10.1146/annurev-immunol-031210-101317
31. Twigg HL, 3rd. Humoral immune defense (antibodies): Recent advances. Proc Am Thorac Soc. 2005;2(5):417-21. https://doi.org/10.1513/pats.200508-089JS
32. Quinti I, Soresina A, Guerra A, Rondelli R, Spadaro G, Agostini C, et al. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: Results from a multicenter prospective cohort study. J Clin Immunol. 2011;31(3):315-22. https://doi.org/10.1007/s10875-011-9511-0
33. Park JE, Beal I, Dilworth JP, Tormey V, Haddock J. The HRCT appearances of granulomatous pulmonary disease in common variable immune deficiency. Eur J Radiol. 2005;54(3):359-64. https://doi.org/10.1016/j.ejrad.2004.09.005
34. Mechanic LJ, Dikman S, Cunningham-Rundles C. Granulomatous disease in common variable immunodeficiency. Ann Intern Med. 1997;127(8 Pt 1):613-7. https://doi.org/10.7326/0003-4819-127-8_Part_1-199710150-00005
35. Touw CM, van de Ven AA, de Jong PA, Terheggen-Lagro S, Beek E, Sanders EA, et al. Detection of pulmonary complications in common variable immunodeficiency. Pediatr Allergy Immunol. 2010;21(5):793-805. https://doi.org/10.1111/j.1399-3038.2009.00963.x
36. Landau LI, Phelan PD. The spectrum of cystic fibrosis: A study of pulmonary mechanics in 46 patients. Am Rev Respir Dis. 1973;108(3):593-602.
37. Chen Y, Stirling RG, Paul E, Hore-Lacy F, Thompson BR, Douglass JA. Longitudinal decline in lung function in patients with primary immunoglobulin deficiencies. J Allergy Clin Immunol. 2011;127(6):1414-7. https://doi.org/10.1016/j.jaci.2011.03.041
38. Rich AL, Le Jeune IR, McDermott L, Kinnear WJ. Serial lung function tests in primary immune deficiency. Clin Exp Immunol. 2008;151(1):110-3. https://doi.org/10.1111/j.1365-2249.2007.03550.x
39. Alachkar H, Taubenheim N, Haeney MR, Durandy A, Arkwright PD. Memory switched B cell percentage and not serum immunoglobulin concentration is associated with clinical complications in children and adults with specific antibody deficiency and common variable immunodeficiency. Clin Immunol. 2006;120(3):310-8. https://doi.org/10.1016/j.clim.2006.05.003
40. Detkova D, de Gracia J, Lopes-da-Silva S, Vendrell M, Alvarez A, Guarner L, et al. Common variable immunodeficiency: Association between memory B cells and lung

diseases. Chest. 2007;131(6):1883–9. https://doi.org/10.1378/chest.06-2994

41. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119(7):1650–7. https://doi.org/10.1182/blood-2011-09-377945
42. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: Division into distinct clinical phenotypes. Blood. 2008;112(2):277–86. https://doi.org/10.1182/blood-2007-11-124545
43. The United States Immunodeficiency Network (USIDNET) webpage [Available from: https://usidnet.org/registry-data/stats-registry-enrollment/.
44. ESID Registry Network Reporting Tool public webpage Available from: https://cci-reporting.uniklinik-freiburg.de/#/.
45. Aghamohammadi A, Rezaei N, Yazdani R, Delavari S, Kutukculer N, Topyildiz E, et al. Consensus Middle East and North Africa registry on inborn errors of immunity. J Clin Immunol. 2021;41(6):1339–51. https://doi.org/10.1007/s10875-021-01053-z