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## Retrospective Study

## High-resolution computed tomography findings in humoral primary immunodeficiencies and correlation with pulmonary function tests

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## Abstract

## AIM

To compare high-resolution computed tomography (HRCT) findings between humoral primary immunodeficiencies (hPIDs) subtypes; to correlate these findings to pulmonary function tests (PFTs).

## METHODS

We retrospectively identified 52 consecutive adult patients with hPIDs who underwent 64-row HRCT and PFTs at the time of diagnosis. On a per-patient basis, an experienced radiologist recorded airway abnormalities (bronchiectasis, airway wall thickening, mucus plugging, tree-in-bud, and air-trapping) and parenchymal-interstitial abnormalities (consolidations, ground-glass opacities, linear and/or irregular opacities, nodules, and bullae/cysts) found on HRCT. The chi-square test was performed to compare the prevalence of each abnormality among patients with different subtypes of hPIDs. Overall logistic regression analysis was performed to assess whether HRCT findings predicted obstructive and/or restrictive PFTs results (absent-to-mild *vs* moderate-to-severe).

## RESULTS

Thirty-eight of the 52 patients with hPIDs showed common variable immunodeficiency disorders (CVID), while the remaining 14 had CVID-like conditions (*i.e.*, 11 had isolated IgG subclass deficiencies and 3 had selective IgA deficiencies). The prevalence of most HRCT abnormalities was not significantly different between CVID and CVID-like patients ( $P > 0.05$ ), except for linear and/or irregular opacities (prevalence of 31.6% in the CVID group and 0 in the CVID-like group;  $P = 0.0427$ ). Airway wall thickening was the most frequent HRCT abnormality found in both CVID and CVID-like patients (71% of cases in both groups). The presence of tree-in-bud abnormalities was an independent predictor of moderate-to-severe obstructive defects at PFTs (Odds Ratio, OR, of

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18.75,  $P < 0.05$ ), while the presence of linear and/or irregular opacities was an independent predictor of restrictive defects at PFTs (OR = 13.00;  $P < 0.05$ ).

## CONCLUSION

CVID and CVID-like patients showed similar HRCT findings. Tree-in-bud and linear and/or irregular opacities predicted higher risks of, respectively, obstructive and restrictive defects at PFTs.

**Key words:** Bronchiectasis; Multidetector computed tomography; Common variable immunodeficiency; Immunologic deficiency syndromes; Respiratory function tests

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**Core tip:** Humoral primary immunodeficiencies (hPIDs) are a group of conditions characterized by impaired antibody production and presenting with recurrent respiratory infections, autoimmune diseases, and malignancy. Chest high-resolution computed tomography (HRCT) is the imaging technique of choice for detecting, characterizing, and quantifying lung complications in these patients. The aims of this study were to compare HRCT findings in 52 patients with hPIDs subtypes (common variable immunodeficiency disorders - CVID vs CVID-like), and evaluate whether these findings may predict pulmonary function tests results. CVID vs CVID-like patients showed comparable HRCT findings. The presence of tree-in-bud and linear and/or irregular opacities were independent predictors of, respectively, significant obstructive and restrictive defects.

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## INTRODUCTION

Humoral primary immunodeficiencies (hPIDs), also known as primary predominantly antibody deficiencies, constitute the most common subgroup of primary immunodeficiency disorders (about 50% of diagnoses)<sup>[1]</sup>. hPIDs encompass a spectrum of conditions characterized by impaired antibody production, manifesting with recurrent respiratory tract infections, increased susceptibility to autoimmune diseases, and malignancy<sup>[1,2]</sup>. Common variable immunodeficiency disorders (CVID) are the most clinically significant group of hPIDs (with a prevalence of about 1:25000-1:50000 subjects). These disorders show distinct clinical and laboratory phenotypes associated with low levels of IgG and IgA and/or IgM<sup>[3,4]</sup>. CVID onset is during adult life in 70% of the cases, generally occurring between 20 and 40 years of age<sup>[5,6]</sup>. Other hPIDs are often referred as "CVID-like" conditions: these conditions are in most cases asymptomatic and include selective IgA deficiency (the most frequent hPID, with a prevalence of 1/600 in white people) and isolated IgG subclass deficiency<sup>[2,7,8]</sup>.

Overall, thoracic complications develop in 60% of patients with hPIDs, representing the leading cause of morbidity and mortality. Chest high-resolution computed tomography (HRCT) is the imaging technique of choice for detecting, characterizing, and quantifying lung complications, as well as for evaluating the response to therapy<sup>[1,9,10]</sup>. It is generally accepted that the initial evaluation of newly diagnosed patients should include HRCT and pulmonary function tests (PFTs). Early identification of respiratory complications provides a baseline assessment of lung involvement, allows prompt treatment to reduce the number of pulmonary infections, and impacts on quality of life and mortality, the latter being influenced by both structural and functional pulmonary impairment<sup>[5,11,12]</sup>.

Several studies have reported HRCT findings in hPIDs; these findings include non-infective airway disorders (*i.e.*, bronchiectasis, airway wall thickening, and air trapping), pulmonary infections, diffuse lung parenchymal diseases [*e.g.*, Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD), and organising pneumonia], and thoracic neoplasms (*e.g.*, lymphoma)<sup>[10,13-16]</sup>. However, most papers



refer only to CVID patients, and report that HRCT abnormalities are present in more than 90% of those patients<sup>[9,17]</sup>. While some Authors reported that the severity of HRCT abnormalities was not significantly different between CVID and CVID-like paediatric patients<sup>[18,19]</sup>, to the best of our knowledge no studies have addressed this issue in adult patients. Demonstrating a difference between CVID and CVID-like patients may influence the time intervals between HRCT examinations during follow-up in these 2 subgroups of hPIDs. In addition to this, previous studies assessing a correlation between HRCT findings and PFTs results demonstrated contradictory results<sup>[9,17,18,20]</sup>.

The purpose of this study was twofold: (1) to compare HRCT pulmonary findings in adult patients among different subgroups of hPIDs (*i.e.*, CVID and CVID-like); and (2) to assess whether HRCT findings predict PFTs results.

## MATERIALS AND METHODS

### *Study population and PFTs*

Our referring Ethical Committee approved this study. The need for informed consent was waived due to the retrospective design of the study. By performing a computerized search, we identified 56 adult patients who received a definite diagnosis of hPIDs, in accordance with the European Society for Immunodeficiencies criteria<sup>[21]</sup>, in our tertiary referral centre and between 2012 and 2016. Diagnosis was performed after a history of previously undefined respiratory disease ranging from 1 to 5 years in duration. All patients underwent HRCT and PFTs within one month from diagnosis as a part of the diagnostic workflow performed at our institute. Accordingly, hereinafter we are going to refer to the HRCT performed at the time of diagnosis as baseline HRCT. Four patients were excluded from the study due to infectious respiratory disease at the time of HRCT (clinically unstable disease) or unavailability of the PFTs results. Therefore, the final population included 52 patients and had the following distribution of disease subtypes: 38 CVID, 11 isolated IgG subclass deficiency, and 3 selective IgA deficiency cases.

Lung function was evaluated according to the criteria of the European Respiratory Society/American Thoracic Society task force<sup>[22]</sup>. The following parameters were measured with a spirometer (Vmax 29c; Sensor Medics, Yorba Linda, CA, United States): Forced expiratory volume in one second (FEV<sub>1</sub>), forced vital capacity (FVC), vital capacity (VC), peak expiratory flow (PEF), and total lung capacity (TLC). Obstructive ventilatory defects were diagnosed when the reduced FEV<sub>1</sub>/VC ratio was below the 5<sup>th</sup> percentile of the predicted value; restrictive ventilatory disorders were diagnosed when a reduction in TLC below the 5<sup>th</sup> percentile of the predicted value was detected in the presence of a normal FEV<sub>1</sub>/VC ratio. The severity of ventilatory defects was assessed using a six-point scale (absent, mild, moderate, moderately severe, severe, and very severe)<sup>[23]</sup>. For the purposes of analysis, patients with obstructive or restrictive defects were classified in two groups: (1) patients with absent-to-mild defects (*i.e.*,  $\geq 70\%$  of predicted values); and (2) patients with moderate-to-severe defects (*i.e.*,  $< 70\%$  of predicted values).

### *HRCT examinations*

HRCT examinations were performed with a 64-row MDCT scanner (Discovery HD 750, GE Healthcare, Milwaukee, WI, United States), with the patient in the supine position. The whole thorax was scanned volumetrically at suspended full inspiration using the following acquisition parameters: tube potential, 120 kV; tube current modulation range, 150-400 mA (based on a Noise Index set at 18.4); rotation time, 0.8 s; detector configuration, 64 mm  $\times$  0.625 mm; reconstructed section thickness and reconstructed interval, 1.25 mm; field of view according to patient size. In 32/52 patients an additional end-expiratory volumetric scan with the same parameters was also acquired.

Images were reconstructed using a high-spatial-frequency algorithm, and displayed with lung parenchyma (level, -500 HU; width, 1500 HU) and mediastinum windowing (level, 50 HU; width, 350 HU).

### *Image analysis*

A radiologist with 8 years of experience in pulmonary imaging, blinded to patient history and lung function, reviewed the HRCT examinations on a picture archiving and communication system workstation (SuiteSensa Ebit srl, Esaote Group Company, Genoa, Italy). Post-processing techniques, including Multiplanar Reconstruction (MPR), Maximum Intensity Projection (MIP) and Minimum Intensity Projection (MinIP), were available to complement the analysis of thin source images.

For each patient, the reader recorded two classes of abnormalities: airway abnormalities (*i.e.*, airway wall thickening, tree-in-bud, bronchiectasis, mucus plugging, and air trapping), and parenchymal-interstitial abnormalities (*i.e.*, linear and/or irregular opacities, nodules, consolidations, ground-glass opacities, and bullae/cysts). Radiological features were evaluated according to the Fleischner Society glossary<sup>[24]</sup>. In particular, “linear and/or irregular opacities” describe any linear opacity of irregular thickness that does not respect the lung architecture<sup>[9]</sup> and has been reported as being a key feature of lung disease in CVID patients.

Any individual abnormality was scored using a double three-point scale (with a total score ranging from 2 to 6), for coding two aspects simultaneously: (1) extension, with 1 = involvement of a single pulmonary lobe, 2 = two-to-three lobes involved, 3 = more than three lobes involved; and (2) conspicuity in the most involved lobe, with 1 = mild, 2 = moderate, and 3 = severe. As to include in the analysis only findings that are reasonably related to hPIDs, the minimum required total score for an abnormality was 3.

### Statistical analysis

We calculated the per-patient prevalence of each of the aforementioned HRCT abnormalities in the overall population and in different subgroups of hPIDs patients, *i.e.*, the CVID group *vs* CVID-like group (the latter including both isolated IgG subclass deficiencies and selective IgA deficiencies). Main clinical features (age, duration of symptoms before definite diagnosis, and ventilatory defects) and prevalence of HRCT abnormalities were compared between the two groups using, respectively, the *u*-Mann-Whitney and  $\chi^2$  tests. A logistic regression analysis (stepwise approach) was performed to assess whether the HRCT findings could predict a significant obstructive or restrictive defect at PFTs on the overall study population. As variables we used each of the aforementioned airway abnormalities and parenchymal-interstitial abnormalities. Obstructive and restrictive defects were defined as relevant only if they were of moderate-to-severe nature, and not if they were absent-to-mild. Air trapping was excluded from the model since HRCT additional expiratory scan was not available for all patients. Analysis was performed with a commercially available software (MedCalc version 12.5.0.0, MariaKerke, Belgium). The  $\alpha$  level was set to 0.05.

## RESULTS

### Study population and PFTs results

Of the 52 hPIDs patients 37 were females and 15 were males, with a mean age of  $53.9 \pm 12.7$  years. Thirty-eight of the 52 patients (73%) were included in the CVID group, and 14/52 patients (27%) were in the CVID-like group. No significant differences between the two groups were found in terms of age (mean  $54.9 \pm 12.9$  years in the CVID group *vs*  $51 \pm 11.9$  years in the CVID-like group) and average duration of symptoms before definite diagnosis of hPIDs (2 years, range 1-3, in the CVID group *vs* 4 years, range 1-5, in the CVID-like group,  $P > 0.05$ ). None of the patients underwent HRCT before hPIDs diagnosis. Standard CTs were available for 15 of the 52 patients (one examination each) and had been performed 2-4 years before the HRCT at the time of hPIDs diagnosis.

The results of the PFTs show that almost half of the patients (25/52, 48.1%) had ventilatory defects (Table 1). Three patients in the CVID group had concomitant moderate-to-severe obstructive defects and restrictive defects. None of the patients in the CVID-like group showed restrictive defects. No statistically significant differences were found between the two subgroups of hPIDs in terms of prevalence of obstructive (CVID: 44.7% *vs* CVID-like: 42.9%,  $P = 0.8474$ ) and restrictive defects (CVID: 13.1% *vs* CVID-like: 0%,  $P = 0.2052$ ).

### Distribution of HRCT abnormalities in the study groups

We recorded a high prevalence of HRCT findings, with one or more abnormalities detected in 47/52 hPIDs patients (90.4%). The prevalence of specific airway abnormalities was not significantly different between the CVID and CVID-like groups ( $P > 0.05$ , Table 2). Airway wall thickening was the most commonly found abnormality and showed a comparable prevalence in both groups (71.0% in the CVID group and 71.4% in the CVID-like group, Figure 1).

Regarding HRCT parenchymal-interstitial abnormalities, linear and/or irregular opacities were present in 31.6% of the patients in the CVID group and in none of those in the CVID-like group, with borderline significance ( $P = 0.0427$ , Table 2). Nodules were the most frequent finding in both groups, with a prevalence of 50.0% (Figure 2).

**Table 1** Pulmonary function tests results *n* (%)

	Obstructive defect				Restrictive defect			
	Absent	Mild	Relevant <sup>†</sup>	Any	Absent	Mild	Relevant <sup>†</sup>	Any
CVID ( <i>n</i> = 38)	21 (55.3)	10 (26.3)	7 (18.4)	17 (44.7)	33 (86.9)	1 (2.6)	4 (10.5)	5 (13.1)
CVID-like ( <i>n</i> = 14)	8 (57.1)	2 (14.3)	4 (28.6)	6 (42.9)	14 (100)	0 (0)	0 (0)	0 (0)
All patients ( <i>n</i> = 52)	29 (55.8)	12 (23.1)	11 (21.2)	23 (44.2)	47 (90.4)	1 (1.9)	4 (7.7)	5 (9.6)

Data are presented as number of patients with percentages in parentheses.

<sup>†</sup>Moderate-to-severe defect. CVID: Common variable immunodeficiency disorder; CVID-like: Including isolated IgG subclass deficiency and selective IgA deficiency.

### Correlation between HRCT abnormalities and PFTs

The distributions of HRCT-detected airway and parenchymal-interstitial abnormalities according to severity of ventilatory defects assessed at PFTs are reported in Tables 3 and 4.

Regarding HRCT-detected airway abnormalities, both mucus plugging ( $P = 0.0112$ , Figure 3) and tree-in-bud ( $P = 0.0014$ , Figure 4) were found to be significantly associated with a relevant obstructive defect assessed at PFTs. However, on multivariate analysis, tree-in-bud was the only independent predictor ( $P = 0.0027$ ) of relevant obstructive defect, with an odds ratio (OR) of 18.75 (95%CI: 2.76-127.52).

Additionally, regarding HRCT-detected parenchymal-interstitial abnormalities, the presence of linear and/or irregular opacities (Figure 5) was the only predictor of relevant restrictive defect both at univariate ( $P = 0.0029$ ) and multivariate analysis ( $P = 0.0344$ ; OR, 13.00; 95%CI: 1.21-139.97).

## DISCUSSION

Pulmonary abnormalities in hPIDs adult patients were common in our series: Only 9.6% of our patients had negative HRCTs at the time of diagnosis, a finding in agreement with the literature (range 4%-17%)<sup>[9,17,25]</sup>. The prevalence of most of airways and parenchymal-interstitial findings was not significantly different between the CVID and the CVID-like groups. Similarly, PFTs results were comparable between the two subtypes of hPIDs, showing a larger prevalence of obstructive defects (45% in the CVID group and 43% in the CVID-like group) over restrictive defects (13% in the CVID group and 0 in the CVID-like group). These findings are in agreement with the previously reported prevalences in CVID patients (9%-53% for obstructive defects and 5%-34% for restrictive defects)<sup>[9,17,26,27]</sup>. Conversely, to the best of our knowledge, this is the first study reporting prevalences in adult CVID-like patients. Overall, our findings support the hypothesis that neither imaging nor PFTs can reliably differentiate between the two groups of CVID and CVID-like patients. One might argue that the relevance of this result is impaired by the relatively small population included in the present study. However, our series reflects the rarity of both conditions, and is one of the largest published reports on HRCT as far as we know.

Of note, linear and/or irregular opacities were more frequently found in CVID patients (32%) than in CVID-like patients (0), although statistical significance was borderline ( $P = 0.0427$ ). Gregersen *et al*<sup>[9]</sup> highlighted the importance of this abnormality in CVID adult patients, both because of its frequency (about 52% of cases) and its close association with impaired gas diffusion. In line with the relevant literature<sup>[11,28]</sup>, we found that only one HRCT abnormality, linear and/or irregular opacities, was a predictor of significant restrictive defects. This result emphasizes the importance of prompt identification of this abnormality at baseline evaluation. Overall, our results support the assumption that CVID-like patients are clinically and immunologically comparable to CVID patients<sup>[18,29]</sup>, although the latter show more frequently radiological abnormalities associated to interstitial disease (*i.e.*, linear and/or irregular opacities).

It is likely that the prevalence of different HRCT findings might reflect the effects of the specific disease on the lungs in CVID and CVID-like patients. The most frequent findings in our cohort were bronchiectasis (69.2%) and airway wall thickening (71.2%, Figure 2), and are in line with those previously reported in adult patients (range 40%-70% for bronchiectasis and 68%-75% for airway wall thickening)<sup>[9,10,17,25,26]</sup>. Such a high prevalence can be explained by the cumulative effect of respiratory tract infections<sup>[17,30,31]</sup>. Other common findings in our study were nodules (found in 50% of





**Figure 1 Airway wall thickening.** A 65-year-old male patient with common variable immunodeficiency disorder. High-resolution computed tomography shows diffuse airway wall thickening in the right middle and lower lobes (straight arrows); centrilobular and tree-in-bud nodules in the right lung are also detected (curved arrow).

patients *vs* 29%-55% reported in literature)<sup>[9,17,25]</sup> and mucus plugging (in 44.2% of patients). We did not differentiate among various types of nodules, since their characteristics reflect a wide spectrum of conditions (including infectious diseases, previous infections or lymphoproliferative and/or granulomatous conditions) that cannot be histologically confirmed in most patients<sup>[14,25]</sup>. We believe that the high prevalence of nodules should be considered as an epiphenomenon of other coexisting pulmonary abnormalities rather than a definite hallmark of CVID or CVID-like hPIDs. However, the finding of mucus plugging mirrors more specifically the inflammation of large airways<sup>[9]</sup>, with a reported prevalence in hPIDs ranging between 25% and 35%<sup>[9,17]</sup>. Last, air trapping was frequent (50%) in the subgroup of patients for whom an expiratory scan was available. Although incomplete, the prevalence we describe is in the range of those previously reported in CVID patients (45%-63%)<sup>[9,17,25]</sup>.

Concerning the less frequent HRCT findings, we detected tree-in-bud abnormalities in 19% of the patients, similarly to what reported by Tanaka *et al*<sup>[25]</sup> (20%) in a study assessing a CVID population. This sign reflects a spectrum of both endobronchiolar and peribronchiolar disorders<sup>[24]</sup>. The main causes of tree-in-bud findings in the general population are reported to be acute or chronic infections mainly from nontuberculous mycobacteria and bacteria (*e.g.*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*)<sup>[32,33]</sup>. Previous studies demonstrated the presence of potentially pathogenic bacteria (and viruses) in the lungs of patients with clinically stable hPIDs<sup>[34]</sup>. In our series, most of the tree-in-bud cases were of infectious origin, albeit asymptomatic, at the time of HRCT. The majority of these patients (80%) showed coexisting bronchiectasis, a major predisposing factor for infections<sup>[32]</sup>. Follicular bronchiolitis (FB) is another cause of tree-in-bud sign detected at HRCT<sup>[35,36]</sup>. FB is a reactive pulmonary lymphoid disorder reported in CVID patients, is presumably related to recurrent pneumonia, and is characterized by the development of lymphoid follicles and germinal centres with peribronchial/peribronchiolar distribution<sup>[37]</sup>. In our population, 2 of the 10 cases with tree-in-bud abnormalities were CVID patients who developed GLILD, a condition in which FB is a typical finding<sup>[38,39]</sup>. In addition, consolidation was found in 27% of our study population (*vs* 17%-64% reported in the literature) and ground-glass opacities in 25% of the patients (*vs* 12%-34% in the literature)<sup>[9,10,17,25]</sup>. Although the nature of most of these abnormalities remained undetermined, it is likely that they represent the effects of subclinical or previous infections, thus not requiring specific radiological work-up in the absence of clinical suspicion of lymphoma or cancer.

In patients with CVID, HRCT was proven to detect silent progression earlier than PFTs, because of its capability to assess even subtle structural abnormalities<sup>[34,40]</sup>. Not surprisingly, alterations detected by PFTs are less frequent than those detected by HRCT<sup>[40]</sup>, an observation confirmed in our study that also includes CVID-like patients (prevalence was 48.1% by PFTs *vs* 90.4% by HRCT). This observation raises some questions on how to follow up the patient after baseline evaluation. Current recommendations suggest PFTs intervals of 6-12 mo, and HRCT intervals ranging from 1 to 5 years<sup>[11,17]</sup>. By multivariate analysis, we found that detection of tree-in-bud abnormalities predicts obstructive defects (OR 18.75), and detection of linear and/or irregular opacities predicts restrictive defects (OR 13.00). By contrast, none of the other, more frequent findings were independent predictors of obstructive or restrictive defects. This observation supports previous data on CVID showing a moderate correlation between PFTs and HRCT results, as well as the idea that these

**Table 2** Prevalence of high-resolution computed tomography-detected abnormalities in the two humoral primary immunodeficiencies subtypes (CVID and CVID-like), and comparison between the two groups *n* (%)

Abnormality	All patients <i>n</i> = 52	CVID <i>n</i> = 38	CVID-like <i>n</i> = 14	<i>P</i> -value (CVID vs CVID-like)
Airway abnormalities				
Bronchiectasis	36 (69.2)	27 (71)	9 (64.3)	0.8964
Airway wall thickening	37 (71.2)	27 (71)	10 (71.4)	0.7501
Tree-in-bud	10 (19.2)	6 (15.8)	4 (28.6)	0.8464
Mucus plugging	23 (44.2)	16 (42.1)	7 (50)	0.8888
Air trapping <sup>1</sup>	16 (50)	12 (52.2)	4 (44.4)	0.8557
Parenchymal-interstitial abnormalities				
Consolidation	14 (26.9)	11 (28.9)	3 (21.4)	0.8495
Ground-glass opacity	13 (25)	12 (31.6)	1 (7.1)	0.1487
Nodules	26 (50)	19 (50)	7 (50)	1
Linear and/or irregular opacities	12 (23.1)	12 (31.6)	0 (0) <sup>a</sup>	0.0427
Bullae/cysts	5 (9.6)	5 (13.2)	0 (0)	0.3695

<sup>a</sup>*P* < 0.05.<sup>1</sup>Values are calculated on the 32 patients (23 CVID + 9 CVID-like) for whom additional expiratory scan was acquired. Chi-square test: CVID vs CVID-like patients; CVID: Common variable immunodeficiency disorders; CVID-like: Including isolated IgG subclass deficiency and selective IgA deficiency.

two examinations assess different aspects of the disease<sup>[40]</sup>. Of note, Maarschalk-Ellebrouck *et al*<sup>[17]</sup> found a poor correlation between detection of tree-in-bud abnormalities and PFTs. However, these authors evaluated tree-in-bud abnormalities in a combined score with mucus plugging, which impairs a direct comparison with our findings. Our results suggest that morphological assessment with HCRT might be postponed as much as possible to maximize cost-effectiveness and reduce radiation exposure. A possible exception to this might be the case of patients showing tree-in-bud or linear and/or irregular opacities: Scheduling HRCTs at shorter intervals for these patients might provide a reliable morphological counterpart of pulmonary function. Our hypothesis is extrapolated from the observation of baseline examinations in our population; therefore, further studies with a more specific purpose and a prospective design should be performed to confirm this statement.

We acknowledge that our study has some limitations. First, an HRCT supplementary expiratory scan was not available in 38% of the patients because of the retrospective nature of the study. Hence, we were not able to include air trapping as a variable in the logistic regression analysis to predict PFTs results. Previous studies found a significant correlation between air trapping and airway obstruction both in children and in adult patients with CVID<sup>[9,20]</sup>. While we acknowledge that we should have included air trapping to study both CVID and CVID-like groups, we believe that most of the relevant HRCT findings support our conclusions. Second, we did not consider the extent and/or distribution of individual HRCT findings in the prediction analysis of PFTs results. The use of dedicated HRCT scoring systems, which were originally developed for CVID patients and/or for paediatric populations only, could help studying this issue also in adult patients with CVID and CVID-like conditions<sup>[9,17,18,20]</sup>. Third, we were not able to assess the radiologic evolution of the disease over time because of the lack of previous HRCTs, which could have been used for a comparison with the baseline HRCT. However, our study actually reflects the clinical reality, in which a delay between the onset of respiratory infections-related symptoms and the definite diagnosis of hPIDs is common (median of 8 years in adults aged over 30 years old, according to The United Kingdom Primary Immunodeficiency Registry<sup>[41]</sup>). In this scenario, the first HRCT is frequently performed only at the time of diagnosis.

In conclusion, we found no significant difference in the prevalence of most of HRCT findings or PFTs abnormalities between CVID and CVID-like conditions. Our results support the hypothesis that these two conditions are comparable hPIDs subtypes and candidate to similar management. The detection of tree-in-bud abnormalities was found to be an independent predictor of obstructive defects assessed at PFTs, while the detection of linear and/or irregular opacities was an independent predictor of restrictive defects assessed at PFTs. Our observations suggest that patients showing these findings might benefit from more frequent HRCTs during follow-up as to evaluate the morphological abnormalities associated with their function impairment.

**Table 3** Distribution of high-resolution computed tomography-detected airway abnormalities according to the severity of obstructive defect at pulmonary function tests in the overall study population, and results of logistic regression analysis for prediction of moderate-to-severe obstructive defects at PFTs *n* (%)

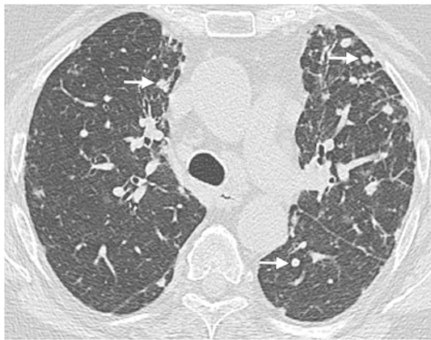
Abnormality	Absent	Mild	Moderate	Severe	Univariate analysis	Multivariate analysis
	<i>n</i> = 29	<i>n</i> = 12	<i>n</i> = 9	<i>n</i> = 2	<i>P</i> -value	<i>P</i> -value (odds ratio)
Bronchiectasis	19 (66.5)	9 (75)	7 (77.8)	1 (50)	NS	NS
Airway wall thickening	20 (69)	9 (75)	6 (66.7)	2 (100)	NS	NS
Tree-in-bud	2 (6.9)	2 (16.7)	5 (55.6)	1 (50)	0.0014	0.0027 (18.75)
Mucus plugging	8 (27.6)	8 (66.7)	5 (55.6)	2 (100)	0.0112	NS

NS: Non-significant.

**Table 4** Distribution of high-resolution computed tomography-detected parenchymal-interstitial abnormalities according to the severity of the restrictive defects at pulmonary function tests in the overall study population, and results of logistic regression analysis for prediction of moderate-to-severe restrictive defects at PFTs *n* (%)

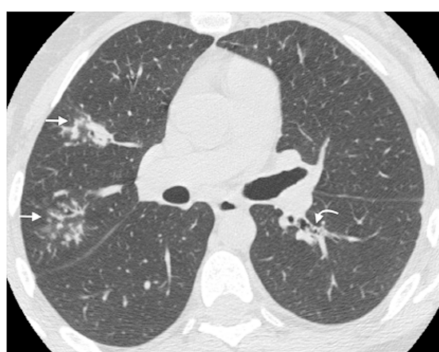
Abnormality	Absent	Mild	Moderate	Severe	Univariate analysis	Multivariate analysis
	<i>n</i> = 47	<i>n</i> = 1	<i>n</i> = 4	<i>n</i> = 0	<i>P</i> -value	<i>P</i> -value (odds ratio)
Consolidation	11 (23.4)	1 (100)	2 (50)	0 (0)	NS	NS
Ground-glass opacity	10 (21.3)	1 (100)	2 (50)	0 (0)	NS	NS
Nodules	23 (48.9)	1 (100)	2 (50)	0 (0)	NS	NS
Linear and/or irregular opacities	8 (17)	1 (100)	3 (75)	0 (0)	0.0029	0.0344 (13.00)
Bullae/cysts	5 (10.6)	0 (0)	0 (0)	0 (0)	NS	NS

NS: Non-significant.

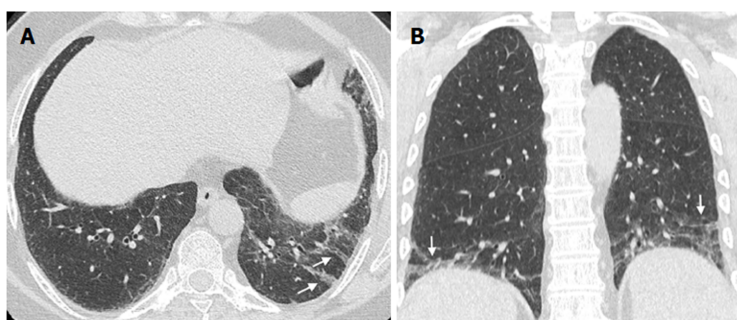
**Figure 2 Nodules.** A 64-year-old female patient with common variable immunodeficiency disorder. High-resolution computed tomography shows multiple, small nodules with peribronchial and perifissural location in the upper and lower lobes of both lungs (arrows). A diagnosis of granulomatous and lymphocytic interstitial lung disease was subsequently made.



**Figure 3 Mucus plugging.** A 65-year-old male patient with common variable immunodeficiency disorder. Para-coronal 2-mm minimum intensity projection high-resolution computed tomography image shows mild bronchiectasis with extensive mucus plugging in the left lower lobe (arrow).



**Figure 4 Tree-in-bud.** A 40-year-old female patient with isolated IgG2 subclass deficiency. High-resolution computed tomography shows centrilobular and tree-in-bud nodules in the right upper lobe (straight arrows); small mucus plugging in the left lower lobe is also detected (curved arrow).



**Figure 5 Linear and/or irregular opacities.** A 66-year-old female patient with common variable immunodeficiency disorder. A: High-resolution computed tomography shows patchy areas of ground-glass opacity, along with reticulation and linear and/or irregular opacities (arrows) in both lower lobes; B: Coronal reformatted image shows the peripheral and basal-predominant distribution of the findings (arrows).

## ARTICLE HIGHLIGHTS

### Research background

Common variable immunodeficiency disorders (CVID) are the most clinically significant group of humoral primary immunodeficiency diseases (hPIDs), manifesting with recurrent respiratory tract infections and increased susceptibility to autoimmune diseases and malignancy. Other hPIDs are often termed “CVID-like” conditions, and include selective IgA deficiency and isolated IgG subclass deficiency. The initial evaluation of patients newly diagnosed with hPIDs should include high-resolution computed tomography (HRCT) and pulmonary function tests (PFTs).

### Research motivation

To the best of our knowledge no previous studies assessed whether HRCT findings differ in terms of prevalence among the two subtypes of hPIDs in adult patients. Demonstrating a difference between CVID and CVID-like patients may influence the time intervals between HRCT examinations during follow-up in these 2 subgroups of hPIDs. Moreover, previous studies assessing a possible correlation between HRCT findings and PFTs results demonstrated contradictory results.

### Research objectives

The purpose of this study was twofold: (1) to compare HRCT pulmonary findings in adult patients with different subgroups of hPIDs (*i.e.*, CVID *vs* CVID-like); and (2) to assess whether HRCT findings predict PFTs results.

### Research methods

We included 52 adult patients (38 CVID and 14 CVID-like) who received a definite diagnosis of hPIDs and underwent HRCT and PFTs within one month from the time of diagnosis. One pulmonary radiologist, blinded to patient history and lung function: (1) reviewed the HRCT examinations; (2) recorded two classes of abnormalities, namely airway abnormalities and/or parenchymal-interstitial abnormalities; and (3) scored all abnormalities according to their extension and conspicuity. We calculated the per-patient prevalence of each HRCT abnormality in the overall population and in both subgroups of hPIDs patients, (CVID and CVID-like groups). We performed a logistic regression analysis to assess whether HRCT findings were predictive of a relevant obstructive or restrictive defect at PFTs on the overall study population.

### Research results

Of the 52 hPIDs patients, 37 were females and 15 were males, with a mean age of  $53.9 \pm 12.7$  years. We found a high prevalence of HRCT findings (90.4% patients had one or more abnormalities). The prevalence of each of the airway abnormalities considered was not significantly different between the CVID and CVID-like group. Regarding HRCT-detected parenchymal-interstitial abnormalities, the only relevant result was the finding of linear and/or irregular opacities, showing a prevalence of 31.6% in the CVID group and 0 in the CVID-like group, with borderline significance. The presence of tree-in-bud abnormalities was an independent predictor of obstructive defects at PFTs (Odds Ratio, OR, of 18.75,  $P < 0.05$ ), while the presence of linear and/or irregular opacities was an independent predictor of restrictive defects at PFTs (OR = 13.00;  $P < 0.05$ ).

### Research conclusions

No previous research compared the prevalence of HRCT findings in different subtypes of hPIDs adult patients. After dividing hPIDs patients in CVID *vs* CVID-like groups, we observed no significant difference in the prevalence of most of airways and parenchymal-interstitial findings between the two groups. This observation supports the hypothesis that these two groups represent comparable hPIDs subtypes, and are candidate to similar management. Tree-in-bud and linear and/or irregular opacities were found to be independent predictors of, respectively, obstructive and restrictive defects on PFTs.

### Research perspectives

Our results suggest that morphological assessment with HRCT might be delayed as much as possible to maximize cost-effectiveness and reduce radiation exposure. A possible exception to this might be the case of patients showing tree-in-bud or linear and/or irregular opacities: Scheduling HRCTs at shorter intervals for these patients might provide a reliable morphological counterpart of pulmonary function. Further prospective studies with a proper design are needed to confirm this hypothesis in the follow-up period.

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