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Lung function trajectories in Common Variable Immunodeficiencies: an observational retrospective multicenter study

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Ethics Statement

This study involving human participants was reviewed and approved by “Comitato Etico delle Province di Treviso e Belluno”. The patients/participants provided their written informed consent to participate in this study.

ABSTRACT

Background: Respiratory disease is a frequent cause of morbidity and mortality in Common Variable Immunodeficiencies (CVIDs), however lung function trajectories are poorly understood.

Objective: To determine lung physiology measurements in CVID, their temporal trajectory and association with clinical and immunological parameters.

Methods: Retrospective study from 5 Italian centres. CVIDs patients with longitudinal Pulmonary Function Tests (PFTs) measurements and available chest CT scan, were included**.** Applying the ERS/ATS 2021 standard, PFTs were expressed as percentile value (pct) within the normal distribution of healthy individuals, with the 5th pct identified the lower limit of normal (LLN). The association of lung function with clinical and immunological parameters was investigated.

Results: 185 CVIDs patients were included. 64% had at least one lung comorbidity (bronchiectasis 41% and Granulomatous Interstitial Lung Diseases 24%). At first spirometry, the median FEV1 was 3.07 L [IQR 2.40 - 3.80], placing at the 32nd pct [6th-61st], and the median FVC was 3.70 L [3.00 - 4.54], placing at the 29th pct [7th-49th]. 23% of patients had an FEV1 < LLN and 21% had an FVC < LLN. Switched-memory B cells <2% were associated with both FEV1<LLN (OR 7.58) and FVC<LLN (OR 3.55). In 112 patients with at least 5 years of PFT follow-up, we found no significant difference between measured and predicted annual decline of FEV1 (25.6 vs 20.7 mL/year) and FVC (15.6 vs 16.2 mL/year).

Conclusion: Our findings suggest that lung volumes of the majority of CVID patients placed in the lower third of normal distribution of healthy individuals. After diagnosis the rate of lung decline was not accelerated.

Keywords: Common Variable Immunodeficiencies; Pulmonary function tests; Global Lung Function Initiative (GLI); B cells subtype; Chronic Obstructive Pulmonary Disease (COPD); Bronchiectasis; Granulomatous Lymphocytic Interstitial Lung Disease (GLILD)

Clinical Implications

A comprehensive assessment of lung function, combined with the characterization of different immunological backgrounds, may help to identify specific disease phenotypes in CVIDs and drive a tailored therapeutic approach.

Capsule summary

Our findings suggest that the majority of CVIDs patients had baseline lung volumes placed in the lower third of the normal distribution of healthy population, but their overall rate of annual decline during immunoglobulin replacement therapy is not significantly higher than predicted.

Abbreviations

CVID: Common Variable Immunodeficiencies; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; GLILD: Granulomatous Lymphocytic Lung Disease; PFTs: Pulmonary function tests; DLCO: diffusing capacity for carbon monoxide; CT: Computed tomography scan; PID: Primary Immunodeficiencies; ESID: European Society for Immunodeficiencies; IgRT: Immunoglobulin Replacement Therapy; COPD: Chronic Obstructive Pulmonary Disease; IgTL: IgG-trough level; ILA: Interstitial Lung Abnormalities; GOLD: Global Initiative for Chronic Obstructive Lung Disease; GLI: Global Lung Function Initiative; ATS/ERS: American Thoracic Society and European Respiratory Society; pct: percentile value; FEV1: Forced Expiratory Value in one second; FVC: Forced Vital Capacity; TLC: Total Lung Capacity; IQR: Interquartile ranges; OR: Odds Ratio; CI: confidence intervals; Switched-memory B cells: SM B cells; Marginal zone B cells: Mz B cells%; ys: years;

INTRODUCTION

Common Variable Immunodeficiencies (CVIDs) are the most frequent symptomatic antibody deficiencies diagnosed in adulthood, affecting about 14 in 100.000 individuals [1].
These immunodeficiencies are characterised by hypogammaglobulinemia with a marked reduction of IgG, IgA and/or IgM serum levels and poor response to vaccinations [2,3].
The associated clinical manifestations are extremely variable and are due to both a lack of function and an aberrant and dysregulated hyper-function of the immune system. Thanks to the efficacy of immunoglobulin replacement therapy in preventing the recurrence of severe infections, nowadays non-infective complications are the major cause of death [4].
A common feature of these disorders is the impact on the respiratory system, with relevant morbidity and mortality [5,6].
The involvement of the respiratory system may be related on one side to a vicious circle involving recurrent infections, inflammation and tissue damage/remodelling with consequent development of bronchiectasis, and, on the other side, to immune-mediated interstitial lung diseases [7].
These comorbidities may lead to long-term impairment of lung architecture and function [8,9].
In particular, bronchiectasis has been identified as one of the comorbidities associated with the greatest disability burden and the Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) as one of the comorbidities associated with higher risk of mortality [10].
Pulmonary function tests (PFTs) including spirometry with measurement of diffusing capacity for carbon monoxide (DLCO), together with high-resolution chest Computed tomography scan (CT) are part of the initial work-up and of the follow-up schedule of CVIDs patients, with PFTs routinely repeated every year [8].
To date, there are no studies that have focused on assessing lung function impairment of CVIDs patients compared to the healthy population. Moreover, longitudinal analysis of lung function has been described only in small cohorts of CVIDs patients, with mixed results [11,12].
Recently, a paper published by Sperlich et al. highlighted the impact of bronchiectasis on lung function in a cohort of 110 CVIDs patients and underlined that CVIDs with bronchiectasis had worse lung function and a higher rate of lung function decline compared to those without bronchiectasis [13].
Considering the current younger age at diagnosis and the increasing life expectancy, a better understanding of the impact of CVIDs on lung function and its decline is needed to establish an early, personalised follow-up and refine therapeutic strategies.
In this retrospective observational study, we considered the pulmonary function of CVIDs patients in the context of the general population. We also investigated for clinical and immunological parameters associated with respiratory function impairment and the impact of different comorbidities on lung function and its decline.

METHODS

Study design

This observational retrospective multicenter study involved 5 Italian referral centres for Primary Immunodeficiencies (PID): Padua, Rome, Cagliari, Brescia and Turin. Patient inclusion criteria were CVIDs diagnosis according to European Society for Immunodeficiencies (ESID) criteria [3], age of

18 or older at the time of enrolment, availability of the reports of at least two Pulmonary Functions Tests (PFTs) performed with an interval of at least one year and one chest CT scan and signature of the informed consent. The study was approved by the Local Ethical Authority.

Data collection

For each patient, we collected the age at diagnosis, at disease onset (defined as beginning of symptoms ascribable to CVIDs) and at Immunoglobulin Replacement Therapy (IgRT) initiation.
We then collected the immunological parameters at diagnosis, including the value of IgG, IgA and IgM, vaccination response and the B cells subtype analysis according to Euroclass [14], history of smoke and professional exposure and the presence of the following lung comorbidities: bronchiectasis, Interstitial Lung Abnormalities (ILA) at CT scan, including those with a clinical-radiological picture consistent with GLILD, asthma, and Chronic Obstructive Pulmonary Disease (COPD), defined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [15]. Finally, we recorded the results of PFTs performed between 1995 and 2023, including the IgRT dosage, use of antibiotic prophylaxis and IgG-trough level (IgTL) for the first and last PFT.

Lung function test interpretation

We used the Global Lung Function Initiative (GLI) reference equations [16] of the American Thoracic Society and European Respiratory Society (ERS/ATS) to calculate the predicted value (for a healthy individual of the same age, sex, height and ethnicity) and the z score. From the z score we identified the corresponding percentile value (pct) in the normal distribution of healthy individuals of the same age, sex, height and ethnicity. The predicted value corresponds to the 50^{th} pct.
Following the ERS/ATS 2021 interpretations standard, we reported lung function parameters values as percentiles. The GLI reference range identifies the distribution of values that are expected in a healthy population and so the lower limit of normal (LLN) enables identification of a cut-off to define results that are outside the range of values typically observed in health. According to ERS/ATS standards a z score < -1.645 (5^{th} pct) was identified to be below the lower limit of normal (LLN). Of note, at 5^{th} pct there is a 5% chance that the results in a healthy individual would be at or below this level [17].

Estimation of annual decline in lung function parameters

Starting from individual measured values over the time of Forced Expiratory Value in one second (FEV1) and of Forced Vital Capacity (FVC) and the corresponding predicted values calculated with the GLI equations, we estimated the annual rates of decline lung volumes considering the first spirometry as baseline. To consider the lack of independence due to repeated measurements for each subject, linear mixed effects models were used to estimate annual rates of decline in FEV1 and FVC both for predicted and measured values. For this analysis we included only patients with at least 5 years of follow-up between the first and last available PFTs.

Statistical Analysis

The continuous variables were summarised using medians, interquartile ranges [IQR], and the categorical ones as percentages. Mann-Whitney U was used for the comparison of unpaired continuous data and Chi-squared test was used for categorical data. Binomial logistic regression

models were fitted to calculate odds ratios (OR) with 95% confidence intervals (CI) in univariate and multivariate analysis.

For patients with at least 5 years of follow up, linear mixed effects models were used to calculate annual decline in FEV1 and FVC (ml/year), both for predicted and measured values, considering the first spirometry as baseline. The models assumed random intercept and random slope to take into account between-subject heterogeneity and estimated the slope (annual decline) using all PFTs results recorded. This analysis was performed on the whole sample and for different subgroups of patients categorised by the presence of the main lung comorbidities and smoke exposure.

The model was also adjusted for height, sex, smoking, age at first PFT, GLILD and bronchiectasis, to estimate the impact of these covariates on the value of FEV1, FVC and their decline (see supplementary methods for further details).

The analyses were performed using R software version 4.3.2 and Jamovi software Version 2.3.28.0.

RESULTS

Patients

We enrolled 185 CVIDs patients, of which 96 (52%) were female. The median age at CVIDs diagnosis was 35 years (ys) [22-44 ys] and at disease onset was 21 ys [8-35 ys]. The median time between the disease onset and the beginning of IgRT was 8 ys [2-17 ys].
118 patients (64%) had a history of lung disease: 75 (41%) had bronchiectasis, of which 50 (27% of the total) without overlapping GLILD, 13 (7%) had asthma, 35 (19%) had received a diagnosis of COPD, of which 16 (9% of the total) without any known risk factors, and 63 (34%) had CT evidence of ILA, of which 45 (24% of the total) had a definite diagnosis of GLILD. 54 patients (29%) had multiple lung comorbidities.
56 (30%) patients had a history of smoking and 14 (8%) of professional exposure.
Demographic features are summarized in Supplementary Table 1

Lung function at first available spirometry

The median age at first available spirometry was 40 ys [30-52 ys] with a median time since CVIDs diagnosis of 3 ys [1-11 ys]; 135 (73%) patients had already begun IgRT.
At first available spirometry, the cohort had a median FEV1 of 3.07 L [2.40 - 3.80 L], placing at the 32^{nd} pct [6^{th}-61^{st} pct] in the normal distribution of healthy individuals, and a median FVC of 3.70 L [3.00 - 4.54 L], placing at the 29^{th} pct [7^{th}-49^{th} pct].
Of note, 43 (23%) patients had a FEV1 < LLN, 39 (21%) had a FVC < LLN and 28 (15%) patients had both FEV1 < LLN and FVC < LLN *(For details see Figure 1).*

Patients with FEV1 < LLN had a lower serum level of IgA (6 vs 9 mg/dL; p=0.03) and of switched-memory (SM) B cells% (0.7% vs 3.0%; p<0.001) and a higher CD21 low B cells% (11% vs 6%; p=0.05). Similarly, the group with a FVC < LLN had lower IgA (6 vs 9 mg/dL; p=0.048) and SM B cells% (1.0% vs 2.7%; p=0.004); IgG serum level was also lower (236 vs 293 mg/dL; p=0.026). We did not find any other difference in the immunological features and in the dosage of IgRT. *(See Table I for details)*
Not being under IgRT at the time of the first available spirometry was not associated with either FEV1 < LLN (OR 1.09; 95%CI 0.45-2.62) or FVC < LLN (OR 0.72; 95%CI 0.30-1.70). Also, comparing

patients with both FEV1 and FVC < LLN with the remaining ones we found lower SM B cells% (0.7% vs 2.6%; p=0.007), without other differences in the immunological features *(See Table 2 in the supplementary materials).*
Moreover, a severely reduced percentage of SM B cells (<2%) was significantly associated with FEV1 < LLN (OR 7.58; 95%CI 2.64-21.75), FVC < LLN (OR 3.55; 95%CI 1.35-9.33) and with concomitant presence of both FEV1 and FVC < LLN (OR 6.16; 95%CI 1.66-22.88).

Lung function trajectories

To investigate temporal trends in lung function we analysed a group of 118 patients with at least 5 years of spirometric follow-up data available. 6 of these patients were excluded because they had been treated with immunosuppressive drugs for GLILD, with lung function improvement, before final spirometry.
In the final group of 112 patients, 58 were female (52%) and the median age at CVIDs diagnosis was 34 ys [22-41 ys]. 75 patients (67%) had at least one known lung comorbidity with a similar distribution of pulmonary comorbidities and baseline lung volumes compared to the whole sample *(For details See supplementary results).*
The median time between the first and most recent spirometry was 7 years [6-10 ys].
At most recent spirometry, this subgroup had a median FEV1 absolute value of 2.79 [1.99 - 3.76 L], placing at the 28^{th} pct [2^{nd} - 51^{st} pct] in the normal distribution of healthy individuals, and a median FVC absolute value of 3.54 [2.68 - 4.56 L], placing at the 30^{th} pct [6^{th} - 55^{th} pct].
Of note, 30 (27%) patients had a FEV1 < LLN, 25 (23%) had a FVC < LLN and 23 (21%) had both FEV1 < LLN and FVC < LLN. *(For details see Figure 1 in Supplementary materials).*
Similarly to the first spirometry, the group with value of FEV1 below LLN had a significantly lower serum level of IgA (5 vs 15 mg/dL; p=0.016) and of SM B cells% (1 vs 3; p=0.045). Additionally, we found a lower percentage of marginal zone (Mz) B Cells (3.5 vs 11.2; p=0.031).
When comparing FVC < LLN and FVC > LLN groups, we found, in the group with a FVC below LLN, a lower percentage of SM B cells (0.9 vs 3; p=0.006) and a higher percentage of CD21low B cells (11.1 vs 5.0; p=0.016) *(For details see Table II).*

Of note, as for the first spirometry, comparing the group of patients with both FEV1 and FVC < LLN with the remaining patients, we found a significantly lower percentage of SM B cells (0.9 vs 3.3; p=0.004) *(For details see Table 3 in the supplementary materials).*
Again, a severely reduced percentage of SM B cells (<2%) was significantly associated with FEV1 < LLN (OR 3.51; 95%CI 1.14-10.70), FVC < LLN (OR 6.00; 95%CI 1.73-20.77) and with concomitant presence of both FEV1 and FVC < LLN (OR 7.49; 95%CI 1.90-29.50).
Interestingly, the IgTL was significantly lower in the FEV1 < LLN group (678 vs 799 mg/dL; p=0.008) and tendentially lower in the FVC < LLN group (694 vs 797 mg/dL; p=0.094); while there was no significant difference in terms of IgRT dosage.
Finally, we found no association between ongoing antibiotic prophylaxis and FEV1< LLN (OR 1.45; 95%CI 0.48-4.37) or FVC< LLN (OR 1.56; 95%CI 0.48-5.07).

We then evaluated the impact of lung comorbidities on lung function and its decline for the previously defined subgroup of 112 patients with at least a 5-years interval between first and last spirometry. Table III summarised the lung volumes at baseline and at last available PFTs, categorising patients according to the main lung comorbidity *(See Table III).*

A total of 498 PFTs, with a mean of 4.4 PFTs per patient, were analysed to assess the annual decline of FEV1 and FVC.

The annual decline estimated using a linear mixed effects model was 25.6 mL/year for FEV1 and 15.6 mL/year for FVC, without any significant difference between the measured and the predicted one (even if we found a trend towards significance for FEV1). In the same way, we also calculated the annual decline of FEV1 and FVC for different subgroups of patients categorised by the presence of the main lung comorbidities and smoke exposure *(For details see Table IV)*.

Patients without a known lung comorbidity and without history of smoke exposure had the lowest rate of decline. Patients with a history of smoke exposure and patients with COPD had a significantly higher value of measured FEV1 and FVC decline in comparison with the predicted one *(For details see Table IV)*.

Considering that the COPD group had both lower baseline lung volume and greater lung function decline, in a post-hoc analysis we compared the immunological and clinical features of COPD group with remaining patients. We found in COPD a significantly lower level of serum IgA (4 vs 15 mg/dL; p=0.029), of IgM (13 vs 25 mg/dL; p=0.007) and of peripheral blood MZ B cells% (4.0 vs 11.6; p=0.021), and a later age at diagnosis (39 vs 33 years; p=0.049). Of note, those patients with a COPD without smoke history, also had a significantly greater diagnostic (10.5 vs 7.0 years; p=0.028) and therapeutic delay (20.0 vs 8.0 years; p=0.008) compared to all the other enrolled patients. *(For details see Table 4 in Supplementary Materials).*

A total of 18 (69%) patients with a COPD, of which 10 without smoke history, also had CT evidence of bronchiectasis. In a multivariate analysis considering bronchiectasis, GLILD and smoke we found that only the presence of bronchiectasis was associated with COPD (OR 3.55; 95%CI 1.31-9.60) (*For details see Table 5 in Supplementary materials).*
Indeed, the presence of bronchiectasis was associated with a FEV1 < LLN at last available spirometry (OR 2.84; 95%CI 1.19-6.76), even when we excluded patients with concomitant presence of GLILD (OR 2.74; 95%CI 1.06-7.05).

Linear mixed effects model was then adjusted for covariates (gender, smoking, height, age at first PFT, bronchiectasis, GLILD) to estimate the impact of different covariates on the value of FEV1 and its decline. We found that patients with bronchiectasis had a significant lower FEV1, (on average – 304.9 mL, (95%CI – 543.2; -63.5 mL p=0.015) than patients without bronchiectasis. The model did not show the smoke and GLILD variables to be statistically significant. The "net" annual decline of FEV1, independently of the effects due to the other variables, was -26.8 ml, 95%CI [-40.1, -13.5]. *(See Table V).* On the other hand, the same model for FVC did not show a statistically significant impact of bronchiectasis, GLILD and smoke *(For details see Table 6 in Supplementary materials).*

Total Lung Capacity (TLC) analysis

140 patients had at least one spirometry including the measurement of Total Lung Capacity (TLC), performed after a median period of 4 ys [1-12 years] from the CVIDs diagnosis. The median value of TLC at first available spirometry was 5.40 L [4.67-6.59 L], with a median z score of -0.275 [-0.956; 0.347], corresponding to the 39th pct [17th-64th]. Twenty (14%) patients had a TLC < LLN.
102 patients had performed a second PFT with TLC after a median period of 5 ys [4-9 ys]. Among all comorbidities, we found that only GLILD was associated with TLC < LLN at last PFT (OR 4.25 95%CI; 1.45-12.4) *(For details see Supplementary results and Table 7)*.
In order to estimate the trend of TLC over time, we analysed 47 patients that had performed a second spirometry with TLC after at least 5 years (range 5-10). Notably, at first available measurement

patients with GLILD had a median TLC at 16th pct, which dropped to 5th pct at the second spirometry. *(Data summarised in Table VI)*

Diffusing capacity for carbon monoxide (DLCO) analysis

A total of 147 patients had at least one spirometry that included the diffusing capacity for carbon monoxide (DLCO) value. The median time between CVIDs diagnosis and first DLCO was 6 ys [1-12 ys]. The median value of DLCO was 20.6 mmHg/min [17.4-26.5 mmHg/min], with a median z score of -0.713 [-1.980; 0.123], corresponding to the 24th pct [2nd-55th], and 41 (28%) patients DLCO < LLN.

A total of 95 patients had performed a second PFT with DLCO after a median time of 6 ys [3-8 ys]. Among all comorbidities we found that only GLILD was associated with DLCO < LLN at last available PFT (OR 3.45 95%CI 1.31-9.09) *(For details See Supplementary Results Table 8).*

In order to estimate the trend of DLCO during the time, we considered 44 patients that had performed a subsequent spirometry with DLCO from a restricted interval of 5 to 10 years after baseline. Remarkably, at first available measurement patients with GLILD had a median DLCO at 11th pct, which dropped to 3rd pct at the second spirometry *(Data summarised in Table VII).*

DISCUSSION

We report the largest CVIDs cohort specifically studied for lung function and its decline. We identify that in our multi-center retrospective cohort, although baseline lung volumes were reduced, the subsequent rate of FEV1 and FVC decline was not accelerated.

At the first available PFT, our patients were typically in the lower third of the normal distribution of healthy individuals for both FEV1 and FVC and in the lower half for TLC. Moreover, 23% had a value lower than LLN of FEV1, 21% of FVC and 14% of TLC. These findings are consistent with an impact of CVID and related complications on lung volumes and function. DLCO, a parameter that reflects alveolar-capillary membrane integrity, was also in the lower third of the normal distribution, with 28% of patients presenting a pathological value.

Notably, our study showed that patients with baseline lung volumes lower than LLN had significantly lower levels of IgA, IgG and SM B cells%, with a tendentially higher percentage of CD21low B cells. These immunological parameters have already been reported as associated with specific pulmonary comorbidities; in particular, lower IgG and IgA and a higher percentage of CD21low B cells with GLILD, [18,19] whereas lower IgA and IgG with bronchiectasis [20]. We also observed that a severely reduced percentage of SM B cells (<2%) [14] led to a seven-fold increased risk of FEV1 lower than LLN and a three-fold increased risk of FVC lower than LLN at baseline. Similarly, it led to a three-fold increased risk of FEV1 lower than LLN and a six-fold increased risk of FVC lower than LLN at last PFT. This data is in line with another previous study in which a lower percentage of SM B cells, reflecting a more severe B cell impairment, was associated with a worse clinical outcome of respiratory and intestinal involvement [21].

The analysis of 498 PFTs in 112 CVID patients with at least 5 years of respiratory function follow-up, showed a median annual decline of 25.6 ml/year for FEV1 and 15.6 ml/year for FVC. Unlike the previous study by Chen Y et al., which reported a rate of decline approximately double compared to the healthy non-smoking adult population, with an average decline of 36 mL/year for FEV1 and 39

mL/year for FVC, we did not find a significant difference between the measured and the predicted annual decline. Moreover, we found that patients with no lung co-morbidities or exposure present a functional decline over time in line with that predicted in the general population. In that study, the data were collected before 2010 and only 29 CVID patients from Australia were included. [11]. A more recent study from Sperlich et al., with a likely closer temporal range of data collection to our study, calculated an annual FEV1 decline of 18.25 ml/year in a cohort of 67 patients, excluding those affected by GLILD. In our patients, excluding GLILD, we found a slightly higher rate of measured FEV1 decline, 23.9 mL/year, but without a significant difference from the predicted one.

In our cohort, 64% of the patients had at least one known lung comorbidity. The prevalence of bronchiectasis (41%) was similar to what has already been reported in the literature [20,22], while the number of patients with a GLILD diagnosis (24%) was slightly higher in comparison with previous reports showing a prevalence of 10-20% [23,24].
Bronchiectasis were associated with a prevalent obstructive pattern with lower value of FEV1 whereas GLILD was associated with restrictive pattern and interstitial dysfunction, with lower value of TLC and DLCO. Interestingly, observing the trend of TLC and DLCO in the GLILD group, the median percentile dropped, reaching values lower than LLN at the last PFTs for both. These data confirmed the importance of performing comprehensive PFTs, including DLCO and TLC, supporting the role of these lung parameters as markers in the diagnosis and in the assessment of treatment response in GLILD [25].
Using a linear mixed-effect model to investigate the impact of different covariates (gender, smoking, height, age at first PFT, bronchiectasis, GLILD) on the value of FEV1 we found that in patients with bronchiectasis the mean FEV1 was stably lower than in those without bronchiectasis. On the other hand, similarly to Sperlich et al., patients with bronchiectasis had a median FEV1 decline of 22.1 mL/year, but the measured decline was not significantly higher in comparison with the predicted one [13]. Considering that all patients in our cohort were under IgRT, our data seemed consistent with previous ones showing effectiveness of IgRT in preventing infections, and subsequent development/extension of bronchiectasis, thus reducing the progression of lung impairment [26,27].

We noticed that among all, patients with a COPD functional phenotype at last PFT had a lower baseline lung volume, with a median value of FEV1 at the LLN, and a concomitant significantly higher decline of lung volumes in comparison with predicted decline, reaching 65.4 mL/year for FEV1 and 39.7 mL/year for FVC. Data were similar, although not significantly different from predicted, also when considering patients without a history of smoke (68.0 mL/year for FEV1 and 31.6 mL/year for FVC), in which COPD was presumably related to CVID itself. Interestingly, COPD patients had lower levels of IgA, IgM and Mz B cells percentage, probably reflecting a deeper immunological defect, especially in the mucosal immunity and in the T-independent response. This particular immunological background cannot be rescued by IgRT alone. Indeed, lower IgA levels were already identified as one of the risk factors for development of pneumonia despite IgRT [28] and a lower percentage of IgM Memory B cells led to a more severe alteration in anti-polysaccharide response [29,30]. Moreover, an impairment in IgA and IgM response to vaccination has been associated with higher prevalence of bronchiectasis and chronic lung diseases [31]. All these data may support the need for a more tailored approach to these patients: the absence of IgA could be counterbalanced by shorter immunoglobulin replacement intervals, addition of antibiotic prophylaxis [32] and, theoretically, nebulized IgA [33].
Furthermore, at present the IgTL and the personalization of IgRT dosage is mainly driven by weight, infection burden and evidence of organ damage [34,35]. Starting from our finding that patients with normal FEV1 at last PFT had higher IgTL, we could speculate that patients with severely reduced

SM B cells %, showing baseline FEV1 and FVC lower than LLN, might benefit from higher IgRT dosage in order to achieve higher IgTL. Indeed, a possible beneficial role of IgRT on lung function, but limited to small airways, has been already suggested by previous studies [36].

The main limitation of our study is the retrospective design, which limited the quality of data collection, with some missing data, particularly regarding DLCO and TLC measurements. Moreover, the evaluated population was only Caucasian, avoiding any potential influence of ethnicity [37], and there was no categorization according to lung-comorbidity severity and to the extent of smoke exposure.

However, to our knowledge, this is the first study specifically focusing on CVID lung function and its decline which were evaluated according to the last ERS/ATS 2021 interpretations standard [17] and using the GLI formula [16].

CONCLUSION

In conclusion, our study underlines the importance of a comprehensive lung function evaluation at CVIDs diagnosis and during the follow-up to identify specific disease phenotypes and possibly drive a tailored therapeutic approach.

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TABLES

Table I. *Comparison of lung volumes, clinical and immunological features at diagnosis in patients' groups identified according to FEV1 < LLN and > LLN and to FVC < LLN and > LLN at first available spirometry.*

	FEV1 < LLN	**FEV1 > LLN**	**p value**	**FVC <LLN**	**FVC >LLN**	**p value**
Absolute value (L)	2.05 (1.43-2.62)	3.32 (2.68-3.99)	***<0.001**	2.47 (2.19-3.04)	3.97 (3.40-4.84)	***<0.001**
% of predicted	64.8 (48.9-72.2)	97.0 (89.1-105.0)	***<0.001**	67.0 (58.7-74.1)	95.0 (89.5;103)	***<0.001**
Age at diagnosis (ys) n 185	37 (22-45)	35 (22-44)	0.934	37 (22-40)	34 (22-45)	0.775
Age at first PFR (ys) n 185	40 (35-55)	40 (28-51)	0.265	43 (37-52)	40 (29-52)	0.336
Diagnostic delay (ys) n 181	7.0 (2.0-14.8)	7.0 (2.0-14.5)	0.954	8.0 (2.5-18.0)	7.0 (2.0-14.0)	0.383
IgRT delay (ys) n 169	7.5 (2.8-22.3)	8.0 (2.0-17.0)	1.000	8.0 (4.5-21.5)	8.0 (2.0-16.0)	0.496
IgG (mg/dL) n 168	256 (51-373)	280 (169-389)	0.107	236 (75-369)	293 (172-397)	***0.026**
IgA (mg/dL) n 168	6 (0-21)	9 (3-27)	***0.032**	6 (0-20)	9 (4-27)	***0.048**
IgM (mg/dL) n 168	18 (4-33)	21 (8-35)	0.239	19 (5-28)	20 (8-37)	0.284
B cells% n 150	7.5 (2.6-10.8)	8.0 (3.5-12)	0.738	8.0 (3.5-12.5)	8.0 (3.1-11.9)	0.747
SM B cells% n 118	0.7 (0.0-1.4)	3.0 (1.1-6.4)	***<0.001**	1.0 (0.0-2.5)	2.7 (1.0-6.4)	***0.004**
Cd21low B cells% n 118	11 (5.3-22.9)	6.0 (3.0-14.8)	***0.050**	9.9 (4.7-15.4)	6.0 (3.0-17.0)	0.439
Mz B cells% n 118	4.0 (1.7-8.9)	8.3 (2.2-18.8)	0.079	4.0 (1.8-7.3)	8.7 (2.3-17.8)	0.068
IgRT mg/kg/month n 128	345 (323-400)	306 (243-400)	0.080	354 (302-418)	313 (248-389)	0.112

Mann-Whitney U test. Data are summarised as medians and interquartile ranges.

555 ***Table II.*** *Comparison of lung volumes, clinical and immunological features at diagnosis in patients'*
556 *groups identified according to FEV1 <LLN and >LLN and to FVC <LLN and >LLN at last available*
557 *spirometry.*
558

	FEV1 <LLN	**FEV1 >LLN**	**p value**	**FVC <LLN**	**FVC >LLN**	**p value**
Absolute value (L)	1.68 (1.39-2.02)	3.35 (2.70-3.94)	***<0.001**	2.44 (2.25-2.71)	4.18 (3.26-4.86)	***<0.001**
% of predicted	62.2 (46.7-70.9)	95.6 (90.1-103)	***<0.001**	69.5 (59.1-72.6)	97.4 (88.2-103)	***<0.001**
Age at last PFR (ys) n 112	46 (35-60)	48 (36-58)	0.757	44 (35-61)	48 (36-58)	0.563
Age at diagnosis (ys) n 112	33 (16-40)	34 (22-42)	0.690	32 (14-45)	35 (22-41)	0.413
IgRT delay (ys) n 98	9.0 (4.0-20.0)	9.0 (4.0-16.5)	0.895	8.0 (3.0-14.0)	10.0 (4.8-19.3)	0.530
Diagnostic delay (ys) n 111	8.0 (3.0-17.0)	7.0 (2.0-14.0)	0.704	7.0 (3.0-14.0)	8.0 (2.0-16.0)	0.670
IgG (mg/dL) n 100	299 (204-382)	279 (157-382)	0.849	286 (200-393)	300 (199-393)	0.569
IgA (mg/dL) n 100	5 (0-30)	15 (6-31)	***0.016**	7 (0-31)	14 (5-29)	0.264
IgM (mg/dL) n 100	23 (6-41)	21 (9-45)	0.679	32 (19-52)	19 (7-44)	0.319
B cells % n 95	8.0 (3.8-13.8)	8.5 (4.5-13.3)	0.702	5.0 (2.7-9.8)	9.0 (5.0-14.0)	0.124
SM B cells % n 82	1.0 (0.1-5.0)	3.0 (1.2-6.4)	***0.045**	0.9 (0.1-1.3)	3.0 (1.2-6.2)	***0.006**
CD21low B cells% n 82	9.0 (3.5-31.4)	5.2 (2.7-10.1)	0.114	11.1 (4.7-50.7)	5.0 (2.7-9.2)	***0.016**
Mz B cells % n 82	3.5 (1.9-7.0)	11.2 (3.1-22.0)	***0.031**	3.9 (2.2-7.3)	10.7 (2.6-22.0)	0.093
IgRT (mg/kg/mths) n 94	370 (320-517)	366 (291-404)	0.155	370 (311-449)	396 (300-410)	0.486
IgTL (mg/dL) n 96	678 (608-816)	799 (713-900)	***0.008**	694 (630-829)	797 (703-896)	0.094

559 *Mann-Whitney U test. Data are summarised as medians and interquartile ranges.*
560

Table III. *Summary of lung volumes at baseline and last available PFTs, divided according to the main lung comorbidity.*

	FEV1 First measured (L)	FEV1 First z score	FEV1 First pct	FVC First measured (L)	FVC First z score	FVC First pct
All (n 112)	3.06 (2.38-3.89)	-0.458 (-1.55 ; 0.116)	32th (6th – 55th)	3.82 (3.01-4.71)	-0.533 (-1.30 ; -0.032)	30th (10th - 49th)
CVID-NLS (n 17)	4.02 (2.99-4.28)	-0.269 (-0.603 ; 0.173)	39th (27th -57th)	4.54 (3.64-5.00)	-0.421 (-0.654 ; -0.057)	34th (26th-48th)
Bronchiectasis (n 35)	2.79 (1.75-3.55)	-1.17 (-2.64 ; - 0.240)	12th (0.4th -41st)	3.49 (2.45-4.09)	-0.865 (-2.18 ; -0.146)	19th (1st - 44th)
GLILD (n 24)	2.62 (2.26-3.52)	-1.11 (-1.95 ; -0.114)	13rd (2nd-45th)	3.54 (2.92-4.24)	-0.964 (-2.01 ; -0.181)	17th (2nd - 43rd)
COPD (n 26)	2.32 (1.76-3.25)	-1.66 (-2.78 ; -0.352)	5th (0.3th -36th)	3.04 (2.44-4.14)	-1.13 (-2.18 ; -0.398)	13rd (1st-35th)
Smoke (n 39)	3.14 (2.34-3.82)	-0.490 (-1.90 ; 0.168)	31st (3rd-57th)	4.07 (3.07-5.08)	-0.699 (-1.22 ; 0.143)	24th (11th-56th)
	FEV1 Last measured (L)	**FEV1 Last z score**	**FEV1 Last pct**	**FVC Last measured (L)**	**FVC Last z score**	**FVC Last pct**
All (n 112)	2.79 (1.99-3.76)	-0.569 (-1.96 ; 0.0135)	28th (2.5th- 51st)	3.54 (2.68-4.56)	-0.520 (-1.54 ; 0.123)	30th (6th – 55th)
CVID-NLS (n 17)	3.91 (3.15-4.25)	-0.258 (-0.579 ; 0.149)	39th (28th – 56th)	4.64 (3.65-5.22)	-0.189 (-0.814 ; 0.077)	43rd (21st ; 53rd)
Bronchiectasis (n 35)	2.38 (1.69-3.34)	-1.15 (-2.65 ; -0.448)	13rd (0.4th- 33rd)	3.19 (2.46-4.13)	-0.913 (-1.70 ; -0.427)	18th (4th; 33rd)
GLILD (n 24)	2.68 (1.88-3.46)	-0.955 (-2.08 ; -0.283)	17th (2nd - 39th)	3.21 (2.59-4.18)	-0.834 (-1.98 ; 0.081)	20th (2nd, 53rd)
COPD (n 26)	1.59 (1.39-2.74)	-2.21 (-3.41 ; -0.957)	1st (0.03th - 17th)	2.69 (2.29-4.02)	-1.19 (-2.44 ; 0.095)	12th (0.7th; 54th)
Smoke (n 39)	2.75 (1.91-3.46)	-0.943 (-2.14 ; -0.055)	17th (1.6th – 48th)	3.56 (2.62-4.58)	-0.499 (-1.53 ; 0.140)	31st (6th; 56th)

Definitions: CVID-NLS = CVID patients without history of lung comorbidities and smoke exposure; Bronchiectasis = excluding patients with concomitant GLILD; Smoke = including both active and former smokers.

Table IV: *Comparison between the measured and predicted decline of FEV1 and FVC in the whole group and in the comorbidities related subgroups obtained from the linear mixed effects model.*

	Linear mixed effects model					
	FEV1 decline measured (mL/year) [95% CI]	**FEV1 decline predicted (mL/year) [95% CI]**	**p**	**FVC decline measured (mL/year) [95% CI]**	**FVC decline predicted (mL/year) [95% CI]**	**p**
All (n 112)	-25.6 [-37.1, -14.1]	-20.7 [-25.3, -16.1]	0.055	-15.6 [-27.8, -3.4]	-16.2 [-21.9, -10.4]	0.537
CVID-NLS (n 17)	-10.4 [-35.9, +15.2]	-16.9 [-32.1, -1.8]	0.322	-2.2 [-44.9, +40.6]	-9.3 [-27.8, +9.2]	0.413
Bronchiectasis (n 35)	-22.1 [-40.3, -4.2]	-16.2 [-25.5, -6.8]	0.194	-13.2 [-33.3, +6.0]	-10.9 [-22.7, +0.9]	0.944
GLILD (n 24)	-31.8 [-66.6, +3.1]	-24.5 [-34.9, -14.0]	0.480	-21.5 [-52.9, +9.9]	-20.8 [-33.8, -7.8]	0.976
COPD (n 26)	-65.4 [-94.6, -36.1]	-26.9 [-35.0, -18.8]	**0.017**	-39.7 [-66.4, -13.0]	-25.9 [-37.1, -14.6]	**0.048**
Smoke (n 39)	-38.3 [-58.1, -18.5]	-26.7 [-32.2, -21.2]	**<0.001**	-35.6 [-55.0, -16.2]	-24.3 [-32.1, -16.6]	**<0.001**
COPD-no Smoke (n 12)	-68.0 [-125.5, -10.59]	-31.92 [-35.7, -28.2]	0.291	-31.6 [-74.7, 11.6]	-33.3 [-37.9, -28.7]	0.843
All without GLILD (n 88)	-23.9 [-35.5, -12.3]	-19.6, [-24.8, -14.5]	0.08	-14.0 [-27.1, -0.9]	-14.7 [-21.2, -8.2]	0.545

Mann-Whitney U test was used for measured vs predicted comparison.
Definitions: CVID-NLS = patients without history of lung comorbidities and smoke exposure; Bronchiectasis = excluding patients with concomitant GLILD; Smoke = including both active and ex-smokers; COPD-noSmoke = patients with COPD functional phenotype without history of smoke exposure; All without GLILD = all patients without history of GLILD.

Table V: *Final mixed effects model for FEV1*

Variable		Estimate (mL)	95%CI Lower (mL)	95%CI Upper (mL)	p
Time (continuous variable in year)		**- 26.80**	**- 40.08**	**-13.53**	**<0.001**
Sex (ref. male)	**Female**	**-452.38**	**- 776.96**	**- 127.80**	**0.006**
Age at first spirometry (continuous variable in year)		**- 29.21**	**- 37.54**	**-20.88**	**<0.001**
Height (continuous variable in cm)		**+50.07**	**+ 34.30**	**+65.84**	**<0.001**
Smoke (ref. No)	Yes	+1.83	-242.84	+246.50	0.988
Bronchiectasis (ref. No)	**Yes**	**-304.87**	**-543.23**	**-63.51**	**0.012**
GLILD (ref. No)	Yes	-14.67	-297.01	+267.67	0.919

95% Confidence Intervals and p-values were computed using a Wald t-distribution approximation.
Time: years from the first spirometry.

Table VI. *TLC in 47 patients who performed a second spirometry at a restricted interval of 5 to 10 yrs after baseline.*

	TLC 1st	z score 1st	Pct 1st	TLC Last	z score Last	Pct Last
All (n 47)	5.70 (4.65;6.93)	-0.073 (-0.778;0.259)	47th (22th;60th)	5.50 (4.84;6.65)	-0.564 (-1.58;0.089)	29th (6th;54th)
No-GLILD (n 33)	6.00 (5.02;7.17)	0.027 (-0.476;0.237)	51th (32nd;59th)	6.19 (5.01;6.76)	-0.266 (-0.822;0.063)	40th (21st;53rd)
GLILD (n 14)	5.51 (4.26;6.02)	-0.980 (-1.70;0.227)	16th (5th;59th)	4.96 (3.88;6.17)	-1.70 (-2.44; 0.006)	5th (0.7th-50th)

Table VII: *DLCO in 44 patients who performed a second spirometry at a restricted interval of 5 to 10 yrs after baseline.*

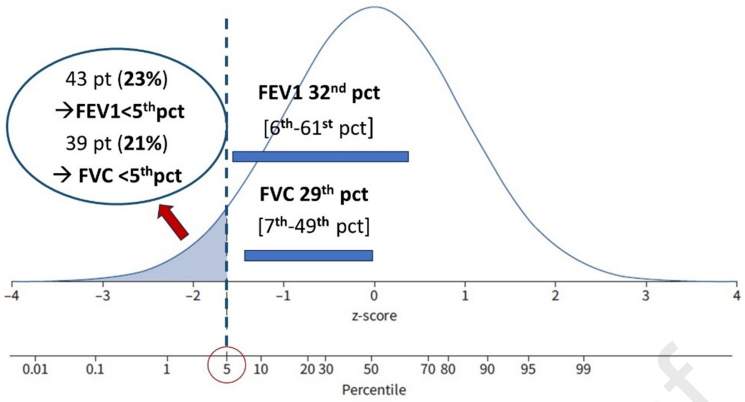
	DLCO 1st (mL/mmHg/min)	z score 1st	Pct 1st	DLCO Last	z score Last	Pct Last
All (n 44)	23.5 (18.7;27.2)	-0.706 (-1.24;0.04)	24th (11st;52th)	20.7 (17.1-25.2)	-0.833 (-1.74;-0.159)	20th (4th;44th)
No-GLILD (n 31)	24.4 (20.3;28.6)	-0.279 (-1.04;0.369)	39th (15th;64th)	22.2 (18.8;26.7)	-0.677 (-1.17;-0.123)	25th (12th;45th)
GLILD (n 13)	18.5 (15.2;20.7)	-1.24 (-3.18;-0.748)	11st (0.1th;23rd)	18.0 (14.1;20.3)	-1.910 (-3.09;-0.752)	3rd (0.1th;23rd)

FIGURE LEGENDS

Figure 1: *Lung volume at first available spirometry.*

The table summarized the absolute value, the percentage of predicted, the z score and the corresponding percentile of FEV1 and FVC at first available spirometry.
The 5th pct (z score -1.645) identifies the lower limit of normal (LLN).

Figure 1



	Absolute value (L)	Percentage of predicted (%)	z score	Percentile
FEV1	3.07 (2.40 - 3.80)	94.0 (79.8-103.0)	-0.470 (-1.540; 0.275)	32nd (6th - 61st)
FVC	3.70 (3.00 - 4.54)	92.7 (82.3-99.8)	-0.553 (-1.460; -0.014)	29th (7th - 49th)