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ORIGINAL RESEARCH

Single-Breath Simultaneous Measurement of DL_{NO} and DL_{CO} as Predictor of the Emphysema Component in COPD – A Retrospective Observational Study

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Background: Chronic Obstructive Pulmonary Disease (COPD) is a respiratory condition characterized by heterogeneous abnormalities of the airways and lung parenchyma that cause different clinical presentations. The assessment of the prevailing pathogenetic components underlying COPD is not usually pursued in daily practice, also due to technological limitations and cost.

Aim: To assess non-invasively the lung emphysema component of COPD by the simultaneous measurement of DL_{NO} and DL_{CO} via a single-breath (sDL_{NO} and sDL_{CO}).

Methods: COPD patients aged ≥40 years of both genders were recruited consecutively and labelled by computed tomography as "with significant" emphysema (>10% of CT lung volume) or "with negligible" emphysema otherwise. Current lung function tests such as sDL_{NO}, sDL_{CO} and Vc (the lung capillary blood volume) were measured. All possible subsets of independent spirometric and diffusive parameters were tested as predictors of emphysema, and their predicted power compared to each parameter alone by ROC analysis and area under the curve (AUC).

Results: Thirty-one patients with "significant emphysema" were compared to thirty-one with "negligible emphysema". FEV_1 and FEV1/FVC seemed to be the best spirometric predictors (AUC 0.80 and 0.81, respectively), while sDL_{CO} and Vc had the highest predicted power among diffusive parameters (AUC 0.92 and 0.94, respectively). sDL_{CO} and Vc values were the parameters most correlated to the extent of CT emphysema. Six subsets of independent predictors were identified and included at least one spirometric and one diffusive parameter. According to goodness-to-fit scores (AIC, BIC, log-likelihood and pseudo R^2), RV coupled with sDL_{CO} or Vc proved the best predictors of emphysema.

Conclusion: When investigating the parenchymal destructive component due to emphysema occurring in COPD, sDL_{NO}, sDL_{CO} and Vc do enhance the predictive power of current spirometric measures substantially. sDL_{NO}, sDL_{CO} and Vc contribute to phenotype of the main pathogenetic components of COPD easily and with high sensitivity. Organizational problems, radiation exposure, time and costs could be reduced, while personalized and precision medicine could be noticeably implemented.

Keywords: COPD, parenchymal destruction, emphysema, lung capillary blood volume, simultaneous single-breath NO and CO diffusing capacity, precision medicine

Introduction

Chronic obstructive pulmonary disease (COPD) is a pathological condition of the lung that is characterized by persistent respiratory symptoms (cough, expectoration, dyspnea) due to heterogeneous disorders affecting the airways and/or the lung parenchyma to a variable extent.[1] Though characterized by significant progression and by huge epidemiological and socio-economic impact worldwide,[2–4] Nevertheless, COPD is described as a preventable and treatable condition.[1]

It is known since long ago that the pathogenetic components underlying COPD can variably involve all structures of lung units, such as the conductive airways, the small airways and/or the alveoli, the capillary vasculature included.[5–7]

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Such a pathogenetic heterogeneity entails different clinical presentations of COPD: the clinical phenotypes of COPD.[8–19] Different COPD phenotypes can be obviously characterized by variable responses to therapeutic regimens due to the variable extent of reversible and irreversible components of structural disorders occurring in the lung, and consequently different short- and long-term outcomes can be expected. Unfortunately, respiratory conditions characterized by the predominant airway involvement and those where the parenchymal destruction is prevailing are currently included in the same comprehensive term "COPD", both in clinical practice and in the vast majority of RCTs.

In the aim of defining the right pattern of lung function occurring in COPD and the existence of some destructive parenchymal components, measurements of diffusing capacity for carbon monoxide (DL_{CO}) are currently recommended together to the assessment of static and dynamic volumes, forced flows, airway resistances, and residual volume. However, due to the slow binding of CO with intracapillary hemoglobin (Hb), usual measurements of DL_{CO} are considered to be insufficient for distinguishing the structural abnormalities affecting the diffusing conductance of alveolar structure (DM) from those mainly affecting the vascular side of alveolar membrane.

Even if presently limited by the still poor awareness of physicians, the simultaneous single-breath assessment of nitric oxide diffusing capacity (sDL_{NO}) and of carbon dioxide (sDL_{CO}) has been specifically recommended together with the measure of the lung capillary blood volume (Vc) in order to overcome these limits.[20–23]

Aim of the present study was to investigate the contribution of the single-breath simultaneous measurements of sDL_{NO} and sDL_{CO} and related parameters (namely, the sDL_{NO}/sDL_{CO} ratio and Vc) in phenotyping COPD non-invasively and at low-cost in terms of the underlying parenchymal destructive components involving the vascular side of the alveolar membrane.

Methods

Study Design

COPD patients aged ≥40 years of both genders, in stable condition, non or former smoker, and without steroid use were retrospectively enrolled. Exclusion criteria were as follows: (1) patients aged <40 years; (2) the presence of major comorbidities affecting the diffusion measurements, such as: anemia (blood Hb <12g/L), heart failure, lung fibrosis, vasculitis, liver and renal failure, diabetes; (3) bronchial asthma and other asthma components (ACO); (4) the presence of COVID-related parenchymal abnormalities; (5) the presence of physical limitations and/or cognitive impairment enabling procedures for lung function tests; (6) the refusal of the informed consent; (7) COPD in non-stable conditions and without any steroid treatment over the last six weeks; (8) patients characterized by a forced expiratory volume in 1 sec. (FEV_1) reversibility ≥ greater or equal to 12% from baseline after salbutamol 400 mcg.

Computed tomography (CT; Siemens 64 slice) was performed in all patients and two radiologists quantified independently the % extent of emphysema in the whole lungs. The extent of emphysema was reported as the mean % of lung volume calculated by both the radiologists in each patient (% CT volume). Patients were labelled as COPD "with significant emphysema" only when emphysema destruction was involving at least >10% of their whole lung volume, otherwise patients were labelled as COPD "with negligible emphysema". Usual spirometric parameters and current DL_{CO} measures also contributed to the patients' characterizations in terms of lung function. The single-breath simultaneous sDL_{NO} and sDL_{CO} measures were assessed for the first time with the aim to investigate and quantify the structural impairment of lung parenchyma due to the emphysema component in COPD.

Data Collected

Parameters collected were as follows: age (in years), gender, body mass index (BMI), Hb (in g/L), vital capacity (VC), forced vital capacity (FVC), FEV_1, FEV_1/FVC ratio, residual volume (RV), DL_{CO}, sDL_{NO}, sDL_{CO}, sDL_{NO}/sDL_{CO} ratio, and Vc. All parameters were reported as % predicted and corresponding z-score values.

Spirometric volumes, flows, and RV were obtained by means of a Plethysmography Platinum DX Elite (MedGraphics, Saint Paul, MN, USA). DL_{CO} measurements were carried out in agreement with the specific standards for single-breath carbon monoxide uptake in the lung.[24] The simultaneous assessment of sDL_{NO}, sDL_{CO} and related parameters was obtained by means of the "Stand-Alone" Hypair Compact System (MGC Diagnostics International, Sorinnes, Belgium) that allows the simultaneous assessment of DM and Vc as a function of the standard single-breath

method. This method is based on the principle by Roughton and Forster[25] of two reactions for THETA fractions: one for CO and the other one for NO, according to the values fixed in the ERS/ATS Task-Force 2017[24] during the usual single breath maneuvers. Due to the use of an electrochemical analyzer for NO, the usual DL_{CO} measure apnea time duration of 10 sec is reduced for DL_{NO} around 5 sec. Two gas mixtures are required for these measures: i) helium (He) 14%; CO 0.280%; oxygen (O2) 18–21, and nitrogen (N2), and ii) nitric oxide in nitrogen (NO in N2) 400 ppm. According to standard procedures, measure of DL_{CO} and DL_{NO} required breath-hold times of 10 and 5 sec, respectively.[26–28]

Statistical Analysis

A prespecified sample size calculation was performed based on the mean difference of spirometric and diffusive parameters according to the formula for unmatched samples $n=2(z_{1-\alpha}+z_{1-\beta})^2/\Delta^2$, where α=5% and β=20% are the type I and II errors, respectively, and Δ is the standardized mean difference defined as the mean difference *d* of each parameter between the two groups divided by its standard deviation. Conservatively, it was assumed that for each parameter the mean value in the group "COPD with significant emphysema" was 10–20% lower than the mean value in the group "COPD with negligible emphysema" (for RV and sDL_{NO}/sDL_{CO} ratio, it was assumed an increase of 10–20%). The standard deviation of the mean difference was calculated assuming (1) that the standard deviation of each parameter in both groups was equal to 20–40% of the mean value and (2) a plausible linear correlation ρ=0.5 for each parameter between the two groups. According to these assumptions, about 10–27 patients per group should be enrolled in the study.

Continuous data were presented as means and standard deviation (SD), while gender as absolute and relative frequencies. Differences assessed in baseline between the two subsets of patients were tested by non-parametric Wilcoxon test (for continuous variables) and Fisher's exact test (for gender). Differences in lung function parameters were estimated by a generalized linear model (gamma family) adjusting for all the characteristics available at enrollment. Results were reported as adjusted mean difference (AMD) and confidence intervals (CI). Moreover, the relationship between lung parameters and the % CT volume was also investigated by using the same generalized linear model, including % CT volume as continuous independent variable instead of the presence of significant emphysema. In this case, results were presented as adjusted mean variation (in each parameter) for every 10% increment in the value of % CT volume ($AMV_{10\%}$).

Receiver Operating Characteristic (ROC) curves and area under the curve (AUC) were used to identify the parameters able to classify emphysema with the highest predicting power. Youden's criterion was used to establish optimal cut-off values with sensitivity, specificity, and diagnostic odds ratios (DOR) also reported.

Finally, regression analysis was performed to identify possible subsets of predictors that conjointly could be able to classify emphysema better than each parameter alone. The following algorithm was applied:

1. Correlation matrix of all spirometric (ie, FEV_1, VC, FEV_1/FVC, RV) and diffusive (ie, current DL_{CO}, sDL_{CO}, sDL_{NO}, sDL_{CO}/sDL_{NO} ratio, and Vc) parameters considered in the analysis was calculated using Bonferroni correction for multiple comparisons;[29]
2. Based on correlation matrix, all the possible subsets of independent (ie, uncorrelated) predictors were selected and used as covariates in a series of logistic regression models; specifically, each subset was defined such that all pairwise comparisons among variables in the same subset must be non-significant ($p > 0.05$);
3. Stepwise selection was used to extract, from each subset, the minimal set of predictors;
4. For each model, an overall score was created using the coefficient estimated from logistic regression (standardized between 0 and 100) and its predicting power was tested via ROC analysis.

In the base case, parameters were included in each model as % predicted. A scenario analysis by using z-scores instead of % predicted was also conducted.

All models were adjusted by age, sex, BMI and Hb levels at enrollment and their goodness to fit was evaluated using Akaike's information criterion (AIC), Bayesian information criterion (BIC), log-likelihood and pseudo R^2. Lower values of AIC and BIC and higher values of log-likelihood and pseudo R^2 indicate better fit models. A p value <0.05 was considered statistically significant. All statistical calculations were carried out by means of STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Ethics

The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session of May 2, 2021. This study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent prior to enrollment.

Results

A total of 62 patients were included in the analysis: 31 patients with a CT documented parenchymal damage due to emphysema involving >10% of their lung parenchyma (mean extension 31.3%, SD = 9.7), and 31 patients with a negligible emphysema extension (3.7%, SD = 4.4) (Table 1).

The two groups were well matched by age (p = 0.9382) and Hb (p = 0.8376) distribution, while the BMI seemed to be lower in patients with significant emphysema (mean BMI: 24.5 vs 27.5, p = 0.0019). Moreover, the proportion of male was lower in patients with significant emphysema (48.4% vs 71.0%, p = 0.060) (Table 1). Mean FEV_1 reversibility was 1.8% (SD = 0.4), undistinguishable between the two groups (p = 0.96).

The comparisons of lung parameters among the two groups are reported in Table 2. When compared to values from patients with negligible emphysema, mean values for FEV_1, VC, FEV_1/FVC, DL_{CO}, sDL_{CO}, sDL_{NO}, and Vc obtained in

Table 1 Baseline Characteristics of Patients

Parameters	COPD with Negligible Emphysema	COPD with Significant Emphysema	p-value
n	31	31	
Mean age (SD)	73.8 (8.9)	74.6 (7.8)	0.9382
Male (%)	22 (71.0%)	15 (48.4%)	0.060
Mean BMI (SD)	27.5 (3.6)	24.5 (4.6)	0.0019
Mean Hb (SD)	13.9 (0.6)	13.9 (0.4)	0.8376
% CT emphysema volume (SD)	3.7 (4.4)	31.3 (9.7)	<0.0001

Abbreviations: BMI, body mass index; Hb, hemoglobin; SD, standard deviation.

Table 2 Comparison of Diffusive and Spirometric Parameters Between COPD Patients Without and with Emphysema

Parameters	COPD with Negligible Emphysema	COPD with Significant Emphysema	AMD (95% CI)	p-value
FEV_1	67.1 (7.5)	50.7 (15.5)	−15.5 (−23.0 to −8.0)	<0.001
VC	89.7 (16.9)	76.6 (8.9)	−12.4 (−19.2 to −5.5)	<0.001
FEV_1/FVC	64.0 (10.3)	51.7 (9.2)	−11.0 (−16.1 to −5.8)	<0.001
RV	108.0 (38.4)	159.9 (57.9)	49.5 (23.4 to 75.7)	<0.001
DL_{CO}	71.1 (16.9)	43.3 (14.3)	−26.5 (−35.1 to −17.8)	<0.001
sDL_{CO}	70.6 (15.3)	39.0 (10.6)	−30.8 (−37.9 to −23.7)	<0.001
sDL_{NO}	77.7 (18.9)	52.4 (17.3)	−26.0 (−35.7 to −16.4)	<0.001
sDL_{NO}/sDL_{CO} ratio	112.7 (10.2)	130.8 (19.1)	15.8 (8.0 to 23.7)	<0.001
Vc	56.8 (11.7)	27.6 (10.4)	−27.1 (−34.0 to −20.2)	<0.001

Abbreviations: AMD, adjusted mean difference (adjustment for age, sex, BMI, and Hb).

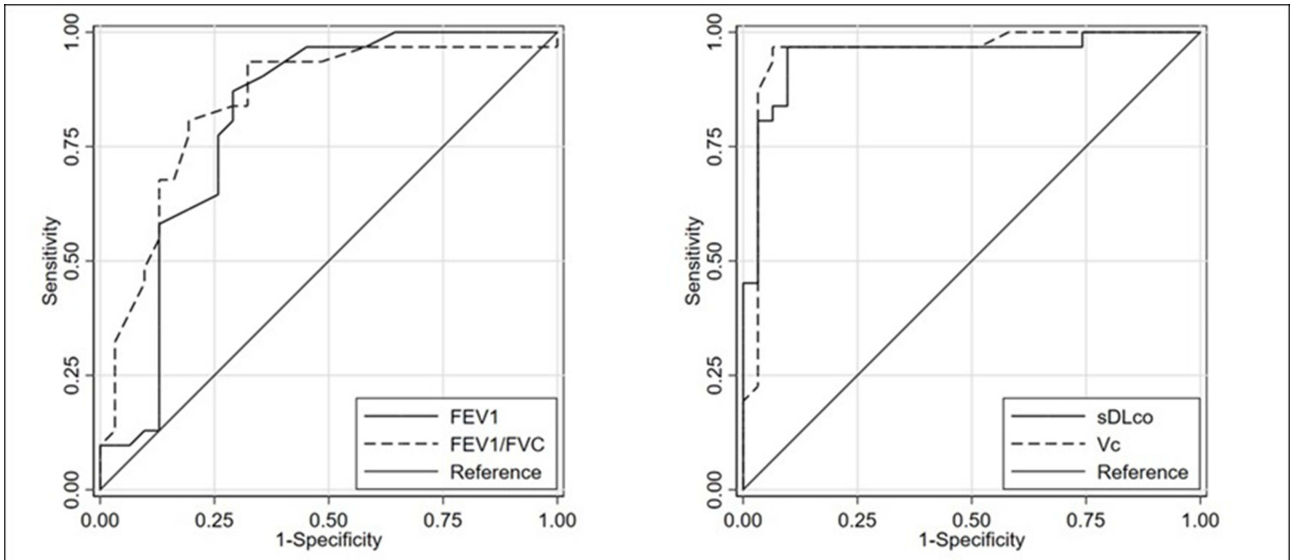
those with significant emphysema were significantly lower ($p < 0.001$) while corresponding values for RV and the sDL_{CO}/sDL_{NO} ratio were significantly higher ($p < 0.001$). Same results were obtained using parameters expressed in terms of z-score (Table S1 in Supplementary material).

According to the results of generalized linear regression versus the % CT volume, every 10% increment in the % CT volume seemed to be associated with a significant decrement in FEV_1, VC, FEV_1/FVC, DL_{CO}, sDL_{CO}, sDL_{NO}, and Vc and a significant increment in RV and the sDL_{CO}/sDL_{NO} ratio (Table S2 in Supplementary material). However, the magnitude of the variation was generally more pronounced in the diffusive parameters with respect to spirometric parameters (with the exception of RV). Moreover, the linear correlation with % CT volume is high (R^2>0.7) for sDL_{CO} and VC, moderate (R^2 0.4–0.6) for DL_{CO}, sDL_{NO} and sDL_{NO}/sDL_{CO} ratio, and low (R^2<0.3) for all the spirometric parameters (Figure 1).

According to the ROC analysis, almost all parameters were characterized by high AUC, sensitivity and specificity (Figure 2). Among spirometric parameters, FEV_1 and FEV1/FVC seemed to be the best predictors (AUC 0.79 and 0.81, respectively). However, the predicted power of diffusive parameters was generally superior, Specifically, sDL_{CO} and Vc had the highest predicted power (AUC 0.94 and 0.95, respectively), followed by DL_{CO} and sDL_{NO} (AUC 0.79).

Diffusive and spirometric parameters were highly correlated (Table S3 in Supplementary material). However, 6 subsets of uncorrelated variables were identified. After variable selection by using a stepwise algorithm, the results of the final 6 logistic regression models are reported in Table 3. All models include at least one spirometric parameter and one diffusive parameter (reported as % predicted).

According to goodness-to-fit scores, models 5 and 6 had the lowest AIC and BIC (Table 3 and Figure 3) and the highest log-likelihood and pseudo R^2. Pseudo R^2 of models 2 and 3 were also high and comparable with the value of model 5 and 6. However, both models 2 and 3 were penalized because they are not parsimonious models (the models with the highest number of covariates needed such as, 4 parameters), while the other models, with the exception of models 3 and 6, only require 2 covariates.



Variables	AUC	Cut-off	Sensitivity	Specificity	DOR
FEV_1	0.79 (0.70 to 0.88)	60.5 (54.6 to 66.4)	0.87 (0.69 to 1)	0.71 (0.50 to 0.92)	0.89 (0.84 to 0.95)
VC	0.74 (0.65 to 0.83)	90.5 (82.2 to 98.8)	0.48 (0.23 to 0.74)	0.99 (0.79 to 1)	0.92 (0.87 to 0.97)
FEV_1/FVC	0.81 (0.72 to 0.90)	59.3 (54.2 to 64.3)	0.81 (0.64 to 0.97)	0.81 (0.64 to 0.96)	0.86 (0.79 to 0.93)
RV	0.74 (0.65 to 0.84)	117 (75.6 to 158.4)	0.84 (0.56 to 1)	0.65 (0.38 to 0.91)	1.02 (1.01 to 1.04)
DL_{CO}	0.79 (0.70 to 0.88)	56.5 (46.0 to 67.0)	0.74 (0.55 to 0.94)	0.84 (0.65 to 1)	0.90 (0.85 to 0.95)
sDL_{CO}	0.94 (0.88 to 0.99)	50.5 (43.7 to 57.4)	0.97 (0.88 to 1)	0.90 (0.81 to 0.99)	0.84 (0.77 to 0.91)
sDL_{NO}	0.79 (0.71 to 0.87)	73.5 (53.9 to 93.1)	0.68 (0.44 to 0.91)	0.90 (0.65 to 1)	0.93 (0.90 to 0.96)
sDL_{NO}/sDL_{CO} ratio	0.77 (0.68 to 0.87)	123.5 (116 to 131)	0.61 (0.39 to 0.83)	0.94 (0.69 to 1)	1.09 (1.04 to 1.14)
Vc	0.95 (0.90 to 1)	39.5 (35.5 to 43.5)	0.97 (0.90 to 1)	0.94 (0.86 to 1)	0.82 (0.75 to 0.90)

Figure 1 Relationships between % CT volume of emphysema and all variables of lung function.

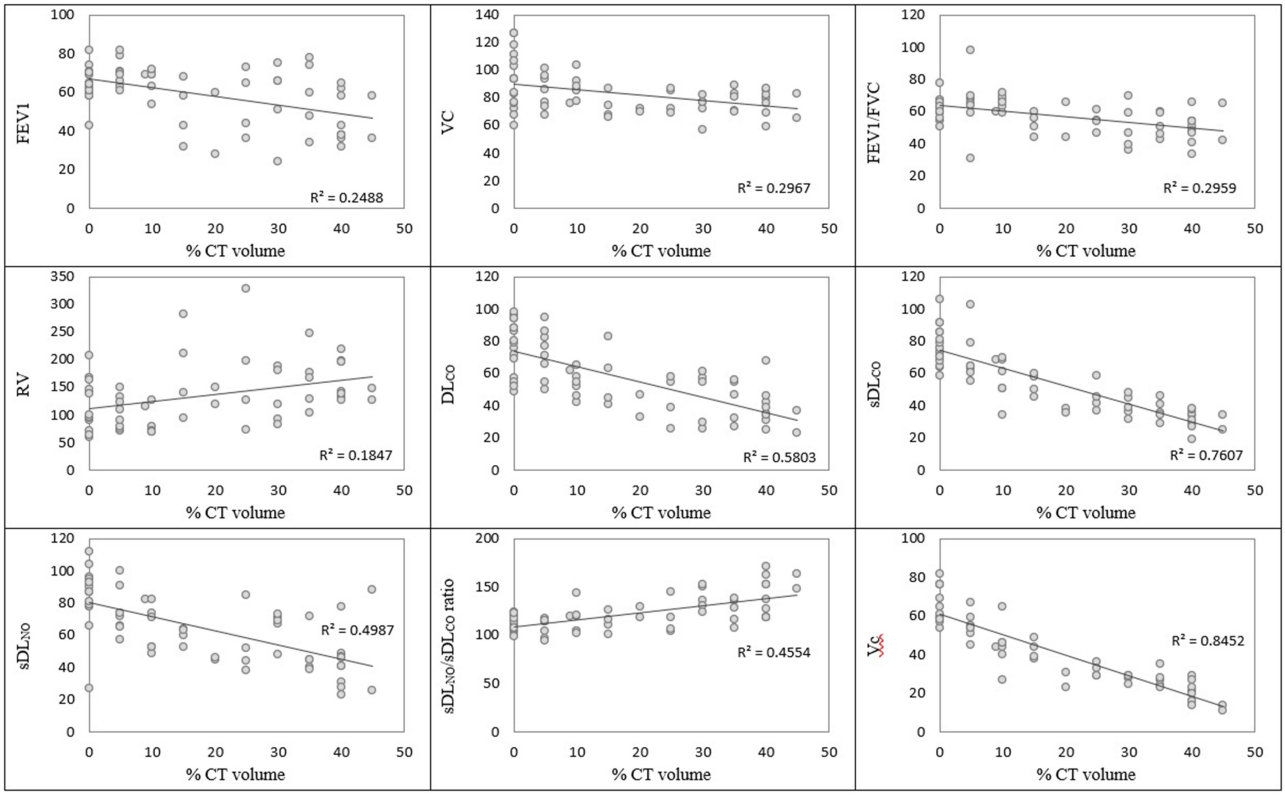


Figure 2 ROC and AUC analysis.
Abbreviations: AUC, area under the curve; DOR, diagnostic odds ratio.

Finally, based on ROC analysis, all models (with the exception of model 1) had better predicted power (AUC > 0.90), sensitivity (>0.87) and specificity (>0.90) than each lung parameter alone (Figure 4).

Additionally, the scenario analysis based on z-scores (instead of % predicted) confirmed the results of the base case (Table S4, Figures S1 and S2).

Table 3 Reduced Logistic Models, Results Were Presented as Odds Ratio and 95% Confidence Intervals

Predictors	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
FEV_1	0.85 (0.78 to 0.94)					
VC		0.84 (0.72 to 0.99)	1.03 (1.00 to 1.06)			
FEV_1/FVC		0.82 (0.7 to 0.96)				
RV				1.04 (1.02 to 1.06)	1.03 (1 to 1.06)	1.03 (1.00 to 1.06)
DL_{CO}				0.84 (0.76 to 0.93)		
sDL_{CO}					0.82 (0.74 to 0.91)	
sDL_{NO}		0.91 (0.84 to 0.97)	0.89 (0.84 to 0.95)			
sDL_{NO}/sDL_{CO} ratio	1.14 (1.05 to 1.23)	1.13 (1.04 to 1.23)	1.13 (1.04 to 1.22)			
Vc						0.81 (0.73 to 0.91)

(*Continued*)

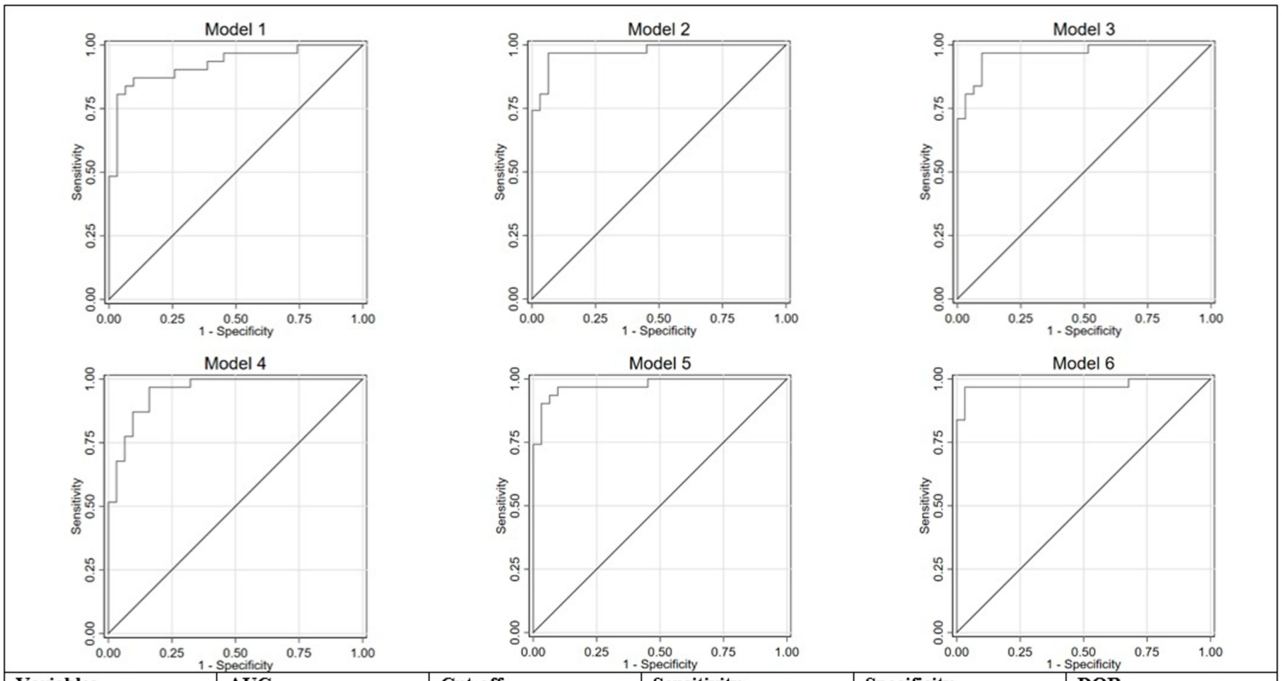
Table 3 (Continued).

Predictors	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Goodness to fit statistics						
AIC	47.698	36.073	39.656	38.936	30.213	29.876
BIC	54.079	46.708	48.164	45.317	36.594	36.258
Log-likelihood	−20.849	−13.036	−15.828	−16.468	−12.106	−11.94
Pseudo R^2	0.515	0.697	0.6317	0.617	0.718	0.722

Discussion

COPD is a chronic and progressive respiratory condition characterized by different clinical presentations that can recognize heterogeneous pathogenetic determinants.[1,5,7] The identification of the prevailing structural damage (such as, the prevailing obstruction rather than the prevailing parenchymal destruction – emphysema) would be of great clinical value as the therapeutic options, the strategy of management, the short- and long-term therapeutic outcomes, and the overall impact of COPD can result substantially different.[13,17,30]

Though warmly recommended since long ago, the parametrical recognition of the prevailing structural disorders underlying COPD (variably mixed in many cases) is not usually pursued in clinical practice and is not required in the vast majority of RCTs, likely due to technological limitations of many centers and because time-consuming and expensive. In general, a much more simplistic approach is currently privileged.[31] In fact, only a few simple spirometric parameters are currently used (namely, FEV_1 and FVC) even if biased by a too poor sensitivity and specificity in



Variables	AUC	Cut-off	Sensitivity	Specificity	DOR
Model 1	0.89 (0.81 to 0.96)	46.4 (32.5 to 60.30)	0.87 (0.74 to 1)	0.90 (0.82 to 0.99)	1.07 (1.04 to 1.10)
Model 2	0.95 (0.90 to 1)	58.1 (46.0 to 70.2)	0.97 (0.90 to 1)	0.94 (0.85 to 1)	1.08 (1.04 to 1.12)
Model 3	0.94 (0.88 to 0.99)	37.9 (14.9 to 61.0)	0.97 (0.89 to 1)	0.90 (0.81 to 1)	1.07 (1.04 to 1.10)
Model 4	0.90 (0.83 to 0.97)	37.3 (13.0 to 61.5)	0.97 (0.87 to 1)	0.84 (0.71 to 0.97)	1.06 (1.03 to 1.10)
Model 5	0.94 (0.89 to 0.99)	45.1 (15.8 to 74.4)	0.94 (0.85 to 1)	0.94 (0.86 to 1)	1.07 (1.04 to 1.11)
Model 6	0.97 (0.93 to 1)	38.2 (15.2 to 61.2)	0.97 (0.90 to 1)	0.97 (0.91 to 1)	1.08 (1.04 to 1.12)

Figure 3 Comparison of the 6 logistic models (the size of each circle is proportional to the Log-likelihood ie, bigger circles represent higher goodness to fit).

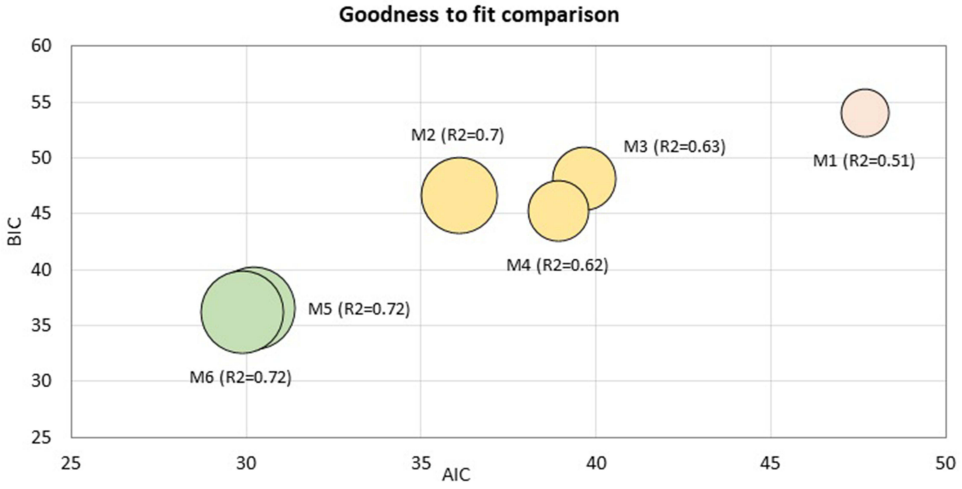


Figure 4 ROC and AUC analysis for the six models.
Abbreviations: AUC, area under the curve; DOR, diagnostic odds ratio.

describing the complexity and the heterogeneity of events characterizing COPD properly.[11,32–36] In particular, FEV_1 alone is not specific enough for recognizing all the structural changes occurring within the airways and/or the lung parenchyma and variably contributes to support COPD-related disorders and clinical signs.[13] Moreover, the FEV_1/FVC ratio, though widely used as the main diagnostic criterion for defining a persistent airflow limitation, is known to correlate with COPD patients' symptoms only partially.[37] However, FEV_1/FVC, further to minimize the extent of the current flow limitation (it actually represents the ratio between two forced volumes, and not between a forced and a static volume as the true Tiffeneau index would require) proved poorly related to changes in elastic recoil and parenchymal changes occurring in COPD.[38,39]

Parenchymal changes due to emphysema components can variably occur in COPD. Further to alterations and collapse of peripheral airways, they basically consist of destruction of lung parenchyma septa, thus involving both the alveolar and the vascular side of respiratory lung units at variable extent. In general, the presence of emphysema can be suggested by the lung function profile, usually characterized by a greater increase of static lung volumes, a dramatic reduction of forced flows and of DL_{CO}, and variable disorders in blood gas exchange, while dyspnea tends progressively to become the prevailing clinical sign.[36,40,41]

As the lung function assessment of emphysema components in COPD is infrequent in daily practice and in RCTs mostly due to technological limitations, organizational aspects, and cost,[42–44] the chest computed tomography (CT) is presently regarded (even if of limited use in daily practice for this purpose) as the most suitable method for detecting and assessing the extent of emphysema in COPD patients.[20–22]

However, the prevailing site of structural changes in the lung units (namely, occurring at the alveolar rather than at the vascular side of diffusing membrane) is only episodically investigated in COPD patients, and clinical consequences are unfrequently considered and discriminated. In other words, if the recognition of the different pathogenetic determinants underlying COPD remains insufficient and generic, as much generic and unspecific still remains the comprehensive term "COPD" for labeling the vast majority of cases.[45]

Nevertheless, the assessment of structural changes occurred within the parenchymal septa would contribute substantially to a proper comprehension of COPD and then to a more effective management of this complex respiratory condition. In our opinion, the investigational opportunity recently provided by the single-breath simultaneous assessment of the sDL_{NO}/sDL_{CO} ratio, and Vc represents a significant step forward from this point of view, also when considering that any back tension interference is avoided and that the presence of NO does not affect the measured DL_{NO} or DL_{CO}. When compared obtained with current DL_{CO} measures, this recent non-invasive lung function method seems actually to provide superior and more specific information on the type, site and extent of structural changes caused by emphysema-related parenchymal damage in COPD, thus contributing to its phenotyping.

In other words, this diagnostic procedure seems to validate with high sensitivity and specificity the hypothesis that the loss of microvascular structures involving the diffusion membrane would correspond to the emphysema phenotype of COPD in these cases, though to a variable extent. It should be emphasized that the CT imaging was corresponding to the values of these novel and specific diffusive parameters in all patients investigated.

When compared to cut-off values from normal individuals,[46] the very low values of sDL_{CO}, sDL_{NO}/sDL_{CO} ratio and Vc assessed in a not negligible proportion of those patients previously labelled as "emphysema patients" by their CT imaging clearly show that the microvascular blood volume is substantially impaired and reduced within their lung parenchyma. As their peculiar diffusive pattern is of variable extent, it would also contribute to easily rank the patients' extension and severity of emphysema components in these cases and then to easily phenotype their COPD by its prevailing pathogenetic component. However, in those patients where the involvement of the airways represents the prevailing lung function pattern, either the sDL_{NO}/sDL_{CO} ratio and Vc prove preserved. A lower destructive component can then be presumed with a higher probability in these cases that would be more properly identified as "obstructive chronic bronchitis" with a negligible or absent emphysema component.

In the present study, six different combinations of independent lung parameters were tested in order to detect the presence of emphysema in COPD patients. RV and the sDL_{NO}/sDL_{CO} ratio were the most frequent predictors (they appeared in 3 and 4 models over 6, respectively). When compared to each spirometric or diffusive parameter alone, the combination of at least one spirometric and one novel diffusive parameter proved much more effective and was associated with a greater predictive power, sensitivity and specificity in all models. In particular, RV coupled with sDL_{CO} or Vc was associated with a sensitivity >0.90 and a specificity of 0.97, respectively. Models based on spirometric and diffusive parameters calculated as % predicted or those based on z-scores lead to superimposable conclusion.

The present paper has some points of weakness: a) the study consists of a pivotal monocentric research project, and the sample size was then limited; b) the threshold for "significant emphysema" was empirically stated by CT imaging. Point of strength are: a) the study represents, to the best of our knowledge, the very first investigation designed for assessing and comparing non-invasively the pattern of pulmonary microvascular loss in COPD with different extent of parenchymal destruction due to emphysema; b) novel parameters that investigate simultaneously both the alveolar and the vascular side of lung diffusion (namely, the sDL_{NO}/sDL_{CO} ratio and Vc) were adopted for the first time in the clinical setting with the aim to phenotype the main pathogenetic components of COPD; c) proper and strict statistical models were adopted.

Conclusions

The single-breath simultaneous assessment of sDL_{NO}, sDL_{CO} and related parameters (namely, the sDL_{NO}/sDL_{CO} ratio and Vc) may contribute significantly to the easy recognition and assessment of the emphysema component in COPD) that are usually neglected in daily clinical practice. A rapid phenotyping of COPD can then be easily achieved only by adding the, simultaneous assessment of sDL_{NO} and sDL_{CO} to some basic spirometric indices (namely RV).

As this diagnostic procedure is simple to obtain, not time-consuming, and at low cost, it would be recommended for investigating COPD more properly in clinical practice and also in RCTs, particularly when different therapeutic strategies should be investigated in homogeneous clusters of patients.

The rapid discrimination of the prevailing structural damage (such as, obstructive and/or destructive) underlying COPD would also be of critical value in terms of those personalized therapeutic actions to be taken in the perspective of a more effective "precision medicine".

Ethics

The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session of May 2, 2021. This study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent prior to enrollment.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Celli B, Fabbri L, Criner G, et al. Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. *Am J Respir Crit Care Med*. 2022;206(11):1317–1325. doi:10.1164/rccm.202204-0671PP
2. Mannino DM, Higuchi K, Yu TC, et al. Economic burden of chronic obstructive pulmonary disease by presence of comorbidities. *Chest*. 2015;147:199–201.
3. Dal Negro RW. COPD: the annual cost-of-illness during the last two decades in Italy, and its mortality predictivity power. *Healthcare*. 2019;7 (1):35. doi:10.3390/healthcare7010035
4. Iheanacho I, Zhang S, King D, Rizzo M, Ismaila AS. Economic burden of Chronic Obstructive Pulmonary Disease (COPD): a systematic literature review. *Int J Chron Obstruct Pulmon Dis*. 2020;15:439–460. doi:10.2147/COPD.S234942
5. Snider GL. Chronic obstructive pulmonary disease: a definition and implications of structural determinants of airflow obstruction for epidemiology. *Am Rev Respir Dis*. 1989;140(3_pt_2):S3–8. doi:10.1164/ajrccm/140.3_Pt_2.S3
6. Fabbri LM, Romagnoli M, Corbetta L, et al. Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2003;167(3):418–424. doi:10.1164/rccm.200203-183OC
7. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350 (26):2645–2653. doi:10.1056/NEJMoa032158
8. Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest*. 2003;124(2):474–481. doi:10.1378/chest.124.2.474
9. Marsh SE, Travers J, Weatherall M, et al. Proportional classifications of COPD phenotypes. *Thorax*. 2008;63(9):761–767. doi:10.1136/thx.2007.089193
10. Sobradillo P, Garcia-Aymerich J, Agusti A. Clinical phenotypes of COPD. *Arch Bronchopneumol*. 2010;46:s8–11. doi:10.1016/S0300-2896(10)70056-9
11. Han MK, Agusti A, Calverly PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med*. 2010;182(5):598–604. doi:10.1164/rccm.200912-1843CC
12. Vestbo J. COPD: definition and phenotypes. *Clin Chest Med*. 2014;35(1):1–6. doi:10.1016/j.ccm.2013.10.010
13. Sheikh K, Coxon H, Parraga G. This is what COPD looks like. *Respirology*. 2016;21(2):224–236. doi:10.1111/resp.12611
14. Rogliani P, Ora J, Puxeddu E, Cazzola M. Airflow obstruction: is it asthma or is it COPD? *Int J Chron Obstruct Pulmon Dis*. 2016;11:3007–3013. doi:10.2147/COPD.S54927
15. Calle Rubio M, Casamor R, Miravitlles M. Identification and distribution of COPD phenotypes in clinical practice according to Spanish COPD Guidelines: the FENEPOC study. *Int J Chron Obstruct Pulmon Dis*. 2017;9(12):2373–2383. doi:10.2147/COPD.S137872
16. Fragoso E, Andre S, Boleo-Tome JP, Arelas V, Munha J, Cardoso J. Understanding COPD: a vision on phenotypes, comorbidities and treatment approach. *Rev Port Pneumol*. 2016;22(2):101–111. doi:10.1016/j.rppnen.2015.12.001
17. Siafakas N, Corlateanu A, Fouka E. Phenotyping before starting treatment in COPD? *COPD*. 2017;14(3):367–374. doi:10.1080/15412555.2017.1303041
18. Segal LN, Martinez FJ. Chronic obstructive pulmonary disease subpopulations and phenotyping. *J Allergy Clin Immunol*. 2018;141(6):1961–1971. doi:10.1016/j.jaci.2018.02.035
19. Polverino F, Sam A, Guerra S. COPD: to be or not to be, that is the question. *Am J Med*. 2019;132(11):1271–1278. doi:10.1016/j.amjmed.2019.04.047
20. Guenard H, Varene N, Vaida P. Determination of lung capillary blood volume and membrane diffusing capacity by measurement of NO and CO transfer. *Respir Physiol*. 1987;70(1):113–120. doi:10.1016/S0034-5687(87)80036-1
21. Borland CDR, Hughes JMB. Lung diffusing capacities (DL) for nitric oxide (NO) and carbon monoxide (CO): the evolving story. *Compr Physiol*. 2020;10:73–97.
22. Gibson QH, Roughton FJW. The kinetics and equilibria of the reactions of nitric oxide with sheep haemoglobin. *J Physiol*. 1957;136(3):507–524. doi:10.1113/jphysiol.1957.sp005777
23. Giraud X, Le-Dong NN, Hogben K, Martinot JB. The measurement of DLNO and DLCO: a manufacturer's perspective. *Respir Physiol Neurobiol*. 2017;241:36–44. doi:10.1016/j.resp.2017.02.006
24. Graham BL, Brusasco V, Burgos F, et al. ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. 2017;49 (1):1600016. doi:10.1183/13993003.00016-2016
25. Roughton FJ, Forster RE. Relative importance of diffusion and chemical reaction in determining rate of exchange of gases in the human lung. *J Appl Physiol*. 1957;11(2):290–302. doi:10.1152/jappl.1957.11.2.290
26. Barisone G, Brusasco V. Lung diffusing capacity for nitric oxide and carbon monoxide following mild-to-severe COVID-19. *Physiol Rep*. 2021;9 (4):e14748. doi:10.14814/phy2.14748
27. Borland CD, Dunningham H, Bottrill F, et al. Significant blood resistance to nitric oxide transfer in the lung. *J Appl Physiol*. 2010;108 (5):1052–1060. doi:10.1152/japplphysiol.00904.2009
28. Zavorsky GS, Hsia CCW, Hughes MB, et al. Standardisation and application of the single-breath determination of nitric oxide uptake in the lung. *Eur Respir J*. 2017;49(2):1600962. doi:10.1183/13993003.00962-2016

29. Woolson RF, Clarke WR. *Statistical Methods for the Analysis of Biomedical Data*. Second ed. New York: John Wiley & Sons. Inc; 2002.
30. Fletcher CM, Peto R. The natural history of chronic airflow obstruction. *Br Med J*. 1977;1(6077):1645–8A. doi:10.1136/bmj.1.6077.1645
31. Segreti A, Stirpe E, Rogliani P, Cazzola M. Defining phenotypes in COPD: an aid to personalized healthcare. *Mol Diagn Ther*. 2014;18 (4):381–388. doi:10.1007/s40291-014-0100-9
32. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis management and prevention of COPD, 2023
33. Macklem PT, Mead J. Resistance of central and peripheral airways measured by a retrograde catheter. *J Appl Physiol*. 1967;22(3):395–401. doi:10.1152/jappl.1967.22.3.395
34. Pinto LM, Alghamdi M, Benedetti A, Zaihara T, Landry T, Bourbeau J. Derivation and validation of clinical phenotypes for COPD: a systematic review. *Respir Res*. 2015;16(1):50. doi:10.1186/s12931-015-0208-4
35. Global initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Accessed: March 30, 2015. Available from: http://www.goldcopd.org/uploads/users/files/GOLD.
36. Lange P, Halpin DM, O'Connell DE, MacNee W. Diagnosis, assessment, and phenotyping o, COPD beyond FEV1. *Int J Chron Obstruct Pulmon Dis*. 2016;11(Spec Iss):3–12. doi:10.2147/COPD.S85976
37. Dal Negro RW, Carone M, Cuttitta G, on behalf of the CLIMA Study Group, et al. Prevalence and clinical features of most frequent phenotypes in the Italian COPD population: the CLIMA Study. *Multidiscip Respir Med*. 2021;16:790. doi:10.4081/mrm.2021.790
38. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax*. 2001;56(11):880–887. doi:10.1136/thorax.56.11.880
39. Puente-Maestu L, Stringer WW. Hyperinflation and its management in COPD. *Int J Chron Obstruct Pulmon Dis*. 2006;1(4):381–400. doi:10.2147/copd.2006.1.4.381
40. Janson C, Malinovschi A, Amaral AFS, et al. Bronchodilator reversibility in asthma and COPD: findings from three large population studies. *Eur Respir J*. 2019;54(3):1900561. doi:10.1183/13993003.00561-2019
41. Burrows B, Fletcher CM, Heard BE, Jones NL, Wootliff JS. The emphysematous and bronchial types of chronic airways obstruction. A clinicopathological study of patients in London and Chicago. *Lancet*. 1966;87(7442):830–835. doi:10.1016/S0140-6736(66)90181-4
42. Pistolesi M, Camiciottoli G, Paoletti M, et al. Identification of a predominant COPD phenotype of COPD in clinical practice. *Respir Med*. 2008;102 (3):367–376. doi:10.1016/j.rmed.2007.10.019
43. BOLD Collaborative Research Group, the EPI-SCAN Team, the PLATINO Team, and the PREPOCOL Study Group, Lamprecht B, Soriano JB, Studnicka M, et al. Determinants of underdiagnosis of COPD in national and international surveys. *Chest*. 2015;148(4):971–985. doi:10.1378/chest.14-2535
44. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. *Respirology*. 2016;21(1):14–23. doi:10.1111/resp.12660
45. Axelsson M, Backman H, Nwaru BI, et al. Underdiagnosis and misclassification of COPD in Sweden - A Nordic Epilung study. *Respir Med*. 2023;217:107347. doi:10.1016/j.rmed.2023.107347
46. Dal Negro RW, Turco P, Povero M. Phenotyping lung function disorders in respiratory Long-COVID. *Brit J Multidiscip Adv Studies: Health Med Sci*. 2023;4(3):71–83. doi:10.37745/bjmas.2022.0219