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Ventilation Heterogeneity in Asthma and COPD: The Value of the Poorly Communicating Fraction as the Ratio of Total Lung Capacity to Alveolar Volume

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Keywords
Ventilation heterogeneity · Asthma · Chronic obstructive pulmonary disease · Poorly communicating fraction · Multiple-breath nitrogen washout

Abstract
Background: The ventilation heterogeneity (VH) is reliably assessed by the multiple-breath nitrogen washout (MBNW), which provides indices of conductive (S_{cond}) and acinar (S_{acin}) VH as well as the lung clearance index (LCI), an index of global VH. VH can be alternatively measured by the poorly communicating fraction (PCF), that is, the ratio of total lung capacity by body plethysmography to alveolar volume from the single-breath lung diffusing capacity measurement. ***Objectives:*** Our objective was to assess VH by PCF and MBNW in patients with asthma and with COPD and to compare PCF and MBNW parameters in both patient groups. ***Method:*** We studied 35 asthmatic patients and 45 patients with COPD. Each patient performed spirometry, body plethysmography, diffusing capacity, and MBNW test. ***Results:*** Compared to COPD patients, asthmatics showed a significantly lesser degree of airflow obstruction and lung hyperinflation. In asthmatic patients, both PCF and LCI and S_{acin} values were significantly lower than the corresponding ones of COPD patients. In addition, in both patient groups, PCF showed a positive correlation with LCI ($p < 0.05$) and S_{acin} ($p < 0.05$), but not with S_{cond}. Lastly, COPD patients with PCF >30% were highly likely to have a value ≥2 of the mMRC dyspnea scale. ***Conclusions:*** These results showed that PCF, a readily measure derived from routine pulmonary function testing, can provide a comprehensive measure of both global and acinar VH in asthma and in COPD patients and can be considered as a comparable tool to the well-established MBNW technique.

Introduction

In healthy individuals, the uniform distribution of minute ventilation can minimize the work of breathing and maximize the efficiency of the lung as a gas exchanger [1]. Nonuniform distribution of inspired gas within the lung, termed ventilation heterogeneity (VH), occurs in patients with asthma [2, 3] or with chronic obstructive pulmonary disease (COPD) [4], even in those with mild severity degree of disease, thereby being a fundamental

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impairment of lung function. It is of note that in asthmatic patients, the degree of VH was found to be linked to the degree of airway hyperresponsiveness, a hallmark feature of disease [5] and to asthma control [6]. In addition, in patients with COPD, the uneven ventilation distribution was found to be a sensitive marker of early physiological impairment [7, 8] and disease progression [9].

The VH can be routinely and reliably assessed by both single- and multiple-breath nitrogen washout (SBNW and MBNW) techniques [10]. The advantage of using MBNW rather than SBNW consists of the possibility to anatomically locate the airway impairment in the conducting airways or in the distal small airways, since MBNW can provide indices of conductive (S_{cond}) and acinar (S_{acin}) VH in addition to the lung clearance index (LCI), considered as an index of global VH [11–14]. Despite its sensitivity, the SBNW is not specific to distal small airway dysfunction, and changes in any of the generations of the conducting airways can affect phase III slope [12]. Furthermore, the SBNW showed a lower reproducibility than that of MBNW [11]. On the other hand, it is of note that both techniques are not entirely easy to perform [11, 12, 14, 15].

Interestingly, an alternative and easy to perform physiological measurement of VH, the so-called "poorly communicating fraction" (PCF) [16, 17], has been successfully evaluated in COPD patients. The PCF is the ratio of total lung capacity (TLC) derived from plethysmography to alveolar volume (VA) [16, 17]. VA is the maximum alveolar volume that is traced by the inert gas inhaled during a single breath from residual volume to TLC through an inspiratory vital capacity maneuver. VA is usually derived from the single-breath lung diffusion capacity for the carbon monoxide (DL_{CO}) maneuver [18]. In COPD patients, the PCF was found to be moderately related to the ventilation defect measured by pulmonary functional magnetic resonance imaging [17] and was able to predict exercise intolerance [16]. In a large cohort of mixed patients with respiratory symptoms requiring pulmonary function testing assessment, PCF was related to airway response to methacholine challenge [19]. However, up to now, PCF has not been specifically addressed to evaluate VH in asthmatic patients and has not been compared to other routine and well-established measurements of VH, such as the MBNW technique. The aim of the present study was, therefore, to assess VH by means of PCF and of MBNW technique in asthmatic patients and in patients with COPD, enrolled in clinically stable conditions, and to evaluate the relationship between PCF and MBNW parameters in both patient groups.

Materials and Methods

Subjects

Patients with asthma diagnosed according to the GINA criteria [20] and patients with COPD diagnosed according to the GOLD criteria [21] were eligible to take part in the study and were prospectively recruited from our Lung Function Outpatient Clinic. Asthmatic and COPD patients with (a) an exacerbation in the 8 weeks prior to enrollment, (b) other coexisting lung diseases (restrictive diseases or bronchiectasis), and (c) severe comorbidities, such as uncontrolled cardiovascular disease or cancer, were excluded. In each patient, age, gender, BMI (kg/m^2), smoking habit, and current therapy were recorded.

In asthmatic patients, the disease control was assessed by using the Italian version of the Asthma Control Test (ACT) [22]. In COPD patients, the subjective impact of the disorder on the lifestyle of these patients and the daily living activity-related dyspnea were assessed by the COPD Assessment Test (CAT) score (Italian version) [23] and the Italian version of the 5-point MRC scale modified by the ATS [24], respectively. All patients performed spirometry, body plethysmography, diffusing capacity, and MBNW test.

The study protocol was approved by the Ethics Committee for the Province of Parma, Italy, and was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki. All enrolled patients gave their informed consent.

Spirometry, Body Plethysmography, and Diffusing Capacity

In all patients, spirometry and body plethysmography were performed by using a flow-sensing spirometer and a body plethysmograph connected to a computer for data analysis (V_{max} 22 and 6200; SensorMedics, Yorba Linda, CA, USA) [25]. FEV_1 and FVC were recorded and expressed as absolute values (L) and percentage of predicted value (% pred.); FEV_1/FVC, expressed as a ratio, was taken as an index of airway obstruction.

Thoracic gas volume was measured by body plethysmography with the subject panting against a closed shutter at a frequency slightly <1 Hz and their cheeks supported by their hands. TLC (as absolute value in L and as % pred.) was obtained as the sum of thoracic gas volume and linked IC. IC/TLC, expressed as a ratio, was taken as an index of hyperinflation of the lung at rest.

At least 3 measurements were made for each spirometry and lung volume variable to ensure reproducibility, and the highest value was used in subsequent calculations. The flow-sensor was calibrated before each test using a 3-L syringe.

DLco (% pred.), the CO transfer coefficient (K_{CO}, % pred.), and VA (as absolute value in L and as % pred.) were measured by the single-breath method using a mixture of carbon monoxide and methane and were measured at least in duplicate [18]. PCF was calculated by means of the following formula: 1 – (VA/TLC) (%) [16, 17].

Multiple-Breath Nitrogen Washout

MBW testing was performed according to a standard procedure [26]. In brief, patients were asked to wear a nose clip and were seated with their lips sealed tightly around the mouthpiece, which was connected to a gas analyzer (EXHALYZER® D; ECO MEDICS AG, Dürnten, Switzerland). They inhaled 100% oxygen from end-expiratory lung volume while breathing with a fixed tidal volume and respiratory rate, helped by a visual breathing pattern feedback, until the nitrogen concentration in the exhaled volume

Table 1. Demographic and lung function characteristics of 35 asthmatic patients (22 females) and 45 COPD patients (13 females)

	Asthmatic patients		COPD patients		*p* value
Age, years	54±14	(21–77)	68±8	(51–82)	*0.001*
BMI, kg/m^2	27±4	(18–39)	26±3	(17–33)	*0.045*
TLC, % pred.	105±12	(83–126)	122±16	(87–154)	*0.001*
FEV_1, % pred.	93±16	(64±135)	53±20	(26±106)	*0.001*
FEV_1/VC, %	71±9	(49–88)	46±11	(27–68)	*0.001*
IC/TLC, %	48±6	(30–58)	31±8	(18–48)	*0.001*
DL_{CO}, % pred.	90±12	(70–116)	56±17	(21–94)	*0.001*
K_{CO}, % pred.	97±18	(64–144)	67±20	(30–108)	*0.001*
VA, % pred.	96±11	(64–117)	87±17	(52–121)	*0.007*
PCF, %	11±7	(1–30)	29±13	(0–64)	*0.001*
LCI	11.6±3.3	(7.6–19.1)	14.4±3.6	(7.6–25.1)	*0.001*
S_{cond}, L^{-1}	0.023±0.014	(0–0.053)	0.027±0.024	(0–0.112)	*0.399*
S_{acin}, L^{-1}	0.146±0.105	(0.015–0.387)	0.458±0.173	(0.100–0.847)	*0.001*

Values are expressed as mean ± SD (range). TLC, total lung capacity; VA, alveolar volume; PCF, poorly communicating fraction; LCI, lung clearance index.

reached 1/40th or 2.5% of the initial concentration of the resident nitrogen in the lungs for 3 consecutive breaths. Each test lasted about from 2 to 10 min and was performed at least 2 times to ensure the reproducibility.

From MBNW testing, we obtained LCI, S_{cond}, S_{acin}, and ventilated FRC (FRC_{MBNW}). LCI was obtained as a ratio between the cumulative expired volume of the inert gas over the FRC_{MBNW}. S_{cond} and S_{acin} (in L^{-1}) were derived from phase III slopes of the nitrogen spirogram, and their value increases when VH increases [26].

Statistical Analysis

A Shapiro-Wilk test was used to assess the normality of distribution in all variables. Data were reported as means ± standard deviation for the variables with normal distribution and as median [25th–75th percentile] for those with a nonnormal distribution. An unpaired *t* test, a Mann-Whitney test, and Pearson's χ^2 test were used for comparisons when appropriate. Relationships between variables were assessed by Pearson correlation coefficient (*r*) or by Spearman's rank correlation coefficient (ρ), depending on the distribution. A linear regression analysis was performed for those values that showed a significant correlation. The ROC curve method [27] was used to plot the true-positive rate (sensitivity) in function of the false-positive rate (100 − specificity) for a cutoff point of PCF with respect to mMRC ≥2 as the threshold value. A *p* value <0.05 was considered significant.

Results

We consecutively studied 35 patients (22 females) with clinically stable asthma, aged between 21 and 77 years, and 45 patients (13 females) with clinically stable COPD, aged between 51 and 82 years. Demographic characteristics of the asthmatic and COPD patients are shown in Table 1.

At study entry, asthmatic patients were receiving short-acting β_2-agonists prn (25%) or long-acting β_2-agonists plus inhaled corticosteroids (75%), and 15% were smokers or ex-smokers. Moreover, COPD patients were receiving long-acting β_2-agonists (98%), inhaled steroids (80%), and long-acting muscarinic antagonists (78%); all of them were smokers or ex-smokers.

Asthmatics were significantly younger and had a greater BMI than COPD patients (Table 1). Median [25th–75th percentile] and range values of ACT in asthmatics and of CAT and mMRC in COPD patients were 23 [21–25] and 12–25 and 11 [6–15] and 4–26 and 1 [1–2] and 0–3, respectively.

As compared to COPD patients, asthmatic patients showed a significantly lesser degree of airflow obstruction and lung hyperinflation (Table 1). In addition, in asthmatic patients, both PCF and LCI and S_{acin} values were significantly lower than those of COPD patients (Table 1). Both in asthmatics and in COPD patients, PCF showed a negative correlation with FEV_1/FVC ($r = -0.478$, $p = 0.004$, and $r = -0.523$, $p = 0.0001$) and IC/TLC ($r = -0.414$, $p = 0.014$, and $r = -0.604$, $p = 0.0001$) and no correlation with K_{CO}.

With respect to MBNW parameters, both in asthmatic patients and in COPD patients, PCF showed a positive correlation with LCI ($r = 0.397$, $p = 0.018$, and $r = 0.477$,

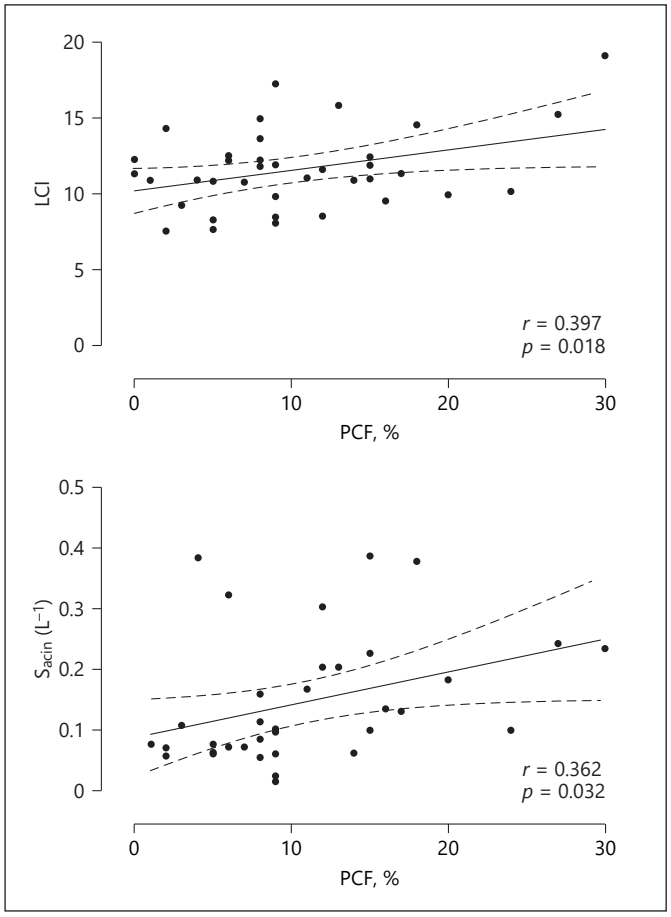

Fig. 1. Relationship between PCF and LCI (upper panel) and S_{acin} (lower panel) in 35 asthmatic patients. Regression analysis showed that LCI = 0.15 × PCF (%) + 9.93 (r^2 = 0.157) and S_{acin} (L^{-1}) = 0.0054 × PCF (%) + 0.087 (r^2 = 0.131). PCF, poorly communicating fraction; LCI, lung clearance index.

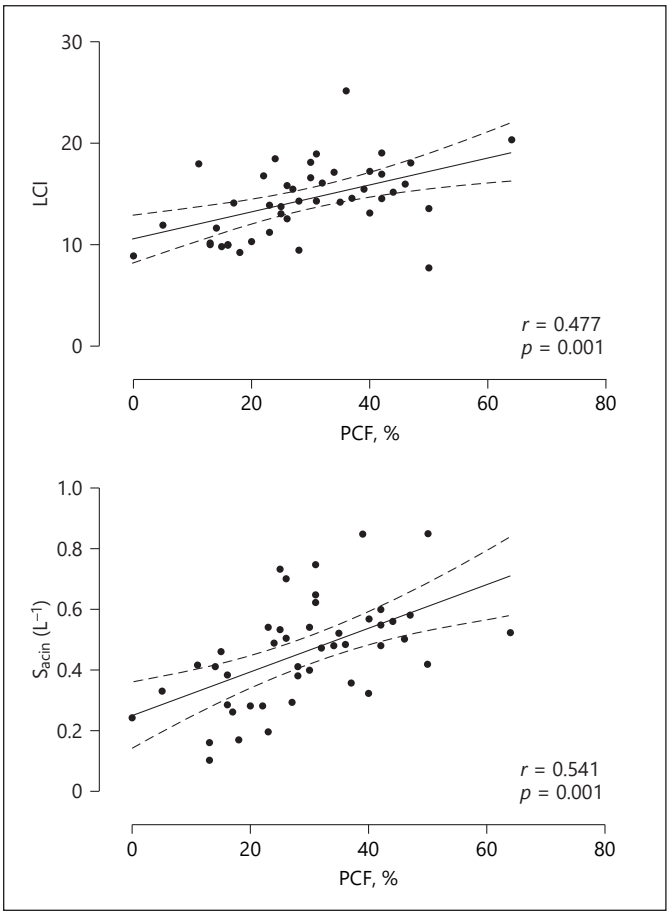

Fig. 2. Relationship between PCF and LCI (upper panel) and S_{acin} (lower panel) in 45 COPD patients. Regression analysis showed that LCI = 0.133 × PCF (%) + 10.53 (r^2 = 0.227) and S_{acin} (L^{-1}) = 0.0072 × PCF (%) + 0.25 (r^2 = 0.293). PCF, poorly communicating fraction; LCI, lung clearance index.

p = 0.001) and S_{acin} (r = 0.362, p = 0.032, and r = 0.541, p = 0.001), but no correlation with S_{cond} (shown in Fig. 1, 2). Regression analysis showed that LCI = 0.15 × PCF (%) + 9.93 (r^2 = 0.157) and LCI = 0.133 × PCF (%) + 10.53 (r^2 = 0.227) in asthmatic and COPD patients, respectively, and S_{acin} (L^{-1}) = 0.0054 × PCF (%) + 0.087 (r^2 = 0.131) and S_{acin} (L^{-1}) = 0.0072 × PCF (%) + 0.25 (r^2 = 0.293) in asthmatic and COPD patients, respectively.

PCF was not related to ACT in asthmatics or to CAT in COPD patients, whereas it was positively related to mMRC in COPD patients (ρ = 0.439, p = 0.002). Additionally, according to the ROC curve method, the plot of the true-positive rate in function of the false-positive rate for a cutoff point of PCF with respect to an mMRC ≥2 as the threshold value showed 0.763 area under curve value (p = 0.009). A cutoff point, which maximized sensitivity and specificity, was PCF >30% (0.91 sensitivity and 0.71 specificity). In addition, in COPD patients, the ratio between the number of patients with mMRC ≥2 and that of patients with mMRC <2 was significantly higher in patients with PCF >30% as compared to that of patients with PCF ≤30% (10/12 vs. 1/22; χ^2 = 10.288, p = 0.002) (shown in Fig. 3).

Discussion

In the present study, we assessed VH by means of PCF and MBNW testing in a cohort of clinically stable patients, consisting of asthma patients and COPD patients,

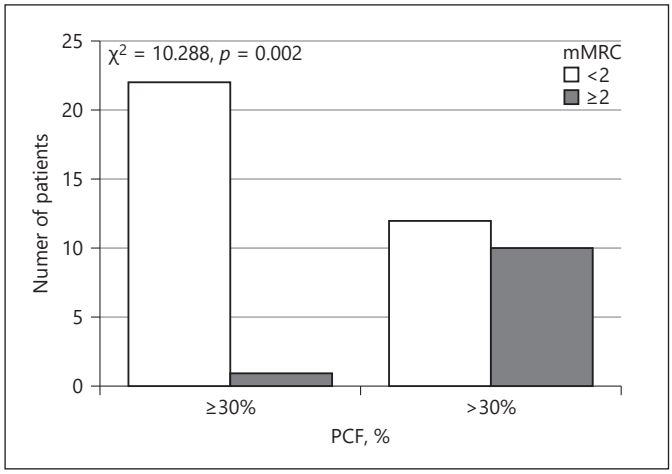

Fig. 3. Number of patients categorized by mMRC <2 or ≥2 in relation to PCF value ≤30% or >30%. The ratio between the number of patients with mMRC ≥2 and that of patients with mMRC <2 was significantly higher in patients with PCF >30% as compared to that of patients with PCF ≤30% (10/12 vs. 1/22; $\chi^2 = 10.288$, $p = 0.002$). PCF, poorly communicating fraction.

and we evaluated PCF as related to MBNW parameters in both patient groups. We found that asthmatic patients significantly differ in PCF and in LCI and S_{acin} values, but not in S_{cond} values, as compared to COPD patients. In addition, we found that PCF was significantly related to LCI and S_{acin} in both patient groups, but not to S_{cond}. Lastly, in COPD patients, PCF was strictly linked to the daily living activity-related dyspnea assessed by means of the mMRC scale.

In patients with obstructive pulmonary disease, VH is a very common, if not a peculiar, finding and is a result of uneven behavior of mechanical time constants, that is, the product of resistance multiplied by compliance, which consequently may induce asynchronous and inhomogeneous ventilation [28]. Inert gases dilution testing can provide relevant information regarding inspired gas misdistribution, incomplete gas mixing, and trapped gas volume [29, 30]. These tests are based on the notion that the fraction of an inert gas, such as helium or methane, recovered at the end expiration is inversely related to the number of lung units effectively participating in alveolar ventilation [29, 30]. Consequently, VH can be simply inferred by the extent to which VA derived from the DL_{CO} manoeuver underestimates TLC derived from plethysmography and can be expressed as PCF [16, 17].

In the present study, we found that asthmatic patients had less VH, measured by PCF, as compared to that of COPD patients. This result is not surprising given that in comparison with COPD patients, our asthmatic patients had a lesser degree of airflow obstruction and lung hyperinflation, which in turn can alter the uniformity of the mechanical time constant distribution. As expected, in our study, PCF was significantly related to the parameters of airflow obstruction and lung hyperinflation in both patient groups.

Interestingly, when assessed by means of MBNW, a significant difference was found between asthmatics and COPD patients in terms of acinar, expressed as S_{acin}, but not conductive VH, expressed as S_{cond}. It is of note that in a cross-sectional study by Jarenbäck et al. [31], COPD patients had increased S_{acin} but not S_{cond} values, when compared to those of both healthy subjects and smoking controls. Furthermore, it is worth noting that the S_{cond} values of our asthmatic and COPD patients were similar to those reported by Jarenbäck et al. [31] in COPD patients and controls. The finding of an increased VH in the acinar, but not conductive airways, in patients with asthma or with COPD, is plausible since the pathophysiology of both obstructive diseases is mostly located in the distal district of the lung.

In this study, we compared PCF to the MBNW test, which is a standardized measure of VH, and may be reliably used into the routine clinical practice [10]. We found that PCF was significantly related to LCI and to S_{acin} in both patient groups, but not to S_{cond}, and we provided the corresponding regression equations. Accordingly, PCF can be considered as a comprehensive measure of both global and acinar VH in asthma and in COPD patients. This finding is in line with the assumption that there may be 3 distinct causes of a low VA, when related to TLC: (1) incomplete alveolar expansion, (2) loss of lung units, and (3) poor mixing with misdistribution of inspired gas [30]. The 3 causes may coexist, and causes 2 and 3 can occur in patients with obstructive pulmonary disease [30].

In our COPD patients, PCF was significantly associated with the score of the mMRC scale. Notably, COPD patients with PCF >30% were highly likely to have an mMRC value ≥2, which is considered as a threshold for separating "less breathlessness" from "more breathlessness," when breathlessness is linked to the daily living activities [21]. Interestingly, a key finding of a previous study by Neder et al. [17] in a large cohort of COPD patients was the significant relationship between increased PCF, higher dyspnea score at the end of progressive exercise, and poorer exercise tolerance. Taken together, our results and those of the study by Neder et al. [17] show that PCF is a readily available physiological marker of lung mechanics impairment relevant to dyspnea on exertion.

A limitation of this study is that the cohort of asthmatics lacks severe patients, and conversely the cohort of patients with COPD lacks patients with mild disease. Accordingly, our results cannot be generalized to the entire population of asthma and COPD patients. However, the patient population considered in this study reflects the population of asthma patients and of patients with COPD, who usually refer to our outpatient clinic, and was not a result of a selection process.

In conclusion, the present study showed that PCF can be considered as a comparable tool to the MBNW test in the assessment of VH both in patients with asthma and in patients with COPD. In this context, it is worth noting that in order to measure the ventilation distribution heterogeneity, the MBNW is a more accurate but also more time-consuming test than PCF, which is on the contrary a measurement readily derived from routine pulmonary function testing. Further studies are required to ascertain the physiological meaning of PCF in different disease stages and whether or not this test is informative enough in making treatment decision for individualized patient care.

Statement of Ethics

This study was conducted in accordance with Good Clinical Practice and the current version of the revised Declaration of Helsinki (WMA Declaration of Helsinki). The study protocol was approved by the Ethics Committee of the Province of Parma, Italy. Written informed consent was obtained from each patient prior to enrollment.

Conflict of Interest Statement

All authors declare no conflicts of interest.

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Author Contributions

Roberta Pisi, Marina Aiello, and Giuseppina Bertorelli: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing – original draft (equal), and writing – review and editing (equal). Luigino Calzetta, Annalisa Frizzelli, Veronica Alfieri, and Giovanna Pisi: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing – original draft (equal), and writing – review and editing (equal). Alfredo Chetta: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (lead), investigation (equal), methodology (equal), project administration (equal), resources (lead), software (equal), supervision (equal), validation (equal), visualization (equal), writing – original draft (equal), and writing – review and editing (equal).

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