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Prevalence of Small-Airway Dysfunction among COPD Patients with Different GOLD Stages and Its Role in the Impact of Disease

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Keywords

Chronic obstructive pulmonary disease · Small-airway dysfunction · GOLD classification · COPD Assessment Test · Impact of disease

Abstract

Background: In chronic obstructive pulmonary disease (COPD) patients, small-airway dysfunction (SAD) is considered a functional hallmark of disease. However, the exact role of SAD in the clinical presentation of COPD is not yet completely understood; moreover, it is not known whether SAD may have a relationship with the impact of disease. ***Objectives:*** To evaluate the prevalence of SAD among COPD patients categorized by the old and the new GOLD classification and to ascertain whether there is a relationship between SAD and impact of disease measured by the COPD Assessment Test (CAT) questionnaire. ***Methods:*** We prospectively enrolled COPD outpatients from the University Hospital of Parma. Using the impulse oscillometry system (IOS), we assessed the fall in resistance from 5 to 20 Hz (R5–R20), reactance at 5 Hz (X5), and resonant frequency (F_{Res}) as markers of peripheral airway dysfunction. According to R5–R20 ≥0.07 or <0.07, the cohort was also categorized in patients with and without SAD, respectively. ***Results:*** We studied 202 patients. In both GOLD classifications, a progressive increasing distribution of R5–R20 and F_{Res} was reported with a decreasing of X5. Moreover, there was a significant correlation between R5–R20 and CAT ($r = 0.527$, $p < 0.001$). Finally, the presence of SAD (OR 11.96; 95% CI 4.53–31.58; $p < 0.001$) and use of ICS + LABA + LAMA (OR 5.31; 95% CI 1.88–15.02; $p = 0.002$) were independent predictors of higher impact (CAT score ≥10). ***Conclusion:*** In COPD patients, the presence of SAD, as assessed by IOS, progressively increases with GOLD classifications and it is closely related to the high impact of disease on health status.

Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide prevalent disease [1]. In 2006, according to international guidelines (Global Initiative for Chronic Obstructive Lung Disease, GOLD) [2], spirometric measurements defined by the forced expiratory volume in the 1st second (FEV_1) were required for the diagnosis and severity of COPD (GOLD stages 1, 2, 3, and 4). Considering COPD as a complex and heterogeneous disease requiring a multifaceted approach [3], in 2011, the GOLD Committee [4] proposed a new multidimensional system evaluating different degrees of severity by identifying 4 risk categories or groups (GOLD A, B, C, and D). Other than the FEV_1, this approach considers the history of previous ex-

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acerbations and the perceived impact of COPD on patients as new categorical variables [4]. Dyspnoea (measured by the modified Medical Research Council [mMRC] score) and health status (measured by the COPD Assessment Test [CAT] score) were then respectively considered to discriminate patients with more impact (mMRC score ≥2 and CAT score ≥10) from patients with less impact (mMRC score 0–1 and CAT score <10) [4].

In COPD patients, the small airways represent the key sites of airflow obstruction [5], and small-airway dysfunction (SAD) is considered a functional hallmark of disease [6, 7]. Although in COPD patients a significant correlation between SAD and quality of life (measured by St. George's Respiratory Questionnaire, SGRQ) and dyspnoea perception (measured by mMRC scale) [8] may occur, the exact role of SAD in the clinical presentation of COPD is not yet completely understood [9]. Moreover, it is not known whether SAD may have a relationship with the impact of disease.

In the context of lung function evaluation, the impulse oscillometry system (IOS), a type of forced oscillation technique, was recently proposed as a better way of detecting SAD than standard spirometry. In fact, while FEV_1 is mainly able to measure expiratory flow at high and mid volume [10], IOS provides measures of both proximal and distal airway resistance [11]. In COPD patients, IOS is useful to detect early phases of disease [12] or bronchodilator responsiveness [13], to define different subgroups of patients according to airflow obstruction [14], and to examine the effect of bronchodilator drugs [15].

Our study hypothesis was that, in COPD patients, SAD measured by IOS increases progressively according to the severity of disease assessed by both the old and new GOLD classifications. Therefore, the primary aim of our study was to evaluate the prevalence of SAD among COPD patients categorized by the old and new GOLD classifications. Moreover, the secondary aim was to ascertain whether or not there is a relationship between SAD and impact of disease on health status measured by the CAT questionnaire.

Material and Methods

Study Design and Cohort

This observational study was conducted at the University Hospital in Parma (Italy) over a period of 26 months between January 2014 and February 2016. The sampling method was systematic, and all patients who met criteria for COPD according to the GOLD guidelines [4] and were admitted to our outpatient clinic were considered for the study. We enrolled patients with: (a) a smoking history of ≥20 pack-years; (b) a postbronchodilator FEV_1/forced vital capacity (FVC) ratio of <0.7; and (c) a regular treatment over a period of 6 months. We excluded patients with: (a) an exacerbation in the 4 weeks prior to enrolment; (b) patients with another coexistent lung disease (asthma or bronchiectasis); (c) patients with severe comorbidities associated to COPD, such as unstable cardiovascular diseases or cancer; and (d) patients unable to perform all functional tests requested.

The study protocol was approved by the Ethics Committee for the Province of Parma, Italy (reference number: 44221/2014), and conducted in accordance with good clinical practices and the Declaration of Helsinki. All enrolled patients gave their informed consent.

General Measurements

In all patients, the following measures were recorded at enrolment: anthropometric variables (age, sex, and body mass index [BMI]), smoking habit (current/former) and number of packs per year, Charlson Index (score), number of previous exacerbations per year, CAT score (Italian version) [16], use of domiciliary medications (short-acting β-agonists; inhaled corticosteroids [ICS]; long-acting β-agonists [LABA]; and long-acting muscarinic antagonists [LAMA]). We used the CAT score [16], but not the mMRC scale, in order to assess symptoms and categorize COPD patients according to the new GOLD classification [4].

Spirometry and Reversibility Testing

Patients were advised to avoid inhaled bronchodilators 12 h before spirometry and reversibility testing. A flow-sensing spirometer connected to a computer for data analysis (Vmax 22 and 6200; SensorMedics, Yorba Linda, CA, USA) was used to measure lung parameters. FEV_1, FVC, and forced expiratory flow in the middle half of the patient's exhaled volume ($FEF_{25–75}$) were recorded and expressed as absolute values (liters) and as a percentage of predicted value (% pred.). The FEV_1/FVC value was recorded and expressed as a ratio. Functional residual capacity was measured by body plethysmography (Vmax 22 and 6200; SensorMedics). Total lung capacity (TLC) was obtained as the sum of functional residual capacity and the linked inspiratory capacity (IC). Residual volume (RV) was obtained by subtracting vital capacity from TLC. At least 3 measurements were taken for each spirometry and lung volume variable to ensure reproducibility.

Participants underwent spirometry before and 15 min after inhaling salbutamol (400 μg) from a metered-dose inhaler with a valve-bearing spacer device. The bronchodilator responsiveness was expressed as a percentage change relative to the prebronchodilator value of FEV_1 (ΔFEV_1, %) and FVC (ΔFVC, %). A change after bronchodilator administration of 12% and 0.2 L increasing in FEV_1, FVC, or in both characterized the presence of flow responsiveness, volume responsiveness, and flow-and-volume responsiveness, respectively [17].

Impulse Oscillometry System

Following standard recommendations [18], IOS was performed using the Jaeger MasterScreen-IOS (Carefusion Technologies, San Diego, CA, USA). Patients were asked to wear a nose clip and were seated during tidal breathing with their neck slightly extended and their lips sealed tightly around the mouthpiece, while firmly supporting their cheeks with their hands. At least 3 trials were performed, each lasting 30 s, and mean values were chosen.

Table 1. General characteristics of the study sample

	Total sample (n = 202)	Patients with SAD[1] (n = 149)	Patients without SAD[1] (n = 53)	p value
Age, years	67.4±9.2	68.4±8.7	64.7±10.2	0.011
Male/female gender	152/50 (75/25)	111/38 (74/26)	41/12 (77/23)	0.678
BMI	26.8±4.2	27.2±4.1	25.9±4.3	0.057
Current/former smoker	82/120 (41/59)	55/94 (37/63)	27/26 (51/49)	0.074
Packs/year	40 [26.2; 57.9]	45 [29; 60]	40 [22.8; 50]	0.109
Charlson index score	5 [4; 6]	5 [4; 6]	5 [3; 6]	0.716
FEV_1, L	1.4 [1.1; 1.9]	1.29 [1.01; 1.64]	1.95 [1.68; 2.47]	<0.001
FEV_1, % pred.	55.0±20.1	49.4±17.5	70.6±18.9	<0.001
FVC, L	2.7 [2.2; 3.4]	2.54 [2.19; 3.09]	3.61 [3.02; 3.97]	<0.001
FVC, % pred.	78.8±20.1	73.8±18.2	93.0±18.3	<0.001
FEV_1/FVC, %	54.4 [45.6; 61.2]	51.5 [43.9; 57.5]	60.3 [51.4; 64.7]	<0.001
FEF_{25-75}, L/s	0.56 [0.41; 0.84]	0.48 [0.37; 0.66]	0.78 [0.63; 1.16]	<0.001
FEF_{25-75}, % pred.	20.8 [15.2; 31.1]	19.3 [13.7; 25.8]	30.6 [21.7; 39.2]	<0.001
RV, % pred.	156 [122.5; 188.9]	163.9 [126.8; 193.2]	130 [117.2; 164]	0.004
TLC, % pred.	115.1±17.9	115.6±18.4	113.8±16.8	0.554
RV/TLC	0.52±0.11	0.54±0.10	0.45±0.9	<0.001
IC/TLC	0.34±0.08	0.33±0.08	0.38±0.07	<0.001
GOLD stage I/II/III/IV	54/89/48/11 (27/44/24/5)	26/68/44/11 (17/46/30/7)	28/21/4/0 (53/40/7/0)	<0.001
GOLD stage A/B/C/D	70/43/23/66 (35/21/11/33)	34/38/14/63 (23/26/9/42)	36/5/9/3 (68/9/17/6)	<0.001
ΔFEV_1, %	7.4±8.9	8.4±9.4	4.5±6.7	0.006
ΔFVC, %	5.5±8.4	6.8±8.9	2.2±5.8	0.001
CAT total score	10 [6.7; 16]	12 [9; 17]	8 [5; 9]	<0.001
R5–R20, kPa × s × L^{-1}	0.15 [0.06; 0.27]	0.20 [0.14; 0.30]	0.03 [0.01; 0.04]	<0.001
X5, kPa × s × L^{-1}	–0.23 [–0.36; –0.13]	–0.30 [–0.40; –0.20]	–0.11 [–0.14; –0.09]	<0.001
F_{Res}, Hz	22.2 [16.7; 26.6]	24.0 [21.4; 28.5]	12.9 [10.4; 15.7]	<0.001
No medications	82 (41)	53 (36)	29 (55)	0.015
SABA	7 (3)	7 (5)	0 (0)	0.108
ICS + LABA	36 (18)	32 (21)	4 (8)	0.023
LABA + LAMA	19 (9)	13 (9)	6 (11)	0.578
ICS + LABA + LAMA	58 (29)	44 (29)	14 (26)	0.667

Data are shown as number of patients (%), means ± SD, or medians [1st quartile; 3rd quartile], unless otherwise stated.

SAD, small-airway dysfunction; BMI, body mass index; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow in the middle half of the patient's exhaled volume; RV/TLC, residual volume to total lung capacity ratio; IC/TLC, inspiratory capacity to total lung capacity ratio; CAT, COPD Assessment Test; R5–R20, fall in resistance from 5 to 20 Hz; X5, reactance at 5 Hz; F_{Res}, resonant frequency; SABA, short-acting β-agonists; ICS, inhaled corticosteroids; LABA, long-acting β-agonists; LAMA, long-acting muscarinic antagonists.

SABA includes salbutamol; ICS includes fluticasone and budesonide; LABA includes formoterol, salmeterol, indacaterol, and vilanterol; and LAMA includes tiotropium, glycopyrronium, and umeclidinium.

[1] SAD was defined according to the R5–R20 cutoff of ≥0.07 kPa × s × L^{-1} (see Methods).

Respiratory resistances at 5 and 20 Hz (R5 and R20, in kPa × s × L^{-1}) were used as indices of total and proximal airway resistance, respectively, and the fall in resistance from 5 to 20 Hz (R5–R20, in kPa × s × L^{-1}) was considered to be an index for the resistance of peripheral airways. Moreover, reactance at 5 Hz (X5, in kPa × s × L^{-1}) and resonant frequency (F_{Res}, in Hz) were considered representative markers of peripheral airway dysfunction. An R5–R20 cutoff of 0.07 kPa × s × L^{-1} was chosen to define the presence of SAD [19].

Statistical Analysis

A Shapiro-Wilk test was used to assess the normality of distribution in all variables. Data were reported as medians (1st quartile; 3rd quartile) for continuous variables with nonnormal distribution or means ± standard deviation (SD) for those with normal distribution. Number of patients (%) was used for categorical variables. Categorical variables were compared using the χ^2 test or the Fisher exact test and continuous variables with the t test or the nonparametric Mann-Whitney test. Univariate and multivariate regression analyses were performed to identify variables associated

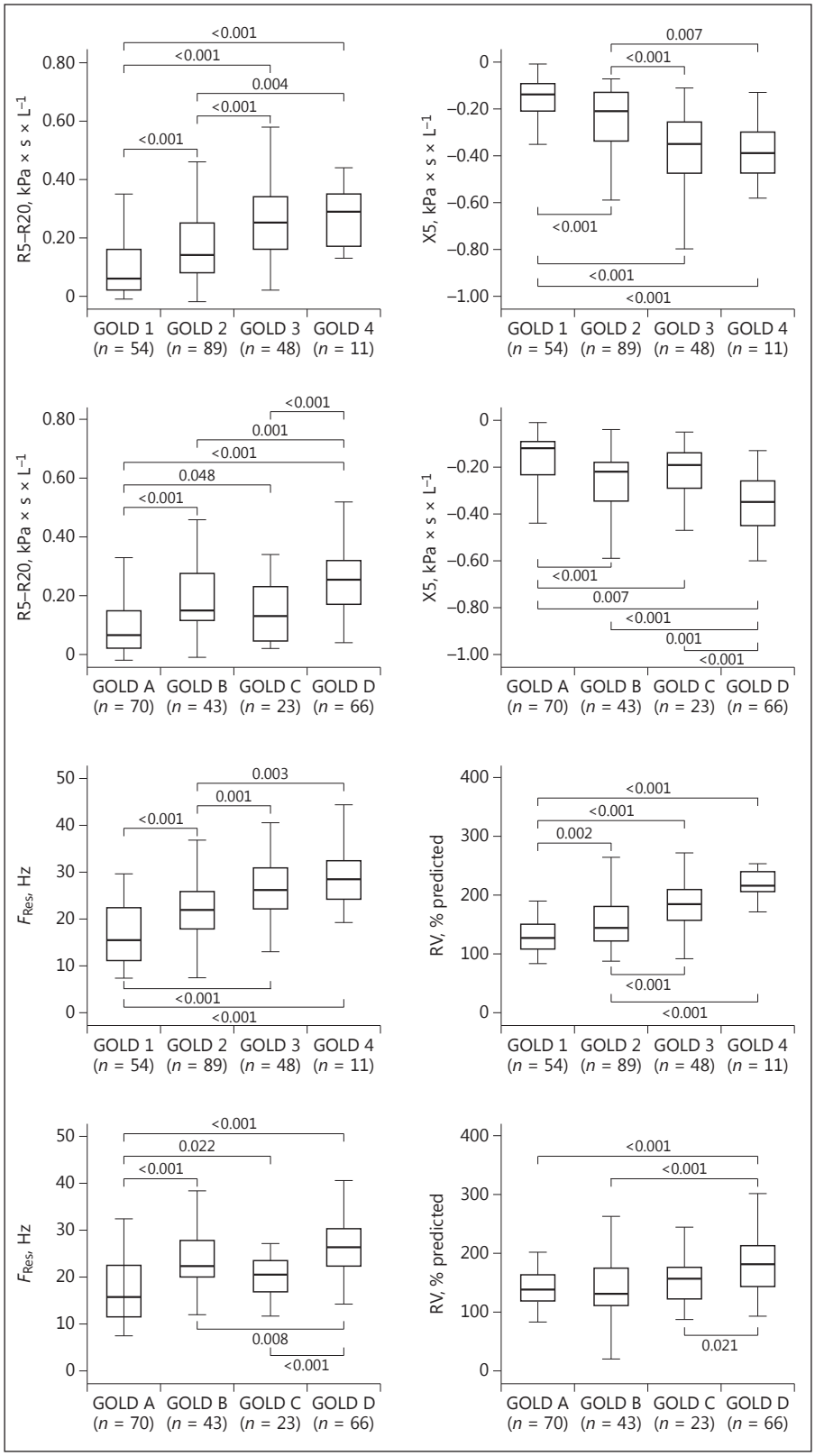

Fig. 1. Distribution of peripheral airway dysfunction markers among patients with different GOLD stages. R5–R20, fall in resistance from 5 to 20 Hz; X5, reactance at 5 Hz; F_{Res}, resonant frequency; RV, residual volume.

with a CAT score ≥10 (the dependent variable). The following variables were included in the univariate analysis: age, gender (female/male), BMI, smoking habit (former/current), packs/year, Charlson index, FEV_1 (>50 and ≤50% pred.), FVC (% pred.), $FEF_{25–75}$ (% pred.), RV/TLC, IC/TLC (≤0.25 and >0.25), presence of flow responsiveness (no/yes), presence of volume responsiveness (no/yes), presence of flow-and-volume responsiveness (no/yes), and presence of SAD (no/yes). Variables that showed significant results ($p < 0.1$) were included in the corresponding multivariate regression stepwise model. Variables that correlated strongly ($r > |\pm 0.3|$) were excluded from the multivariate analyses. The receiver operating characteristic curve method [20] was used to plot the true positive rate (sensitivity) in function of the false-positive rate (specificity) for different cutoff scores of CAT with respect to R5–R20 as a threshold value. A p value <0.05 was considered significant. All analyses were performed with IBM SPSS Statistics 23.0 (Armonk, New York, NY, USA).

Results

Our study cohort included 202 adult stable COPD patients (75% male, mean age 67 years) with on average a moderate degree of airflow obstruction (mean ± SD, FEV_1 55 ± 20% pred.). All data on general characteristics of the patients are reported in Table 1. According to the defined cutoff value of 0.07 kPa × s × L^{-1} for R5–R20, the entire cohort was categorized in patients with (74%) and without (26%) SAD, respectively. Age, pulmonary function (FEV_1, L and % pred., FVC, L and % pred., FEV_1/FVC, $FEF_{25–75}$, L/s and % pred., RV/TLC, and IC/TLC), old and new GOLD classifications, bronchodilator responsiveness (ΔFEV_1 and ΔFVC), CAT total score, prevalence of patients not on domiciliary medications and use of ICS + LABA, and all measurements related to peripheral airway dysfunction (R5–R20, X5, F_{Res}) were those variables significantly different between patients with and without SAD. The other variables showed no differences between groups.

Distributions of SAD among COPD patients classified according to the old and the new GOLD stages (GOLD 1, 2, 3, 4 and GOLD A, B, C, D) are shown in Figure 1. Related to variables of peripheral airways dysfunction in both GOLD staging system, we noted progressive and increasing values of R5–R20 (kPa × s × L^{-1}) and F_{Res} (Hz), as well as of RV (% pred.) with a reduction of X5 (kPa × s × L^{-1}). We also found no difference in the mean values of R5–R20 and RV between patients belonging to the GOLD B stage and those belonging to the GOLD C stage. Furthermore, when the patients were categorized according to the 0.07 kPa × s × L^{-1} cutoff value, 38 out of 43 participants in the GOLD B group (88%) and 14 out of 23 participants in the GOLD C group (61%) had a R5–R20 value higher than 0.07 kPa × s × L^{-1} ($\chi^2 = 6.78$, $p = 0.009$) (Fig. 2).

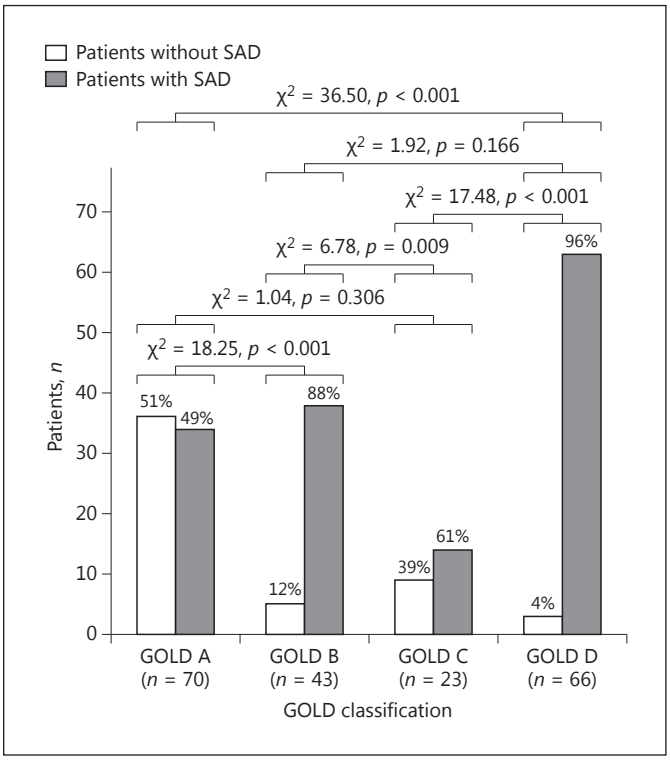

Fig. 2. Distribution of patients with and without SAD according to the new GOLD classification.

Figure 3 shows the scatterplot of a significant and positive correlation ($r = 0.527$, $p < 0.001$) between R5–R20 in kPa × s × L^{-1} and CAT total score. The analysis of distribution between the presence of SAD and CAT, categorized by a score of <10 or ≥10, reports a significant value ($\chi^2 = 43.68$, $p < 0.001$) (Fig. 4). The number of patients with high scores (score 3, 4, and 5) for each item of CAT is reported in Figure 5. A significant correlation was found between RV values and CAT scores in all patients (Spearman's rho 0.199, $p = 0.007$).

Table 2 reports the univariate and multivariate logistic regression model predicting the high impact of disease (CAT score ≥10). While in the univariate model age (odds ratio [OR] 1.03; 95% CI 1.00–1.06; $p = 0.070$), BMI (OR 1.07; 95% CI 1.00–1.15; $p = 0.044$), packs/year (OR 1.02; 95% CI 1.00–1.03; $p = 0.007$), IC/TLC ≤0.25 (OR 6.46; 95% CI 2.13–19.55; $p = 0.001$), FEV_1 ≤ 50% pred. (OR 4.49; 95% CI 2.23–9.03; $p < 0.001$), presence of SAD (OR 11.84; 95% CI 5.18–27.06; $p < 0.001$), presence of

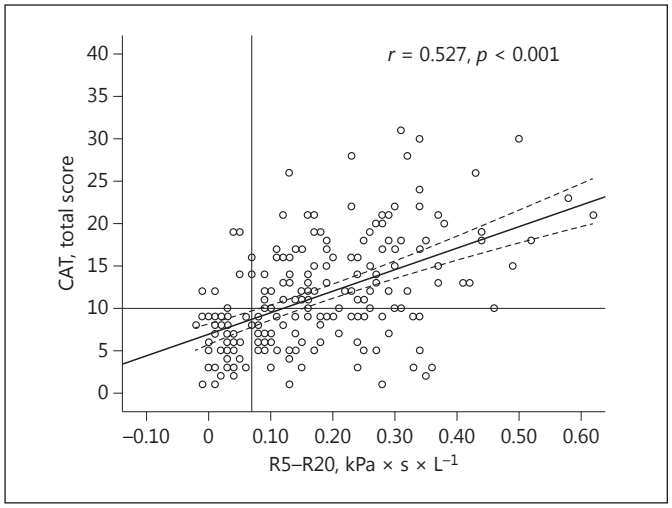

Fig. 3. Scatterplot between R5–R20 and CAT total score. The continuous line and dashed lines indicate mean and 95% confidence intervals, respectively. The vertical and horizontal lines indicate the cutoffs of R5–R20 (0.07 kPa × s × L^{-1}) and CAT score (10), respectively.

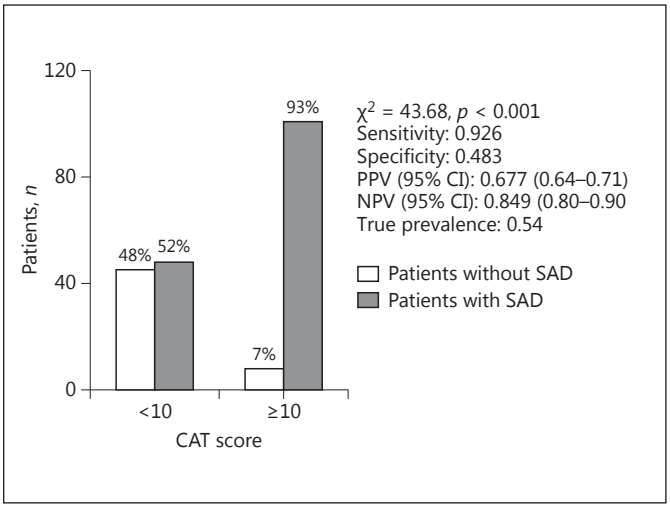

Fig. 4. Distribution of SAD and CAT. Percentage calculated with patients in each category. PPV, positive predicted value; NPV, negative predicted value; CI, confidence interval.

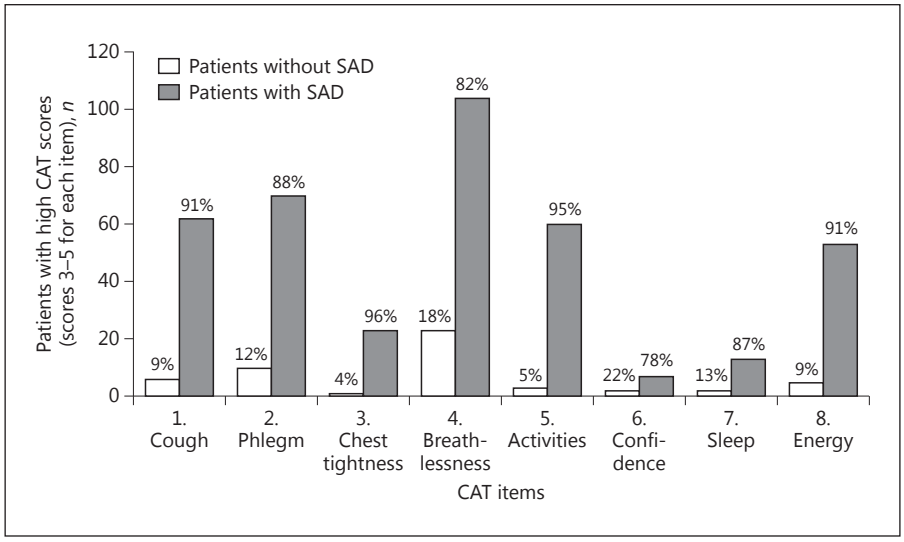

Fig. 5. Number of patients with high impact on health status in each single item of CAT. Percentage calculated with patients in each category.

volume responsiveness (OR 2.69; 95% CI 1.13–6.37; p = 0.025), and ICS + LABA + LAMA (OR 4.48; 95% CI 2.14–9.35; $p < 0.001$) were the predicted variables, in the multivariate analysis the presence of SAD (OR 11.96; 95% CI 4.53–31.58; $p < 0.001$) and the use of domiciliary ICS + LABA + LAMA (OR 5.31; 95% CI 1.88–15.02; p = 0.002) showed an independent predictive role.

The receiver operating characteristic curve calculated to establish the value of CAT and able to identify the presence of SAD (Fig. 6) showed an area under the curve of 0.783 (standard error [SE] 0.035; 95%CI 0.715–0.851; $p <$ 0.001) with a CAT score cutoff value of 9.5 (sensitivity 0.678, specificity 0.849).

Discussion

Our observational study on stable COPD patients demonstrates that there is a progressive increase in peripheral airway dysfunction among patients with differ-

Table 2. Univariate and multivariate logistic regression model predicting the probability to have a CAT score ≥10

Variables	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age (years)	1.03	1.00–1.06	0.070	0.99	0.96–1.04	0.866
Sex (male vs. female)	0.65	0.34–1.24	0.190			
BMI	1.07	1.00–1.15	0.044	1.08	0.99–1.17	0.077
Smoking habit (current vs. former)	1.06	0.61–1.87	0.829			
Packs/year	1.02	1.00–1.03	0.007	1.01	1.00–1.03	0.082
Charlson index score	1.06	0.81–1.27	0.493			
IC/TLC (≤0.25 vs. >0.25)	6.46	2.13–19.55	0.001			
FEV_1 % pred. (≤50 vs. >50)	4.49	2.23–9.03	<0.001	1.22	0.47–3.15	0.677
Presence of SAD (yes vs. no)	11.84	5.18–27.06	<0.001	11.96	4.53–31.58	<0.001
Presence of flow responsiveness (yes vs. no)	0.49	0.19–1.23	0.129			
Presence of volume responsiveness (yes vs. no)	2.69	1.13–6.37	0.025	1.65	0.60–4.58	0.334
Presence of flow-and-volume responsiveness (yes vs. no)	2.18	0.74–6.43	0.159			
Domiciliary medications						
No medications (reference)	1	–	–			
SABA	3.91	0.71–21.36	0.116	2.30	0.39–13.44	0.353
ICS + LABA	1.95	0.88–4.32	0.098	1.16	0.48–2.83	0.739
LABA + LAMA	1.40	0.51–3.84	0.506	1.43	0.42–4.87	0.559
ICS + LABA + LAMA	4.48	2.14–9.35	<0.001	5.31	1.88–15.02	0.002

The number of patients (% of total sample) with flow, volume, and flow-and-volume responders was: $n = 21$ (10.4%), $n = 30$ (14.9%), and $n = 17$ (8.4%), respectively. Hosmer and Lemeshow goodness-of-fit test, $p = 0.778$ for multivariate analysis.

OR, odds ratio; CI, confidence interval. For other abbreviations, see Table 1.

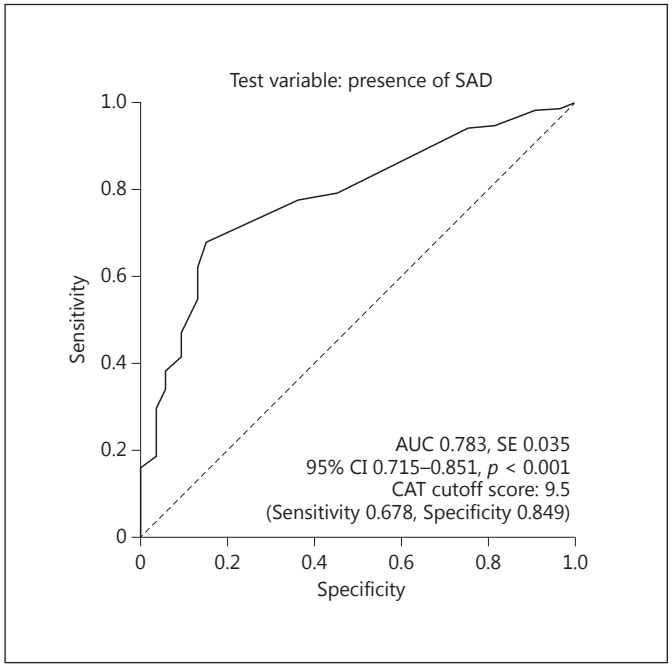

Fig. 6. Receiver operating characteristic curve for CAT calculated with presence of SAD as test variable. The dashed line indicates the reference line. AUC, area under the curve; SE, standard error.

ent GOLD stages evaluated by both GOLD staging systems (both the old and the new systems). Moreover, SAD correlates closely with the level of impact of COPD on perceived health status of patients evaluated by CAT score, which is an independent significant predictor of higher impact (CAT score ≥10).

Role of Cutoff Defining SAD in Our Study

Our study shows that in the majority of the patients (74%), it was possible to identify SAD according to the cutoff of 0.07 kPa × s × L^{-1} [19]. A previous observational study [13] on moderate COPD patients recently demonstrated a higher prevalence (80%), but it was calculated with another cutoff (0.03) reported from the literature [21]. Our current choice for a higher cutoff (0.07 and not 0.03) takes into account 2 aspects: (1) to have a reasonable certainty of the presence of SAD, and 0.07, as previously reported [19], represents a conservative upper limit of normality for R5–R20; and (2) to have a model, similar to asthmatics [22, 23], that identifies a portion of patients who have poor control of the disease and could require the use of as-needed medications, such as short-acting β-agonists. In fact, although COPD

is considered not entirely reversible to airflow obstruction disease [2] that may show significant bronchodilator responsiveness [24], the assessment of SAD may be considered a functional marker useful to evaluate improvements of treatment and to identify flow and volume responders [13], and this despite an absence of a change in FEV_1 [25]. However, while in patients with asthma the role of SAD as a therapeutic target for extrafine formulations is consolidated by an increasing peripheral airways drug deposition [26], in COPD this role is not yet fully established, although improvements in air trapping and dyspnoea perception [27] and in other patient-related outcomes [28] have been demonstrated. Finally, the possibility to have a methodology such as IOS that is able to provide evaluation of the treatment effect in COPD patients [15, 29, 30] may open functional and clinical scenarios in the opportunity to target pharmacotherapy and make progress towards to personalized management [3].

Despite everything, the prevalence of COPD patients with SAD categorized with 0.03 kPa × s × L^{-1} was 83% in our sample, similar to that recorded previously [13] and the results on the distribution and the model of prediction were not different in comparison to a cutoff of 0.07 kPa × s × L^{-1} (data not reported).

On the other hand, among our patient sample, an appreciable number of patients showed normal IOS values. This finding is not surprising. Interestingly, in a previous study in a large cohort of healthy and COPD individuals assessed by IOS, 40, 34 and 29% of the patients with measurable parameters of R5–R20, X5, and the area of low-frequency reactance from 5 Hz (AX5), respectively, showed values that fell within the normal range [14]. Taken together, our and Crim et al.'s [14] results suggest that a minority of COPD patients may represent a distinct clinical subtype sharing less impairment in spirometry as well as normal values in respiratory system resistance and reactance when assessed by IOS. It is of note that, although in COPD patients the smaller conducting airways represent the major site of obstruction, the inflammation associated with the chronic bronchitis subtype is commonly found in the epithelium of the central airways, where the inflammatory process extends along the gland ducts into the mucus-producing glands [31]. Therefore, it is conceivable that in the patients without SAD, the dysfunction of cartilaginous airways may be mainly due to enlarged bronchial mucus glands and goblet metaplasia of the airway epithelial lining [32].

SAD and GOLD Classifications

Although it has been proved that the old GOLD classification based on spirometric measures predicts mortality better than the new GOLD classification [33], the latter provides a different approach to COPD [4]. The new approach includes 2 dimensions of the disease: the risk of future exacerbation and the impact of the disease [4]. A previous study has demonstrated in 50 smokers that the slope of phase III of the single-breath nitrogen test (SBN_2T), another marker of early detection of SAD, increased and correlated closely with the severity of airway obstruction graded according to the old GOLD classification [34]. Our study provides the first evidence that the degree of peripheral airway dysfunction is strictly correlated to the severity of COPD not only evaluated by FEV_1 but also by multidimensional variables defining classes of risk (Fig. 1, 3, 4).

In the present study, we also found that there was no difference in the mean values of R5–R20 and of RV between patients belonging to the GOLD B and those belonging to the GOLD C stages. However, when the patients were categorized according to the presence of SAD as expressed by a R5–R20 cutoff value of 0.07 kPa × s × L^{-1}, the number of the patients with SAD, as compared to those without SAD, was significantly higher in the GOLD B than in the GOLD C stage (Fig. 2). This result further strengthens the association between symptoms and SAD in COPD and, additionally, might have some implications about the treatment of the patients of the GOLD B stage. Interestingly, a previous study showed that in a large cohort of COPD patients, despite having milder spirometry impairment, the patients belonging to the GOLD B stage showed no differences in hospitalization and mortality rates compared to the patients of the GOLD C stage [35].

SAD and CAT

CAT is a short, easy-to-use, self-administered questionnaire able to measure the health-related impact of COPD patients also across different countries [36]. In clinical practice, CAT is able to distinguish among patients with exacerbation of COPD [37], patients with different degrees of severity [37], and patients with associated comorbidities [37]. Moreover, CAT has demonstrated its validity as a prognostic measure [38, 39]. In the present study, we found a close relationship between SAD and CAT (Fig. 3). This finding is in line with previous studies that have demonstrated direct correlations between SAD and the total score of SGRQ [8] as well as between CAT and SGRQ [40]. It is not excluded, moreover,

that the severity of the airflow obstruction of the COPD patients can influence the CAT score [4, 37] (see also Fig. 1).

The presence of SAD is a determining factor in the categorization of patients with a high impact of disease (CAT score ≥10). In fact, we proved that there is a significant distribution ($\chi^2 = 43.68$, $p < 0.001$; Fig. 4) with a high prevalence of SAD among patients with high impact (93%). Moreover, to corroborate the link between SAD and the impact of COPD, the presence of SAD, in comparison to patients without SAD, is a significant variable predicting the higher impact and this independently from FEV_1 (Table 2). The discrimination value between patients with and without SAD is a score of 9.5 (Fig. 6). As described above, with regard to the possibility to identify in COPD patients a bronchodilator responsiveness phenotype [13, 41] suitable for a personalized pharmacotherapy, we may speculate that in selected patients with SAD and with a higher impact of disease (CAT score >9.5 or simply ≥10 as reported from guidelines), may find use also for COPD patients similarly to asthma [42] an as-needed therapeutic approach with extra-fine formulations.

Strengths and Limitations

To the best of our knowledge, our research is the first one investigating the distribution of SAD in COPD patients in different GOLD stages and its role in the impact of disease. Thus, the major strengths are the prospective and consecutive nature of the data collection and the statistical approach, utilizing SAD as an independent variable predicting more symptomatic patients. On the contrary, a limitation is that we conducted our research at a single center; further multicenter studies are needed to confirm our results.

In conclusion, our study demonstrates that in COPD patients there is a progressive and increasing peripheral airway dysfunction among GOLD stage classifications. Moreover, we demonstrated a strong relationship between SAD as assessed by means of IOS and impact of disease measured by CAT and that SAD is able to identify patients with high disease impact.

Author Contributions

Study concept and design: E.C., R.P., G.B., A.C. Data collection: R.P., M.A., M.V., P.T., A.T. Data analysis and interpretation of the data: E.C., R.P., A.C. Writing the article: E.C., R.P., G.B., A.C. Critical revision of the manuscript: G.B., A.C. Final approval of the manuscript: A.C.

Conflicts of Interest Statement

All authors declare that they have no financial and personal relationships with people or organizations that could inappropriately influence this work.

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