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How to Stage Airflow Limitation in Stable Chronic Obstructive Pulmonary Disease Male Patients?

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Abstract

No study has evaluated the utility of different classifications of chronic obstructive pulmonary disease (COPD) airflow limitation (AFL) in terms of the refined "ABCD" classification of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) or in terms of the impacts on quality of life. This study aimed to compare some relevant health outcomes (i.e., GOLD classification and quality-of-life scores) between COPD patients having "light" and "severe" AFL according to five COPD AFL classifications. It was a cross-sectional prospective study including 55 stable COPD male patients. The COPD assessment test (CAT), the VQ11 quality-of-life questionnaire, a spirometry, and a bronchodilator test were performed. The patients were divided into GOLD "A/B" and "C/D." The following five classifications of AFL severity, based on different post-bronchodilator forced expiratory volume in 1 s (FEV_1) expressions, were applied: $FEV_{1\%pred}$: "light" ($\geq$50), "severe" ($<$50); $FEV_{1z\text{-}score}$: "light" (≥ -3), "severe" (< -3); FEV_1/height^2: "light" ($\geq$0.40), "severe" ($<$0.40); FEV_1/height^3: "light" ($\geq$0.29), "severe" ($<$0.29); and $FEV_{1Quotient}$: "light" ($\geq$2.50), "severe" ($<$2.50). The percentages of the patients with "severe" AFL were significantly influenced by the applied classification of the AFL severity (89.1 [$FEV_{1z\text{-}score}$], 63.6 [$FEV_{1\%pred}$], 41.8 [FEV_1/height^3], 40.0 [$FEV_{1Quotient}$], and 25.4 [FEV_1/height^2]; Cochrane test = 91.49, df = 4). The CAT and VQ11 scores were significantly different between the patients having "light" and "severe" AFL. In GOLD "C/D" patients, only the $FEV_{1Quotient}$ was able to distinguish between the two AFL severities. To conclude, the five classifications of COPD AFL were not similar when compared with regard to some relevant health outcomes.

Keywords

chronic respiratory disease, lung function test, bronchial flows, social disadvantage

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Chronic obstructive pulmonary disease (COPD) is a major public health problem, causing a significant impairment in terms of disability and quality of life (QOL; Daldoul et al., 2013; GOLD., 2019; Khalladi et al., 2017; Rosenberg et al., 2015). Worldwide, COPD ranks among the top five causes of disability. COPD is predicted to become the third leading cause of mortality by 2030 and to be responsible for 7.8% of total deaths in the world (Lopez-Campos et al., 2016; Mathers & Loncar, 2006). The diagnosis of COPD requires confirmation, via spirometry, of airflow limitation (AFL) that is not fully reversible (Celli et al., 2015). Staging COPD AFL in terms of severity is a pioneer step in its management (GOLD., 2019; SPLF., 2010). The AFL staging is a predictor factor of mortality (SPLF., 2010). It is correlated with QOL impairment (Stahl et al., 2005) and has therapeutic implications (SPLF., 2010). Once the

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COPD AFL stage is determined, physicians are required to include their patients into one of the four refined "ABCD" groups of the Global Initiative for Chronic Obstructive Lung Disease (GOLD., 2019; based on dyspnea [Fletcher et al., 1959], number of exacerbations, COPD assessment test [CAT] score [Jones et al., 2009]) and to evaluate their QOL impairment (GOLD., 2019; Ninot et al., 2010, 2013). In practice, two questions related to the diagnosis and staging severity of COPD AFL should be addressed. The first question is almost resolved in the literature (Abdool-Gaffar et al., 2011; Celli et al., 2015; GOLD., 2019; O'Donnell et al., 2008; SPLF., 2010; Yang et al., 2017). A global consensus recommends defining COPD AFL when the post-bronchodilator ratio between forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC; FEV1/FVC ratio) is less than 0.70 (Abdool-Gaffar et al., 2011; Celli et al., 2015; GOLD., 2019; O'Donnell et al., 2008; SPLF., 2010; Yang et al., 2017). The answer to the second question is debatable.

While several scholarly societies agreed on staging COPD using the post-bronchodilator FEV_1 (Abdool-Gaffar et al., 2011; Celli et al., 2004; GOLD., 2019; O'Donnell et al., 2008; SPLF., 2010; Yang et al., 2017), there is no clear consensus on how to express this parameter. In fact, several expressions were proposed (GOLD., 2019; Miller & Pedersen, 2010; Miller et al., 2007; Quanjer et al., 2014). First, according to the GOLD (2019), the FEV_1 should be expressed as the percentage of the predicted value derived from a predictive equation ($FEV_{1\%pred}$). Second, the global lung function initiative proposed to express the FEV_1 as a z-score ($FEV_{1z\text{-}score}$; Quanjer et al., 2014). Third, other methods were advanced, such as standardizing the FEV_1 by the power of height ($FEV_1/height^2$ Miller et al., 2007 or $FEV_1/height^3$ [Miller & Pedersen, 2010]) or by the lowest sex-specific first percentile ($FEV_{1Quotient}$; Miller & Pedersen, 2010). While several studies have tested the value of the aforementioned classifications as predictors of survival and health outcomes (Hegendorfer et al., 2017; Huang et al., 2018; Pedone et al., 2013; Turkeshi et al., 2015), none has evaluated their utilities in terms of the refined "ABCD" assessment tool (GOLD., 2019) or in terms of their impact on the health status (e.g., via some QOL questionnaires such as the CAT [Jones et al., 2009] or the VQ11 [Ninot et al., 2010, 2013]).

Halpin et al. (2019) highlighted that it is time for the medical world to take COPD seriously. For that reason, and taking into account the aforementioned points, the aim of this study was to compare some relevant health outcomes [i.e., the percentages of patients classified GOLD "C/D" and the scores of QOL questionnaires (CAT and VQ11)] between COPD patients having "mild to moderate" and "severe to very severe" AFL according to the aforementioned five COPD AFL classifications.

Patients and Methods

Study Design

This cross-sectional prospective study was conducted at the Department of Physiology and Functional Explorations in (the Farhat HACHED University Hospital, Sousse-Tunisia). The study was performed during 2017 and 2018. Since all the performed tests (spirometry, questionnaires) make up part of the COPD patients' usual health care, there was no need for an ethical committee approval. In the present study, the following precautions were applied: (a) All the patients were individually informed about the study proposes, about their right to refuse to participate and/or to withdraw from participating in the study, and that their data are confidentially protected; and (b) oral consents were taken in the presence of at least one witness.

Sample Size

The study sample size was estimated using the following predictive equation (Kang et al., 2008): $n = (Z_{\alpha/2}^2\ p\ q)/\Delta^2$, where "$n$" was the needed number of COPD patients; "$Z_{\alpha/2}$" was the normal deviate for type I error ($Z_{\alpha/2} = 1.64$ for 10% level of significance); "p" was the population frequency of COPD patients having a "mild or moderate" AFL according to the post-bronchodilator $FEV_{1\%pred}$; "q" was equal to "1 − p"; and "Δ" was the precision, and it was fixed at 0.11. According to Miller et al. (2007), among the 1,086 COPD patients, 435 ($p = 0.40$) had a "mild or moderate" AFL. The insertion of the above data in the predictive equation gave a sample size of 53 patients.

Population

The population source involved all the patients referred to the aforementioned department for a spirometric test during the study period. The target population was COPD patients who accepted to be included. The following inclusion criteria were applied: COPD diagnosis, clinically stable COPD, male sex, age ≥40 years, and tobacco use greater than five pack-years. Patients with cognitive disorder or inability to answer the questions adequately were not included.

Used Questionnaires and Applied Definitions

All the COPD patients answered a questionnaire including three parts: a general questionnaire (Ferris, 1978), the CAT (Jones et al., 2009, 2011), and the VQ11 (Ninot et al., 2010, 2013) QOL questionnaires. The general questionnaire, inspired by the American Thoracic Society (Ferris, 1978), was utilized to collect the following data: demographic data (socioeconomic and schooling levels, marital status), smoking habits, personal medical and surgical histories, current respiratory symptoms (e.g., cough, sputum, dyspnea), exacerbations, and medications. Two socioeconomic (low [e.g., unskilled worker, jobless] and high [e.g., skilled worker, farmer, manager]) and schooling (low [illiterate, primary education] and high [secondary and university education]) levels were arbitrarily determined. The marital status (married, single, divorced, widower) was determined. Tobacco use was evaluated in pack-years. The patients were divided into ex-smokers (patients who stopped smoking 6 months earlier) and current smokers (Soltani & Bchir, 2000). Dyspnea was evaluated according to the modified British Medical Research Council scale and two levels of dyspnea were arbitrarily defined (mMRC <2 or ≥ 2) (Fletcher et al., 1959). The COPD exacerbation was defined as an acute event characterized by deterioration of the patient's respiratory symptoms exceeding normal day-to-day variations and leading to treatment modification (inhaled bronchodilator or corticosteroid, antibiotics) or hospitalization (GOLD., 2019; Kahnert et al., 2018). The validated Arabic version of the CAT was used (Al-Moamary et al., 2011). This eight-item auto-questionnaire aims to quantify the COPD impacts on the health status (Al-Moamary et al., 2011; Jones et al., 2009, 2011). The COPD patients were classified into two groups (CAT score <10 or ≥ 10). The VQ11, a valid French questionnaire providing a reliable measure of QOL, was applied (Ninot et al., 2010, 2013). This questionnaire includes 11 items distributed into three components (functional = 3; psychological = 4; relational = 4). The questions were translated into Arabic (*by* FG *in the authors' list*). The VQ11 score ranges from 11 to 55 and a high score (≥ 22) indicates low QOL.

Anthropometric Data

The decimal age was noted. The height (m) and weight (kg), with heels joined and back straight, were measured using a mechanical scale (Seca Deutschland). The body mass index (BMI, kg/m^2) was calculated. The following corpulence statuses were categorized: underweight (BMI <18.5 kg/m^2), normal weight (BMI: 18.5 to 24.9 kg/m^2), overweight (BMI: 25.0 to 29.9 kg/m^2), and obesity (BMI ≥ 30.0 kg/m^2; Tsai & Wadden, 2013).

Spirometric Measurements, COPD Diagnosis, Refined GOLD "ABCD" Classification

The spirometric tests were performed by experienced technicians. The acceptability and reproducibility criteria were checked twice by trained residents (*IA and HK in the authors list*) based on the international guideline (Miller et al., 2005). The pre- and post-bronchodilator-measured spirometric parameters were expressed in percentage of local predictive equations (Ben Saad et al., 2013). The FVC maneuver and the bronchodilator test are described elsewhere (Ben Saad et al., 2013; Pellegrino et al., 2005).

Diagnosis of COPD was determined from a post-bronchodilator FEV_1/FVC ratio <0.70 (GOLD., 2019). The refined GOLD (2019) "ABCD" classification was applied. It was based on the patient's health status (mMRC scale or CAT score) and on the history of exacerbations including hospitalization (GOLD., 2019). The four groups (A, B, C, and D) were determined and the COPD patients were classified into two subgroups ("A/B" and "C/D").

FEV_1 Expressions and AFL Classifications

The post-bronchodilator FEV_1 was expressed in five ways:

(i) $FEV_{1\%pred}$: percentage of the local predicted value (GOLD., 2019)
(ii) $FEV_{1z\text{-}score}$: calculated as (measured minus predicted) divided by the residual standard deviation of the predicted value (Quanjer et al., 2014)
(iii) FEV_1/height^2: FEV_1 divided by the squared height (Miller et al., 2007)
(iv) FEV_1/height^3: FEV_1 divided by the cubed height (Miller & Pedersen, 2010)
(v) $FEV_{1Quotient}$: absolute value of FEV_1 divided by the sex-specific first percentile (0.5 L for males; Miller & Pedersen, 2010).

Box 1 presents the five AFL classifications, based on the post-bronchodilator FEV_1. For practical reasons (detailed in the Discussion section), the "mild" and "moderate" AFLs were considered as "light" and the "severe" and "very severe" AFLs were considered as "severe" **(Box 1)**.

Statistical Analysis

The quantitative data were expressed as mean $\pm$ standard deviation (95% confidence interval). The qualitative data

Box 1. Numbers of COPD Patients in the Four Severity Stages According to the Five Classifications of AFL.

	"Light"		"Severe"	
Severity of the AFL	Mild	Moderate	Severe	Very severe
AFL classifications (reference)				
$FEV_{1\%pred}$ GOLD. (2019)	≥80% (n = 2)	50% to 80% (n = 18)	30% to 50% (n = 23)	<30% (n = 12)
$FEV_{1z\text{-}score}$ Quanjer et al. (2014)	≥ −2 (n = 3)	−2 to −3 (n = 3)	−3 to −4 (n = 8)	< −4 (n = 41)
FEV_1/height^2 Miller et al. (2007)	≥0.5 (n = 31)	0.4 to 0.5 (n = 10)	0.3 to 0.4 (n = 7)	<0.3 (n = 7)
FEV_1/height^3 Miller and Pedersen (2010)	≥0.38 (n = 18)	0.29 to 0.38 (n = 14)	0.22 to 0.29 (n = 11)	<0.22 (n = 12)
$FEV_{1Quotient}$ Miller and Pedersen (2010)	≥3.38 (n = 19)	2.50 to 3.38 (n = 14)	1.90 to 2.50 (n = 12)	<1.90 (n = 10)

Note. AFL = airflow limitation; COPD = chronic obstructive pulmonary disease; FEV_1 = post-bronchodilator forced expiratory volume in 1 s; n = number; $_{\%pred}$ = % of the predicted value.

were expressed by relative frequency. Comparison between the pre- and the post- bronchodilator spirometric parameters was performed using the Wilcoxon test. The comparison between the percentages of COPD patients having "light" or "severe" AFL, based on the retained five classifications, was carried out via the Cochrane test. When applicable, significant differences between the percentages were tested using the McNemar test. The comparisons of the CAT and the VQ11 scores of COPD patients having "light" or "severe" AFL were performed via the Mann Whitney U test. The comparisons of the percentages between the "light" and the "severe" AFL groups with regard to the COPD patients having low QOL or belonging to GOLD "C/D" were conducted via the chi-square test. The analyses were carried out using the Statistica software (Statistica Kernel version 6; StatSoft, Paris, France). Alpha was set at $p < .05$.

Results

Among the 56 examined male COPD patients, only 1 with a cognitive disorder was not included. Table 1 presents their descriptive data. The COPD patients age ranged from 48.5 to 82.3 years. The number (%) of overweight or obese patients was 25 (45.5). GOLD B and D dominated the GOLD "ABCD" classification (together, they represented 50 [90.9%] patients). Table 2 presents the personal medical and surgical histories of the patients.

Table 3 presents the characteristics of COPD patients divided into two groups ("light" vs. "severe") according to the AFL severities. This table main results were the following:

(i) The percentages of patients with "light" or "severe" AFL were significantly influenced by the applied classification (Cochrane test = 91.49, df = 4, $p < .05$). For the "light" AFL group, the number (%) of patients varied from 6 (10.9%; $FEV_{1z\text{-}score}$) to 41 (74.6%; FEV_1/height^2). The difference was statistically significant between the $FEV_{1\%pred}$ or the $FEV_{1z\text{-}score}$ and the remaining four classifications. However, no statistically significant difference was found between FEV_1/height^2 and FEV_1/height^3 or $FEV_{1Quotient}$, or between FEV_1/height^3 and $FEV_{1Quotient}$.

(ii) The AFL classification based on FEV_1/height^2 and $FEV_{1Quotient}$ did not distinguish the patients according to their CAT scores. For the remaining three classifications, the CAT score of the patients having "severe" AFL was significantly higher than that of the patients having "light" AFL.

(iii) The five AFL classifications distinguished the patients according to their total VQ11 score. The patients having "severe" AFL had a significantly higher score than those having "light" AFL.

(iv) The five AFL classifications distinguished the patients according to their QOL level. The per-

Table 1. Descriptive Data of the 55 COPD Patients.

		Mean ± *SD* or number (%)	95% CI
Anthropometric data and obesity status			
Age (years)		65.6 ± 8.1	[63.4, 67.8]
Height (m)		1.67 ± 0.06	[1.65, 1.69]
Weight (kg)		68 ± 15	[64, 72]
Body mass index (kg/m^2)		24.3 ± 5.5	[22.8, 25.7]
Corpulence status	Underweight	9 (16.4)	
	Normal weight	21 (38.2)	
	Overweight	19 (34.5)	
	Obesity	6 (10.9)	
Demographic data and smoking habits			
Low socioeconomic level		35 (63.6)	
Low schooling level		45 (81.8)	
Marital status (married)		39 (70.9)	
Tobacco smoking (pack-years)		67 ± 44	[55, 79]
Current smokers		23 (41.8)	
GOLD "ABCD" classification, CAT, and VQ11 scores			
GOLD	A	4 (7.3)	
	B	23 (41.8)	
	C	1 (1.8)	
	D	27 (49.1)	
CAT score		20 ±10	[18, 23]
VQ11	Functional	9 ± 3	[8, 10]
	Psychologic	10 ± 4	[9, 11]
	Relational	11 ± 4	[9, 12]
	Total	30 ± 10	[27, 33]
Low quality of life		40 (72.73)	

Spirometric data

	Pre-bronchodilator		Post-bronchodilator	
	Mean ± *SD*	95% CI	Mean ± *SD*	95% CI
FEV_1 (L)	1.34 ± 0.51	[1.21, 1.48]	1.46 ± 0.52	[1.32, 1.60]*
$FEV_{1\%pred}$	40 ± 15	[36, 44]	43 ± 16	[39, 48]*
FVC (L)	2.46 ± 0.67	[2.28, 2.64]	2.63 ± 0.69	[2.45, 2.82]*
$FVC_{\%pred}$	62 ± 16	[58, 66]	67 ± 17	[62, 71]*
FEV_1/FVC (absolute value)	0.54 ± 0.09	[0.51, 0.56]	0.55 ± 0.10	[0.52, 0.57]*
$FEV_{1z\text{-}score}$ (absolute value)			−4.68 ± 1.33	[−5.03, 4.32]
FEV_1/height^2 (L/m^2)			0.52 ± 0.18	[0.47, 0.57]
FEV_1/height^3 (L/m^3)			0.31 ± 0.11	[0.28, 0.34]
$FEV_{1Quotient}$ (absolute value)			2.92 ± 1.04	[2.64, 3.21]

Note. Qualitative data were number (%). Quantitative data were mean ± *SD* (95% confidence interval [CI]). CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; $_{\%pred}$ = percent of the predicted value; VQ11: quality-of-life questionnaire.
**p* <.05: Wilcoxon test: pre-bronchodilator versus post-bronchodilator.

centages of the patients with low QOL were significantly higher in the "severe" AFL group.

(v) Only the $FEV_{1Quotient}$ AFL classification distinguished the patients according to their GOLD

Table 2. Personal Medical and Surgical Histories of the 55 COPD Patients.

Medical history		
Cardiovascular diseases	Stable hypertension	17 (30.9)
	Myocardial infarctions	3 (5.4)
	Pectoral angina	3 (5.4)
	Arrhythmias	3 (5.4)
	Stroke	3 (5.4)
	Heart failure	2 (3.6)
	Total	31 (56.4)
Atopy		19 (34.5)
Dyslipidemia		7 (12.7)
Mellitus diabetes		6 (10.9)
Neoplasm	Lung	2 (3.6)
	Bladder	1 (1.8)
	Total	3 (5.4)
Anemia		2 (3.6)
Pulmonary tuberculosis		1 (1.8)
Dysthyroidism		1 (1.8)
Surgical history		
Abdominopelvic matter		10 (18.1)
Urologic matter		4 (7.2)
Thoracic matter		3 (5.4)
Total		17 (30.9)

Note. Data were number (%). COPD = chronic obstructive pulmonary disease.

"ABCD" groups. The percentage of the patients belonging to GOLD "C/D" was significantly higher in the "severe" AFL group.

Discussion

The present study concluded that the severity of the COPD AFL depended on how the post-bronchodilator FEV_1 was expressed. First, the percentages of the patients with "light" or "severe" AFL were influenced by the applied classification of the AFL severity. Second, only three AFL classifications ($FEV_{1\%pred}$, $FEV_{1z\text{-}score}$, and $FEV_1/height^3$) distinguished the patients according to their CAT scores. Third, only the $FEV_{1Quotient}$ AFL classification distinguished the patients according to their GOLD "ABCD" groups. Finally, the five AFL classifications distinguished the patients according to their QOL level (VQ11 score).

To the extent of the authors' knowledge, the present study is the first to raise the issue of the utility of several AFL classifications in terms of the refined "ABCD" assessment tool and in terms of the impacts on the health status. The other related studies aimed to evaluate the performance of some AFL classifications in predicting the survival (Miller et al., 2007), the all-cause mortality (Hegendorfer et al., 2017; Huang et al., 2018; Miller & Pedersen, 2010; Pedone et al., 2013; Turkeshi et al., 2015), or the risk of some clinical outcomes (e.g., severe acute exacerbation [SAE], unplanned hospitalization, or physical and mental status decline (Hegendorfer et al., 2017; Huang et al., 2018)). Table S1 (Appendix) presents the main results of these studies (Hegendorfer et al., 2017; Huang et al., 2018; Miller & Pedersen, 2010; Miller et al., 2007; Pedone et al., 2013; Turkeshi et al., 2015).

Discussion of Results

The severity of the COPD AFL depended on how the post-bronchodilator FEV_1 was expressed (Table 3). The percentages of the patients with "light" or "severe" AFL were influenced by the applied classification (Table 3). Three ($FEV_{1\%pred}$, $FEV_{1z\text{-}score}$, and $FEV_1/height^3$), one ($FEV_{1Quotient}$), and five ($FEV_{1\%pred}$, $FEV_{1z\text{-}score}$, $FEV_1/height^2$, $FEV_1/height^3$ and $FEV_{1Quotient}$) AFL classifications distinguished the patients according to their CAT scores, their GOLD groups, and their QOL level, respectively (Table 3). The three points mentioned earlier, rarely dealt with in the literature, could influence the adherence of physician to the GOLD guideline. In fact, AFL severity, CAT scores, GOLD "ABCD" groups, and QOL level were shown to be barriers to physicians' guideline adherence (Lopez-Campos et al., 2019). The following text discusses the advantages/disadvantages of the five FEV_1 expressions/classifications.

The classification based on $FEV_{1\%pred}$, by far the most widely used one, has "survived" despite its numerous disadvantages (Kerstjens, 2004). First, since it is influenced by the patients' anthropometric data (Miller et al., 2007), the $FEV_{1\%pred}$ classification may misclassify the COPD AFL severity, especially in the elderly (Fragoso et al., 2011). Second, since it is not based on statistical evidence, the recommended AFL severity thresholds were arbitrarily chosen (Kerstjens, 2004; Vaz Fragoso et al., 2010). To overcome the $FEV_{1\%pred}$ limitations, the z-score method was proposed (Quanjer et al., 1993, 2014). The z-score, which accounts for the age-related differences in pulmonary function, is free from bias related to the patients' ethnicity and/or anthropometric data (Fragoso et al., 2011). Moreover, staging the COPD AFL severity using the $FEV_{1z\text{-}score}$ was associated with all-cause mortality and respiratory symptoms (Fragoso et al., 2011). A recent study, involving older people, compared the proportion of deaths attributed to a reduced FEV_1, when staged by $FEV_{1\%pred}$ (Stages 1 [$\geq$80%], 2 [50%–79%], and 3 [<50%]) and $FEV_{1z\text{-}score}$ (Stages 1 [≥ -1.64], 2 [-2.55 to -1.63], and 3 [< -2.55]; Vaz Fragoso et al., 2019). It appears that the "proportion of deaths attributed to a reduced FEV_1 is best stratified by z-score staging thresholds" (Vaz Fragoso et al., 2019). In the present study, both $FEV_{1z\text{-}score}$ and $FEV_{1\%pred}$ classifications were effective when comparing the patients according to their CAT and VQ11 scores, but not according to GOLD "C/D"

Table 3. Characteristics of the 55 COPD Patients Divided According to the Two AFL Severity Stages Defined Using the Post-Bronchodilator FEV_1 Expressed in Five Ways.

FEV_1 expression	$FEV_{1\%pred}$		$FEV_{1z\text{-}score}$		FEV_1/height^2		FEV_1/height^3		$FEV_{1Quotient}$		
AFL	"Light"	"Severe"	"Light"	"Severe"	"Light"	"Severe"	"Light"	"Severe"	"Light"	"Severe"	
Number (%)	20 (36.4)	35 (63.6)	6 (10.9)	49 (89.1)	41 (74.6)	14 (25.4)	32 (58.2)	23 (41.8)	33 (60.0)	22 (40.0)	*abcdefg
CAT score	16 ± 10	23 ± 9#	9 ± 7	22 ± 9#	19 ± 10	24 ± 9	18 ± 9	24 ± 9#	18 ± 9	24 ± 9	
VQ11 score	23 ± 8	34 ± 9#	19 ± 8	31 ± 10#	27 ± 10	38 ± 7#	25 ± 8	37 ± 9#	25 ± 8	37 ± 9#	
Low QOL	7 (35.0)	33 (94.3)!	1 (16.7)	39 (79.6)!	26 (63.4)	14 (100)!	18 (56.3)	22 (95.7)!	19 (57.6)	21 (95.5)!	
GOLD "C/D"	10 (50.0)	18 (51.4)	4 (66.7)	24 (49.0)	19 (46.3)	9 (64.3)	13 (40.6)	10 (43.5)	13 (39.4)	15 (68.2)!	

Note. Data were number (%) except for the CAT and VQ11 scores, where data were mean ± *SD*. "Light" AFL includes "mild" and "moderate" AFL. "Severe" AFL includes "severe" and "very severe" AFL. AFL = airflow limitation; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; $_{\%pred}$ = percent of the predicted value; QOL = quality-of-life; VQ11: quality-of-life questionnaire.

#$p < .05$ (Mann–Whitney): CAT or VQ11 scores: "light" versus "severe" for the same FEV_1 expression.

!$p < .05$ (chi-square): low QOL or GOLD "C/D": "light" versus "severe" for the same FEV_1 expression.

*$p < .05$ (Cochrane Q test): comparison between the % of COPD patients having "light" or "severe" AFL based on the retained five classifications.

McNemar test:

[a] $FEV_{1\%pred}$ versus $FEV_{1z\text{-}score}$

[b] $FEV_{1\%pred}$ versus FEV_1/height^2

[c] $FEV_{1\%pred}$ versus FEV_1/height^3

[d] $FEV_{1\%pred}$ versus $FEV_{1Quotient}$

[e] $FEV_{1z\text{-}score}$ versus FEV_1/height^2

[f] $FEV_{1z\text{-}score}$ versus FEV_1/height^3

[g] $FEV_{1z\text{-}score}$ versus $FEV_{1Quotient}$

[h] FEV_1/height^2 versus FEV_1/height^3

[i] FEV_1/height^2 versus $FEV_{1Quotient}$

[j] FEV_1/height^3 versus $FEV_{1Quotient}$

(Table 3). Yet, the z-score method still requires the estimation of a predicted value (Miller et al., 2007), which is considered as a limitation. To address the bias resulting from the anthropometric data ($FEV_{1\%pred}$ classification; [GOLD., 2019]) or the need for a reference equation ($FEV_{1\%pred}$ [GOLD., 2019] and $FEV_{1z\text{-}score}$ [Quanjer et al., 2014] classifications), three additional methods (FEV_1/height^2, FEV_1/height^3, and $FEV_{1Quotient}$) were advanced. In this study, both FEV_1/height^2 and FEV_1/height^3 classifications distinguished the patients according to their VQ11 scores and QOL status (Table 3). The FEV_1/height^2, first described as a predictor of mortality (Sorlie et al., 1989), was then proposed as a COPD staging method (Miller et al., 2007). The FEV_1/height^2 classification was a good predictor of all-cause mortality and survival (Huang et al., 2018; Miller & Pedersen, 2010). It was a better tool than $FEV_{1\%pred}$ for expressing lung function deficiency (Miller et al., 2007). Compared to the classification based on the $FEV_{1\%pred}$, Miller et al. (2007) reported that the one based on FEV_1/height^2 classified more patients as having "light" AFL (40.05% and 54.14%, respectively; Table S1). The FEV_1/height^3 classification, compared to the others ($FEV_{1\%pred}$, $FEV_{1z\text{-}scores}$) has two advantages. First, it has a satisfactory model for predicting survival, hospitalization, physical and mental decline, as well as SAE risk (Hegendorfer et al., 2017; Huang et al., 2018; Miller & Pedersen, 2010; Turkeshi et al., 2015). Second, it takes into account the body size variability and does not require reference equations (Turkeshi et al., 2015). However, its capacity to predict mortality is controversial (Huang et al., 2018; Pedone et al., 2013). In this study, although it did not distinguish the patients according to their CAT scores, $FEV_{1Quotient}$ was the only classification that differentiated the patients according to the GOLD "C/D" (Table 3). This classification, first introduced as an alternative to expressing lung function deficiency (Miller & Pedersen, 2010), has been the best model for predicting survival. It outperformed the other classifications in predicting the risk of SAE, hospitalization, as well as physical and mental decline (Hegendorfer et al., 2017; Huang et al., 2018; Miller & Pedersen, 2010; Pedone et al., 2013).

Discussion of Methodology

Unlike the six aforementioned studies (Hegendorfer et al., 2017; Huang et al., 2018; Miller & Pedersen, 2010; Miller et al., 2007; Pedone et al., 2013; Turkeshi et al., 2015; Table S1), the present study opted for a prospective design. This enables describing the disease characteristics in a population over a period of time (1 year for this study). When compared to prospective studies, retrospective ones have some disadvantages (Hess, 2004). First, their level of evidence is low (Hess, 2004). Second, the selection of the control group may be significantly biased (Hess, 2004) and therefore it cannot be representative of the population (Sedgwick, 2014). Third, their outcomes assessment is poorly controlled (Suchmacher & Geller, 2012). Fourth, they require very large sample sizes (Hess, 2004).

In the present study, the COPD patients had almost the same profile observed in real practice in Tunisia (e.g., mean age, smoking habits, and corpulence status; Table 1 [Ben Moussa et al., 2014, 2016; Ben Saad et al., 2008, 2014; Khalladi et al., 2017; Rejeb et al., 2018]). For example, the mean age of the present study patients (66 ± 8 years) was similar to that of COPD patients included in two previous local studies (e.g., 63 ± 9 years [Ben Saad et al., 2008]; 60 ± 10 years [Khalladi et al., 2017]). Moreover, the mean age of this study's COPD patients and their smoking habits were intermediate compared with those reported in similar studies (Table S1).

Similar to this study, some others also used the post-bronchodilator parameters (Miller & Pedersen, 2007, 2010; Pedone et al., 2013). However, while Huang et al. (Huang et al., 2018) used the post-bronchodilator parameters only if available, some other authors (Hegendorfer et al., 2017; Turkeshi et al., 2015) opted for the pre-bronchodilator ones. This makes the comparison between the studies difficult since there are big differences between the pre- and post-bronchodilator parameters (Johannessen et al., 2006; Pérez-Padilla et al., 2007). In this study, as suggested by GOLD (2019), COPD diagnosis was retained when the postbronchodilator FEV_1/FVC ratio was <0.70. In similar studies, the COPD diagnosis criterion was not mentioned in two studies (Hegendorfer et al., 2017; Turkeshi et al., 2015), and it was different in some others (post-bronchodilator FEV_1/FVC ratio < lower limit of normal [Huang et al., 2018; Pedone et al., 2013]; FEV_1/FVC ratio <89% [Miller & Pedersen, 2010; Miller et al., 2007]).

Similar to other related studies (Table S1) and as recommended by scholarly societies (Abdool-Gaffar et al., 2011; Celli et al., 2004; GOLD., 2019; O'Donnell et al., 2008; SPLF., 2010; Yang et al., 2017), grading the severity of COPD AFL in this study was based on the FEV_1. The latter is correlated with COPD severity (SPLF., 2010), the number of exacerbations (Seemungal & Wedzicha, 2014), and the impacts on QOL (Ketata et al., 2013). The FEV_1 is considered as a predictor of mortality (Anthonisen et al., 1986; Siafakas et al., 1995; Traver et al., 1979). Some authors (Coton et al., 2017) proposed a new AFL classification based on the FEV_1/FVC ratio. The latter seemed to be less dependent on ethnicity. It agreed moderately with the $FEV_{1\%pred}$-based classification and gave similar results in terms of QOL, dyspnea, and number of exacerbations (Coton et al., 2017).

Considering the "mild" and "moderate" AFLs as "light" and the "severe" and "very severe" AFLs as "severe" (Box 1) was due to two "practical reasons" related to the small subsample sizes and to a statistical ease. First, in some AFL severity stages, the number of COPD patients was very small (n = 2 for the $FEV_{1\%pred}$ mild stage, n = 3 for the $FEV_{1z\text{-}score}$ mild and moderate stages; Box 1). Second, dealing with four stages of AFL in a single study seems to be difficult. This raises some questions, such as whether the frequencies of some epidemiological and/or clinical data (e.g., corpulence status, QOL levels, CAT scores) in those stages are comparable.

According to the 2001 classification of the World Health Organization, the natural evolution of COPD has three phases: deficiency, incapacity, and social disadvantage WHO (2001). In practice, the assessment of the last phase is based on quantifying the QOL impairment via some specific questionnaires (Jones, 2001). In this study, the CAT (Jones et al., 2009) and the VQ11 (Ninot et al., 2010, 2013) questionnaires were chosen for two reasons. First, these two questionnaires are easier and less time-consuming than other questionnaires and they have simple scoring algorithms (Jones et al., 2011; Ninot et al., 2013). Second, their scores are well correlated with the COPD AFL severity (Ghobadi et al., 2012; Ninot et al., 2013).

The present study has three main limitations. First, the number of included COPD patients (n = 55) "seems" to be relatively low, when compared to similar studies, where n varied from 296 (Huang et al., 2018) to 1,095 (Miller & Pedersen, 2010; Miller et al., 2007; Table S1). This study's sample size was calculated according to a predictive equation (Kang et al., 2008). In practice, calculating the required minimal sample size, a statistically fundamental point for planning a study protocol, provides the study with a sufficient statistical power (Kang et al., 2008). For that reason, this study sample size was closer to the database size (n = 54) used by some authors (Hegendorfer et al., 2017; Turkeshi et al., 2015; Table S1). Second, the convenience sampling might weaken the ability to make generalizations from the present sample to the general population. Third, the diagnosis of cognitive disorder was subjective. It could have been better if an objective tool such as the Mini-Mental State Examination was applied (Tombaugh & McIntyre, 1992).

To conclude, the five classifications of COPD AFL were not similar when compared with regard to some relevant male health outcomes. Therefore, further studies, including large sample sizes, to determine the best method for staging COPD AFL severity should be conducted. Moreover, a global consensus on how to stage COPD AFL should be advanced.

Authors' Note

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Authors' Contributions

IA, FG, HK, and HBS: Literature search, data collection, study design, analysis of data, manuscript preparation, and review of manuscript. All authors read and approved the final manuscript.

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Supplemental Material

Supplemental material for this article is available online.

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