

Original Research Article

Defining and grading an Obstructive Ventilatory Impairment: American Thoracic Society/European Respiratory Society interpretive strategies of 2005 versus 2022

Abstract

Background: The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have issued several updates to their guidelines for lung function testing between 2005 and 2022.

Objective: We aimed to compare ATS/ERS recommendations for 2005(R1) and 2022(R2) in defining Obstructive Ventilatory Impairment (OVI) and in classifying its severity.

Patients and methods: It was a retrospective study including 1129 patients. All patients underwent spirometry with measurement of Forced Expiratory Volume in 1 second (FEV₁) and Forced Vital Capacity (FVC). An OVI was considered according to R1 when FEV₁/FVC ratio is under the Lower Limit of Normal (LLN) and when the z-score of FEV₁/FVC ratio is under -1.645 according to R2. For the severity levels of airflow obstruction: ATS/ERS previously recommended the use of percent predicted FEV₁ with 5 levels using cut values of 70%, 60%, 50% and 35%. Recently updated for z-scores with cut values of -2, -2.5 and -4. Mean age was 54.23±19.23 years.

Results: For defining an OVI, both definitions were comparable (529 patients with OVI). For the severity classification, the following proportions were assessed: 151 mild, 86 moderate, 84 moderately severe, 133 severe and 75 very severe vs 148 mild, 238 moderate, 76 severe and 67 cases having a normal FEV₁ (z-score of FEV₁ above -1.645), which were classified as mild according to R1. Mild OVI(R2) were distributed according to R1 into 74 mild, 51 moderate, 16 moderately severe and 7 severe. Moderate OVI (R2) were dispatched using R1 to 10 mild, 34 moderate, 66 moderately severe, 103 severe and 25 very severe. Severe OVI(R2) were classified as 1 moderate, 2 moderately severe, 23 severe and 50 very severe.

Conclusion: ATS/ERS new and previous recommendations seem to be comparable in defining OVI. However, discrepancies were assessed in classifying its severity.

Key words: Physiology, Respiratory Function Test, Pulmonary Disease, Spirometry, Forced Expiratory Volume, Vital capacity.

1. Introduction:

Pulmonary function tests (PFTs) have played a crucial role in the screening, diagnosis and management of respiratory diseases[1][2]. In order to improve the quality control and interpretation of PFTs, a series of technical standardizations have been published by the American Thoracic Society (ATS) and European Respiratory Society (ERS). TheATS/ERS have issued several updates to their guidelines for lung function testing between 2005 and 2022[3][4].

Interpretation of PFTs is usually based on comparisons of data measured in a patient with reference (predicted) values based on healthy subjects with the same anthropometric data (e.g. sex, age and height) and where relevant ethnic characteristics of the patient being tested [3].

It is accepted that a diagnosis of airflow limitation should be based on an abnormally low ratio of the Forced Expiratory Volume in 1 second (FEV_1) and Forced Vital Capacity (FVC) [5].

In 2005, the ATS/ERS have recommended the use of Lower Limit of Normal (LLN) in interpreting spirometry which is defined as the 5th percentile of a normal population[6]. In practice, the LLN of each spirometric data is obtained by the subtraction of ' $1.64 \times$ residual standard deviation (SD)' from the predicted value [7]. In fact, an Obstructive Ventilatory Impairment (OVI) is defined when FEV_1/FVC ratio is under the LLN. However, the new ATS/ERS recommendations of 2022 consider the LLN as a z-score lower than ' -1.64 '. The Z-score is the signed number of Standard Deviations (SD) by which the value of a measured spirometric data differs from the mean value of what is being predicted[8]. Comparing z-score and LLN in lung function testing is important because they provide different information about the test results. Z-score measures how far a result is from the mean value, while LLN is a cut-off value that separates normal from abnormal results. Z-score is independent of age, height and sex, while LLN is age-dependent [9].

Severity levels of OVI differs between previous and new recommendations. It was previously based on percent predicted value of FEV₁[6]. However, the latest ATS/ERS recommendations consider the use of FEV₁ z-score to classify an OVI[4].

To the best of the authors' knowledge, there are limited data about making a comparison between the two recommendations.

Therefore, we aimed to compare ATS/ERS recommendations for 2005 (R1) and 2022 (R2) in defining an OVI and in classifying its severity.

2. Patients and methods:

2.1 Study design:

A retrospective study was conducted in the department of functional respiratory explorations of Abderrahmane Mami hospital of Ariana, Tunisia. It has included patients who consulted for PFTs during January 2019- March 2023. There was no need for an approval from a hospital ethics committee since spirometry was done as a routine exam.

2.2 Study population:

Patients who underwent technically acceptable and reproducible spirometry maneuvers were included[10], [11], [12].An OVI was defined according to ATS/ERS 2005 when the FEV₁/FVC ratio is under the LLN (Recommendation 1: R1) versus when the z-score of FEV₁/FVC ratio is under -1.645 according to ATS/ERS 2022 (Recommendation 2: R2)[4]. The following severity classifications were applied: R1 which is based on percent predicted FEV₁ with 5 severity levels: mild (>70%), moderate (60-69%), moderately severe (50-59%), severe (35-49%) and very severe (<35%);

R 2 which considers the FEV₁ z-score with 3 severity levels: mild (-2.5 to -1.645), moderate (-2.51 to -4) and severe (<-4)[4]. A z-score is considered normal when it is above (-1.645).

Then comparison of the number of patients obstructed according to R1 with the number obstructed using R2 was performed and identification of a common set of patients who were

obstructed according to both prediction equations to compare the categorization of obstruction severity using both prediction models.

For secondary analysis, the study population was divided into 4 ranges according to age: Class 1 (C1) for aged 5-18 years, Class 2 (C2) aged 18-40 years, Class 3 (C3) aged 40-65 years and Class 4 (C4) aged 65-89 years. Comparisons between different age categories were assessed. Then the total sample was divided into two groups based on severity: G1: severe obstruction vs G2: non-severe obstruction according to FEV1% as well as z-score with cut-off values at 50% and -4, respectively.

2.3 Data collection:

Anthropometric data (age, sex, height and weight) were collected at the enrollment day for all subjects. The ethnic group considered for Tunisian individuals was Caucasian since spirometric data of 840 Tunisian healthy subject were included into the Caucasian group [8].

2.4 Pulmonary function tests:

Spirometry was performed for all patients according to ATS/ERS technical standards. Three key elements are needed to obtain high quality pulmonary function data: accurate and precise instrumentation, a subject capable of performing acceptable and reproducible measurements, and a motivated technologist to elicit maximum performance from the patient [11]. Predicted values and z-scores were derived for each subject in each dataset using prediction equations from the Global Lung Function Initiative (GLI-2012) [5].

2.5 Statistical analysis:

The Kolmogorov Smirnov test was used to analyze variables distribution. For continuous variables, results were expressed by their means \pm SD in case of normal distribution and equal variances. Otherwise, variables were expressed by their medians (1st -3rd quartiles). For categorical variables, frequencies were calculated for descriptive analysis. The Kappa test was

used to assess the agreement level between R1 and R2 in defining an OVI. The chi-2 test was used to compare percentages of OVI and to assess its severity. Significance level was fixed at 0.05. Correlation Pearson test was used for variables with normal distribution, otherwise, the Spearman test was used.

3. Results:

A total of 1129 patients were included with male predominance (sex ratio at 1.58). A description of the total sample was assessed in **table 1**.

Among the entire sample, 70,5% of patient experienced dyspnea, and dyspnea was classified according to the mMRC scale as follows: 25.9% mMRC 1; 32.1% mMRC 2; 9.7% mMRC 3 and 2.8% mMRC 4. The most prevalent reasons for consultation were asthma (38.9%) and Chronic Obstructive Pulmonary Disease (31.7%).

There were correlations between FEV1% and its z-score ($r= 0.976$), FVC and its z-score ($r= 0.924$) **figure 1**. An OVI was observed in 529 (46.8%) subjects according to both recommendations. The agreement level performed with Kappatest to compare the two reference values of LLN and z-score in defining an OVI has found a value of 1.

Main etiologies of OVI were chronic obstructive pulmonary disease (COPD) (54.6%), asthma (32.4%) and other diagnosis such as bronchial dilatation, lung cancer and interstitial lung disease.

For the classification of the disease severity, the following proportions were assessed: 28.5% mild, 16.2% moderate, 15.8% moderately severe, 25.1% severe and 14.1% very severe vs 28% mild, 45% moderate and 14.4% severe. It is crucial to notice that 12.7% of patient with OVI had a FEV1 z-score above -1.645. This group of patients can't be classified among different severity levels using z-score. They were merged into the mild OVI according to R1. It is obvious that discrepancies consisted mainly in grading the severity of an OVI. **Table 2** shows

results of chi 2 test conducted to compare both classifications according to FEV1 z-score and percent predicted FEV1.

In fact, mild OVI (R2) was distributed according to R1 into mild, moderate, moderately severe and severe OVI. Moderate OVI (R2) was dispatched using R1 to mild, moderate, moderately severe, severe and very severe OVI. Severe OVI (R2) was classified as severe and very severe OVI with R1.

Table 3 shows the distribution of the study population according to different age classes (C1, C2, C3 and C4).

By comparing R1 and R2 for the C1 (5-18 years), chi 2 test shows that both recommendations are perfectly similar (measurement of agreement with Kappa = 1) in defining an OVI (24 subjects, 24.2% had an OVD). However, there was a significant difference in grading its severity (Pearson test <0.05). In fact, 7 mild OVI according to R2, were dispatched into 6 mild cases and 1 moderate case according to R1. Then, 5 moderate OVI (R2) were considered mild (1 subject), moderate (1 subject), moderately severe (2 subjects) and severe (1 subject) according to R1. Twelve cases of OVI while having a normal FEV1 z-score (dysanapsis) were considered mild by considering the FEV1%. For C 2 (18-40 years), both definitions overlap in diagnosing OVI in 41 subjects (38.3%, Kappa = 1) and distinction of different severity classes was observed mainly in moderate OVI according to z-score. For C 3 (40-65 years), there was an agreement in terms of definition of OVI between R1 and R2 (52.5%, Kappa = 1). There was a significant difference in terms of grading OVI severity detailed in table 6. For

C 4 (65-89 years), R1 and R2 were concordant in defining an OVI (61.6%, measure of agreement with Kappa at 1). **Table 4** summarizes differences in grading the severity of the disease in this age range.

Table 5 showed that FEV1 z-score underestimated the severity level of OVD. In fact, the chi 2 test concluded that there was no intersection between severe OVI with FEV1 z-score and non-severe OVI with percent predict FEV1, however, 150 patients with severe OVI using percent predicted FEV1 were classified non-severe using FEV1 z-score.

By comparing G1 and G2 according to FEV1%, there was a statistically significant difference in terms of age (64.31 ± 10.27 vs 51.44 ± 20.18 vs, $p < 0.0001$) and mMRC scale (1.94 ± 1.02 vs 1.18 ± 1.05 , $p < 0.0001$), respectively. As well as for FEV1 z-score, there was a significant difference in age (57.21 ± 9.04 vs 53.99 ± 19.80 , $p < 0.05$) and mMRC scale (1.95 ± 0.98 for G1 vs 1.29 ± 1.08 for G2, $p < 0.05$).

The main result of this study was that the LLN and z-score of FEV1/FVC ratio were similar in term of defining an OVI. However, the classification of the OVI using the FEV1 z-score resulted in a change in the severity degrees established by the ATS/ERS recommendations in 2005 using the percent predicted FEV1, particularly for the severe OVI.

4. Discussion:

The main outcome of this study is that the use of z-score in classifying OVI severity doesn't comply well with FEV%. In fact, only 3 stages (mild, moderate and severe) were identified using the z-score and there was a regrouping of different severity stages based on FEV1%, especially for the moderate stage with z-score that had clustered all severity stages with FEV% from mild to very severe. On the other hand, the definition of an OVI using the z-score was in conformity with the use of the LLN. It is important to examine the potential effects of changes in the interpretative strategies of the ATS/ERS over time, and to assess similarities as well as discrepancies between reference values adopted in the interpretation of test results.

4.1 Results discussion:

The present study results showed that ATS/ERS recommendations of 2005 as well as 2022 are matched in defining an OVI. In fact, percentage of patients having airflow limitation was

similar according to both R1 and R2. As found by **QUANJER et al** who had included a larger sample size (17880 subjects) and concluded that ATS/ERS previous diagnostic criterion (LLN of FEV1/FVC ratio) can be replaced with z-score maintaining the same interpretation of the test result [5].

Unlike percent of predicted, the z-score is free from bias due to age, height, sex and ethnic group, and is therefore particularly useful in defining the lower and upper limits of normal and in simplifying uniform interpretation of test results [13]. While the percent predicted of each outcome has a different cut-off, the z-score has the same cut-off of -1.645 for all outcomes across all ages, sex, ethnic groups and spirometric pulmonary function indices [14]. Consequently, an approach that reports spirometric values based on z-scores potentially provides an age-appropriate and clinically valid strategy for evaluating respiratory impairment [15]. Furthermore, the GLI task force released the GLI-2012 spirometric norms from data collected from 72,031 healthy individuals (26 countries) aged 3–95 years and Tunisia has participated with its reference values from 870 Tunisian adults aged ≥ 45 years and were included in the Caucasian group [16].

For the severity categorization, the z-score and FEV1% were different in grading OVI. In fact, five severity levels were considered using FEV1%, however only three stages were defined with z-score and still exist unclassified cases who have a normal FEV1 z-score. Added to that, concordant classes with both definitions (mild, moderate and severe OVI) are not exchangeable. For example, mild OVI (R2) combined mild, moderate, moderately severe and severe OVI with R1, moderate OVI (R2) included all severity levels using R1 and severe OVI (R2) merged moderate, moderately severe, severe and very severe OVI (R1). For the cases with normal FEV1 z-score, they were considered mild using FEV1%. These findings were in line with previous studies conducted by **LINARES-PERDEMO et al**, **VUKOJA et al**, and **CHAIWONG et al**, who have compared different reference equations used to define the LLN

of FEV1 and FEV1/FVC ratio to define an OVI and grade its severity [17][18][19] and concluded that significant differences existed when classifying degree of lung function impairment with different predictive equations in patients with obstructive lung diseases[20]. The meaning of a low FEV1/FVC ratio with a normal FEV1 is unclear. It can be considered according to the ATS/ERS latest recommendations as “dysanaptic” growth of the airways and lung parenchyma [4]. This profile may be associated with the propensity for obstructive lung disease[21]. Several factors have been reported as associated with this pattern in healthy people including male sex, younger age and taller stature, with higher FVC above predicted[4]. Whether this pattern represents airflow obstruction will depend on the prior probability of obstructive disease and possibly on the results of additional tests, such as bronchodilator responsiveness, gas exchange evaluation and measurement of muscle strength or exercise testing[4].

By considering different age classes, R1 and R2 were perfectly similar in diagnosing OVI for all age classes. For the OVI classification, discrepancies were found in all age categories but less for C4, where OVI was nearly classified with both recommendations. In fact, mild OVI (R2) has been remained mild (R1), moderate OVI (R2) was classified as mild, moderate and moderately severe (R1), severe OVI (R2) was classified as severe and very severe (R1).

It was demonstrated in this study that FEV1% overestimates the determination of severe obstruction compared to z-score FEV1 and this finding has been also supported by **Tejero et al** who had found that the adjustment of FEV1 using its z-score underestimated the severity of the airflow limitation in individuals older than age 60[22].

Previous studies have shown that spirometric data such as FEV1 could be a good predictor of survival[23], [24], [25], [26]. Thus, FEV1 z-score could be used to determine the association with objective outcomes such as mortality. The previously recommended severity levels for airflow obstruction considered percent predicted FEV1 with 5 levels. However, this severity

scale was then adapted for z-scores considering 3 levels. The new ATS/ERS standardization for interpretative strategies of pulmonary function tests have reported that the risk of mortality is associated with severity levels using z-score. In fact, z-score cut levels between -1.65 and -2.5 have little difference in risk of death and were therefore merged into a mild group. Individuals with z-score between -2.5 and -4 exhibit a moderate risk of mortality and these categories were therefore merged into the moderate category[4].

The purpose of our current study was not to determine the “best” spirometry prediction equation, but to inform clinicians that there are important differences essentially in grading airway obstruction between the ATS/ERS recommendations of 2005 and 2022. Thus, spirometry prediction equations should not be used interchangeably to define and categorize OVI for all patients, especially when longitudinal studies are needed.

The GLI 2012 reference equations considered by ATS/ERS recommendations of 2022 are a huge step forward, providing a robust reference standard to rationalize the interpretation of spirometry results within and between populations worldwide.

4.2 Strengths and limits:

The strength of our study is that it had included a large database of 1129 patients with different ages (from 5 to 89 years), matching males and females, with several pathologies. Moreover, results were interesting and significant in showing discrepancies between different recommendations established by the ATS/ERS.

One limit of this study is that it was a retrospective analysis of routinely obtained spirometric data of patients who have consulted our department during 2021-2023. Another limitation, is that there is no clear causal link between COVID19 infection and OVI since we have patients who consulted during the pandemic of COVID19.

Abbreviations:

ATS/ERS: American Thoracic Society/ European Respiratory Society

C1: Class 1

C2: Class 2

C3: Class 3

C4: Class 4

COPD: Chronic Obstructive Pulmonary Disease

FEV1: Forced Expiratory Volume in 1 second

FVC: Forced Vital Capacity

GLI: Global Lung Initiative

LLN: Lower Limit of Normal

OVD: Obstructive Ventilatory Disease

PFTs: Pulmonary Function Tests

R1: ATS/ERS Recommendations of 2005

R2: ATS/ERS Recommendations of 2022

SD: Standard Deviation

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Table 1: description of the total sample

Age (years)	54±19
BMI (Kg/m²)	26.75±6.85
FEV1 (L; %; z-score)	2.08±0.88; 74±25; -1.61±1.54
FVC (L; %; z-score)	3.10±2.63; 85±21; -0.94±1.36
Smoking (%)	52
Smoking intensity (Pack/years)	25±34

Table 2: concordance and discordance in grading the severity of an OVD using the FEV1% vs the FEV1 z-score.

Severity according to FEV1 z-score	Total
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		0	1	2	3	
Severity according to FEV1%	1	67	74	10	0	151
	2	0	51	34	1	86
	3	0	16	66	2	84
	4	0	7	103	23	133
	5	0	0	25	50	75
	Total	67	148	238	76	529

OVD: Obstructive Ventilatory Disease, FEV1: Forced Expiratory Volume in one second

Table 3: number of subjects grouped by age

Age-class (years)	5-18	18-40	40-65	65-89
Subjects (%)	9.6	10.3	46.8	33.3

Table 4: comparison of the severity of OVD according to R1 vs R2 in different age classes

		Severity according to R2			
		Normal FEV1 z-score	mild	moderate	Total
Severity according to C1	Mild	12	6	1	19
	Moderate	0	1	1	2

to R1	Moderately severe	0	0	2	2
	Severe	0	0	1	1
	Total	12	7	5	24

C2	mild				Total	
	Normal FEV1 z-score		moderate	severe		
	Mild	10	14	2	0	26
	Moderate	0	0	8	0	8
	Moderately severe	0	0	3	0	3
	Severe	0	0	0	2	2
	Very severe	0	0	0	2	2
	Total	10	14	13	4	41

C3	mild				Total	
	Normal FEV1 z-score		moderate	severe		
	Mild	29	42	5	0	76
	Moderate	0	18	20	1	39
	Moderately severe	0	2	36	2	40
	Severe	0	6	38	16	60
	Very severe	0	0	1	38	39
	Total	29	68	100	57	254

C4	mild				Total	
	Normal FEV1 z-score	Mild	Moderate	Severe		
	Mild	16	12	2	0	30
	Moderate	0	32	5	0	37
	Moderately severe	0	14	26	0	40
	Severe	0	2	64	5	71
	Very severe	0	0	24	10	34
	Total	16	60	121	15	212

R1: ATS/ERS recommendations of 2005? R2: ATS/ERS recommendations of 2022, OVD: Obstructive Ventilatory Disease

Table 5: concordance and discordance between R1 and R2 in classifying severe OVD

		Severe OVD with z-score			Total
		No	Yes		
Severe OVD with FEV1%	No	809	0	809	
	Yes	150	72	222	
Total		959	72	1031	

R1: ATS/ERS recommendations of 2005? R2: ATS/ERS recommendations of 2022, OVD: Obstructive Ventilatory Disease, FEV1: Forced Expiratory Volume in one second.

UNDER PEER REVIEW

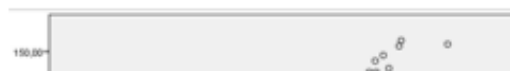
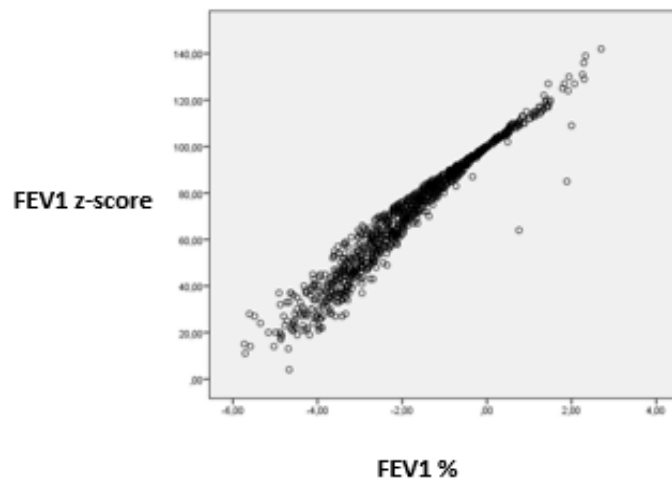


Figure 1: correlations between spirometric parameters and their z-scores.

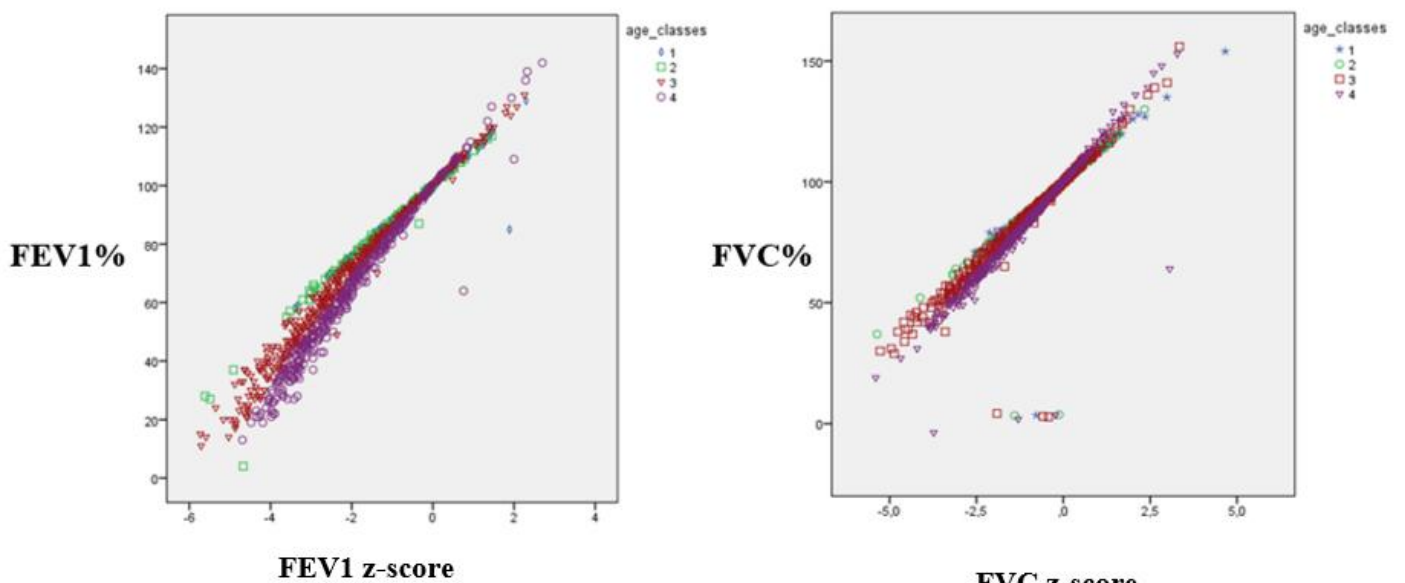


Figure 2: correlations of FEV1 and FVC with their z-scores considering different age-classes

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