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Defining and grading an obstructive ventilatory defect (OVD): 'FEV$_1$/FVC lower limit of normal (LLN) vs. *Z*-score' and 'FEV$_1$ percentage predicted (% pred) vs. *Z*-score'

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ABSTRACT

An obstructive ventilatory defect (OVD) is defined by a low forced expiratory volume/'forced/slow' vital capacity (FEV$_1$/FVC) (e.g. <lower limit of normal (LLN)). However, the LLN can be estimated either by the 90% confidence interval (or the 90th percentile) (American Thoracic and the European Respiratory Societies (ATS/ERS) method) or by the *Z*-score (global lung initiative (GLI) method). In 2014, a new alternative classification (GLI classification) for grading the OVD severity was proposed to replace the 2005-ATS/ERS one. The aims of the present study were to determine, according to the two methods (GLI vs. ATS/ERS), the frequency of participants having an OVD; and to compare the two classifications (GLI vs. ATS/ERS) of OVD severity. This was a prospective study including 1000 participants (mean age = 41 ± 10 years). The OVD was defined according to the ATS/ERS [FEV$_1$/FVC < LLN (=local norms value − 1.64 × residual standard deviation)] and GLI (FEV$_1$/FVC *Z*-score < −1.64) criteria. The following OVD classifications severity were applied: ATS/ERS (FEV$_1$%pred): mild (>70%), moderate (60–69%), moderately severe (50–59%), severe (35–49%), and very severe (<35%) and GLI (FEV$_1$ *Z*-score): mild (≥ −2.0), moderate (−2.0 to −2.5), moderately severe (−2.5 to −3.0), severe (−3.0 to −4.0), and very severe (<−4.0). The frequencies of OVD were 14.4% (ATS/ERS method) and 10.5% (GLI method) ($p < 0.05$). Among the 103 participants having an OVD according to the two methods, the severity classification was mild (34.95% vs. 37.86%, $p < 0.05$), moderate (25.24% vs. 18.45%, $p < 0.05$), moderately severe (23.30% vs. 15.53%, $p = 0.144$), severe (9.71% vs. 20.39%, $p < 0.05$), and very severe (6.80% vs. 7.77%, $p = 0.785$), respectively for the ATS/ERS and GLI classifications. The two OVD definitions were not exchangeable. Moreover, the two grading severity systems misclassified the OVD grades.

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Bronchial obstruction; diagnosis; interpretation; international guidelines

In adults with a prior evidence of lung disease, an obstructive ventilatory defect (OVD) is usually defined by a low ratio between the 1st forced expiratory volume and the 'forced/slow' vital capacity [FEV$_1$/(F)VC] (e.g. <lower limit of normal (LLN)] [1,2]. In practice, once the OVD diagnosis is retained, it is essential to grade its severity into five degrees based on the FEV$_1$ [1,3]. However, nowadays, there is no clear consensus, neither as to what constitutes a LLN, nor as to how express the FEV$_1$.

Two methods were recommended by the American Thoracic and the European Respiratory Societies (ATS/ERS) [1] and by the global lung initiative (GLI) [2], to estimate the LLN. According to the ATS/ERS [1], the LLN can be estimated either as the 90% confidence interval using Gaussian statistics (in case of normal distribution) or with a nonparametric technique, such as the 90th percentile (in case of skewed distribution) [1]. In practice, the 90% LLN of each spirometric data is obtained by the subtraction of '1.64 × residual standard deviation (SD)' from the predicted value [1]. For example, the LLN of FEV$_1$ is equal to 'FEV$_1$ predicted value − 1.64 × residual SD'. While according to the ATS/ERS [1], the aforementioned SD is a fixed value whatever the age, for the GLI [2], it is a coefficient of variation that varies with age and, hence it must be modeled. According to the GLI, the LLN is considered as a *Z*-score lower than '−1.64' [2]. The *Z*-score is derived using the LMS method ['L' for lambda or location (index of skewness), 'M' for mu or mean value, and 'S' for sigma or scatter (coefficient of variation)] and using the generalized additive models for location, scale, and shape (GAMLSS) technique [4]. The principle of the LMS method is that the distribution of the outcome variable **Y** is defined by three age-varying parameters **λ, μ, σ** such that the transformed outcome: $\boldsymbol{Z} = [(\mathbf{Y}/\boldsymbol{\mu})^{\boldsymbol{\lambda}} - 1]/(\boldsymbol{\lambda} \times \boldsymbol{\sigma})$ [5]. The *Z*-score is the signed number of SDs by which the value of a

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measured spirometric data differs from the mean value of what is being predicted, with merely 5% of healthy subjects having a *Z*-score of 1.64 or less [2,6].

The severity of the OVD correlates with the ability to work and function in daily life, morbidity, respiratory complaints, and prognosis, including a fatal outcome [7]. Surprisingly, there is a disagreement between the ATS/ERS and the GLI on the way to express the FEV_1 [1,3]. While the ATS/ERS classification is based on the FEV_1 expressed in percentage of the predicted value (%pred) [1], the GLI new classification is based on the FEV_1 *Z*-scores [3]. This could be a source of confusion [6,8].

The present *Scientific Letter* aimed to ascertain how well the GLI criteria to diagnosis the OVD [2] and to grade its severity [3] fit those recommended by the ATS/ERS [1].

A cross-sectional study including 1000 participants (145 females) was performed in a private function exploration center (http://placesmap.net/TN/centre-international-d-explorations-fonctionnelles-163323/). Measurements were carried by a plethysmograph (Jaeger MasterScreen Body, CareFusion Germany). Local norms [9] were applied to derive the predicted values and the LLN. The *Z*-scores were derived for each participant using norms from the GLI basing specially on developed software [10]. The OVD was defined according to the ATS/ERS [FEV_1/FVC < LLN (=local norms value − 1.64 × residual SD) [1]] and the GLI [FEV_1/FVC *Z*-score < '−1.64' [2]] criteria. The following two severity classifications were applied: ATS/ERS [1] [based on the FEV_1%pred [11,12]: mild (>70%), moderate (60–69%), moderately severe (50–59%), severe (35–49%), and very severe (<35%)]; GLI [based on the FEV_1 *Z*-score [3]: mild (≥−2.0), moderate (−2.5 to −2.0), moderately severe (−3.0 to −2.5), severe (−4.0 to −3.0), and very severe (<−4.0)]. Analyses were carried out using Statistica software (Statistica Kernel version 6; StatSoft, Paris, France). Significance was set at the 0.05 level. Descriptive analysis includes frequencies for categorical variables and mean ± SD for continuous ones. Chi-square test was used to assess the agreement between the presence of OVD or its severity degree according to the two classifications (GLI vs. ATS/ERS). The relationships between the three spirometric data (FEV_1, FVC, and FEV_1/FVC) expressed as %pred and their *Z*-scores were evaluated using the correlation coefficient (r).

The total sample age, height, and weight mean ± SD were, respectively, 41.29 ± 10.30 years, 1.71 ± 0.08 m, and 80.9 ± 12.2 kg. Twenty percent of participants were smokers or ex-smokers. The determined FEV_1 (L, %pred), FVC (L, %pred), and FEV_1/FVC (absolute value, %pred) were, respectively, 3.37 ± 0.79 (84 ± 14%), 4.25 ± 0.89 (90 ± 12%), and 0.79 ± 0.08 (97 ± 9%). According to the GLI norms, their mean ± SD *Z*-scores were, respectively, −0.87 ± 1.04, −0.75 ± 0.93, and −0.26 ± 1.04. There were strong and significant linear relationships between data expressed as %pred and their *Z*-scores (r = 0.9280 for FEV_1, r = 0.9210 for FVC and r = 0.9689 for FEV_1/FVC). The frequencies of participants having an OVD were 14.4% and 10.5%, respectively with the ATS/ERS and the GLI methods ($p < 0.05$). Conformity of OVD diagnosis was found in 103 cases. Among the 144 participants having an OVD according to the ATS/ERS method, 41 were free from OVD according to the GLI method. Among the 105 participants having an OVD according to the GLI method, only two were free from OVD according to the ATS/ERS method. Moreover, the two grading severity systems misclassified the grades of OVD (Pearson Chi-square = 214.095, df = 16, $p < 0.05$). In fact, for the 103 participants having OVD according to the ATS/ERS and the GLI methods, the severity classification was mild (34.95% vs. 37.86%, $p < 0.05$), moderate (25.24% vs. 18.45%, $p < 0.05$), moderately severe (23.30% vs. 15.53%, $p = 0.144$), severe (9.71 vs. 20.39%, $p < 0.05$), and very severe (6.80% vs. 7.77%, $p = 0.785$).

The main result of this study was that the diagnosis and the classification of the OVD using the GLI method [2,3] resulted in a change in the frequencies and the severity degrees established by the ATS/ERS recommendations [1].

It is conventional that a diagnosis of an OVD should be based on an abnormally low FEV_1/(F)VC ratio [3]. Unexpectedly, there is no worldwide consensus on what constitutes a low FEV_1/(F)VC ratio [3,13]. Whereas the ATS/ERS [1] advocated use of the 5th percentile of FEV_1/(F)VC from a healthy population as the LLN, the GLI [2] adopted the *Z*-score value of FEV_1/FVC. According to the GLI [2], unlike %pred the *Z*-score is free from bias due to age, height, sex, and ethnic group. In this study, the two OVD definitions (GLI vs. ATS/ERS) were not exchangeable. The above result was contrary to that found in another larger study (n = 21,191 participants) [3], where the overall prevalence of OVD was identical with the ATS/ERS [1] and the GLI [3] definitions. The authors concluded that this allows reliable reconstruction of ATS/ERS criterion diagnosis by simple replacement of the LLN with *Z*-score [3]. This study findings do not support the above conclusion and confirmed previous result that adopting the GLI norms [2] will have significant effects on the proportions of detection of spirometric defects [11].

The GLI new classification system was described as effortless, simply remembered, and clinically convincing [3]. It seems that it retains formerly established links with clinical results and circumvents biases due to the use of FEV_1%pred [3]. According to Quanjer et al. [3], when merged with the GLI norms [2], it supplies a universal diagnostic standard, gratis of bias due to age, height, sex, and ethnic group. Similar to this study, another one [3] found a robust linear relationship between FEV_1% pred and FEV_1 Z-score (r = 0.99). The authors [3] concluded that this permits unfailing rebuilding of ATS/ERS severity classification cut-off values by simple substitution of FEV_1%pred with Z-score. In addition, they found that using the LLN for FEV_1/(F)VC and Z-scores for FEV_1 of −2, −2.5, −3, and −4 to demarcate severity grades of OVD results in close arrangement with ATS/ERS severity classifications [3]. This study finding do not support the above conclusions. In the cohort study of Tejero et al. [8] (n = 2614 patients with chronic obstructive pulmonary disease (COPD)), based on ATS/ERS [1] and GLI [11] classifications, 33.2% and 35.7% had mild, 39.9% and 36.2% had moderate, 18.5% and 20.9% had severe, and 8.3% and 7.3% had very severe OVD. Like in this study, in the aforementioned one [8], the classification based on Z-score [3] showed little concordance with the ATS/ERS classification [1]: according to the Z-score classification [3], 66.3% of COPD remained with the same severity, while 23.7% worsened and 10.0% improved.

The low percentage of females (14.5%) included in this study, makes the 'generalization' of the findings questionable, and a little bit 'biased'. In order to avoid such biased assessment of outcomes and the sex-related effect on spirometric data [14,15], it was better to include similar percentages of both sexes. However, the observed low percentage of females was similar to that reported in a previous local study where females represented 19.6% of the total sample [11].

In conclusion, the rational behind the remodeled scheme for diagnosing OVD and for classifying spirometric deficiency is interesting. It will afford the occasion for a universal standard for presentation and reading of spirometry. However, in some regions (e.g. North Africa), their application with the GLI norms should be taken with cautions. Again, the GLI group [2] is asked to consider North African population as an individual ethnic group and to create an adjustment factor for it. A larger number of North African participants with OVD or COPD will be needed to analyze the real application of the GLI [3] adjustment on diagnosing OVD and classifying its severity.

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Authors' contributions

RK conceived the study, participated in its design, performed the statistical analysis, and helped to draft the manuscript.

IG conceived the study, participated in its design and helped to draft the manuscript.

SR conceived the study, participated in its design and helped to draft the manuscript

HBS conceived the study, participated in its design, performed the statistical analysis, helped to draft the manuscript and coordinated the study.

All authors read and approved the final manuscript.

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