Spirometry for the diagnosis of airway obstruction in patients with risk factors for COPD: the GOLD and lower limit of normal criteria

Monica Grafino1, Filipa Todo-Bom1, Ana Cristina Lutas1, Jorge Cabral2, Marco Pereira1, João Valença1, Sofia Tello Furtado1

ABSTRACT

Objective: The identification of persistent airway obstruction is key to making a diagnosis of COPD. The GOLD guidelines suggest a fixed criterion—a post-bronchodilator FEV1/FVC ratio < 70%—to define obstruction, although other guidelines suggest that a post-bronchodilator FEV1/FVC ratio < the lower limit of normal (LLN) is the most accurate criterion.

Methods: This was an observational study of individuals ≥ 40 years of age with risk factors for COPD who were referred to our pulmonary function laboratory for spirometry. Respiratory symptoms were also recorded. We calculated the prevalence of airway obstruction and of no airway obstruction, according to the GOLD criterion (GOLD+ and GOLD−, respectively) and according to the LLN criterion (LLN+ and LLN−, respectively). We also evaluated the level of agreement between the two criteria.

Results: A total of 241 individuals were included. Airway obstruction was identified according to the GOLD criterion in 42 individuals (17.4%) and according to the LLN criterion in 23 (9.5%). The overall level of agreement between the two criteria was good (κ = 0.67; 95% CI: 0.52-0.81), although it was lower among the individuals ≥ 70 years of age (κ = 0.42; 95% CI: 0.12-0.72). The proportion of obese individuals was lower in the GOLD+/LLN+ category than in the GOLD+/LLN− category (p = 0.03), as was the median DL CO (p = 0.04). Conclusions: The use of the GOLD criterion appears to be associated with a higher prevalence of COPD. The agreement between the GOLD and LLN criteria also appears to be good, albeit weaker in older individuals. The use of different criteria to define airway obstruction seems to identify individuals with different characteristics. It is essential to understand the clinical meaning of discordance between such criteria. Until more data are available, we recommend a holistic, individualized approach to, as well as close follow-up of, patients with discordant results for airway obstruction.

Keywords: Pulmonary disease, chronic obstructive; Airway obstruction; Spirometry.

INTRODUCTION

As is well known, COPD is a leading cause of mortality and morbidity worldwide. According to the GOLD, COPD is characterized by persistent respiratory symptoms and airway obstruction, defined as an FEV1/FVC ratio < 70%. However, the FEV1/FVC ratio is influenced by sex and age. The fixed cutoff value does not reflect that influence and may misclassify airway obstruction. In view of that, some authors have proposed using the lower limit of normal (LLN), estimated from a reference population that is representative (in terms of age, sex, height, and race), as a more accurate criterion to define airway obstruction.

The true prevalence of COPD is unknown, and its reported prevalence varies considerably across the world due to differences in survey methods, sample characteristics, and diagnostic criteria. Most studies of COPD have been population-based studies including large proportions of individuals without risk factors for COPD (asymptomatic individuals and nonsmokers), have not included post-bronchodilator assessments, or have had both of those issues.

The aim of this study was to assess the prevalence of COPD according to the two different criteria used in order to define airway obstruction (FEV1/FVC ratio < 70% and FEV1/FVC ratio < LLN), as well as to determine the agreement between those two criteria, in a sample of patients with risk factors for COPD. We also assessed the clinical and functional differences between the patients in whom the criteria were concordant and those in whom they were discordant.

METHODS

Sample

This was an observational study including individuals ≥ 40 years of age who presented with key indicators of COPD and underwent spirometry between September...
and December of 2019 at the Pulmonary Function Laboratory of the Hospital da Luz Lisboa, in the city of Lisbon, Portugal. The key indicators of COPD were defined as follows: a smoking history of ≥ 10 pack-years or a history of relevant exposure to dust, vapor, fumes, gases, or chemicals; or chronic respiratory symptoms, including chronic cough, chronic sputum production, dyspnea—defined as a modified Medical Research Council (mMRc) dyspnea scale score ≥ 2 (11)—recurrent lower respiratory tract infections, and wheezing, in a smoker. Individuals who were under treatment with a bronchodilator—long-acting (< 24 h) or short-acting (< 8 h)—were excluded, as were those with a history of asthma, bronchiectasis, interstitial lung disease, or lung resection, as well as those whose symptoms could not be assessed.

The sample size was calculated on the basis of a confidence level of 95% (confidence limits of 5%) and an anticipated frequency in the general population of 14.2%. (12) Thus, the minimum sample size was determined to be 187 subjects.

Demographic characteristics (sex and age), anthropometric data (weight and height), and medical history (smoking habits, history of lung disease, and respiratory symptoms such as chronic cough, chronic sputum production, dyspnea, and wheezing) were obtained from medical records or from the patients themselves, in interviews. Individuals who had quit smoking six months prior to the interview were categorized as former smokers.

**Pulmonary function testing**

The pulmonary function tests included the determination of FEV₁, FVC, and the FEV₁/FVC ratio. If total body plethysmography, with or without single-breath diffusion testing, was performed, RV, TLC, and DLCO (% of predicted) were also recorded, as recommended in international guidelines. (13-15) All pulmonary function tests were performed by certified respiratory technologists trained in the use of the Masterscreen Body/Diffusion system with SentrySuite Software, version 2.21 (Vyaire Medical Inc., Chicago, IL, USA). Hygiene and infection control measures were applied in all patients. Calibration checks were performed, and quality control procedures were followed. All patients were informed about which activities and medications should be avoided or suspended before the pulmonary function tests.

The Global Lung Initiative (GLI) 2012 reference equations were applied for spirometry, (16) and the European Community for Coal and Steel equations were applied for static volumes. (17) All individuals with a pre-bronchodilator FEV₁/FVC ratio < 70% or < LLN underwent bronchodilator reversibility testing, in accordance with international guidelines. (15,17)

The default bronchodilator was albuterol, administered with a metered dose inhaler (100 µg per actuation). A dose of 400 µg was delivered with a valved holding chamber. Post-bronchodilator FEV₁ and FVC were measured 15 min later, the maneuvers being repeated until three acceptable measurements had been obtained. If albuterol was contraindicated, the anticholinergic agent ipratropium bromide (at a total dose of 160 µg with a valved holding chamber) was used. For the individuals receiving ipratropium bromide, the post-bronchodilator maneuvers were performed at 30 min after administration.

Airway obstruction was defined according to the fixed ratio (GOLD criterion) as a post-bronchodilator FEV₁/FVC ratio < 70% and according to LLN as a post-bronchodilator FEV₁/FVC ratio < LLN (designated GOLD+ and LLN+, respectively). Conversely, a post-bronchodilator FEV₁/FVC ratio ≥ 70% was designated GOLD− and a post-bronchodilator FEV₁/FVC ratio ≥ LLN was designated LLN−. The LLN was calculated by using the GLI 2012 equations, (16) in which it is the overall mean predicted value (based on sex, age, race, and height) minus 1.64 times the standard error of the estimate determined in the population-based study on which the reference equation is based (LLN 5% [lower 5th percentile]; z-score, −1.64).

The study was approved by the Ethics in Clinical Research Committee of the Hospital da Luz Lisboa. All participants provided written informed consent.

**Statistical analysis**

A descriptive analysis of the data was performed with RStudio, version 1.3.1056, running R, version 4.0.2 (RStudio Inc., Boston, MA, USA). Quantitative variables were expressed as medians and interquartile ranges, whereas qualitative variables were expressed as absolute and relative frequencies. The Shapiro-Wilk test was used in order to assess the normality of variables. The level of agreement between the two criteria applied to define airway obstruction was assessed by calculating Cohen’s kappa statistic (κ). We defined four categories of agreement between the two criteria: GOLD−/LLN−, GOLD+/LLN−, GOLD+/LLN+, and GOLD−/LLN+. To evaluate between-category differences for the quantitative variables, we used the Kruskal-Wallis test and Dunn’s test with Benjamini-Hochberg correction, whereas we used chi-square tests with Benjamini-Hochberg correction to determine whether there were statistically significant between-category differences for the qualitative variables. Values of p < 0.05 were considered statistically significant.

**RESULTS**

Our study sample included 241 individuals, of whom 134 (55.6%) were male. The median age was 60 years, and the median BMI was 27 kg/m². All of the individuals had a history of smoking, and 136 (56.4%) were still active smokers. Symptoms were present in 105 (43.6%) of the individuals, the most common being chronic cough (observed in 30.3%). When the GOLD criterion for airway obstruction was applied, 42 (17.4%) of the individuals were classified as having COPD, compared with 23 (9.5%) when the...
The overall agreement between the GOLD and LLN criteria to define obstruction was good (κ = 0.67), although there was only moderate agreement among the individuals over 70 years of age (κ = 0.42). As can be seen in Table 2, none of the individuals evaluated fit into the GOLD−/LLN+ category (post-bronchodilator FEV1/FVC ratio < LLN and ≥ 70%). When comparing the three remaining categories, we found that the individuals in the GOLD+/LLN− category were significantly older than those in the GOLD−/LLN− category (p < 0.001), although we found no significant difference in age between the two discordant categories (GOLD−/LLN− and GOLD+/LLN+; p = 0.102). The proportion of obese patients was lowest in the GOLD+/LLN+ category.

Individuals in the GOLD−/LLN− category had fewer symptoms than did those in the other categories. We found no differences between the GOLD+/LLN− and GOLD+/LLN+ categories in terms of presence of symptoms. The proportion of patients with dyspnea (mMRC score ≥ 2) was higher in the GOLD+/LLN− category than in the GOLD−/LLN− category, although the difference was not statistically significant, and the two categories were comparable in terms of other COPD symptoms (Table 1).

The median DLco value was lower in the GOLD+/LLN+ category than in the GOLD−/LLN− and GOLD+/LLN− categories (p < 0.001 and p = 0.038, respectively). We found no statistically significant difference in DLco between the GOLD−/LLN− category and the GOLD+/LLN− category.

**DISCUSSION**

In the present study, we evaluated two different criteria to define airway obstruction in a sample of individuals with risk factors for COPD. The overall prevalence of COPD was higher when the GOLD criterion was applied than when the LLN criterion was applied (17.4% vs. 9.5%), and the concordance between the two criteria was good, albeit weaker in older individuals. The proportion of obese individuals was higher in the GOLD+/LLN− category and in the GOLD−/LLN+ category. Although the individuals in the GOLD+/LLN− category were older than were those in the GOLD−/LLN− category, there was no significant difference in age between the GOLD+/LLN+ category and the GOLD−/LLN− category.

The reported prevalence of COPD varies widely because of differences in survey design, diagnostic criteria, and analytical approaches, which complicate comparisons of the data. In comparison with the findings of another study conducted in the same region of Portugal, which used the Burden of Obstructive Lung Disease protocol/GOLD criteria, the prevalence of COPD was higher in the present study (14.2% vs. 17.4%). That discrepancy could be explained by the differences between the two samples. In the present study, we included only current or former smokers with risk factors for COPD who were referred for pulmonary function testing. Most other studies of this type, including the Burden of Obstructive Lung Disease study, have been population-based studies.

The LLN values are dependent on the chosen reference equation. Therefore, the reported prevalence of COPD is also broad, ranging from 8.2% to 14.0%, depending on the LLN used in order to define airway obstruction; 8.2% when the European Community for Steel and Coal prediction equation is used; 8.6% when the GLI equation is used; 10.0% when the National Health and Nutrition Examination Survey equation is used; and 14.0% when the Copenhagen City Heart Study/Copenhagen General Population Study equation is used. Among elderly individuals, the rate of airway obstruction obtained is lower when the GLI 2012 reference equation is used than when those of the National Health and Nutrition Examination Survey III and the European Community for Steel and Coal prediction equation are used.

In the present study, the number of individuals diagnosed with airway obstruction was higher when we used a fixed criterion for evaluating the post-bronchodilator FEV1/FVC ratio than when we used the LLN-based criterion, a finding that is consistent with those of other studies. The GOLD criterion may overestimate airway obstruction in older individuals and underestimate it in younger individuals. As in other studies, the prevalence of airway obstruction evaluated with the fixed criterion increased with age in our study. However, as was also found in our study, that difference is less pronounced when the LLN criterion is used. We documented good agreement between the two criteria, although the level of that agreement decreased with age, as has previously been reported.

It is unknown what the most appropriate criterion to define obstruction in the diagnosis of COPD is, as well as the clinical meaning of a discordant classification. Because there is no gold-standard criterion, it is impossible to determine which criterion is better. The overdiagnosis in older individuals when the fixed criterion is used can be associated with unnecessary treatments, increased healthcare costs, adverse health effects, and failure to investigate other possible reasons for the complaints. In one systematic review, both criteria appeared to be associated with various clinically relevant outcomes and there were no data to justify a preference for one criterion over the other.

In regard to lung function, we found that the DLco was lower in the discordant for obstruction category than in the discordant for obstruction category, although it was comparable between the discordant for obstruction category and the discordant for no obstruction category. In keeping with our data, other
Table 1. Descriptive statistics and comparison of the categories of agreement between the GOLD and lower limit of normal criteria to define airway obstruction.

| Variable                                | Total (n = 241) | GOLD−/LLN− (n = 199) | GOLD+/LLN− (n = 19) | GOLD+/LLN+ (n = 23) | p*  | p*  | p*    |
|-----------------------------------------|-----------------|-----------------------|---------------------|---------------------|-----|-----|-------|
| Age (years)                             | 52 (17.8)       | 50 (25.2)             | 4 (21.1)            | 4 (17.4)            | 0.17| 0.17| 0.17  |
| Age range (years)                       |                | 40-49                 | 50-59               | ≥ 60-69             |     |     |       |
| BMI (kg/m²)                             | 25.9 (4.8)      | 25.8 (4.7)            | 26.8 (4.9)          | 24.9 (4.6)          | 0.10| 0.10| 0.10  |
| Smoking history (pack-years)            | 27.0 (23.2)     | 25.6 (22.2)           | 31.1 (29.0)         | 20.0 (19.5)         | 0.02| 0.02| 0.02  |
| Symptom score                           | 7.0 (7.0)       | 6.0 (6.0)             | 8.5 (8.5)           | 5.0 (5.0)           | 0.01| 0.01| 0.01  |
| Cough/sputum/wheezing                   | 15 (5.2)        | 13 (6.1)              | 15 (77.8)           | 12 (52.1)           | 0.01| 0.01| 0.01  |
| Dyspnea (mMRC score ≥ 2)               | 23 (9.5)        | 22 (11.1)             | 14 (73.7)           | 11 (47.8)           | 0.01| 0.01| 0.01  |
| Recurrent respiratory infection         | 4 (1.7)         | 3 (1.5)               | 2 (10.5)            | 1 (4.3)             | 0.01| 0.01| 0.01  |
| Wheezing                                | 6 (2.5)         | 5 (2.6)               | 1 (5.3)             | 0 (0.0)             | 0.01| 0.01| 0.01  |
| Pre-BD FEV1 (% predicted)               | 89 (36.6)       | 89 (36.6)             | 91 (91.0)           | 90 (39.1)           | 0.01| 0.01| 0.01  |
| Post-BD FEV1 (% predicted)              | 90 (37.0)       | 89 (36.6)             | 91 (91.0)           | 90 (39.1)           | 0.01| 0.01| 0.01  |

*With Benjamini-Hochberg correction.

J Bras Pneumol. 2021;47(6):e20210124
studies have suggested that lung function (FVC, FEV$_1$, and the FEV$_1$/FVC ratio) is more well preserved in individuals in whom an obstructive pattern is identified according to the GOLD criterion and not according to the LLN criterion,\(^2\) and that such individuals do not show accelerated FEV$_1$ decline.\(^3\) However, the individuals in our discordant for obstruction category (GOLD+/LLN−) also showed some functional characteristics of COPD (e.g., higher RV).

Dyspnea is a cardinal symptom of COPD, although it is nonspecific and could result from other conditions, including heart disease, other lung diseases, and physical deconditioning. Some authors have reported that respiratory symptoms are less common and that potentially significant comorbidities (such as heart disease) are more frequent in "discordant obstructive" cases.\(^4\) There is evidence suggesting that other etiologies should be considered in such cases.\(^5\)

Although we did not thoroughly access comorbidities in our sample, we found that the proportion of obese individuals was higher in the discordant for obstruction category (GOLD+/LLN−), which is in keeping with the findings of other studies that reported a higher frequency of comorbidities in individuals with discordant results for obstruction.\(^6\) However, not all studies have detected such a difference.\(^7\)

We were unable to analyze the second discordant for obstruction category (GOLD−/LLN+), because none of the individuals in our sample fit into that category. That is probably a consequence of the fact that we included only individuals ≥ 40 years of age, given that the GOLD criterion has been shown to underestimate airway obstruction in individuals between 20 and 44 years of age.\(^8\) However, because the diagnosis of COPD is based on key indicators in individuals over 40 years of age and on airway obstruction confirmed by spirometry,\(^1\) the underdiagnosis of airway obstruction in younger individuals according to the GOLD criterion might not be a significant issue.

The present study highlights the debate on how to interpret the FEV$_1$/FVC ratio and the meaning of discordance between different criteria to define obstruction in the COPD diagnosis. We suggest a holistic and individualized approach for patients with discordant results for obstruction,\(^2\) who should be followed closely. Functional, clinical, and radiological aspects beyond spirometry should be considered. Individuals in the GOLD+/LLN− category in our sample had some characteristics of COPD, such as dyspnea (mMRC score ≥ 2) and higher RV. However, that category could also include some healthy elderly individuals and individuals with symptoms due to other diseases (such as obesity and cardiovascular disease). If only the GOLD criterion is applied, it is more likely that patients will undergo unnecessary treatments and that other possible reasons for the complaints will go undiagnosed. We recommend close follow-up of patients with discordant results for obstruction, because it is possible that the LLN criterion underdiagnoses COPD.

**Figure 1.** Prevalence of COPD by sex and age group, according to the GOLD and lower limit of normal (LLN) criteria (for the post-bronchodilator FEV$_1$/FVC ratio) to define airway obstruction.

**Table 2.** Overall agreement and agreement by age group between the GOLD and lower limit of normal criteria to define airway obstruction.

| Category of agreement | Overall | Age group (years) |
|-----------------------|---------|------------------|
|                       | (n = 241) | < 70 (n = 191) | ≥ 70 (n = 50) |
| GOLD−/LLN−, n (%)     | 199 (82.6) | 166 (86.9) | 33 (66.0) |
| GOLD+/LLN−, n (%)     | 19 (7.9) | 8 (4.2) | 11 (22.0) |
| GOLD+/LLN+, n (%)     | 23 (9.5) | 17 (8.9) | 6 (12.0) |
| GOLD−/LLN+, n (%)     | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Level of agreement, $\kappa$ (95% CI)

|                       | (0.52-0.81) | (0.64-0.93) | (0.12-0.72) |

GOLD−: FEV$_1$/FVC ratio ≥ 70%; LLN−: FEV$_1$/FVC ratio ≥ LLN; GOLD+: FEV$_1$/FVC ratio < 70%; LLN+: FEV$_1$/FVC ratio < LLN; and $\kappa$: Cohen’s kappa statistic.

---

J Bras Pneumol. 2021;47(6):e20210124
Spirometry for the diagnosis of airway obstruction in patients with risk factors for COPD: the GOLD and lower limit of normal criteria

or identifies only patients with more advanced COPD. There is a need for studies focusing on the subgroup of patients with FEV1/FVC ratio discordance.

The present study has a number of strengths. We included individuals with risk factors for COPD (current or former smokers ≥ 40 years of age), thus constructing a sample of individuals at higher risk for developing smoking-related airway obstruction. Conversely, we excluded individuals with other respiratory diseases (such as asthma and bronchiectasis) or a history of lung resection, all of which can mimic the symptoms and lung function alterations of COPD, resulting in an overestimation of its prevalence. In addition, we assessed symptoms characteristic of COPD. Furthermore, we used the GLI 2012 reference equations, which provide a robust reference standard. Moreover, bronchodilator reversibility testing was performed in all individuals with airway obstruction on spirometry, whereas most studies of this topic have not included post-bronchodilator assessments or have been population-based studies that included high proportions of individuals without risk factors for COPD (asymptomatic individuals and nonsmokers) and also did not include post-bronchodilator assessments.

Our study has some limitations. We did not have access to data about exposure to harmful agents other than tobacco smoke, such as airborne pollutants (from household fuel burning, occupational sources, and ambient sources), about socioeconomic status, or about comorbidities. In addition, bronchodilator reversibility testing was performed only in subjects with pre-bronchodilator obstruction (FEV1/FVC ratio < 70% or < LLN). However, that may not have made a significant difference, given that only a small proportion (3%) of individuals show obstruction in the post-bronchodilator evaluation after showing no airway reversibility testing was performed only in subjects with pre-bronchodilator obstruction (FEV1/FVC ratio < 70% or < LLN). However, that may not have made a significant difference, given that only a small proportion (3%) of individuals show obstruction in the post-bronchodilator evaluation after showing no airway obstruction on the pre-bronchodilator evaluation, as well as that pre- and post-bronchodilator airway obstruction have been found to predict mortality with a similar degree of accuracy. Furthermore, because our sample size was calculated to assess the prevalence of COPD, the number of individuals in the discordant for obstruction category was small. Moreover, we did not assess the relationship between airway obstruction on spirometry and other COPD outcomes, because we had no access to follow-up data. Finally, the reference values of the GLI 2012 equations were not applied for body plethysmography (which was not evaluable at the beginning of the data collection).

In this study, we assessed two different criteria to define airway obstruction for the diagnosis of COPD in a sample of individuals with risk factors for the disease. We documented a higher prevalence of airway obstruction when the GOLD criterion was applied than when the LLN criterion was applied (17.4% vs. 9.5%). The overall level of agreement between the two criteria was good, although it was lower in the older subjects. The use of different criteria to define airway obstruction seems to identify individuals with different characteristics. It is essential to understand the clinical meaning of discordance between such criteria. Until more data are available, we recommend a holistic, individualized approach to, as well as close follow-up of, patients with discordant results for airway obstruction.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Bethesda: GOLD; c2020 [cited 2021 Mar 9]. Global strategy for the diagnosis, management and prevention of Chronic Obstructive Pulmonary Disease. 2020 report. Available from: https://goldcopd.org/gold-reports/

2. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl. 1992;16:5-40. https://doi.org/10.1183/09041950.92.s1693

3. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159(11):179-187. https://doi.org/10.1164/ajrccm.159.11.9711018

4. Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, et al. Definition of COPD: based on evidence or opinion?. Eur Respir J. 2003;22(2):681-682. https://doi.org/10.1183/09031936.00154307

5. Celli BR, Halbert RJ, Israoka S, Schau B. Population impact of different definitions of airway obstruction. Eur Respir J. 2003;22(2):268-273. https://doi.org/10.1183/09031936.03.0075102

6. Mohamed Hoessein FA, Zanen P, Lammers JW. Lower limit of normal or FEV1/FVC < 0.70 in diagnosing COPD: an evidence-based review. Respir Med. 2011;105(6):307-315. https://doi.org/10.1016/j.rmed.2011.01.008

7. Doorly A, Miller MR, Thomsen SF, Christensen K, Sigsgaard T, Backer V. The impact of different spirometric definitions on the prevalence of airway obstruction and their association with respiratory symptoms. ERJ Open Res. 2017;3(4):00110-2017. https://doi.org/10.1183/23120541.00110-2017

8. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study (published correction appears in Lancet. 2012 Sep 1;380(9844):806).

9. Meteran H, Miller MR, Thomsen SF, Christensen K, Sigsgaard T, Backer V. Underestimation of airflow obstruction among young adults using FEV1/FVC < 70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. Thorax. 2008;63(12):1040-1045. https://doi.org/10.1136/thx.2008.095554

10. Pellegrino R, Brusasco V, Sigsgaard T, Celli BR, et al. Definition of COPD: based on evidence or opinion?. Eur Respir J. 2003;22(2):681-682. https://doi.org/10.1183/09031936.00154307

11. Mohamed Hoessein FA, Zanen P, Lammers JW. Lower limit of normal or FEV1/FVC < 0.70 in diagnosing COPD: an evidence-based review. Respir Med. 2011;105(6):307-315. https://doi.org/10.1016/j.rmed.2011.01.008
11. Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). BMJ. 1960;2:1662.

12. Bárbara C, Rodrigues F, Dias H, Cardoso J, Almeida J, Matos MJ, et al. Chronic obstructive pulmonary disease prevalence in Lisbon, Portugal: the burden of obstructive lung disease study. Rev Port Pneumol. 2013;19(3):96-105. https://doi.org/10.1016/j.rppneu.2012.11.004

13. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26(3):511-522. https://doi.org/10.1183/09031936.05.00034805

14. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung [published correction appears in Eur Respir J. 2018 Nov 22;52(5):]. Eur Respir J. 2017;49(1):1600016. https://doi.org/10.1183/13993003.00016-2016

15. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-e88. https://doi.org/10.1164/rccm.201908-1590ST

16. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-1343. https://doi.org/10.1183/09031936.00080312

17. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of Spirometry. Eur Respir J. 2005;26(2):319-338. https://doi.org/10.1183/09031936.05.00034805

18. Vollmer WM, Gislason T, Burney P, Enright PL, Gulsvik A, Kocabas A, et al. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. Eur Respir J. 2009;34(3):588-597, https://doi.org/10.1183/09031936.0164608

19. Çolak Y, Nordestgaard BG, Vestbo J, Lange P, Altfaj S. Comparison of five major airflow limitation criteria to identify high-risk individuals with COPD: a contemporary population-based cohort. Thorax. 2020;75(11):944-954. https://doi.org/10.1136/thoraxjnl-2020-214559

20. Danielsson P, Olafsdottir IS, Benediktsdottir B, Gislason T, Janson C. The prevalence of chronic obstructive pulmonary disease in Uppsala, Sweden—the Burden of Obstructive Lung Disease (BOLD) study: cross-sectional population-based study. Clin Respir J. 2012;6(2):120-127. https://doi.org/10.1183/1752669X.2011.00257.x

21. Bhatt SP, Sieren JC, Dransfield MT, Washko GR, Newell JD Jr, Stinson DS, et al. Comparison of spirometric thresholds in diagnosing smoking-related airflow obstruction. Thorax. 2014;69(5):499-514. https://doi.org/10.1136/thoraxjnl-2012-202810

22. van Dijk WD, Gupta N, Tan WC, Bourbeau J. Clinical relevance of diagnosing COPD by fixed ratio or lower limit of normal: a systematic review. COPD. 2014;11(1):113-120. https://doi.org/10.3109/15412555.2013.781996

23. Izquierdo Alonso JL, De Lucas Ramos P, Rodríguez Glez-Moro JM; grupo de estudio CONSISTE. The use of the lower limit of normal as a criterion for COPD excludes patients with increased morbidity and high consumption of health-care resources. Arch Bronconeumol. 2012;48(7):223-228. https://doi.org/10.1016/j.arbr.2012.05.002

24. Akkermans RP, Berrevoets MA, Smeule U, Lucas AE, Thoonen BP, Grootens-Stekelenburg JG, et al. Lung function decline in relation to diagnostic criteria for airflow obstruction in respiratory symptomatic subjects. BMC Pulm Med. 2012;12:12. https://doi.org/10.1186/1471-2466-12-12

25. Lamprecht B, Schinholfer L, Kaiser B, Buist SA, Mannino DM, Studnicka M. Subjects with Discordant Airways Obstruction: Lost between Spirometric Definitions of COPD. Pulm Med. 2011;2011:782015. https://doi.org/10.1155/2011/782015

26. Xiong H, Huang Q, Shuai T, Zhu L, Zhang C, Zhang M, et al. Assessment of comorbidities and prognosis in patients with COPD diagnosed with the fixed ratio and the lower limit of normal: a systematic review and meta-analysis. Respir Res. 2020;21(1):189. https://doi.org/10.1186/s12931-020-01450-9

27. Neder JA, Milne KM, Berton DC, de-Torres JP, Jensen D, Tan WC, et al. Exercise Tolerance according to the Definition of Airflow Obstruction in Smokers. Am J Respir Crit Care Med. 2020;202(5):760-762. https://doi.org/10.1164/rccm.202002-0298LE

28. Fortis S, Eberlein M, Georgopoulou D, Cornellas AP. Predictive value of prebronchodilator and postbronchodilator spirometry for COPD features and outcomes. BMJ Open Resp Res. 2017;4(1):e000213. https://doi.org/10.1136/bmjresp-2017-000213

29. Mannino DM, Diaz-Guzman E, Buist S. Pre- and post-bronchodilator lung function as predictors of mortality in the Lung Health Study. Respir Res. 2011;12(1):136. https://doi.org/10.1186/1465-9921-12-136