Original Article

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Quick Response Code:

Website: www.eurasianjpulmonol.com

DOI: 10.4103/ejop.ejop_78_18

The effectiveness of lower limit of normal criteria and cutoff rate of forced expiratory volume in 1 s/forced expiratory volume in 6 s using in the diagnosis of airway obstruction in chronic obstructive pulmonary disease patients diagnosed with fixed ratio

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Abstract:

AIMS: The definition of limited airflow as forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio for chronic obstructive pulmonary disease (COPD) is still controversial. The objective of this study was to compare the prevalence of COPD using fixed ratio and lower limit of normal (LLN) of FEV1/FVC for the presence of airflow limitation and evaluate the performance of FEV1/forced expiratory volume in 6 s (FEV6) in patients diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) fixed ratio.

SUBJECTS AND METHODS: Patients who presented to the pulmonary disease clinic between May 2008 and December 2017 and who were diagnosed with COPD were evaluated retrospectively. The distribution of FEV1/FVC-LLN according to the GOLD fixed ratio was evaluated after the patients were divided based on age groups. A receiver operating characteristics curve was used to determine the best FEV1/FEV6 cutoff value which fit into the FEV1/FVC <LLN, and sensitivity and specificity were calculated.

RESULTS: Of the patients, 165 (85.9%) were male and 27 were female, with a mean age of 64.40 ± 10.66 years (range, 40–85). Among the patients, 11.5% of 61 patients aged 40–60 years, 28.4% of 67 patients aged 61–70 years, and 26.6% of 64 patients aged over 70 years were out of the diagnosis of obstruction according to the fixed ratio of FEV1/FVC >LLN. The cutoff value of FEV1/FEV6 for airway obstruction according to FEV1/FVC <LLN was 0.735 with a sensitivity of 99.3%, a specificity of 95.3%, and area under the curve of 0.900 (95% confidence interval: 0.856–0.944, $P < 0.001$).

CONCLUSIONS: In this study, older patients, particularly, were diagnosed less often with an FEV1/FVC <LLN value calculated according to the Global lung function initiative (GLI) norms, compared to the fixed ratio. In addition, ratio of FEV1/FEV6 of < 0.735 may be useful in the diagnosis of airway obstruction in the early period and may also be used in office-type spirometers, since it is not dependent on a time constant.

Keywords:

Obstruction, ratio of 1 s of forced expiratory volume to 6 s of forced expiratory volume, ratio of 1 s of forced expiratory volume to forced vital capacity, ratio of 1 s of forced expiratory volume to forced vital capacity under the lower limit of normal

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Received: 24-12-2018
Revised: 09-06-2019
Accepted: 22-06-2019
Published: 30-12-2019

How to cite this article: Erdogan G, Sonmez E, Alahdab H. The effectiveness of lower limit of normal criteria and cutoff rate of forced expiratory volume in 1 s/forced expiratory volume in 6 s using in the diagnosis of airway obstruction in chronic obstructive pulmonary disease patients diagnosed with fixed ratio. Eurasian J Pulmonol 2019;21:175-81.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading public health problem worldwide. The mortality and morbidity of COPD has been increasing constantly, resulting in severe incapacity to work and economic burden. Nevertheless, both overdiagnosis and underdiagnosis lead to challenges in daily practice, causing inappropriate patient management. The current COPD guidelines recommend using the ratio between forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) to diagnose patients with chronic respiratory symptoms or to identify those under risk.[1] Either a FEV1/FVC ratio of <0.70 or a FEV1/FVC ratio of under the 5th percentile derived from reference equations or values under the lower limit of normal (LLN) are accepted as indications of limited airflow by spirometry.[2,3] The lambda–mu–sigma method, a new approach, accounts for age-related changes in lung function and representing how spirometric measures change based on predictor variables (age and height) by using spirometric *Z*-scores that incorporate the median (μ). In this equation, sigma (coefficient of variation) representing the spread of reference values; and Lambda (the skewness) representing withdrawal from normality. A *Z*-score of − 1.64 defines the LLN as the fifth percentile of distribution.[4] The Global Lung Initiative (GLI) has published equations that expand the availability of lambda–mu–sigma calculated spirometric *Z*-scores, using data from large reference populations of asymptomatic lifelong nonsmokers.[5] Prevalence studies have demonstrated the mismatch between the fixed ratio and LLN, and that this situation may lead to underdiagnosis or overdiagnosis[6-8]

Recent studies have suggested the use of forced expiratory maneuver decreased to a period of 6 s and the ratio of 1 s of forced expiratory volume to 6 s of forced expiratory volume (FEV1/FEV6). It is suggested that this ratio can be used rather than the FEV1/FVC ratio in common use for the diagnosis of respiratory obstruction in FVC maneuvers. Since it is easy to use both for the patient and the technician and offers such advantages as a decreased total time of the spirometry test and decreased complications of spirometry such as syncope, its use is recommended, particularly for primary care health services and for office type spirometers.[9-12] However, previous studies demonstrated that the criteria accepted for the definition of obstruction based on FEV1/FEV6 vary considerably, and so used the sensitivity and specificity values associated with the receiver operating characteristics (ROC) curve analysis to identify the best cutoff point.[13] Other studies recommended 0.70 ratio for FEV1/FEV6,[14] while the remaining authors used the LLN derived from the reference equations as the best option.[11-13]

In our study first, we aimed to evaluate airflow limitations using LLN as defined by the Global Lung Function Initiative (GLI) compared to the fixed ratio in patients with COPD diagnosed with the fixed ratio according to the Global Obstructive Lung Disease (GOLD) guide, and the secondary aim of the study was to identify a fixed cutoff equivalent to the commonly used fixed ratio of FEV1/FVC <LLN (GLI) for the FEV1/FEV6 ratio.

Subjects and Methods

Patients who were admitted to the Pulmonary Disease Clinic of between May 2008 and December 2017 and who were diagnosed with COPD were analyzed retrospectively using the International Statistical Classification of Diseases and Related Health Problems-10 codes including J44, 0, 1, 8, 9. A total of 192 patients aged >40 years with a postbronchodilator FEV1/FVC of <0.70 according to the GOLD criteria with a smoking history of ≥10 packs of cigarettes per year were accepted as having COPD and were included in the study. The currently adopted spirometer parameters, calculated according to the ECCS'93 predictive norms were converted into the GLI 2012 norms for Caucasian populations using a GLI online excel converter tool on the Internet site of the European Respiratory Society (ERS), and FEV1/FVC-LLN and *Z*-score values were duly obtained (https://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/online-calculator.aspx).

Patients with a FEV1/FVC *Z*-score of lower than −1.64 were accepted as obstructive. Patients were grouped as 40–60 years Group I, 61–70 years Group II, and >70 years Group III. FEV1/FVC-LLN distributions were evaluated by scatterplots graph against fixed ratio. The difference between the FEV1/FVC *Z*-score values of the age groups was compared with the one-way ANOVA test. A ROC curve was used to identify the best FEV1/FEV6 cutoff value which fit into FEV1/FVC <LLN, and sensitivity and specificity were calculated.

Exclusion criteria were as follows

Acute exacerbation of COPD and COPD with complications such as *cor pulmonale* or pneumothorax, coexisting cardiac failure or congenital heart disease, any other significant medical/surgical disease (i.e., narrow-angle glaucoma, prostatic disease, or bladder outlet obstruction), and history of abdominal/thoracic surgery within the past 3 months.

Written informed consent was obtained from each patient. The study protocol was approved by the Institutional Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Spirometry

The pulmonary function tests (PFTs) were performed using the MasterScreen™ spirometer (CareFusion Ltd., Germany). The calibration of the device was carried out with the body temperature and pressure saturated corrections. Tests which met the ERS/American Thoracic Society (ATS) standards were included, and data providing the spirometer test criteria "A" or "B" level were included [Table 1, Recommendations for a standardized pulmonary function report an official ATS technical statement 2017].

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation. The performance of the separate sets of variables was analyzed using two-by-two tables. The ROC analyses were conducted to measure the accuracy of FEV1/FEV6 compared to the FEV1/FVC-LLN and to identify the FEV1/FEV6 cutoff which had the best sum of sensitivity and specificity in the diagnosis of airflow obstruction as defined by the FEV1/FVC < LLN. Continuous variables among age groups were compared by the one-way ANOVA. Statistical significance was accepted at $P < 0.05$.

Table 1: Spirometry quality criteria

Grade	Criteria for adults and older children and for children aged 2-6 years
A	≥3 acceptable tests with repeatability within 0.150 L for age 2-6, 0.100 L, or 10% of highest value, whichever is greater
B	≥2 acceptable tests with repeatability within 0.150 L for age 2-6, 0.100 L, or 10% of highest value, whichever is greater
C	≥2 acceptable tests with repeatability within 0.200 L for age 2-6, 0.150 L, or 10% of highest value, whichever is greater
D	≥2 acceptable tests with repeatability within 0.250 L for age 2-6, 0.200 L, or 10% of highest value, whichever is greater
E	One acceptable test
F	No acceptable tests

Recommendations for a standardized pulmonary function report an official ATS technical statement 2017. ATS: American Thoracic Society

Table 2: Characteristics of the study group

Variables	Mean±SD (minimum-maximum)
Age (years)	64.40±10.66 (40-85)
Female (*n*=27; 14.1%)	62.11±11.82 (42-80)
Male (*n*=165; 85.9%)	65.7±10.1 (40-85)
BMI (kg/m^2)	26.9±5.1 (16.9-49.2)
Tobacco exposure (pack-years)	49.9±20.01 (10-120)
FVC (L)	3.06±0.88 (1.22-5.37)
FVC%	81.14±17.57 (41-120)
FEV_1 (L)	1.73±0.64 (0.63-3.71)
FEV_1%	60.99±8.66 (21-108)
FEV_6 (L)	2.85±0.84 (1.20-5.28)
FEV_1/FVC	0.56±0.11 (0.28-0.70)
FEV_1/FVC LLN (L)	0.69±0.03 (0.59-0.71)
FEV_1/FVC Z-score	−2.55±1.06 (−5.36-0.77)
FEV_1/FEV_6	0.6±0.09 (0.38-0.77)

BMI: Body mass index, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in 1 s, FEV_6: Forced expiratory volume in 6 s, LLN: Lower limit of normal, *Z*-score: Measured - predicted/SD, SD: Standard deviation

Table 3: Analysis of the discordant cases when using the forced expiratory volume in 1 s/forced expiratory volume in 6 s and forced expiratory volume in 1 s/forced vital capacity ratio-lower limit of normal for airway obstruction curves

FEV_1/FEV_6	FEV_1/FVC		Total, *n*
	< LLN, *n* (%)	≥ LLN, *n* (%)	
73.5%	147 (77.8)	42 (22.2)	189
≥73.5%	2 (66.7)	1 (33.3)	3
Total	149 (77.6)	43 (22.4)	192

LLN: Lower limit of normal, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in 1 s, FEV_6: Forced expiratory volume in 6 s

Results

The mean age of the 192 COPD patients was 64.40 ± 10.66 and 165 (85.9%) were male (65.7 ± 10.1). 27 (14.1%) patients were female (62.11 ± 11.82), [Table 2]. 149 patients (77.6%) were diagnosed with COPD with FEV1/FVC <LLN after the conversion of spirometer data of 192 COPD patients, calculated via ECCS prediction's fixed ratio to GLI prediction; meaning that 43 patients (22.4%) were ruled out of COPD diagnosis according to the LLN criterion with FEV1/FVC > LLN [Table 3]. Linear correlation between FEV1/FVC and FEV1/FVC *Z*-score values of the patients who were separated into age groups are indicated with scatterplot [Figures 1-3], significant linear correlation was present between two variables (Group I, II, and III R^2, respectively: 0.980, 0.980, 0.960, $P < 0.001$). When the inconsistency of FEV1/FVC-LLN between the age groups was assessed, FEV1/FVC >LLN was found in 11.5% of 61 patients between 40 and 60 years; in 28.4% of 67 patients between 61 and 70 years and in 26.6% of 64 patients above 70 years of age; it was noted that particularly elderly patients were diagnosed in higher rates [Table 4]. Assessment of FEV1/FVC *Z*-score value differences obtained from the LLN of the patients separated to age groups revealed no significant difference with each other ($P > 0.05$) [Figure 4].

Another aim of our study was to assess the contribution of FEV1/FEV6 parameter to detection of obstructions as an alternative to diagnosing obstructions with FEV1/FVC <LLN value obtained via GLI prediction. Before the analysis of accuracy, a scatterplot graph between FEV1/FEV6 and FEV1/FVC-LLN ratios was constructed, and R^2: 0.900 ($P < 0.001$) was found. ROCC analysis, conducted for the FEV1/FEV6 value that could be predictive of FEV1/FVC <LLN, yielded a cutoff value of 0.735, sensitivity ratio was 99.3% and specificity ratio was 95.3%, and the area under the curve (AUC) was 0.900 [Figure 5]. The positive predictive value of FEV1/FEV6 was 84.8%, and the negative predictive

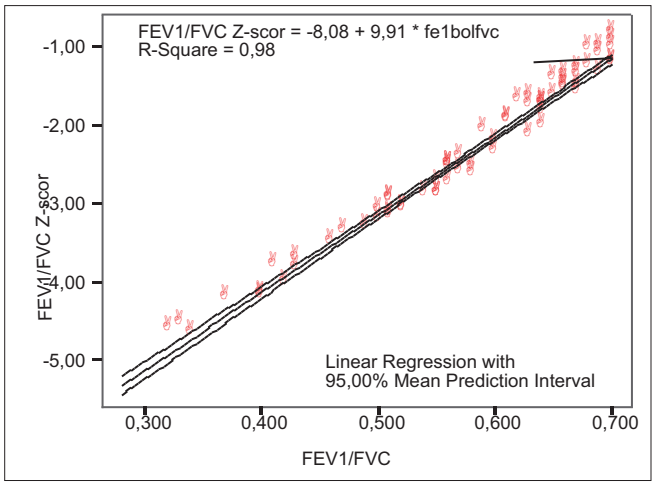

Figure 1: Scatterplot curve for FEV1/FVC and FEV1/FEV *Z*-score values of age Group I. LLN: Lower limit of normal, FVC: Forced vital capacity, FEV: Forced expiratory volume

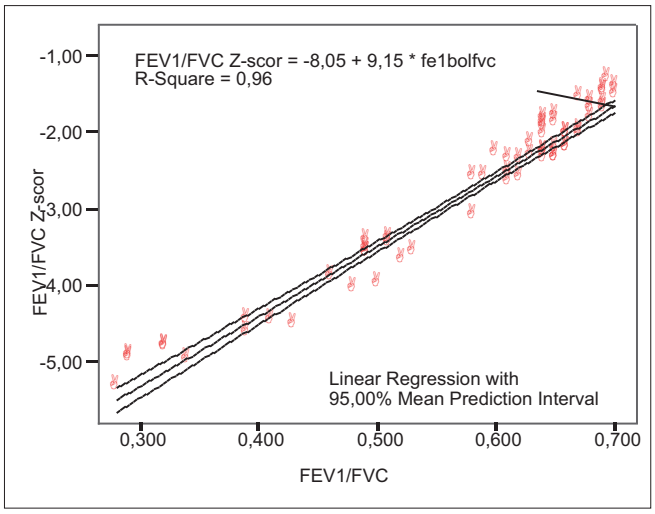

Figure 2: Scatterplot curve for FEV1/FVC and FEV1/FEV *Z*-score values of age Group II. LLN: Lower limit of normal, FVC: Forced vital capacity, FEV: Forced expiratory volume

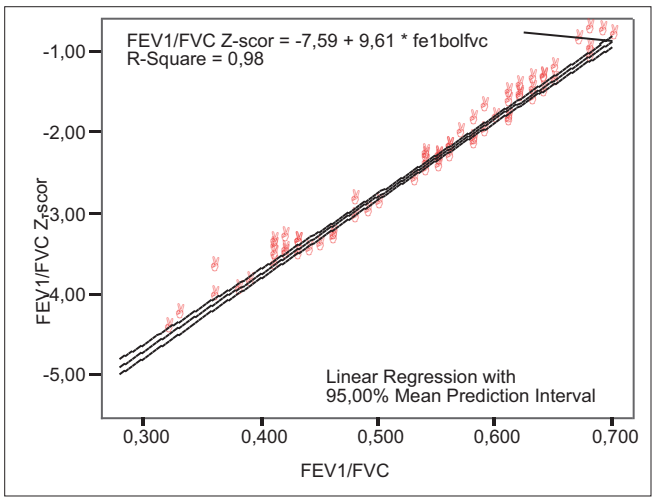

Figure 3: Scatterplot curve for FEV1/FVC and FEV1/FEV Z-score values of age Group III. LLN: Lower limit of normal, FVC: Forced vital capacity, FEV: Forced expiratory volume

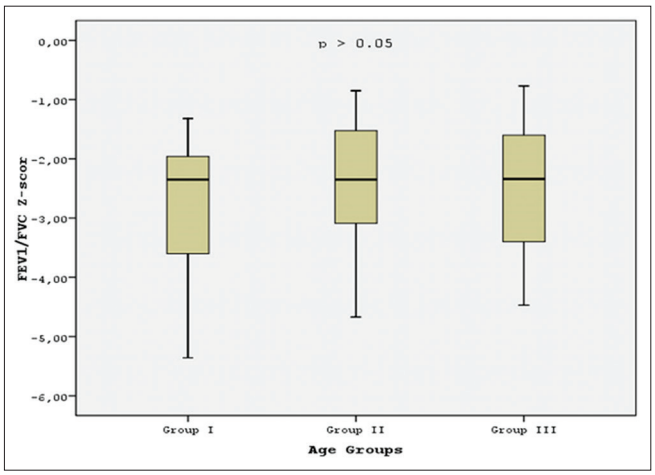

Figure 4: FEV1/FVC *Z*-score values by age groups. FVC: Forced vital capacity, FEV: Forced expiratory volume, Group I: 40–60 years, Group II: 61–70 years, Group III: Age >70 years

Table 4: Analysis of the discordant cases when using the forced expiratory volume in 1 s/forced vital capacity ratio-lower limit of normal between age groups

Age groups	FEV_1/FVC		Total, *n*
	< LLN, *n* (%)	≥ LLN, *n* (%)	
Group 1 (40-60 age)	54 (88.5)	7 (11.5)	61
Group 2 (61-70 age)	48 (71.6)	19 (28.4)	67
Group 3 (>70 age)	47 (73.4)	17 (26.6)	64
Total	149 (77.6)	43 (22.4)	192

LLN: Lower limit of normal, FVC: Forced vital capacity, FEV_1: Forced expiratory volume 1 s

value was 99.7% and an AUC of 0.900 (95% confidence interval: 0.856–0.944 $P < 0.001$). This calculated cutoff value had the specificity and sensitivity to be utilized in diagnosis of obstruction as an alternative to FEV1/FVC-LLN.

Discussion

The primary objective of the present study was to evaluate the diagnostic value of FEV1/FVC <LLN compared to the fixed ratio in patients in different age groups diagnosed with COPD according to the fixed ratio. Our secondary aim was to identify a fixed cutoff equivalent to the commonly used fixed ratio of FEV1/FVC <LLN for the FEV1/FEV6 ratio. We investigated whether FEV1/FEV6 <0.735 value could be considered a valid alternative to FEV1/FVC <LLN for the diagnosis of COPD.

In the study, we attempted to avoid making a new definition of COPD, but rather, we aimed to increase awareness of some of the imperfections of a single fixed cutoff value of FEV1/FVC of 0.7 and an age-adjusted LLN definition. The most recent GOLD guide recommends the

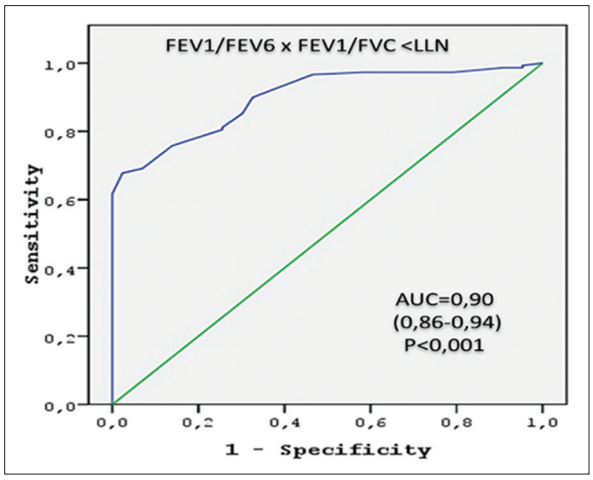

Figure 5: Area under the receiver operator characteristic curves and 95% confidence intervals for the FEV1/FEV6 ratio compared to a FEV1/FVC ratio equal to the LLN. LLN: Lower limit of normal, FVC: Forced vital capacity, FEV: Forced expiratory volume

use of a fixed ratio, as it is derived from the test results of an individual patient and is consistent and independent of reference equations.[15] A total of 297 patients (35.2%) were found to be FEV1/FVC > LLN among 844 patients diagnosed with COPD according to the fixed ratio in a cohort study by the Canada GOLD group which involved 4,882 patients over the age of 40 years and aimed to evaluate the superiority of fixed ratio and LLN in the diagnosis.[16] This ratio was 22.4% in the present study, and the difference was less. The prevalence of COPD in the elderly was found to be significantly lower by LLN in another study comparing the fixed ratio and LLN obtained using the second National Health and Nutrition Examination Survey II reference to determine the prevalence of COPD in a Korean population.[17] Half of the patients over the age of 65 years who were diagnosed using the fixed ratio were over the LLN, and which is considerably higher than the ratio identified in the present study, which was 28.2 in the 60–70 years age group.

Furthermore, the use of the GLI (LLN) equation in the prevalence of airway limitation defined by the GLI in a group of elderly patients in Belgium was found to be 27% lower, compared to the diagnoses based on a fixed ratio.[18] This ratio was found to be the same in the present study, with 26.6% of the group of patients over 70 years of age. In the Pulmonary Risk in South America study involving a large population in the Southern Cone of Latin America, the prevalence of COPD based on the LLN (GLI) criteria was found to be significantly lower than with the FEV1/FVC fixed ratio (GOLD criteria).[19] This discrepancy in the prevalence rates was attributed to the higher percentage of Stage I COPD patients according to the GOLD criteria.

As our secondary objective, it was to identify a fixed cutoff equivalent to the FEV1/FVC < LLN for the FEV1/FEV6 ratio. The spirometer is the most widely used tool for PFTs; however, the FVC maneuver can be challenging for elderly individuals, and a decreased FEV1/FVC fixed ratio is an important indicator of airway obstruction. Glindmeyer *et al*. suggested a posttest criterion based on a fixed time period for the FVC maneuver and reported that the time period required for the result of the FVC to reach 99% was 6.64 s.[20] In more than 80% of all tests, FEV6 was achieved, and the authors suggested that FEV6 was a more repeatable parameter than FVC and that some factors, such as sex and low education level, affected the repeatability of FVC and FEV6.

In another study from China, it was found that a fixed cutoff value of 0.72 for the FEV1/FEV6 ratio could be used as an alternative to FEV1/FVC in the diagnosis of COPD.[21] In a study in Belgium, 0.72 as the best sensitivity and specificity for FEV1/FEV6 was demonstrated to be used in the diagnosis of COPD.[9] Bhatt *et al*. analyzed the efficacy of these two ratios in the diagnosis of COPD using the computed tomographs and morbidity evaluation criteria of COPD in their cohort study including 10,364 patients aged between 45 and 80 years, including smokers and former smokers.[22] They proved the superiority of the 0.73 value obtained for FEV1/FEV6 against the fixed FEV1/FVC < 0.7 ratio in diagnosing the respiratory symptoms and exacerbations associated with COPD. In the population-based, cross-sectional Latin American Project for the Investigation of Obstructive Lung Disease study, which was conducted to determine the prevalence of COPD in patients over 40 years of age, the cutoff value for FEV1/FEV6 for both ratios which was effective against FEV1/FVC and FEV1/FVC-LLN in diagnosing airway obstruction was 0.73.[23] The cutoff value in the aforementioned study was the same in our study. Ünal *et al*. compared the use of FEV1/FEV6 ratio in diagnosing early smoking-related airway obstruction to the GOLD criteria. The study included 53 smoker and 15 healthy individuals. The sensitivity and specificity of FEV1/FEV6 was found to be 87.5% and 98.1, respectively, with a cutoff value of 0.73, similar to that in our study. The low sensitivity value of the mentioned study together with our study can be attributed to the low sample size.[24] To the best of our knowledge, our study is the first to be performed on this subject in the Turkey population.

The current study has limitations. First, we had to compare LLN with only fixed ratio. There is no only other standardized value to define obstruction than fix ratio. Accordingly, it is impossible to identify whether LLN can be preferred over a fixed ratio of FEV1/FVC based on the existing literature. Therefore, we aimed to determine which criterion was better and more clinically appropriate in our population and found that the use of

a fixed ratio in elderly patients resulted in overdiagnosis, compared to LLN, which is consistent with the literature data. Second, since the sample in the present study comprised the test data of patients aged over 40 years and diagnosed with COPD according to the GOLD guideline, no conclusions can be derived about the use of LLN in obstructive patients who are not diagnosed using the fixed ratio or in patients younger than 40 years of age. Thus, controversy still exists regarding which of the methods is more useful.

A single-centered retrospective study with 192 patients is not enough to be generalized to whole country population, so multicentric prospective and randomized studies comparing fixed ratio with LLN criteria are needed.

Conclusions

We found out a subset of elderly patient overdiagnosed as COPD based on fixed ratio but healthy based on LLN criteria; this discrepancy suggests that in elderly people fixed ratio and LLN criteria may be used together to increase the diagnostic accuracy of COPD. As a secondary our study results that the FEV1/FEV6 ratio can be considered an alternative to the FEV1/FVC-LLN approach in the demonstration of early airway obstruction in patients aged 40 years and above with an acceptable sensitivity and specificity. In addition, we suggest that this method is independent of a time constant and is easy to repeat and can be, therefore, easily used in office-type spirometers and primary health-care centers.

Acknowledgment

We would like to thank Prof. Dr. Müzeyyen A.Erk for the mentoring of the article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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