

## Journal club

# Is the GOLD guideline for diagnosing obstruction in COPD discriminatory in predicting severe future COPD-related exacerbations and death?

### Commentary on:

Bhatt SP, *et al.* Discriminative accuracy of FEV<sub>1</sub>:FVC thresholds for COPD-related hospitalization and mortality. *JAMA* 2019; 321: 2438-2447.

## Background

Current Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1] and other major respiratory society guidelines [2] recommend confirming a post-bronchodilator forced expiratory volume in 1 s/forced vital capacity ratio (FEV<sub>1</sub>/FVC) <0.7 for diagnosing COPD in the setting of chronic exposure to noxious inhaled agents. There are advantages to employing a fixed threshold: GOLD has been recommending diagnosing COPD with a fixed ratio <0.7 for >20 years. There is also a huge body of published work in COPD using this threshold, including major worldwide prevalence studies [3]. Disadvantages, however, are that spirometry, in reality, is often only performed pre-bronchodilator; and a submaximal effort is not infrequently obtained, thus overestimating the FEV<sub>1</sub>/FVC. The ratio also falls with age, potentially both underdiagnosing COPD in patients aged <45 years and overdiagnosing in older patients by up to 80% in those aged >80 years [4]. FEV<sub>1</sub>/FVC can also be

pseudonormalised by coexistent restriction, such as a high body mass index [5].

Rather than a fixed threshold, many advocate for the use of a lower limit of normal (LLN) for diagnosing obstruction, where the FEV<sub>1</sub>/FVC is considered abnormal if it is below 1.65 standard deviations from the mean, *i.e.* below the fifth percentile. This would have the advantage of factoring in the mean±SD ratio for each age group and compensating for the age-related decline. Moreover, previous research has suggested that an FEV<sub>1</sub>/FVC <LLN may also be more discerning than FEV<sub>1</sub>/FVC <0.7 with regards to the risk of severe COPD-related events, disease progression and mortality, as it incorporates demographics including age, sex, height and race in determining normal values [6, 7].

BHATT *et al.* [8] have retrospectively interrogated a large database of all patients at baseline spirometry to determine which FEV<sub>1</sub>/FVC thresholds and/or the LLN were the best predictors of future severe COPD events.

## Methods

Four datasets from US general-population atherosclerosis studies that recorded spirometry at baseline from 1987 to 2000 were combined and interrogated. In two populations, the participants

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were aged >44 years [9, 10]; in one, they were aged >65 years [11]; and the fourth, they were aged >70 years [12]. Only pre-bronchodilator spirometry measurements of a minimum standard were included. Predicted values for FEV<sub>1</sub>/FVC were generated from age, sex, height and race, and for LLN, values below the fifth percentile were considered as obstructed. The primary outcome was a composite of COPD-related hospitalisation and mortality. Maximum follow-up was up to 2016. The sensitivity and specificity of various FEV<sub>1</sub>/FVC thresholds, and the LLN in predicting these events were compared.

## Results

24207 subjects were assessed spanning 340757 person-years of follow-up. Mean age was 63 years, with 14% of participants aged >75 years and an almost equal sex split. 69% were non-Hispanic white and 24% African American. 63% were current or former smokers with a mean 22-pack-year smoking history. 2027 (8.4%) patients already had a diagnosis of COPD and 1368 (5.7%) had a diagnosis of asthma. Follow-up was for a median of 15 years post-enrolment (range 9–21 years).

Employing the LLN threshold, 3646 (15%) people had airflow obstruction, which was a similar prevalence to an FEV<sub>1</sub>/FVC threshold of <0.66. Many more people (6261, 26%) had obstruction as defined by the FEV<sub>1</sub>/FVC <0.70 threshold. The authors concluded that the <0.70 threshold was not inferior to and no less accurate than other fixed thresholds, and was in fact superior to the LLN in predicting which patients later developed a severe COPD crisis.

## Commentary

In this large retrospective epidemiological study, we have a snapshot baseline FEV<sub>1</sub>/FVC from which we are trying to extrapolate future risk, over a median of 15 years, of severe acute COPD events. The <0.70 threshold appeared statistically to be the most predictive for assessing future risk of severe exacerbations and was not inferior to other fixed ratios or the LLN. However, it has long been recognised that using a fixed ratio of <0.70 may underestimate airflow limitation in younger individuals, a population in which preventive measures could be employed, and may overestimate airflow limitation in older individuals, in whom unnecessary treatment results in increased healthcare costs and may cause adverse health effects [13].

However, there are a number of important observations to make regarding this study. First, we have no clinical details regarding the participants, and the diagnosis of COPD involves both symptoms and the demonstration of obstructed physiology.

Secondly, 1689 (43%) of the 3925 severely exacerbating COPD patients had a baseline FEV<sub>1</sub>/FVC >0.7 with 387 (10%) having a baseline ratio >0.8, suggesting a major sensitivity issue. Employing the LLN to diagnose obstruction was more stringent and identified only 60% of subjects compared to the fixed ratio of <0.7. It would therefore appear to be more specific and with multiple spirometry readings over 10–15 years, as you would have in normal clinical practice, it may perform better than the fixed ratio. Thirdly, another issue raised by the authors themselves is that all their spirometries were pre-bronchodilator and so the possibility of asthma or asthma/COPD overlap was not excluded. Fourthly, the mean age of baseline spirometry at study entry was 63 years. Two of the studies recruited subjects aged >44 years with 28% of these patients aged 44–55 years at study entry. The mean age at COPD admission and death in other large studies is 73–75 years and 75–79 years respectively [14, 15]. In older subjects, the LLN may have performed better. At a study population level, however, 9.4% of the subjects with a baseline FEV<sub>1</sub>/FVC >0.7 (17946) suffered a severe COPD exacerbation compared to 2236 (35.7%) of the 6261 subjects with an FEV<sub>1</sub>/FVC <0.7, suggesting that the latter were clearly at much higher risk. We also know that 3389 (86%) of the exacerbating subjects were ex- or current smokers, which is reassuring in terms of disease process, but we do not know how many continued to smoke or had ongoing exposure to other chronic airway irritants.

## Implications for practice

Whilst patients with baseline spirometry, with an FEV<sub>1</sub>/FVC <0.7 were 3.5 times more likely to suffer a severe exacerbation of COPD than those with a ratio of >0.7, the positive predictive value remains low; hence, spirometry alone clearly cannot be used to detect all individuals at risk of COPD-related events. The basis of predictive modelling suggests that model accuracy increases with the inclusion of more variables but in reality, physicians are limited to history and presence for any given patient. In this and other similar studies and meta-analyses, the LLN of the FEV<sub>1</sub>/FVC ratio appears to underestimate COPD with recent longitudinal studies suggesting that the fixed ratio of <0.70 is a better criteria on for diagnosing airway obstruction in case finding studies, allowing earlier diagnosis of COPD and acting as a better predictor of severe exacerbations and mortality than LLN [8, 16, 17]. There is also a school of thought that although adult smokers suspected of having COPD reportedly have no increased risk of respiratory morbidity or all-cause mortality until the ratio falls below the age-corrected LLN (even if it is >0.7), the combined assessment of the <0.7 fixed ratio and the LLN might provide more accurate management in early COPD; hence, different criteria may need to be used

in different populations [18–21]. Although there are important limitations in this paper, as with all population-based epidemiological studies, it provides important real-world information that can be used in the clinical setting to prognosticate this patient group and highlights that further research efforts are warranted to provide guidance to practising clinicians in different clinical settings.

In summary, although both the fixed ratio of  $FEV_1/FVC < 0.70$  and the LLN, as currently

used to define airflow limitation, have their own limitations in different clinical settings, the comprehensive, longitudinal, population-based data presented by BHATT *et al.* [8], along with data from others, demonstrate support for adhering to guideline recommendations to continue to use the familiar fixed  $FEV_1/FVC$  of  $< 0.70$  as the threshold for diagnosis of airway obstruction to avoid underdiagnosis and missing patients who would benefit from COPD care.

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## Conflict of interest

M.J. McDonnell has nothing to disclose. M. Harrison has nothing to disclose. R.M. Rutherford has nothing to disclose.

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