Diagnosing COPD: High Time for a Paradigm Shift

In this issue of RESPIRATORY CARE, Vaz Fragoso et al[1] and Aggarwal et al[2] make important contributions to the ongoing discussion on how to properly diagnose COPD. Let us put the problem in perspective.

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In the past there was a growing concern that many cases of COPD went undetected and that generally too little effort was spent in diagnosing COPD, a disease syndrome relatively unknown to the public, or to public health and government officials. Because of this, the United States National Heart, Lung, and Blood Institute and the World Health Organization formed the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[3] which issued recommendations for diagnosing and managing COPD. Spirometrically-determined airflow limitation was proposed as the key measurement for identifying COPD. The definition of airflow limitation, however, still leads to controversy.

An abnormally low ratio of FEV_1 to FVC is universally accepted as indicating airflow limitation: the hallmark of COPD. In adults the FEV_1, FVC, and FEV_1/FVC fall with age, and not at the same rate for men and women. Therefore, various organizations[4-7] have recommended using the lower fifth percentile from a population of healthy never-smokers as the lower limit of normal (LLN). Hence, an $FEV_1/FVC < LLN$ is compatible with airflow limitation. This approach is scientifically valid and in keeping with the way results from the chemistry laboratory have been interpreted for decades in clinical practice. However, despite the widespread availability of computers that can perform the calculation, the GOLD committee judged that using the LLN was too complicated for doctors and recommended a fixed FEV_1/FVC of 0.70 as the cutoff for diagnosing COPD. They also recommended the use of percent-of-predicted FEV_1, with 80% separating mild from moderately severe COPD. In healthy subjects the LLN for FEV_1/FVC falls well below 0.70 above age 45 years, so the fixed-ratio method ($FEV_1/FVC < 0.70$) is heavily biased by age, and to a lesser extent by height, sex, and, possibly, ethnic group. The use of $FEV_1 < 80\%$ of predicted, probably first advocated by Bates and Christie,[8] has similarly been shown to be highly biased by age.[9,10] More than 30 years ago, Sobol wrote: "Nowhere else in medicine is such a naïve view taken of the limit of normal."[11]

Hardie et al[12] were the first to point out the massive (up to 50%) over-diagnosis of COPD in elderly healthy never-smokers that can occur with the fixed ratio. Many other authors subsequently confirmed this, and pointed out that the fixed ratio also leads to under-diagnosis in younger subjects.[13] Essentially, the disagreement is about interpreting an $FEV_1/FVC < 0.70$ but $> LLN$. If such a ratio could be shown to entail a higher risk of premature death, hospitalization, or other ill health effects, that would end the discussion in favor of the GOLD guidelines. So far, however, all the published evidence points the other way. In a literature review, Hoesein et al[14] compared subjects with an $FEV_1/FVC < 0.70$ but $> LLN$ to those with normal lung function, and posited that LLN might miss subjects at risk of hospitalization and death. Their conclusion hinged exclusively on a paper by Mannino et al,[15] who found that GOLD stage 1 was associated with higher risk of premature death. However, Mannino et al misinterpreted their own results: the adjusted odds ratio (CI 0.96–1.3) was not different from that in healthy controls. Their reported increased hazard ratio for hospitalization[15] also failed under scrutiny, as Mannino et al conceded that "the measure of COPD-related hospitalizations was too inclusive."[16] Thus, Hoesein's conclusion[14] also collapses. Recently, this same flaw crept into another study,[17] which found that about 34% of a cohort who had at least one hospital admission for COPD did not meet the spirometric definition of COPD prior to hospitalization. Curiously, rather than concluding that this underlines the severe limitations of using administrative data[18,19] confounded by cardiovascular and other diseases, Garcia-Aymerich et al concluded that GOLD stage 1 represents an increased risk of COPD hospitalization and subsequent mortality.[17] An administrative or hospital diagnosis of COPD can be very biased, again appearing to be too inclusive,[16] and does not warrant that conclusion.

The relative risk of death in GOLD stage 1 in a Swedish population was elevated in female smokers, but not in men, and not in female and male former or never smokers.[20] After adjustment for potential confounders, the hazard ratio for all-cause mortality in older participants in the National Health and Nutrition Examination Survey III was significantly elevated only at an $FEV_1 <$ 5th percentile, regardless of GOLD stage,[21] and GOLD stage 1 was not

associated with a higher prevalence of respiratory symptoms. Compared to the percentile approach, the risk of death and of respiratory symptoms in subjects with GOLD stage 2 was also poorly classified,[21] which confirmed a previous report[22] that the GOLD criteria were not adequate for correctly placing individual subjects into disease stage categories that relate to survival. GOLD stage 1 in asymptomatic subjects is not associated with dyspnea, accelerated FEV_1 decline, respiratory care utilization, or quality-of-life scores, compared to a reference group.[23] In a clinical population there is bound to be less misdiagnosis than in a normal population, because of the higher disease prevalence. In Aggarwal et al's study,[2] which compares the fixed ratio to the LLN in a large male clinical population, the fixed ratio underestimated the prevalence of airflow limitation by 13% in the 21–40-year age range, and overestimated it by 16% in the 40–95 year age range. In another large clinical study, 24% were misclassified by the fixed ratio.[24]

There is no high-quality evidence that an FEV_1/FVC < 0.7 but $>$ 5th percentile represents disease, or increased risk of death. Conversely, values below the 5th percentile do imply increased risk. Vaz Fragoso et al raised the bar by substituting the biased fixed ratio[25] with a novel technique, the lambda-mu-sigma method with the lower limit of normal as the 5th percentile of the distribution of Z scores (LMS-LLN_5), pioneered by Stanojevic et al.[26,27] This method takes into account that the relationship between the predictor variables (eg, age, height, sex) and spirometry measurements is not linear, and that reference values are not normally distributed and do not have constant variability. They found that only individuals with an FEV_1/FVC less than LMS-LLN_5 had a higher risk of all-cause mortality and higher prevalence of respiratory symptoms. Vaz Fragoso et al[1] found that in 2 cohorts of white older patients within the National Health and Nutrition Examination Survey III and the Atherosclerosis Risk In Communities study, the cutoffs that were associated with a significantly higher risk of respiratory symptoms and death were an FEV_1/FVC below the LMS-LLN_5, and a reduced FVC (FEV_1/FVC $>$ LMS-LLN_5 and FVC $<$ LMS-LLN_5), which suggests restrictive-pattern rather than airflow limitation.

Arising from published evidence, a letter from 152 scientists and clinicians and 13 organizations requested that the GOLD guidelines be modified.[28,29] The GOLD committee has acknowledged that the fixed ratio leads to overdiagnosis and misclassification,[3] but argued that the frequent use of the guidelines justifies leaving them unchanged,[30,31] disregarding clinical evidence. If we accept that GOLD stage 1 does not represent respiratory disease (as discussed above), it is not surprising that no evidence has been published to show that any intervention, other than smoking cessation, has any effect. In a recently published guideline, the initiation of inhaled bronchodilator in patients who have respiratory symptoms is therefore recommended only if FEV_1 is $< 60\%$ of predicted.[32] Indeed, the low FEV_1—and not FEV_1/FVC—has been shown to be a very significant risk factor for death.[33-36]

That international societies issue disparate guidelines, advocating both the fixed ratio[32] and the LLN,[4-6] is an important impediment to progress in COPD research, leads to subject-selection bias, and wastes money and resources. More extensive use of spirometry is needed to detect airflow limitation, but guidelines should not cause any patients to be incorrectly diagnosed with COPD, which imposes the psychological burden of a disease with a poor prognosis.

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