Diagnosis of Chronic Obstructive Pulmonary Disease: Breathing New Life into an Old Debate

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The demonstration of airflow obstruction on spirometry is essential and necessary for the diagnosis of chronic obstructive pulmonary disease (COPD). Considerable controversy exists on whether to use a fixed threshold of less than 0.70 for the ratio of forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) or the lower limit of normal (LLN) derived from population-based normative data adjusted for age, sex, and ethnicity (1). This age-old controversy resurfaces often, and the lulls in the battle are not a result of resolution, but fatigue and stalemate. A number of recent studies have reexamined this issue to test whether using one threshold over the other makes any difference for diagnosis and for prediction of respiratory outcomes (2). Common arguments made in favor of the LLN include that the fixed threshold results in underdiagnosis of airflow obstruction in younger adults and overdiagnosis in older adults, that it is a statistically sound model that accepts a 5% error rate but is more specific, especially given the influence of age on lung function, and that its greater specificity results in avoiding unnecessary treatment of individuals. Counterarguments supporting the fixed threshold include its simplicity, that it does not rely on data derived from large populations that vary widely from region to region and are expensive to measure, the ease of comparisons between groups and over time, and that using postbronchodilator values considerably improves the negative likelihood ratio.

A series of studies in the prior decade suggested that the fixed threshold did not

measure up to the LLN and resulted in misdiagnosis (2). However, these studies used the LLN as the gold standard, and it was to only be expected that the comparator did not meet the standard. Recent studies have used a “neutral” gold standard and pitted the thresholds against each other, using computed tomography measures of structural lung disease, respiratory morbidity, and mortality as meaningful parameters. These studies showed that participants in the “intermediate zone,” disease-positive by fixed threshold but not by LLN, have a greater degree of structural disease on computed tomography (2, 3), higher respiratory morbidity (4), greater frequency of exacerbations (4), and higher mortality on follow-up compared with subjects with normal lung function by both criteria (5, 6). These findings raised the question as to whether these participants in the intermediate category warrant therapy if they have active disease in terms of symptom burden or exacerbations.

In this month’s issue of the *AnnalsATS*, Calverley and colleagues (pp. 200–208) add more fuel to the fire by reexamining this question in the context of a pharmacotherapeutic clinical trial by testing whether entry criteria affected study outcomes (7). They analyzed data from 17,072 participants from the Tiotropium Safety and Performance in RespiMat (TIOSPIR) trial that examined the safety and efficacy of tiotropium formulations, and who were originally enrolled based on the fixed threshold. Calverley and colleagues found that 10.6% of enrollees would have been excluded if they had used

the LLN for study inclusion. They report that participants with FEV₁/FVC below the LLN had a lower incidence of major cardiac events, but not cardiac or all-cause mortality, and a greater frequency of moderate and severe exacerbations compared with those in the intermediate zone. This study is important for several reasons. Although the results focus on the LLN group, the LLN threshold is more stringent and specific, and all participants in this study who met LLN criterion also met the fixed threshold criterion. The higher exacerbation frequency in the LLN group is thus not a surprise. Although on the surface it appears that the intermediate group had lower respiratory morbidity, a closer look reveals that their respiratory burden was not trivial. The intermediate category reported symptoms such as productive cough and dyspnea as frequently as the LLN group. Approximately 40% of participants in this group reported a moderate to severe exacerbation over approximately 2.3 years of follow-up, and the exacerbation frequency was two-thirds to three-quarters that of the LLN group. Although not the focus of this study, it is now well established that COPD is associated with cardiovascular disease (8), and the higher burden of cardiac events in the intermediate group raises concerns for missed opportunities for detection and risk stratification if we relied on LLN alone. In addition, there was no difference in treatment effects irrespective of LLN classification, suggesting the intermediate group derives benefit from tiotropium, and likely other long-acting bronchodilators.

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Figure 1. The mean predicted and lower limit of normal (LLN) values for the ratio of forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) over time for a representative Caucasian man who is 70 inches tall. LLN trends are shown for three reference populations: the Knudson reference equations from 1976, the National Health and Nutrition Examination Survey (NHANES) III Hankinson equations from 1999, and the Global Lung Index (GLI) look-up references from 2012. The LLN curve runs parallel to the expected mean for the older curves and almost parallel for the GLI values that rely on the more advanced λ , μ , σ method. This application of the overall SD, or even stratified SDs for narrower age ranges, results in a disproportionate lowering of the LLN in older adults who already have a lower predicted mean. Although not currently recommended, note that the LLN for the Knudson reference does not fall below 0.70 at any age.

There are some limitations to the current study that should be considered. First, the enrollment criteria included FEV_1 percentage predicted lower than 70%, thus increasing the specificity for airflow obstruction. This may also have resulted in excluding a number of participants who would be positive by the fixed threshold, but negative by LLN. Second, the criteria used postbronchodilator data for all comparisons, and LLN is based on prebronchodilator values. This is not a trivial issue, as Tilert and colleagues showed that the prevalence of airflow obstruction using postbronchodilator fixed ratio can be equal to, or even lower than, when prebronchodilator LLN is used (9). The authors add to the literature by demonstrating that there were no treatment

differences between the intermediate category and LLN. However, the study lacked controls without airflow obstruction by either criterion, which would have been the ideal comparison group.

This study adds another dimension to the fixed versus LLN saga. The intermediate category is real, and subjects in this group are not healthy. Although the decision to use fixed or LLN criteria depends on the desired sensitivity and specificity, and may vary according to the intended purpose, we need to reexamine this issue, which has led to so much confusion in the pulmonary community, not to mention in primary practice. Although studies show an age-related decline in FEV_1 , recent studies suggest this age-related decline is

neither uniform nor inevitable (10). There are multiple paths to get to impaired lung function, and whether aging is a way to get there is not without debate. Reference values are now drawn from progressive larger populations and using increasingly sophisticated statistical methods. However, they still suffer from how normality is defined before enrollment, affecting generalizability, the cross-sectional data from which longitudinal assumptions are made, and the assumptions of homoscedasticity of variance, which is likely to disproportionately affect older adults and thus lower the LLN in the older age groups (Figure 1). At a time when half the COPD population is estimated to remain undiagnosed, we should cast a wider net and identify more subjects at risk for or with COPD. Recent studies suggest that a number of subjects with high pretest probability but who do not meet criteria for airflow obstruction have a substantial symptom burden and also show evidence of structural disease on computed tomography (11, 12). Whether these subjects will benefit from therapy is being investigated (ClinicalTrials.gov identifier: NCT02867761), and the current study suggests a slightly worse off intermediate category derives benefit from bronchodilator therapy.

These data reiterate that there is really no need to rigidly classify subjects based on a single number. In practice, a commonsense approach based on considering risk factors and pretest probability, and perhaps a short therapeutic trial for those who are borderline, might be the solution. Relying on symptoms to support the diagnosis is insufficiently reliable, as unlike cough and exacerbations, dyspnea is dependent on the level of exertion. More objective scores for determining pretest probability will help underscore practitioners' confidence in diagnosis. The current study highlights the need for trials focusing on this intermediate zone clinical phenotype. As to epidemiologic prevalence studies that rely on one or the other threshold, however, opportunities for improvement abound. Whether the fixed threshold should be lower than the expert-recommended 0.70 or the LLN should be raised to include a greater proportion of the population with respiratory morbidity is a battle for another day. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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