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## ⊕ A Rising STAR in Chronic Obstructive Pulmonary Disease or More Deckchair Rearrangement?

In the 18th century, Carl Linne, the Swedish physician and botanist commonly referred to as Linnaeus, developed a rational system of classifying plants. This process of classifying organisms, initially on the basis of their physical attributes and now underpinned by scientifically robust studies of their phenotype and genotype, was of great interest to the Founding Fathers of the United States and has been a powerful tool for understanding disease. It was a logical step to use one or more of these defining features to evaluate the severity of a condition, as has been done in the case of patients with chronic obstructive pulmonary disease (COPD). Here spirometry has been the objective characteristic studied, and several arbitrary cut points based on the observed reduction in FEV<sub>1</sub> were selected to define the extent to which impaired lung mechanics and hence structural lung

damage is present (1). These broad groupings define people with different clinical outcomes, especially for mortality, where FEV<sub>1</sub> percent predicted is still the strongest predictive variable (2, 3). For the last 25 years, the most widely adopted approach is that of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), where COPD is defined by the presence of an FEV<sub>1</sub>/FVC ratio of 0.7 (70% or less) and severity (or GOLD stage) is based on the FEV<sub>1</sub> percent predicted; GOLD 1 is an FEV<sub>1</sub> 80% predicted or greater; GOLD 2, 79–50% predicted; GOLD 3, 49–30% predicted; and GOLD 4, below 30% predicted (4).

Recently, Bhatt and colleagues suggested an alternative approach that uses the defining characteristic of airflow obstruction to grade severity in their Staging of Airflow Obstruction by Ratio (STAR) system (5). Again, four grades were created, STAR 1 being a ratio of 60–70%; STAR 2, 50% to <60%; STAR 3, 40% to <50%; and STAR 4, <40%. They validated this system in the large COPDGene (Genetic Epidemiology of COPD Study) observational cohort and two COPD cohorts from Philadelphia, comprising a total of 12,149 individuals with detailed clinical data, and they compared the new system with the conventional GOLD grading. The system produced similar

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outcomes for grades 2–4 despite differences in the composition of each group. However, STAR 1 subjects had a significantly higher mortality and worse outcomes than nonobstructed people, which was not true for those classified as having GOLD 1 COPD. In an accompanying editorial, I suggested that data from a wider range of people with more ethnic diversity would be helpful (6). That request has now been met in a full paper (pp. 1308–1316) and two research letters (pp. 1374–1376 and pp. 1376–1379) in this issue of the *Journal* (7–9). These data not only provide confirmation of the original STAR proposal but also give us more insight into how these differences between the groups might arise and inform how we might use this system.

Backman and colleagues report an analysis of the National Health and Nutrition Examination Survey representative general population sample from 2007 through 2012, in which 14,123 people aged 18–80 (mean age, 45 yr; 52% never smoked) underwent prebronchodilator spirometry, and those over 40 completed a Medical Research Council breathlessness questionnaire (7). Bronchodilator testing was performed in 997 of 1,521 people with airflow obstruction, with the highest subsequent FEV<sub>1</sub> being reported. In view of the low numbers of grade 4 people, groups 3 and 4 were combined. The presence of a modified Medical Research Council dyspnea scale score and the risk of mortality in the period to the end of 2019 were evaluated. The distribution of GOLD and STAR grades are shown in the Figure 1. There was good agreement between the systems, with a Kendall Tau B for concordance of 0.46 and a C-statistic for mortality prediction of 0.81. This is not surprising, given the clear relationship between the FEV<sub>1</sub>/FVC and FEV<sub>1</sub> percent predicted below 60% seen in Figure 1 of Backman’s paper, because this is where most of the mortality signal lies. As in the original report by Bhatt and colleagues, GOLD 1 stage did not distinguish the risk of dying from that in people without obstruction, whereas STAR 1 grading did. The same was true for identifying the report of some breathlessness, most clearly in the unadjusted data. The STAR system performed as well as GOLD among people of different ethnicities, although the subgroup numbers were too small to permit analysis by individual grades. Similarly,

analysis using the lower limit of normal (LLN) FEV<sub>1</sub> as the reference value and including or excluding people with PRISm (preserved ratio impaired spirometry) did not influence the results.

Two other shorter reports add further to these findings. In the Rotterdam study reported by Bertels and colleagues, prebronchodilator FEV<sub>1</sub> was measured in 5,459 adults with follow-up data from 2009 to 2022 (98% White; mean age, 69.2 yr; 14.7% with COPD) and mortality established (8). Almost 75% of participants were not smoking when studied. The distributions of GOLD and STAR stages are shown in the figure below. Again, there was good overall agreement between the systems, and again differences in mortality risk were seen in STAR 1 but not GOLD 1 relative to the nonobstructed comparator population. The current use of tobacco did not influence the outcome of this analysis. Bhatt and colleagues complement these data with a new analysis of their original COPDGene dataset based on the recommended severity classification of the European Respiratory Society/American Thoracic Society for the interpretation of lung function (9). They studied 10,134 people (mean age, 59.5 yr; 32% African American) with reproducible post-bronchodilator spirometry who were followed for vital status for a median of 9.3 years. This analysis compared the four STAR grades with a modification of the Global Lung Initiative boundaries for the LLN of FEV<sub>1</sub>, grade 1 being obstructed in people with an FEV<sub>1</sub> >1.65; grade 2, –1.65 to –2.5; grade 3, –2.5 to –4.0; and grade 4, less than –4.0. Obstruction was defined as an FEV<sub>1</sub>/FVC of 0.7 as in the primary analysis and below the LLN in an additional sensitivity analysis. Once more, the overall level of agreement in terms of mortality risk was high, but there was a difference between STAR 1 and GOLD 1 groups, with the latter just failing to reach statistical significance in the adjusted model compared with the healthy comparator group. Substituting the LLN of the ratio for the fixed ratio did not affect these findings.

Each of these reports has strengths and limitations. The National Health and Nutrition Examination Survey and Rotterdam data sets are population samples with somewhat different age structures and risk of COPD, although similar percentages of obstructed people were identified in each. By design, COPDGene included more people with COPD and a predominantly smoking study population. COPDGene also reported post-bronchodilator data, unlike the other studies, which is important when considering the GOLD 1 group. Despite these differences, the overall findings are in good agreement, with the STAR system showing definite monotonic differences in the mortality experience of each group, unlike the GOLD approach. STAR is easy to apply, is physiologically rational, avoids biases in the way normative data are collected, and is reproducible between clinical settings, regardless of the ethnicity or smoking status of those studied. Thus, STAR would appear to be in the ascendant.

Yet, there is still one area we need to understand better before recommending a wholesale change in the severity classification, and this is reflected in the title of this editorial. An everyday metaphor for a futile task, at least in the United Kingdom, is “to rearrange the deckchairs on the Titanic,” where the resulting pattern is pleasing but wholly unrelated to the important issues at hand. One of the striking features seen when comparing the systems is the reclassification of subjects from GOLD grades 2 and 3 to STAR grade 1 (*see* Figure 1). This is likely to explain the differing mortality and predictive power of STAR 1 versus GOLD 1 because there more people with a lower FEV<sub>1</sub> in the STAR 1 group. A subsidiary analysis by Bertels and colleagues (8) is informative in this regard. Among the 244 STAR 1

Backman et al [7]		Bertels et al [8]			
n=14,123/1521		N=5,459/802			
STAR %	GOLD %	GOLD %	STAR %		
1 8.2	1 5.9	1 7.6	1 11.2		
2 2.0	2 4.2 59%	2 6.3 67%	2 2.6		
3/4 0.8	3/4 0.7 12.5%	3/4 1.4 17%	3/4 0.9		

**Figure 1.** The distribution of chronic obstructive pulmonary disease severity by Staging of Airflow obstruction by Ratio (STAR) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria in two new studies. N=total number of participants and number affected by chronic obstructive pulmonary disease. Percent is the percentage of the total study population in that grade. Figures in red refer to the percentage of individuals at grading reclassified to STAR 1.

people with an FEV<sub>1</sub> at or below 80% predicted (the boundary for GOLD 1), the hazard ratio for mortality was 1.9 compared with 1.1 in the 365 people above 80% predicted. In the 17 people who moved from GOLD 2 to STAR 1, the hazard ratio was 1.9. These data should be examined in the other data sets to confirm if the same is true and whether we are simply shuffling the deckchairs and potentially disguising a group of GOLD 1 subjects at low risk of experiencing an adverse event.

Fortunately, there is no need for immediate action. Both systems have utility, and, as Backman and colleagues note, current decisions about treatment are based on symptoms and exacerbation risk rather than severity of airflow limitation (4). What is also clear from all these analyses, whether conducted using statistically robust methods of classifying abnormal lung function or the more familiar categories based on the degree to which FEV<sub>1</sub> falls below that expected, is that obstruction and its accompanying loss of FEV<sub>1</sub> is at the heart of COPD prognostication and is likely to remain so until some other index of structural lung damage supersedes it. ■

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## ⦿ Race-Neutral z-Score Classification of Airflow Obstruction: A Measured Step Forward

Current pulmonary function guidelines recommend a race-neutral approach to spirometry interpretation and the use of z-score thresholds to classify the severity of lung function impairment (1, 2). However, it is unclear how these recommendations impact both severity classification and the discrimination of meaningful patient outcomes in specific disease states compared with traditional interpretive strategies.

The race-neutral approach involves adopting the Global Lung Function Initiative (GLI) Global reference equations, which weigh all four self-identified ancestral origin groups in the original GLI dataset (i.e., White, Black, Northeast Asian, and Southeast Asian) as equal contributors (3). A recent American Thoracic Society (ATS) statement recommending the use of these race-neutral equations

stems from the understanding that race—a social construct—should not imply biological differences and that adjusting for race may obscure modifiable socioenvironmental factors and perpetuate health disparities.

Current European Respiratory Society and ATS technical standards also recommend transitioning from fixed percent predicted thresholds to z-scores to classify the severity of airflow obstruction (2). z-scores, which account for the normal distribution of lung function, measure how many standard deviations an individual result deviates from the mean (4). A z-score of  $-1.645$ , referred to as the lower limit of normal, has long been used by some to define abnormalities such as airflow obstruction (i.e. where the FEV<sub>1</sub>/FVC ratio is less than the lower limit of normal) (5). The use of z-score thresholds for different severities of airflow obstruction removes the risk of age-, sex-, and height-related bias, and recommended thresholds ( $-1.645$  to  $-2.5$  as mild,  $-2.5$  to  $-4.0$  as moderate, and  $< -4.0$  as severe) have been shown to correlate with mortality risk (2, 4). In contrast, many studies involving patients with chronic obstructive pulmonary disease (COPD) over the past decades have used Global Initiative for Chronic Obstructive Lung Disease–National

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