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SPIROMETRIC CRITERIA FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN CLINICAL TRIALS OF PHARMACOTHERAPY

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Abstract

Clinical trials of pharmacotherapy in chronic obstructive pulmonary disease (COPD) often include older persons with moderate-to-severe airflow-obstruction, as defined by the Global Initiative for chronic Obstructive Lung Disease (GOLD). In this context, spirometric airflow-obstruction establishes COPD. Because GOLD misidentifies COPD and its severity in older persons, we set out to apply more age-appropriate spirometric criteria from the Global Lung function Initiative (GLI) in a prior clinical trial of COPD pharmacotherapy, specifically the Towards a Revolution in COPD Health (TORCH) trial — N=6,112, mean age 65 years. In the TORCH trial, which enrolled GOLD-defined moderate COPD (26.2%, n=1,200) and GOLD-defined severe COPD (73.8%, n=4,511), the GLI reclassification yielded a higher frequency of severe COPD (89.6%, n=5,474), the inclusion of restrictive-pattern (6.9%, n=420) and, in turn, a very low frequency of moderate COPD (3.5%, n=212). These GLI reclassification results suggest that GOLD-based enrollment criteria for the TORCH trial may have assembled a cohort that was: 1) less likely to respond to COPD pharmacotherapy, given the greater representation of severe COPD, very minor representation of moderate COPD, and inclusion of a non-obstructive spirometric impairment (restrictive-pattern); and 2) more likely to have medication-related adverse events, given the inappropriate use of COPD pharmacotherapy in misidentified COPD (restrictive-pattern). We therefore propose that future clinical trials of COPD pharmacotherapy should consider GLI criteria for defining COPD, including a greater representation of GLI-defined moderate COPD.

Keywords

Spirometry; COPD; Pharmacotherapy

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DECLARATION OF INTEREST

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INTRODUCTION

Clinical trials of pharmacotherapy in chronic obstructive pulmonary disease (COPD) often include older persons with moderate-to-severe airflow-obstruction, as defined by spirometric criteria from the Global Initiative for chronic Obstructive Lung Disease (GOLD).[1] In this context, spirometric airflow-obstruction establishes COPD. As an illustrative example, the clinical trial of Towards a Revolution in COPD Health (TORCH), which evaluated salmeterol plus fluticasone, had enrolled 6,112 participants with a mean age of 65 years and GOLD-defined moderate-to-severe COPD.[1] The latter was established spirometrically by a pre-bronchodilator ratio of the forced expiratory volume in 1-second (FEV_1) to forced vital capacity (FVC) of ≤0.70, with severity subsequently established by a pre-bronchodilator FEV_1 of <60 percent predicted (%Pred).[1]

However, prior work has shown that using a threshold ratio of 0.70 for FEV_1/FVC or expressing FEV_1 as %Pred has serious age-related limitations.[2–15] Consequently, the TORCH trial may have misidentified COPD and its severity, perhaps explaining why the effect of salmeterol plus fluticasone on the primary outcome of mortality did not achieve statistical significance, as compared with placebo (hazard ratio 0.825 [95% confidence interval: 0.681, 1.002], p=0.052).[1] Moreover, concerns are raised regarding adverse effects from the inappropriate use of COPD pharmacotherapy in misidentified COPD. Specifically, the TORCH trial showed that the probability of having pneumonia occurred more frequently in those receiving salmeterol plus fluticasone, as compared with placebo (19.6% vs. 12.3%, respectively, p<.001).[1]

To better establish age-appropriate definitions of spirometric impairments, including that of COPD and restrictive-pattern, an alternative approach has been proposed by the Global Lung function Initiative (GLI).[2] The GLI approach uses the Lambda-Mu-Sigma (LMS)[3] method to calculate spirometric Z-scores, rigorously accounting for age-related changes in lung function, including increased variability in spirometric performance. In clinical practice, Z-scores are routinely reported in bone mineral density testing and the LMS method is widely applied to pediatric growth charts.[3,16]

Accordingly, using data on 6,112 participants from the TORCH trial (available at clinicalstudydatarequest.com), we have cross-tabulated the frequency distributions of GOLD and GLI defined spirometric impairments. Because the mean age of the TORCH cohort was 65 years, we hypothesized that the GOLD-based enrollment criteria of the TORCH trial would misidentify COPD and its severity, relative to GLI-defined spirometric criteria. To our knowledge, the current study provides the first GLI reclassification of a clinical trial of COPD pharmacotherapy, wherein the enrollment of participants was based on the commonly used GOLD criteria for moderate-to-severe COPD.[1]

METHODS

As noted earlier, the TORCH trial enrolled 6,112 participants with a mean age of 65 years (standard deviation ±8 years) and established COPD by using pre-bronchodilator spirometric criteria.[1] The use of pre-bronchodilator measures offers several advantages, given that older

persons may have a reduced capacity to perform multiple FVC maneuvers (pre- and post-bronchodilator) and may have an adverse response to a bronchodilator, and given that post-bronchodilator measures may have limited clinical relevance in distinguishing COPD from asthma and low reproducibility over time.[17–21] In addition, diagnostic thresholds for spirometric interpretation are based on reference populations that have only recorded the equivalent of pre-bronchodilator measures.[2,3]

For the current study, in order to cross-tabulate frequency distributions across all spirometric categories, we further stratified the severity of TORCH-defined COPD by applying GOLD-based FEV_1 %Pred thresholds: ≥80 for mild; 50–79 for moderate; and <50 for severe.[22] The FEV_1 %Pred was calculated as [measured/predicted] × 100%, with predicted values obtained from reference equations.[2] Importantly, the calculation of FEV_1 %Pred does not account for the age-related increased variability in spirometric performance.[2–4]

Next, we reclassified the TORCH cohort using GLI-based spirometric criteria: normal spirometry was defined by Z-scores for FEV_1/FVC and FVC, both ≥−1.64; COPD by Z-scores for FEV_1/FVC <−1.64; and restrictive-pattern by Z-scores for FEV_1/FVC ≥−1.64 but FVC <−1.64.[2,3] A Z-score of −1.64 established the lower limit of normal (LLN), as the 5th percentile of distribution.[2,3] COPD severity was then stratified by FEV_1 Z-scores: ≥−1.64 for mild; <−1.64 but ≥−2.55 for moderate; and <−2.55 for severe.[8–10,23] A Z-score of −2.55 defined the 0.5 percentile distribution.[8–10,23] Prior work has shown that these spirometric Z-score thresholds have a strong mathematical, physiological, and clinical rationale, including validation in multiple cohorts (e.g., Genetic Epidemiology of COPD study [COPDGene], Cardiovascular Health Study [CHS], Third National Health and Nutrition Examination Survey [NHANES-III], and in a large cohort of patients referred to a pulmonary function testing laboratory).[2–10,23]

We acknowledge the availability of an alternative 5-level, Z-score stratification for airflow-obstruction.[24] This approach, however, yields small sample sizes for very severe COPD,[11,24,25] and establishes mild COPD at FEV_1 Z-scores ≥ −2.00,[24] thus including a heterogeneous group of participants with FEV_1 <LLN and FEV_1 ≥LLN, respectively (given that the LLN is defined by a Z-score of −1.64). Most often, mild COPD is defined by a decreased FEV_1/FVC (<LLN) but normal FEV_1 (≥LLN).

Because the current study used existing de-identified data that were publicly available, it was granted exemption from participant consent and ethical approval by the institutional review board of Yale University.

RESULTS

As shown in the accompanying Table, the frequency of severe COPD increased from 73.8% (n=4,511) when established by GOLD criteria to 89.6% (n=5,474) when established by GLI criteria — due largely to GOLD-defined moderate COPD being reclassified as GLI-defined severe COPD. In addition, 6.9% (n=420) of participants with GOLD-defined moderate or severe COPD were reclassified as having GLI-defined restrictive-pattern. Other reclassifications by GLI were infrequent (n=9). As a result of these reclassifications, the

frequency of moderate COPD decreased from 26.2% (n=1,600) when established by GOLD criteria to only 3.5% (n=212) when established by GLI criteria.

DISCUSSION

Because the mean age of the TORCH cohort was 65 years, we had hypothesized that the GOLD-based enrollment criteria of the TORCH trial would misidentify COPD and its severity, relative to GLI-defined spirometric criteria. In support of this hypothesis, our subsequent results have shown that the GLI reclassification of the TORCH trial yielded a substantially higher frequency of severe COPD (89.6% vs. 73.8% by GOLD), the inclusion of participants with restrictive-pattern (6.9%) and, in turn, a very low frequency of moderate COPD (3.5% vs. 26.2% by GOLD).

The GLI reclassification results of the TORCH trial suggest that the GOLD-based enrollment criteria assembled a cohort of participants that was less likely to respond to COPD pharmacotherapy, for two reasons. First, as compared with GLI-defined moderate COPD, prior work has shown that GLI-defined severe COPD is an especially advanced stage of disease, associated with 5-fold higher odds of having dyspnea and poor respiratory health related quality-of-life, 3-fold higher odds of having emphysema (as defined by volumetric chest computed tomography [CT]), and 3-fold higher risk of incident COPD hospitalization.[8,10] Second, prior work has shown that GLI-defined restrictive-pattern is unlikely to be an obstructive phenotype of COPD, because it is not associated with CT-measured air trapping or emphysema,[8] nor associated with hyperinflation (as measured by static lung volumes).[23]

We acknowledge that the current study simply reports descriptive results regarding the spirometric enrollment of participants in a clinical trial of COPD pharmacotherapy. Nonetheless, when considered within the context of prior work that has established a strong mathematical, physiological, and clinical rationale for GLI-defined spirometric categories across multiple cohorts,[2–10,23] the current study raises concerns over the continued use of GOLD-based enrollment criteria in clinical trials of COPD pharmacotherapy.

In particular, GOLD-based enrollment criteria have serious age-related limitations when applied in clinical trials involving middle-aged or older persons.[2–15] First, the GOLD fixed-ratio threshold of 0.70 for FEV_1/FVC will under-diagnose COPD in persons aged <50 years (since the FEV_1/FVC can be >0.70 but <LLN), but over-diagnose COPD in persons aged >50 years (since the FEV_1/FVC can be <0.70 but >LLN).[2,3] Second, FEV_1 %Pred thresholds for defining COPD severity assume incorrectly that a given value is equivalently low or high for all persons.[4] For example, in a white male of average height, a given value of 80%Pred for FEV_1 will correspond to the 6th and 14th percentile distribution of the reference population at ages 40 and 70 years, respectively.[4] Stated differently, at a given percentile distribution (as defined by Z-scores), the %Pred value for FEV_1 will decrease with advancing age.[11] As a result of these limitations, prior work has shown high rates of misclassification for GOLD-defined spirometric impairments, including COPD and restrictive-pattern.[5–7,9,10,12–15] The current study, however, is the first to show GOLD-based misclassification of COPD and its severity, specific to a study population enrolled in a clinical trial of COPD pharmacotherapy.

We therefore propose that future clinical trials of COPD pharmacotherapy should consider GLI criteria for defining COPD, including a greater representation of GLI-defined moderate COPD. The latter level of severity is clinically meaningful, as it confers statistically significant associations with multiple adverse health outcomes (as compared with GLI-defined normal spirometry), and likely represents an earlier stage of disease that may be more responsive to COPD pharmacotherapy (as compared with GLI-defined severe COPD).[8–10,23] Importantly, our results also suggest that the exclusion of GLI-defined restrictive-pattern from clinical trials could potentially decrease the inappropriate use of COPD pharmacotherapy, including related adverse drug effects such as pneumonia or a cardiovascular event.

CONCLUSION

The GLI reclassification of the TORCH trial yields a substantially higher frequency of severe COPD, the inclusion of a non-obstructive spirometric impairment (restrictive-pattern) and, in turn, a very low frequency of moderate COPD. These GLI reclassification results suggest that GOLD-based enrollment criteria for the TORCH trial may have assembled a cohort that was less likely to respond to COPD pharmacotherapy and more likely to experience medication-related adverse effects.

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Table

Baseline frequency distributions of spirometric classifications by GLI, cross-tabulated with the original TORCH classification of GOLD-defined COPD (N=6112)

Original TORCH Classification of GOLD-defined COPD[a,b]		GLI Spirometric Classification[d]					
		Normal	COPD[a]			Restrictive- Pattern	Total
			Mild	Moderate	Severe		
		No. (%)					
COPD:	Mild[c]	0	1 (<1)	0	0	0	1 (<1)
	Moderate	3 (<1)	0	206 (3.4)	1156 (18.9)	235 (3.8)	1600 (26.2)
	Severe	0	0	6 (<1)	4320 (70.7)	185 (3.0)	4511 (73.8)
Total	No. (%)	3 (<1)	1 (<1)	212 (3.5)	5476 (89.6)	420 (6.9)	6112 (100)

Abbreviations: COPD, chronic obstructive pulmonary disease; GLI, Global Lung Initiative; GOLD, Global initiative for chronic Obstructive Lung Disease; TORCH, Towards a Revolution in COPD Health trial; %Pred, percent predicted.

[a] In the TORCH trial, the pre-bronchodilator spirometric classification of airflow-obstruction established COPD.

[b] Entry criteria for the TORCH trial included GOLD-defined moderate-to-severe airflow-obstruction (COPD), established by a pre-bronchodilator $FEV_1/FVC \leq 0.70$ and $FEV_1 < 60\%$Pred. In the current study, the severity of airflow-obstruction (COPD) was further stratified by GOLD-based, pre-bronchodilator FEV_1 %Pred: ≥80 for mild, 50–79 for moderate, and <50 for severe.[22] FEV_1 %Pred was calculated as [measured/predicted] × 100%, with predicted values obtained from reference equations.[2]

[c] One TORCH participant had a %Pred value for FEV1 that exceeded the enrollment criterion of <60%Pred.

[d] Using pre-bronchodilator GLI-calculated Z-scores,[2] normal spirometry was established by Z-scores for FEV_1/FVC and FVC, both ≥−1.64, while airflow-obstruction (COPD) was established by Z-scores for FEV_1/FVC <−1.64 and restrictive-pattern by Z-scores for FEV_1/FVC ≥−1.64 but FVC <−1.64.[2,3] A Z-score of −1.64 defined the lower limit of normal as the 5^{th} percentile of distribution.[2,3] The severity of airflow-obstruction (COPD) was then stratified by GLI-calculated Z-scores for FEV_1: ≥−1.64 for mild, <−1.64 but ≥−2.55 for moderate, and <−2.55 for severe.[8–10,23] A Z-score of −2.55 defined the 0.5 percentile distribution.[8–10,23]