Assessment of hyperinflation: comparison of Global Lung Function Initiative and European Community for Steel and Coal lung volume reference equations

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In many individuals, the GLI- and ECSC-derived reference values for residual volume differ substantially. To replace the current ECSC-derived ⩾175% predicted to select potential lung volume reduction patients, a GLI-derived z-score of ⩾2.9 can be used. https://bit.ly/48cLQSh

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Abstract

Background Assessment of static hyperinflation severity is crucial to identify COPD patients eligible for lung volume reduction. The current recommendation of residual volume ⩾175% predicted may need to be reconsidered owing to potential differences between the Global Lung Function Initiative (GLI) and the European Community for Steel and Coal (ECSC) reference equations for residual volume and concerns about using percentage of predicted.

Methods We compared the residual volume reference values derived from the GLI and ECSC equations using mathematically simulated data and used a receiver operating characteristic curve to establish a new GLI-derived z-score cut-off for residual volume using body plethysmography data from patients with severe COPD.

Results The GLI reference equation for residual volume consistently yields a lower predicted residual volume for individuals with an average or below-average height (females ⩽163 cm and males ⩽177 cm). Our clinical cohort consisted of 1011 patients with COPD (graded using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria as 38% GOLD 3 and 59% GOLD 4). In this cohort, a GLI-derived residual volume z-score of ⩾2.9 could accurately replace the ECSC-derived 175% predicted cut-off and a z-score of ⩾3.5 was established for the 200% predicted cut-off.

Conclusion There are substantial differences in predicted residual volume values between the GLI and ECSC equations, with the GLI generally yielding a lower predicted residual volume in the majority of individuals. A GLI-derived residual volume z-score of ⩾2.9 could be used to replace the currently used cut-off of ⩾175% predicted to identify potential lung volume reduction candidates.

Introduction

In 2021, the Global Lung Function Initiative (GLI) presented their new, all-age reference equations for static lung volumes in individuals of European ancestry [1]. Before the development of these reference equations, none of the previously published reference equations for static lung volumes was officially recommended by the American Thoracic Society (ATS) or European Respiratory Society (ERS). However, in European clinical practice, the most commonly used reference equations for static lung volumes are the ones proposed by the European Community for Steel and Coal (ECSC) in 1993 [2, 3]. Comparing the GLI- to the ECSC-derived reference values showed similar results for functional residual capacity and total lung capacity (TLC) [1]. However, for residual volume (RV), distinct differences were observed [1].

Static lung hyperinflation is the result of parenchymal destruction (emphysema) and inflammation of the small airways, which are associated with a reduction in elastic recoil of the lungs, expiratory airflow limitation and air trapping [4, 5]. COPD, particularly the emphysematous phenotype, is a major cause of lung hyperinflation [5]. Nonetheless, lung hyperinflation can also be found in association with other pulmonary diseases, including asthma and cystic fibrosis [6, 7]. Currently, the reference technique to assess and quantify hyperinflation is body plethysmography. In case of lung hyperinflation there is a reduction in inspiratory capacity and an elevation of the functional residual capacity, TLC and RV [8]. As the disease progresses, the increase in RV exceeds that of TLC, resulting in an increase in the RV/TLC ratio [8]. Comparing the measured value to a reference value helps the interpretation and standardisation of pulmonary function outcomes. Common clinical practice is to divide the measured value by the reference value to get a % predicted value. However, this method is now strongly discouraged by the ATS and ERS considering that the % predicted value does not account for the observed age-dependent variability within healthy individuals. Therefore, the ERS and ATS now recommend the use of z-scores, lower and upper limits of normal [9]. Switching from the ECSC to the GLI reference equations and to the use of z-scores instead of % predicted may have clinical implications, especially in the context of patient selection for lung volume reduction treatments.

Surgical and bronchoscopic lung volume reduction (BLVR) options are guideline-recommended treatments for a carefully selected group of patients with advanced emphysema and substantial hyperinflation, and who remain highly symptomatic despite optimised conventional medical treatment [10, 11]. Lung volume reduction therapies aim to reduce static hyperinflation and subsequently improve pulmonary function, exercise capacity and quality of life [12–14]. Consequently, one of the main selection criteria is the presence of "sufficient" hyperinflation. Although there is no widely accepted definition of sufficient hyperinflation, the general consensus among experts is that a post-bronchodilator RV of 175% predicted or higher and an absolute RV/TLC ratio of 55% or higher indicates possible candidates for BLVR using endobronchial valves (Zephyr, PulmonX Corp., Redwood, CA, USA) or lung volume reduction surgery [13–15]. For patients with a more homogeneous distribution of emphysema, a RV ⩾200% predicted is generally recommended [16]. With the change in references equations for lung volumes and the switch from % predicted to z-scores, these recommendations need to be reconsidered.

Therefore, the objectives of this study were to evaluate the difference between the GLI- and ECSC-derived reference values for RV and the effect of sex, age and height on this difference, and to identify a novel RV threshold that can be used in the context of lung volume reduction patient selection and that adheres to the current ATS/ERS recommendations (*i.e.* using the GLI reference equations and z-scores) [9].

Methods

Simulation of ECSC and GLI reference equations

To assess the difference between the GLI- and ECSC-derived reference values for RV and the effect of sex, age and height on this difference, we calculated the RV reference values for individuals of European descent with ages ranging from 18 to 80 years. For height we used the median and corresponding percentiles derived from the latest World Health Organization (WHO) growth chart for the age of 19 years [17]. Although our analyses are targeted at adults, we assumed that height at age 19 years is representative for adults, also considering that the median heights from this WHO growth chart were equal or very similar to the median heights found in our study population (described below).

Study population

Data were collected from patients who were enrolled into our "Groningen Severe COPD Cohort" and who underwent body plethysmography. The Groningen Severe COPD Cohort included patients with COPD who were referred to and evaluated at the University Medical Center Groningen (UMCG) (Groningen, the Netherlands) between August 2014 and August 2019 for their eligibility for a lung volume reduction intervention. This cohort was approved by the ethics committee of the UMCG (EC number: 2014/102, trial registration number at ClinicalTrials.gov: NCT04023409) and all patients provided written informed consent.

All pulmonary function tests were performed post-bronchodilator and in accordance with the most recent ERS/ATS technical guideline at the time of testing [2]. The flow-volume measurements were obtained using a pneumotachograph (Masterscreen PRO or PNEUMO, Vyaire Medical, Mettewa, IL, USA) and the lung volume measurements using a body plethysmograph (Masterscreen PRO). Height and weight were measured prior to pulmonary function testing and age at testing was obtained by subtracting the visit date from the date of birth. The flow-volume measurements were converted using the GLI 2012 reference equations [18] and the lung volume measurements using both the ECSC 1993 and the GLI 2019 reference equations [1, 3].

The majority of the included patients (99.5%) were of European descent. The other patients (0.5%) were of mixed or other descent. The GLI reference equations were derived using only individuals of European descent but, considering that in clinical practice the GLI reference values are most likely used for all individuals, we decided to keep all patients in our analysis. Furthermore, one patient was over the age of 80 years, the maximum age for which a reference value is available in the GLI reference equation, but this patient was also kept in the analysis and the reference value extrapolated; this is not recommended by the ERS/ATS task force but is also done in clinical practice.

Statistical analysis

Categorical data are presented as count (%) and continuous data as mean±SD or median (interquartile range (IQR)) where appropriate. All differences between GLI- and ECSC-derived values are reported as GLI minus ECSC. Bland–Altman plots were generated to illustrate the agreement between the ECSC- and GLI-derived RV % predicted. Receiver operating characteristic curves were used to determine the optimal new cut-off for RV using GLI-derived z-scores compared to the previously used ECSC-derived 175% and 200% predicted. The optimal cut-off is determined based on the highest score for the Youden index, which combines sensitivity and sensitivity into a single measure. All statistical analysis were performed using R (www.r-project.org).

Results

Simulation of ECSC and GLI reference equations

Figure 1 illustrates the difference between the GLI- and ECSC-derived reference values for RV across different ages and heights based on mathematical simulation data. There is no systematic difference between the two reference values for RV, but they are strongly dependent on the combination of sex, age and height. For individuals of median height (177 cm for males and 163 cm for females) or shorter, the GLI-derived reference value is consistently lower. For individuals with an above-median height, the GLI-derived reference value can be higher than the ECSC-derived reference value but this is dependent on age.

Study population

The Groningen Severe COPD Cohort enrolled 1030 patients and body plethysmography data were obtained from 1011 of these patients (98%). The demographic characteristics are shown in table 1. All included patients met the ATS/ERS recommended criterium for airflow limitation (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio below the lower limit of normal [9]) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline diagnostic criterium for COPD (post-bronchodilator FEV_1/FVC ratio <0.7 [10]). The majority of patients had severe to very severe airflow obstruction (38% COPD GOLD 3 and 59% GOLD 4). Median age was 62 years (range 36–81 years), and the average height was 164 cm (range 145–182 cm) for included females and 177 cm (range 155–200 cm) for included males.

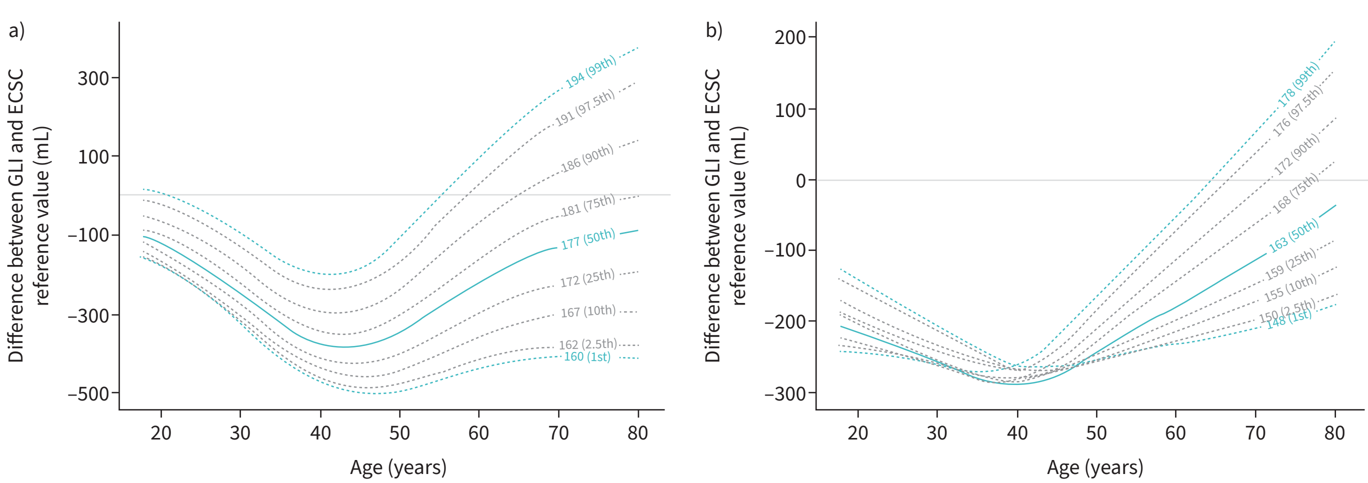

FIGURE 1 Difference in residual volume reference values between the Global Lung Function Initiative (GLI) and the European Community for Steel and Coal (ECSC) for individuals of European descent between the age of 19 and 80 years. Height isopleths are based on the World Health Organization growth chart for individuals of 19 years of age. The percentiles are displayed between brackets. The difference is depicted as GLI-derived reference value minus ECSC-derived reference value. a) Males and b) females.

TABLE 1 Demographic characteristics of the patients included in the study

Subjects (n)	1011
Sex	
Female	662 (65.5)
Male	349 (34.5)
Age (years)	63 (57–67)
BMI (kg·m^{-2})	24.3±4.2
Smoking status[#]	
Never-smoker	2 (0.2)
Current smoker	23 (2.3)
Former smoker	982 (97.5)
Pack years[¶]	40 (30–50)
GOLD grade	
GOLD 1	1 (0.1)
GOLD 2	30 (3.0)
GOLD 3	385 (38.1)
GOLD 4	595 (58.9)
SGRQ (total score)[+]	58.8±13.5
FEV_1	
Absolute (L)	0.75 (0.59–0.96)
z-score	−4.39±0.70
% predicted	27 (22–34)
FVC	
Absolute (L)	2.67±0.92
z-score	−1.84±1.27
% predicted	73±18
FEV_1/FVC ratio (%)	31±7
RV	
Absolute (L)	4.61±1.11
z-score (ECSC-1993)	6.70±2.61
z-score (GLI-2019)	3.96±1.35
% predicted (ECSC-1993)	218±47
% predicted (GLI-2019)	235±56
TLC	
Absolute (L)	7.31 (6.53–8.59)
z-score (ECSC-1993)	2.99±1.32
z-score (GLI-2019)	1.96±1.43
% predicted (ECSC-1993)	133 (124–143)
% predicted (GLI-2019)	122 (111–141)
RV/TLC ratio (%)	61 (55–67)

Data are presented as n (%), mean±SD or median (interquartile range), unless otherwise indicated. All pulmonary function outcomes were measured post-bronchodilator and lung volumes were measured using body plethysmography. BMI: body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; SGRQ: St George's Respiratory Questionnaire (a validated questionnaire to assess health-related quality of life in patients with COPD with scores ranging from 0 to 100, where higher scores indicate a worse quality of life); FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; ECSC: European Community for Steel and Coal; GLI: Global Lung Function Initiative; TLC: total lung capacity. [#]: n=1007; [¶]: n=980; [+]: n=972.

Mean RV was 4.61±1.11 L. The RV % predicted was significantly higher when the GLI reference value was used compared to the ECSC, with a mean difference of 17 percentage points (95% CI 16–18, $p<0.001$, t-test). Bland–Altman plots comparing the ECSC- and GLI-derived RV % predicted are shown in figure 2, which highlight the impact of sex and the magnitude of difference from "normal" on the difference in % predicted.

New RV cut-off

In our study population, a GLI-derived z-score of ⩾2.9 was found to be the optimal cut-off to replace the ECSC-derived ⩾175% predicted cut-off with a sensitivity of 94.4% and specificity of 96.6% (figure 3a). For the ECSC-derived RV ⩾200% predicted, a GLI-derived z-score ⩾3.5 was found to be the optimal cut-off with a sensitivity of 91.4% and specificity of 93.3% (figure 3b).

Figure 4 illustrates the association between the ECSC-derived RV % predicted and the GLI-derived RV z-score for the patients in our cohort and if a patient eventually received BLVR using endobronchial valves or

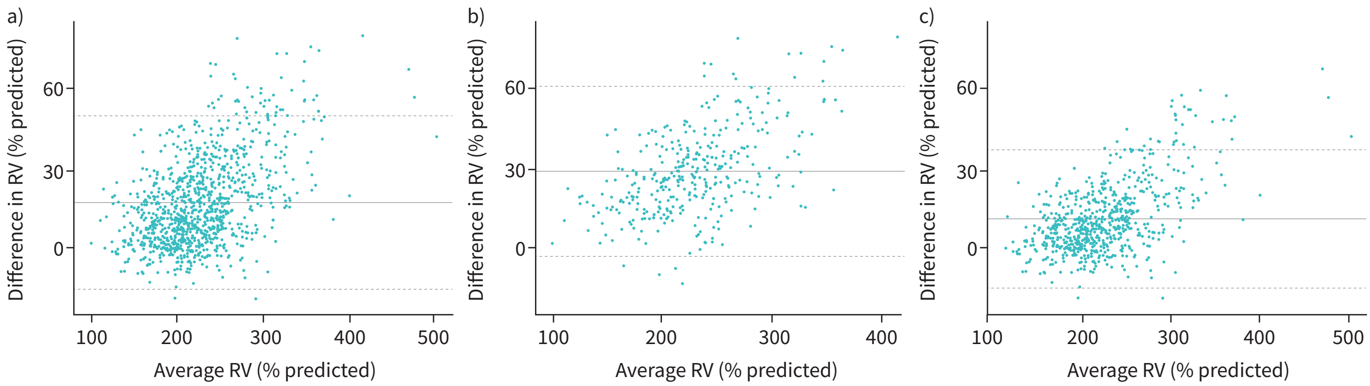

FIGURE 2 Bland–Altman plots of the agreement between the residual volume (RV) % predicted derived from the Global Lung Function Initiative (GLI) and the European Community for Steel and Coal (ECSC) equations. a) Overall; mean difference of 17 percentage points (limits of agreement: −16 to 50). b) Males (n=349); mean difference of 29 percentage points (limits of agreement: −3 to 61). c) Females (n=662); mean difference of 11 percentage points (limits of agreement: −15 to 37). Difference outcomes are displayed as GLI minus ECSC.

coils. In total, 201 patients had a GLI-derived z-score <2.9, of whom only 13 received BLVR. Of these 13 patients, six had a ECSC-derived RV ⩾175% predicted (median 182% predicted, range 176–206% predicted). Compared to patients with a GLI-derived z-score <2.9 who did not receive BLVR, the patients who did receive BLVR had a higher median RV/TLC ratio (58%, range 52–64%, *versus* 49%, range 31–73%). Despite having a ⩾175% predicted (ECSC) and z-score ⩾2.9 (GLI), many patients were still not eligible for a BLVR treatment because of other reasons or contra-indications [13, 19].

Discussion

In this study, we conducted a comparative analysis between the newly developed GLI reference equation for RV and the commonly used ECSC reference equation. Additionally, we explored the possibility of defining a new RV threshold to identify candidates who could potentially receive a lung volume reduction treatment; ⩾175% or ⩾200% predicted are currently the most commonly used thresholds. Our findings indicate that the GLI reference equation yields lower reference values for RV when compared to the ECSC equation across the majority of individuals. This trend holds true for individuals of average or below-average height, regardless of age or sex. Notably, for taller individuals, the GLI-derived RV reference value may exceed the ECSC-derived value, contingent upon the combination of sex, age and

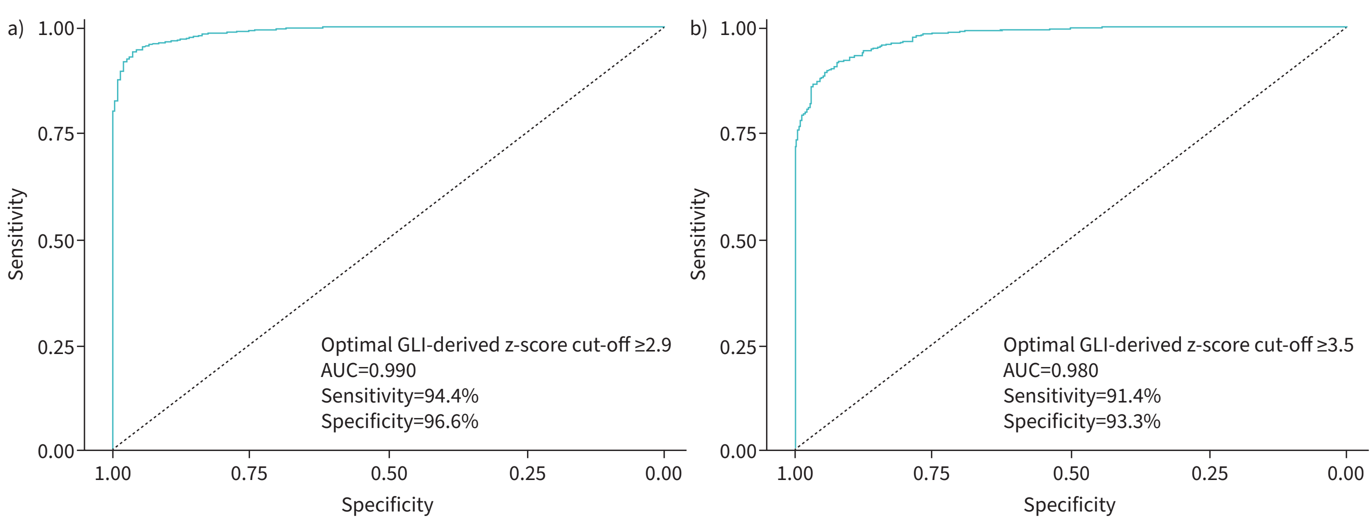

FIGURE 3 Receiver operating characteristic curves for a) European Community for Steel and Coal (ECSC)-derived residual volume (RV) cut-off of ⩾175% predicted and b) ECSC-derived RV cut-off of ⩾200% predicted to the Global Lung Function Initiative (GLI)-derived z-score for RV. AUC: area under the curve.

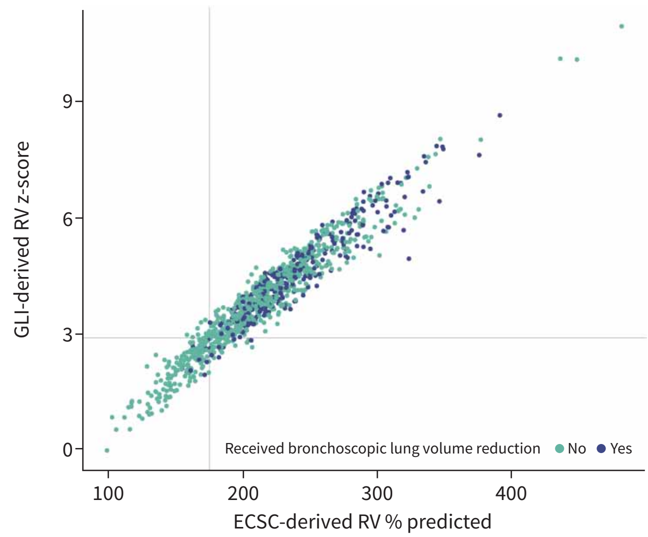

FIGURE 4 Scatterplot of European Community for Steel and Coal (ECSC)-derived residual volume (RV) % predicted and the Global Lung Function Initiative (GLI)-derived RV z-score in our cohort of 1011 COPD patients. The vertical line indicates a RV of 175% predicted based on the ECSC reference value and the horizontal line indicates a RV z-score of 2.9 based on the GLI reference value. The colours indicate if a patient did or did not receive a bronchoscopic lung volume reduction treatment with endobronchial valves or coils.

height. Furthermore, we showed that, in our clinical population, a GLI-derived z-score of ⩾2.9 is a good replacement for the ECSC-derived RV ⩾175% predicted cut-off. Similarly for the ⩾200% predicted cut-off, a GLI-derived z-score ⩾3.5 was found as the best alternative.

For pulmonary function test outcomes, numerous reference equations have been developed using different sample populations and various mathematical models. Small differences in reference values are therefore to be expected and generally of minimal to no clinical importance. However, as already touched on by Hall *et al.* [1], the GLI-derived reference values for RV can differ substantially from other reference equations in individuals with a specific age and height combination. As shown in our study, the GLI reference equation consistently results in a lower RV reference value for individuals with an average or below-average height (females ⩽163 cm and males ⩽177 cm). However, the degree of difference depends on the specific combination of sex, age and height. Furthermore, for individuals with an above-average height, the GLI-derived RV reference value can also be higher. Although the use of % predicted values is discouraged [9], they are still commonly used in clinical practice, mainly because they are easier and more straightforward to interpretate. Our findings illustrate that when centres switch from using the ECSC to the GLI reference equations for lung volumes, higher % predicted values will be observed for individuals of average or below-average height and these differences can be substantial. This indicates that the RV % predicted derived from the ECSC and GLI reference equations cannot be interpreted as if they were the same in the context of assessing hyperinflation severity.

Body plethysmography, or the measurement of lung volumes in general, is not needed to make a specific diagnosis, but it can help to refine a differential diagnosis or improve the characterisation of COPD, especially in patients with severe airflow obstruction [1, 10, 20]. Assessing the severity of static hyperinflation in COPD patients is crucial when lung volume reduction treatments are considered, because these treatments aim to improve patient-related outcomes by reducing hyperinflation [21]. Currently, for most lung volume reduction treatments, an RV of ⩾175% predicted is used as a guideline to identify possible candidates on the basis of sufficient hyperinflation [13, 14]. However, given that the GLI reference equation results in a lower reference value for RV in the majority of individuals and the use of % predicted is discouraged by the ERS and ATS, a novel threshold needs to be defined. We found that the GLI-derived z-score of ⩾2.9 accurately discriminated patients in the same category as the ECSC-derived RV ⩾175% predicted threshold and can therefore be used as a new guideline and as an inclusion criteria in future clinical trials. If a higher RV value is desired, the GLI-derived z-score of ⩾3.5 identifies the same patients as the ECSC-derived ⩾200% predicted threshold with high accuracy.

It is important to note that, outside the context of a prospective clinical trial, the z-score threshold for RV, or more generally a RV threshold value, should only be used as guidance and not as a strict cut-off value for several reasons. First, the current RV threshold recommendation, from which our novel threshold recommendation is derived, is based on an inclusion criterium used in all major lung volume reduction clinical trials [22–28]. To date, for most lung volume reduction treatments, no responder analyses have been done, including endobronchial valve treatment and lung volume reduction surgery. However, it has been shown that patients with a RV below the recommended threshold can significantly benefit from endobronchial valve treatment when there is a clear treatment target lobe [29]. This is supported by a recent cluster analysis from our group which showed that endobronchial valve treatment responders are best distinguished from non-responders by target lobe characteristics rather than pulmonary function measures [30]. While it is encouraging that the GLI-derived z-score of ⩾2.9 accurately categorises patients compared to the previously used value, it emphasises a weakness of using a derived instead of an absolute value, which is that the used reference equation should be clearly reported because the same absolute value can result in a substantially different derived value. Therefore, it could be argued that only the absolute RV/TLC ratio should be used as an inclusion criterium in future lung volume reduction trials.

Our study has limitations. The clinical cohort used in our study (the Groningen Severe COPD Cohort) mainly consists of patients with severe to very severe COPD. This could have affected our findings, especially the comparison between the ECSC-derived % predicted and the GLI-derived z-scores on which we have proposed new threshold values. However, we believe that our cohort accurately represents the general population that is considered for lung volume reduction worldwide. Furthermore, we only compared the newly developed GLI to the ECSC reference equations although more reference equations are available for lung volumes. This was chosen because, to our knowledge, the ECSC reference equations used to be the most commonly used reference equation for lung volumes used in Europe and the ones on which the 175% predicted threshold (and all other RV thresholds) are based. Lastly, in this study we did not try to establish a novel threshold for the 150% predicted cut-off that has been and, in some cases, is still used because the number of patients with an RV <150% predicted was too low to accurately establish a novel threshold.

In conclusion, this study showed significant differences in predicted RV between the GLI and ECSC reference equations, with the GLI generating lower predicted values in the majority of individuals, which would result in higher % predicted values. The discrepancy in predicted RV varied depending on the specific combination of sex, age and height, but consistently showed a lower GLI-derived predicted RV in individuals with an average or below-average height. These findings can have important implications for assessing static hyperinflation in the context of patient selection for lung volume reduction treatments, but in this study we have found that a GLI-derived z-score of ⩾2.9 can accurately substitute the current guideline of 175% predicted or higher to identify patients with sufficiently elevated RV to be possible lung volume reduction candidates.

Provenance: Submitted article, peer reviewed.

Ethics statement: We used data from a clinical cohort that received ethical approval from the ethics committee of the University Medical Center Groningen (EC number 2014/102).

Conflict of interest: D-J. Slebos reports grants or contracts, consulting fees, honoraria, support for attending meetings and receiving materials from PulmonX, PneumRx and Nuvaira, and grants or contracts from Free Flow Medical, all outside the context of the submitted work. All other authors have nothing to disclose.

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