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A Robust Emphysema Severity Measure Based on Disease Subtypes

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Abstract

Rationale and Objectives—We propose a novel single index for the quantification of emphysema severity based on an aggregation of multiple computed tomographic features evident in the lung parenchyma of smokers. Our goal was to demonstrate that this single index provides complementary information to the current standard measure of emphysema, percent emphysema (percent low attenuation areas [*LAA*%]), and may be superior in its association with clinically relevant outcomes.

Materials and Methods—The inputs to our algorithm were objective assessments of multiple emphysema subtypes (normal tissue; panlobular; paraseptal; and mild, moderate, and severe centrilobular emphysema). We applied dimensionality reduction techniques to the emphysema quantities to find a space that maximizes the variance of these subtypes. A single emphysema severity index was then derived from a parametrization of the reduced space, and the clinical utility of the measure was explored in a large cross-sectional cohort of 8914 subjects from the COPDGene Study.

Results—There was a statistically significant association between the severity index and the *LAA* %. Subjects with more severe chronic obstructive pulmonary disease (higher Global initiative for Obstructive Lung Disease stage) tended to have a higher computed tomography severity index. Finally, the severity index was associated with clinical outcomes such as lung function and provided a stronger association to these measures than the *LAA*%.

Conclusions—The method provides a single clinically relevant index that can assess the severity of emphysema and that provides information that is complimentary to the more commonly used *LAA*%.

Keywords

Emphysema severity measure; local histogram analysis

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APPENDIX. SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at doi:10.1016/j.acra.2015.12.021.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by emphysematous destruction of the lung parenchyma. Objective quantification of this process is an important part of disease characterization. Standard methods to do this are based upon a densitometric assessment of the lung parenchyma where a Hounsfield unit threshold is used to delineate emphysematous from nonemphysematous tissue. This measure can be expressed as a fraction but is most commonly reported as the percent low attenuation areas (*LAA*%) (1). Although easy to use for correlative investigation, the *LAA*% does not fully assess the heterogeneous nature of emphysema or its subtypes.

The clinical significance of six features that capture the prevalence of emphysema subtypes (normal tissue [NT]; paraseptal; panlobular; and mild, moderate, and severe centrilobular emphysema) has been previously demonstrated. It has also been shown that these features provide complementary information to *LAA*% (2). However, it becomes increasingly difficult to perform regression analysis as the number of features increases. In addition, it is difficult to appreciate how a variable mixture of these features results in the same level of disease severity. It would therefore be useful to aggregate these multiple features into a single measure without losing information about the individual subtypes. However, currently available methods for the quantification of emphysema on computed tomography (CT) images (3–9) either do not quantify severity based on emphysema subtypes or suffer from low performance and inter-scanner variability.

We sought to examine the clinical utility of a continuous measure of emphysema severity based on six emphysema subtypes (2). This severity index could be obtained via dimensionality reduction of the feature vector that comprises the subtypes (10). Our goal was to determine the clinical correlates of this measure and to compare the strength of these correlations to those obtained using the standard *LAA*%. To do this, we leveraged clinical and radiological data obtained in the COPDGene Study.

MATERIALS AND METHODS

Population

The COPDGene Study is a multicenter investigation focused on the genetic epidemiology of COPD (11). Participants were all current and former smokers with at least 10 pack-years of smoking. Subjects with respiratory conditions other than asthma and COPD were excluded from participation.

Participants in the COPDGene Study underwent inspiratory and expiratory CT scanning (details in the following section) as well as spirometric assessments of lung function before and after the administration of a short-acting bronchodilator (12). Such measures of lung function included the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity obtained according to the American Thoracic Society (ATS) / European Respiratory Society (ERS) standards. Finally, detailed questionnaire data were obtained such as the modified Medical Research Council dyspnea score and the St. George's Respiratory Questionnaire (SGRQ) (13). The modified Medical Research Council dyspnea

score is used to rate participants' shortness of breath ranging from 0 (no dyspnea) to 4 (too breathless to leave the house or when dressing or undressing). The SGRQ is commonly employed to assess health status, where a higher score connotes lower health status.

Clinical and radiological data from 8914 (87%) out of 10,300 COPDGene subjects were included in this analysis. Brigham and Women's Hospital obtained approval from the Partners Human Research Committee, and all subjects provided written informed consent, allowing the use of CT data in this study. An initial training set consisting of the first 2500 subjects of the COPDGene cohort was used to build the model of emphysema severity, which was then tested in the remaining 6414 subjects. There were 102 never-smoking controls in the sample. Table 1 provides a description of the training and testing sets across the Global Initiative for Obstructive Lung Disease (GOLD) stages of disease severity. GOLD stage 0 or at risk indicates absence of COPD, and GOLD stages 1–4 indicate mild, moderate, severe, and very severe disease, respectively.

A subset of the testing data was used for severity score validation. To this end, 40 subjects were selected in such a way that they represent the broad range of emphysema severity as defined by the *LAA*% measure in COPDGene (between 2% and 61%). Patient distributions are 4, 1, 5, 16, and 14 for GOLD stages 0, 1, 2, 3, and 4, respectively.

CT Protocols

Volumetric CT scans were acquired from multiple sites in supine position and without intravenous contrast. Several different scanners were used, with the following protocols: 120 kV peak, 200 mA, and 0.75-mm slice thickness for Siemens scanners; 120 kV peak, 400 mA, and 0.625-mm slice thickness for General Electric scanners; and 120 kV peak, 440 mA, and 0.9-mm slice thickness for Philips scanners. Scans acquired at full inspiration were used in the study. Full inspiration was controlled as per the COPDGene Study protocol (11). The full details of the acquisition parameters for the COPDGene Study can be found in Reference (14).

Emphysema Subtype Features

Input for the emphysema severity model included six parenchymal subtypes (normal, mild, moderate, and severe centrilobular emphysema, panlobular, and paraseptal emphysema). The six subtypes are classified in the following manner (2): First, we obtain training data for each of the subtypes, which consists of square CT regions. For each region of interest, we build a feature vector consisting of a local density histogram obtained using kernel density estimation. We then classify each new CT scan by subdividing it into regions of interest, and then comparing the local histogram of each region to those in the training data using the Least Absolute Deviations (L1) norm. We select the subtype with the highest frequency from the five nearest training neighbors as determined by the distance metric (k-nearest neighbor classification). A representative example of axial CT images and a range of severities for these subtypes are provided in Figure 1.

Severity Index From CT Image Information

A detailed description of the derivation of the severity index is provided as supplementary material. Briefly, we began by extracting the CT-based features that correspond to the prevalence of each of the six emphysema subtypes from the training set of 2500 subjects. Principle components analysis (15) was then performed on those features to extract the first three components and reduce the dimensionality of the data. The result is depicted graphically in Figure 2(a). Visual inspection of this boomerang-like shape suggested that much of the variance of the original data was maintained and that emphysema severity progression (from mild to severe) is based in part on the prevalence of NT. We therefore clustered the data according to prevalence of NT and learned a two-dimensional (2D) space from the six-dimensional original space by maximizing the separation between clusters using linear discriminant analysis (LDA) (16) (Fig 2(b)). Visual inspection of the 2D embedded space suggested that the shape can be modeled by a second-order polynomial curve to form a parametric description of that space.

The resulting dispersion obtained in 2D space suggested that emphysema progression might follow unique paths for each individual. To investigate this, we defined an emphysema severity curve for each COPDGene subject. To do so, we build our model with multiple curves that span the dispersion. We first divide our original severity space into four groups based on the distance along the normal to the curve, n, in 2D space. The intuition is that the closer to 0 the n value is for a given model, the closer the data are to the derived model. For each group, we derive a new model from the subset of training points that belong to that group. We choose to split our space into four groups because it maximizes separability between disease models all while providing an adequate amount of training data per model. An example of a model with four curves is shown in Figure 2(b).

Once the model is built, we can compute the severity for a new patient CT. We first project the emphysema subtype feature vector corresponding to the CT onto the LDA 2D space and obtain a 2D point p_{LDA}. For each of the four curves, the curve-specific severity is then defined as the arc-length along the curve from the upper left point, refered to as origin in Figure 2(b), to the reference point on the curve. The origin is considered the point of mildest emphysema. The reference point on the curve is defined as the projection onto the curve along the polynomial normal of p_{LDA}.

Finally, we obtain a patient-specific disease curve passing through p_{LDA} in LDA space by interpolating over the four curves using the value of n. The final severity index S is then defined as the arc-length along the interpolated curve. This implies that the higher the arc-length, the further we are from the origin along the curve, the higher the severity. A software implementation of this algorithm is available on-line as part of the Chest Imaging Platform (http://chestimagingplatform.org/) under cip_python/phenotypes/emphysema_severity.py.

Statistical Analysis

Data are presented as means and standard deviations or medians and interquartile ranges where appropriate. Linear associations were assessed using Spearman correlation coefficients. P values less than 0.05 were considered statistically significant.

The distributions of *LAA*% and *S* across GOLD stages were compared by performing trend analysis based on the Wilcoxon rank sums test and by computing the coefficient of variation. The association between *LAA*% and *S* by GOLD stage was obtained via a linear regression.

We compared the proposed measure to expert scores using trend analysis based on the Wilcoxon rank sums test. For each of the 40 test cases, two expert clinicians assigned an emphysema severity score by consensus. The score ranges between the values of 0 and 4, where 0 is the lowest severity (no emphysema) and 4 is the highest severity (severe emphysema).

Univariate and multivariate regression models were performed to measure associations between our measure and each of the following clinical measures: FEV_1, distance walked, and SGRQ. These associations were compared to ones obtained using *LAA*%. For the multivariate models, a priori models based on clinical knowledge are used[1] in the models for distance walked and SGRQ, and adjusted for age, gender, race, height, smoking status, and number of pack-years in the model for FEV_1.

RESULTS

Analysis of Severity

Figure 3 shows the distribution of *S* and *LAA*% across GOLD stages. Trend analysis shows a steady increase in *S* along GOLD stages with significant differences across the GOLD stages ($p < 0.0001$). Table 2 shows the coefficient of variation of both *S* and *LAA*% measures across GOLD stages. The coefficient of variation of *LAA*% is considerably higher than that of *S* for all the GOLD stages, suggesting a much higher dispersion. For both *S* and *LAA*%, the coefficient of variation decreases as the GOLD stage increases.

Figure 4 shows the coefficient of determination (R-squared) across GOLD stages following a linear regression between *LAA*% and *S*. An overall R-squared value of 0.654 is obtained between *LAA*% and *S*, and a value of 0.666 is obtained between log(*LAA*%) and *S*. The coefficient of determination is generally increasing across GOLD stages. An analysis of variance shows a linear association between *LAA*% and *S* for each of the GOLD stages ($p < 0.0001$).

Figure 5 shows the distribution of *S* andd *LAA*% by visual assessment score. Trend analysis shows a steady increase in both *S* and *LAA*% along expert index values and significant differences in both *S* ($p < 0.001$) and *LAA*% ($p < 0.0001$) across expert index values.

Associations With Outcomes

Figure 6 shows a plot of the distribution of FEV_1, an important indicator of COPD, and *S*, the proposed severity measure. A regression line fit in red shows a predictable downward trend (R-squared = 0.24).

[1]We adjusted for age, gender, race, body mass index, smoking status, number of pack-years, and FEV_1.

Table 3 shows results of regression models for each of the outcomes and including either *S* or *LAA*%. For both *S* and *LAA*%, statistically significant associations are found with each of the outcomes ($p < 0.0001$). However, for each of the outcomes, the adjusted R-squared is higher in the case of our proposed *S* compared to *LAA*%. This suggests that, prior to adjusting for confounding factors, more of the variation in the outcome is explained by our proposed measure than by *LAA*%.

Table 4 shows results of the multivariate regression models controlling for the covariates. A total of 6220 subjects were used in this analysis (thus excluding normal subjects). We show the two covariates of interest: *S* and *LAA*%. Adjusted R-squared values are predictably higher when both *S* and *LAA*% are included in the model compared to the univariate models. Statistically significant associations are found between *S* and *LAA*% and each of the clinical outcomes ($p < 0.0001$). These associations show that our measure is a statistically significant predictor of the outcomes after adjusting for all the covariates and for *LAA*%. This shows the added benefit of our measure as it provides significant complementary information to *LAA*% and significantly improves associations with clinical indicators of disease severity.

DISCUSSION

We proposed a single emphysema severity measure that aggregates information from multiple features used to classify emphysema subtypes. Dimensionality reduction techniques were used to obtain a 2D space that consists of a linear combination of the original six dimensions. We then computed the proposed emphysema severity measure on 6414 patients and compared the proposed measure to *LAA*%. Trend analysis showed an increase in both *LAA*% and *S* along GOLD stages, predictably showing that cases in later stages of disease tend to have more severe emphysema. *LAA*% was found to have a larger dispersion than *S* when stratified by GOLD, suggesting higher variability in that measure for a given disease stage. We found a wider range in the later disease GOLD stages for *LAA*% compared to earlier stages, whereas the *S* tended to exhibit less variation across the disease spectrum. This resulted in a decrease in the coefficient of variation across disease stages for both *LAA* % and *S*, due to the fact that the coefficient of variation is normalized by the mean. We looked at the coefficient of determination between *LAA*% and *S* across GOLD stages. *S* correlates well with *LAA*% for more advanced stages of disease, and less well for earlier stages of disease. The particularly small interval for *LAA*% for the lower GOLD stages suggests that *S* might have a higher sensitivity in detecting early disease stages.

Both *S* and *LAA*% were shown to have significant associations with expert analysis of severity. A few outliers were observed for both measures, where the measure is high when compared to the expert index. It must be noted that expert manual measurements can suffer from variability. Itra-rater repeat measurements were obtained for the expert classifications, and a kappa coefficient of 0.792 was obtained. In addition, expert classifications were done by looking at extra-pulmonary manifestations in addition to the lungs to obtain a global idea of disease. However, both *LAA*% and *S* are computed only in the parenchymal area and do not take contextual information into account. Thus, based on our knowledge about expert classification, we can hypothesize that an effective emphysema classification scheme would be able to leverage additional contextual information about the patient.

Univariate regression analysis showed that a better model fit was obtained for all outcomes when only our proposed measure was used as opposed to *LAA*%. Multivariate regression analysis showed that although *LAA*% is a predictor of disease outcome, *S* is an independent predictor of disease outcome after adjusting for *LAA*%. This suggests that our proposed severity measure is of added value to *LAA*%, as it provides significant complementary information. This complementary information can help better characterize disease severity. We speculate that the complementary information that our severity measure provides is specific to what each subtype contributes to the severity of emphysema as a whole. Associations were particularly low between the 6-minute walk and both *S* and *LAA*%. The models have not been able to explain the variability for this measure perhaps due to the fact that the variability of the measure itself is inherently high, as it is dependent on the patient's effort. For these reasons, parenchymal measures may never explain more of the variability of the 6-minute walk for the reasons stated previously. In fact, distance walked and SGRQ have shown weak associations with severity measures in the literature (17,18). We believe that finding an emphysema severity measure that would improve these models is beneficial because both distance walked and SGRQ are important indicators of the patient's outcome. In spite of the high variability in both distance walked and SGRQ, our proposed severity measure has still been able to describe more of the variance in the models obtained. Although clearly, more work needs to be done to further improve these models.

Variation in scanned lung volumes can have an effect on intensity-based emphysema measures such as *S* and *LAA*%. We tested the extent of this effect by performing regression analysis on a subset of the COPDGene population that has been scanned twice. The details of this analysis can be found in section 2 of the supplementary material. Although no statistically significant associations were found between change in volume and change in resulting *LAA*% or *S*, higher associations were found between change in volume and change in resulting *LAA*%. We can, however, still see intra-subject variability in our proposed measure across the scans. We plan to study the reasons behind this variability as part of future work.

Changes in scanner can also have an effect on emphysema severity measures. We tested such effects by performing regression analysis between the outcomes and both *S* and *LAA*%, and adding scanner to the covariates. Details of the analysis can be found in section 3 of the supplementary material. We found better associations between the outcomes and our measure compared to *LAA*% after correcting for scanner, and less association between *S* and scanner compared to *LAA*%, although there were statistically significant associations between some outcomes and scanner when both *S* and *LAA*% are included in the model. Further mitigation of the effect of scanner on our measure is the subject of ongoing work.

One limitation of the work is that the automatic emphysema classification scheme that was used has low classification success rates for certain disease subtypes when compared to expert classification (2). In particular, mild centrilobular emphysema was classified with lower success rates than the remaining subtypes. However, we chose this classification scheme based on its speed, simplicity, ease of implementation, and overall competitive performance. When compared to other available methods, its performance was shown to be superior even for the more poorly classified subtypes. More importantly, emphysema

classifications using the chosen method have shown novel associations in a recent genome-wide association study of emphysema phenotypes (19).

CONCLUSIONS

We proposed a method to compute a single emphysema severity measure from CT image-based quantities representing emphysema subtypes. We obtained a manifold from the image-based quantities and used dimensionality reduction to map these quantities onto the severity space. We compared associations between the proposed metric and clinical COPD quantities and those obtained using standard densitometry as a binary classifier of emphysema (*LAA*%). We showed statistically significant associations between our proposed measure and each of the clinical measures analyzed in this study ($P < .0001$), and better associations when our proposed measure is compared to percent emphysema. We also showed that our measure is an independent predictor of the clinical outcomes and provides significant complementary information to *LAA*%. The proposed measure provides a way to compare emphysema severity across a population all while showing associations with clinical outcomes. Future works include exploring methods that would further mitigate the effect of scanner on the characterization of severity, the effect of changes in lung volume on our proposed measure, different dimensionality reduction methods, and extending the measure to three-dimensional space to further improve the associations between the measure and the clinically relevant outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

LAA%	percent low attenuation areas
COPD	chronic obstructive pulmonary disease
FEV_1	forced expiratory volume in 1 second
CT	computed tomography
SGRQ	St. George's Respiratory Questionnaire
2D	two-dimensional

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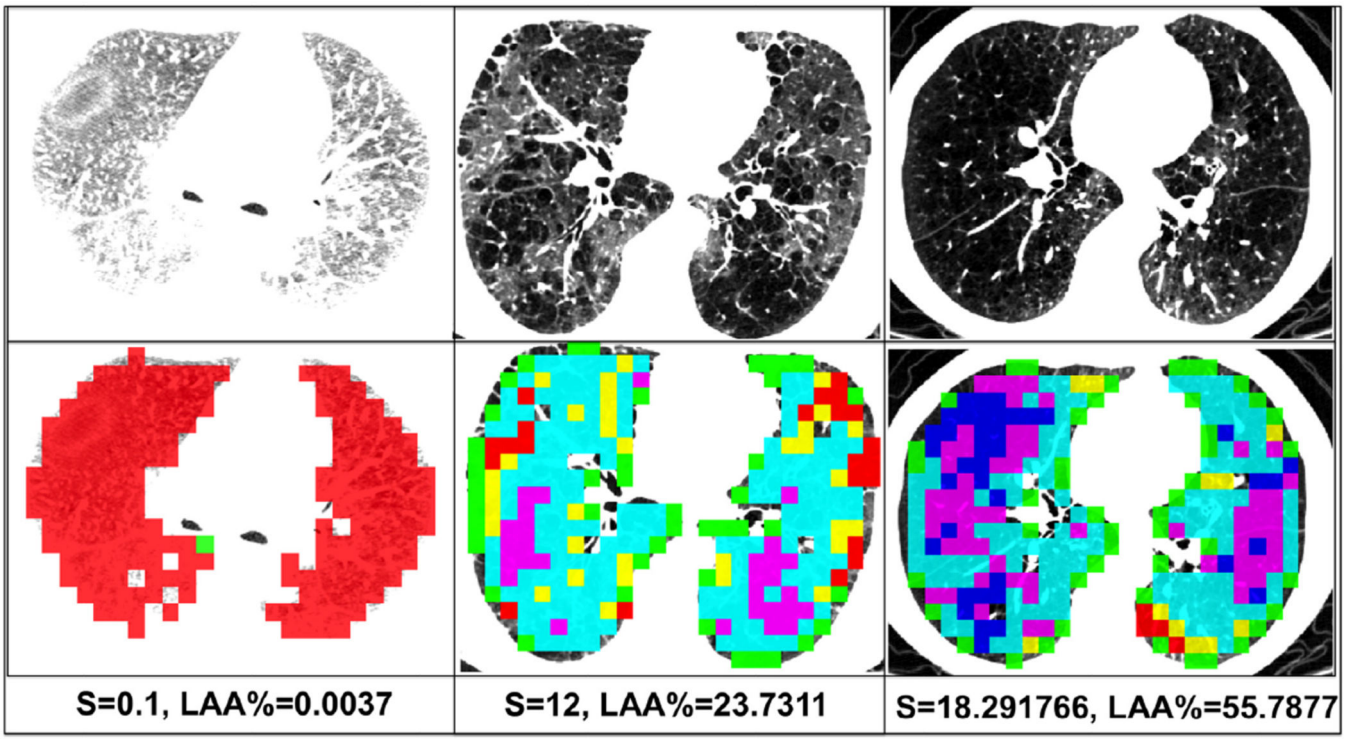

Figure 1.

Computed tomography (CT) slices (*top row*) and their corresponding emphysema classification (*bottom row*). Slices from three patients are shown and range from mild (*left*) to severe (*right*). The emphysema classes have the following color codes: normal parenchyma is red, paraseptal emphysema is green, panlobular emphysema is blue, mild centrilobular emphysema is yellow, moderate centrilobular emphysema is cyan, and severe centrilobular emphysema is purple. (Color version of figure is available online.)

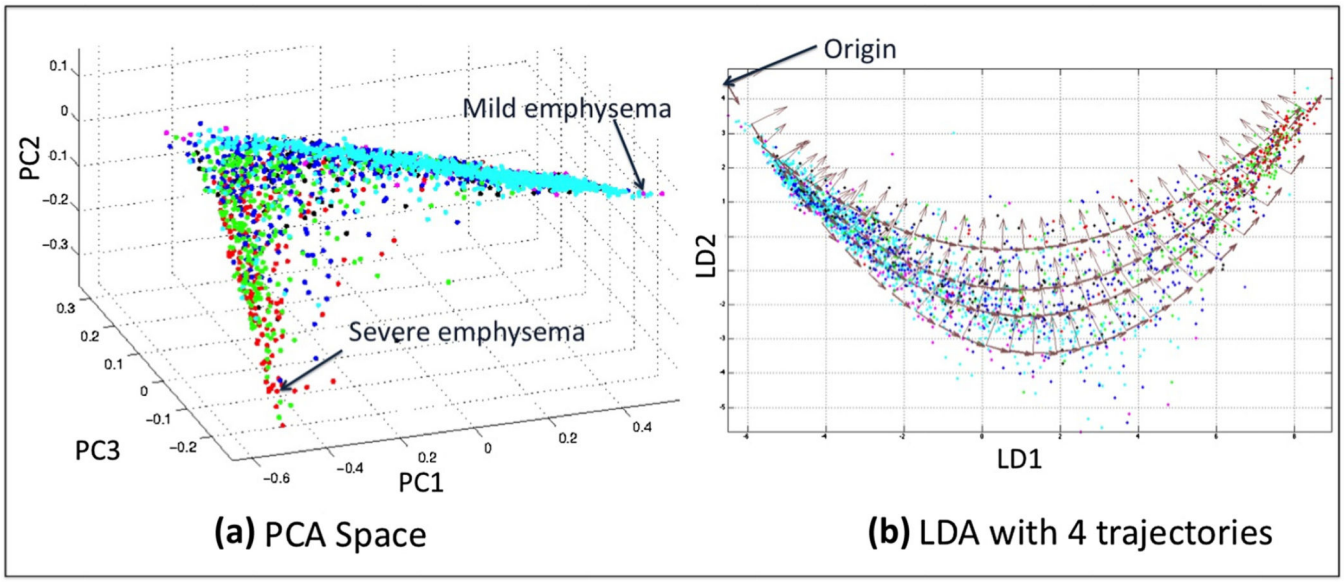

Figure 2.

Derivation of the severity measure *S* from the local histogram emphysema space. The data are projected onto the two spaces shown. Cyan, black, blue, green, and red represent cases with Global Initiative for Obstructive Lung Disease (GOLD) stages 0, 1, 2, 3, and 4, respectively; magenta is for cases with reduced forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). (Color version of figure is available online.)

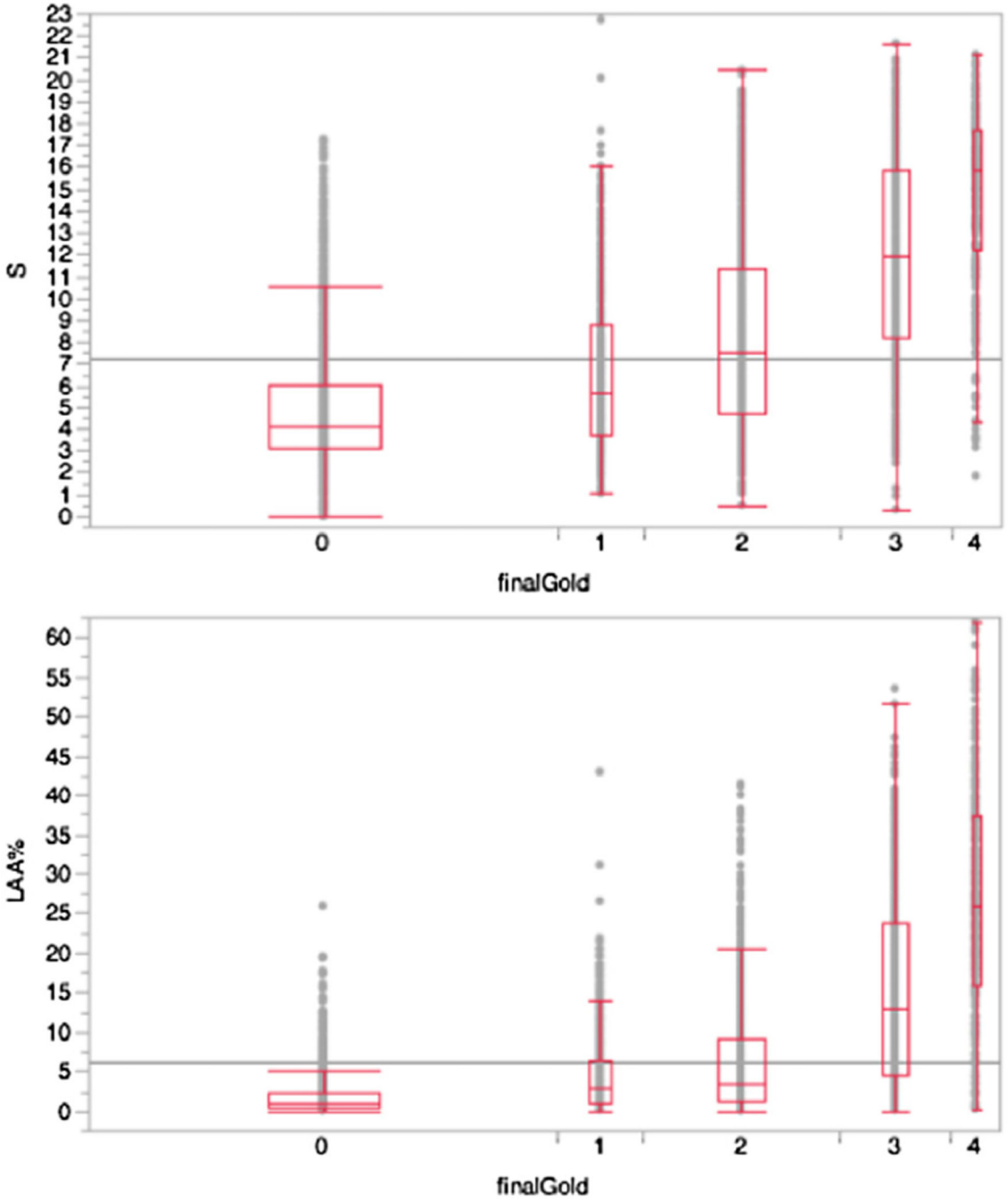

Figure 3.

Distribution of *S* and percent low attenuation areas (*LAA*%) across Global Initiative for Obstructive Lung Disease (GOLD). A gray line shows the mean over all the data.

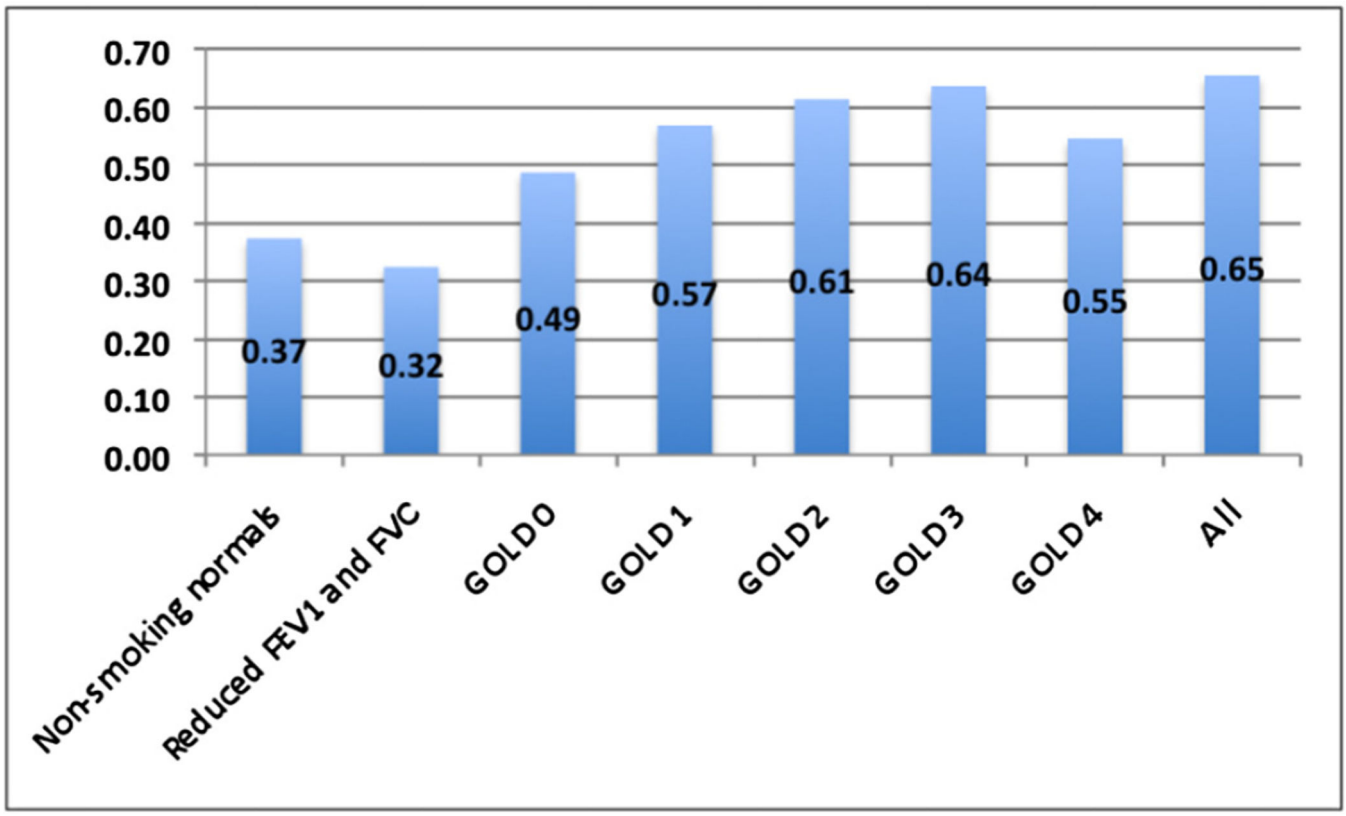

Figure 4.

R^2 between percent low attenuation areas (*LAA*%) and S across Global Initiative for Obstructive Lung Disease (GOLD) stages.

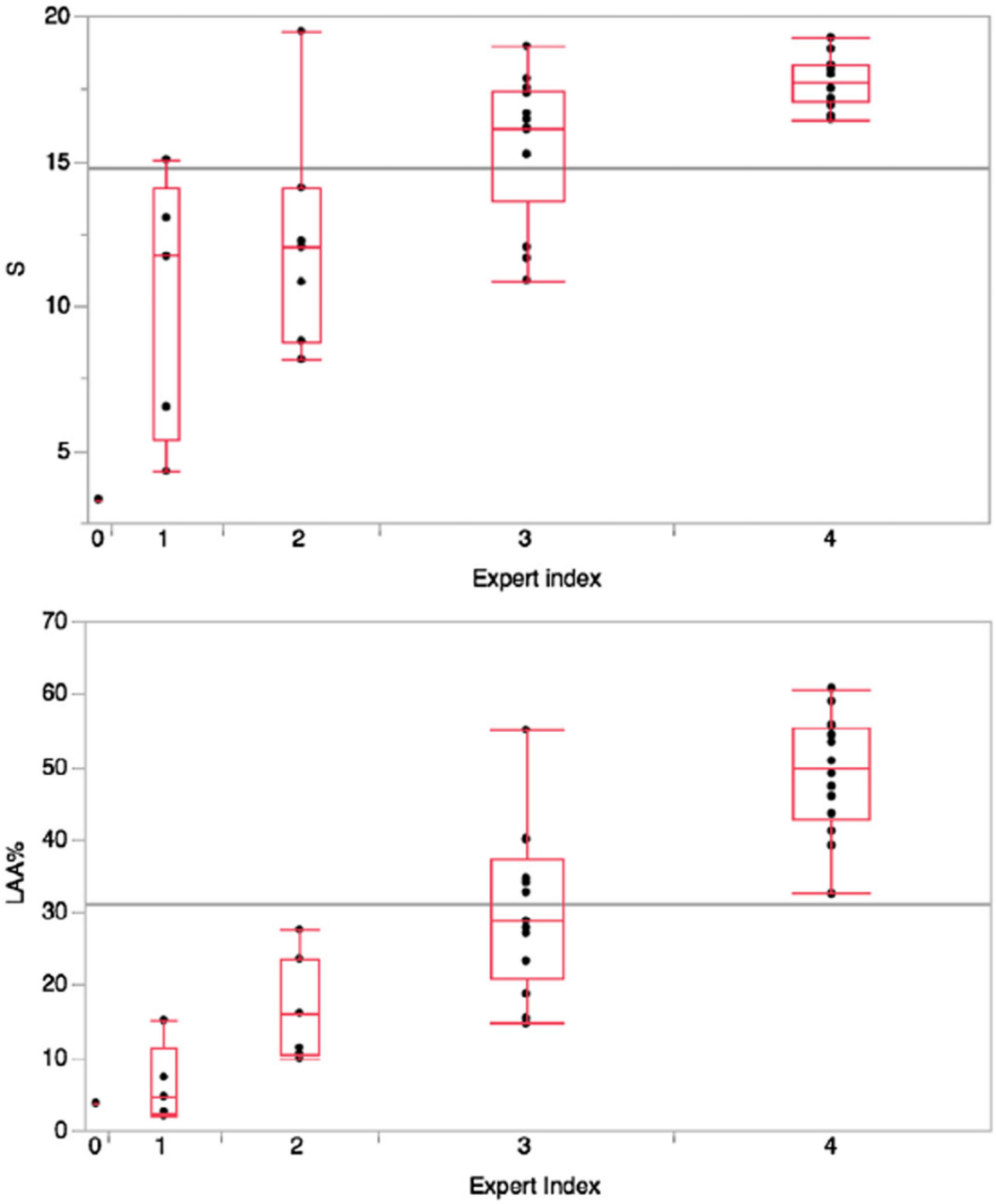

Figure 5.
Distribution of *S* and percent low attenuation areas (*LAA*%) across expert scores. A gray line shows the mean over all the data.

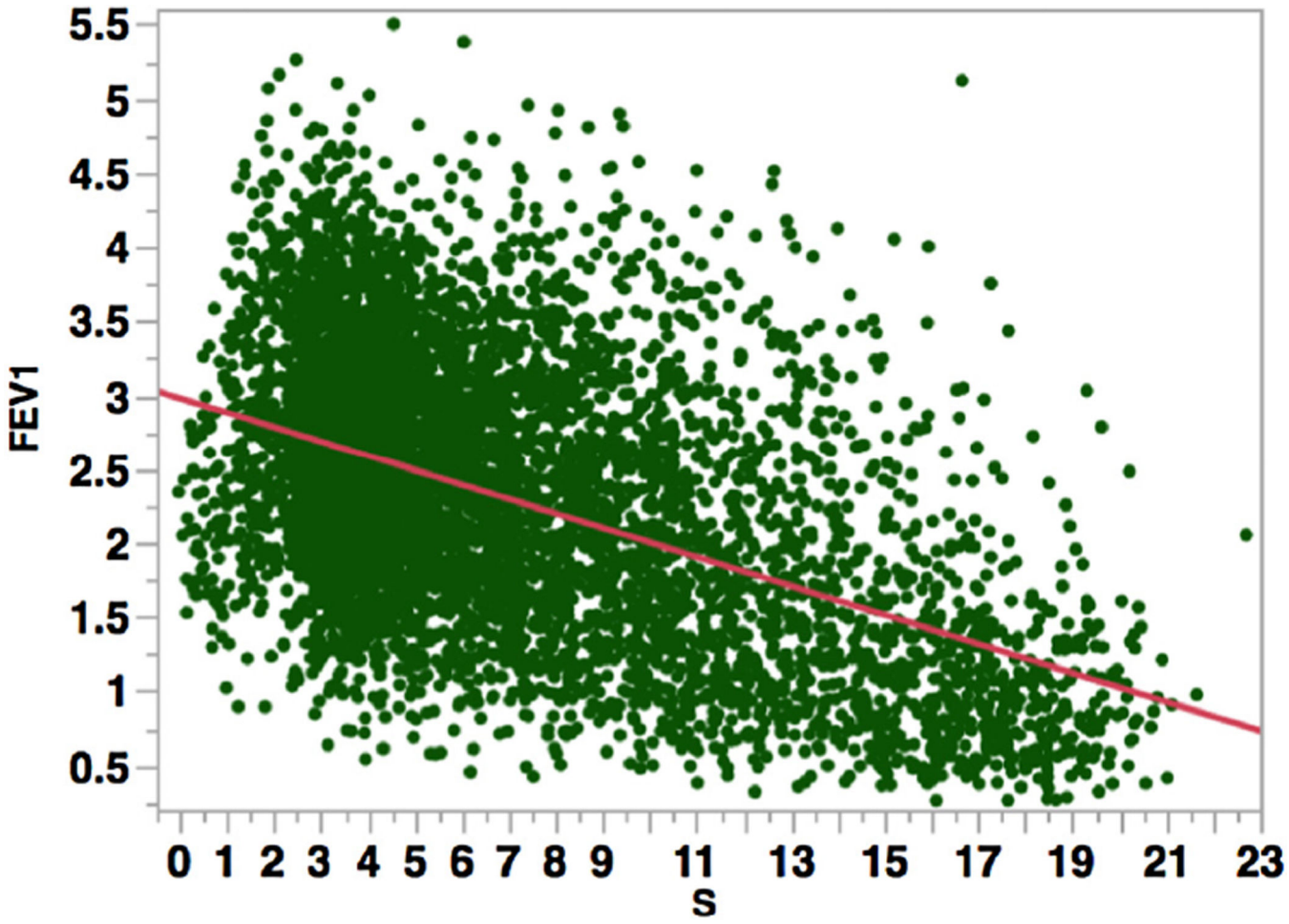

Figure 6.
Distribution of forced expiratory volume in 1 second (FEV_1) and S for the testing data. (Color version of figure is available online.)

TABLE 1

Distribution of *S* and *LAA*% Across GOLD Stages

	Nonsmoking Normal Subjects		Reduced FEV_1 and FVC		GOLD 0		GOLD 1		GOLD 2		GOLD 3		GOLD 4	
Variable	**Train**	**Test**	**Train**	**Test**	**Train**	**Test**	**Train**	**Test**	**Train**	**Test**	**Train**	**Test**	**Train**	**Test**
	n = 0	n = 102	n = 213	n = 804	n = 931	n = 2788	n = 203	n = 505	n = 491	n = 1171	n = 315	n = 660	n = 172	n = 292
Men/Women	—	33/69	103/110	359/445	449/482	1487/1301	105/98	259/246	184/307	537/634	72/243	198/462	16/156	34/258
Age at enrollment	—	60.7 ± 10.3	60.7 ± 8.9	60.1 ± 9.2	58.9 ± 9.1	59.5 ± 9.2	59.4 ± 9.2	58.9 ± 8.7	59.6 ± 8.8	59.7 ± 9.2	60.7 ± 9.0	60.5 ± 9.0	61.2 ± 8.7	61.2 ± 9.1
BMI (kg/m^2)	—	28.4 ± 5.1	31.2 ± 7.3	31.5 ± 7.1	28.5 ± 5.8	29.0 ± 5.7	26.7 ± 4.9	27.0 ± 4.8	28.9 ± 6.0	28.7 ± 6.1	27J ± 6.2	28.1 ± 6.3	25.2 ± 5.5	24.9 ± 5.5
Current smoker	—	0/102	114/99	519/285	489/442	1666/1122	119/84	315/190	296/195	739/432	244/71	499/161	154/18	263/29
Total lung capacity	—	5.4 ± 1.2	4.6 ± 1.1	4.5 ± 1.1	5.4 ± 1.3	5.4 ± 1.3	6.2 ± 1.5	6.1 ± 1.4	5.7 ± 1.4	5.8 ± 1.4	6.1 ± 1.4	6.3 ± 1.5	6.6 ± 1.4	7.0 ± 1.5
LAA%	—	1.9 ± 2.5	1.7 ± 1.9	1.4 ± 2.4	2.6 ± 2.9	1.8 ± 2.4	6.7 ± 6.3	4.7 ± 5.3	8.4 ± 7.9	6.6 ± 7.5	18.0 ± 12.7	15.2 ± 12.2	27.7 ± 13.7	26.4 ± 14.2
*FEV*1pp	—	103.0 ± 13.7	70.6 ± 8.0	70.7 ± 7.9	98.0 ± 11.8	97.5 ± 11.4	91.4 ± 9.3	90.6 ± 8.9	64.9 ± 8.6	65.3 ± 8.4	40.0 ± 5.7	40.4 ± 5.7	22A ± 4.8	23.0 ± 4.6
ATS pack-years	—	39.5 ± 21.0	48.4 ± 28.1	43.7 ± 24.9	43.1 ± 24.4	44.0 ± 25.1	44.8 ± 24.2	44.7 ± 24.8	43.5 ± 23.0	46.2 ± 26.6	43.8 ± 24.9	45.4 ± 25.9	46.4 ± 26.5	45.3 ± 27.2

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; *LAA*%, percent low attenuation areas.

TABLE 2

Statistics for *S* and *LAA*% Across GOLD Stages

Statistic	Emphysema Measure	Nonsmoking Normal Subjects	Reduced FEV_1 and FVC	GOLD 0	GOLD 1	GOLD 2	GOLD 3	GOLD 4
Mean	*S*	4.38	5.30	4.92	6.55	8.36	11.87	14.76
	LAA%	1.92	1.36	1.81	4.74	6.55	15.16	26.36
Minimum	*S*	0.61	0.15	−0.02	1.04	0.50	0.29	1.81
	LAA%	0.02	0.00	0.00	0.02	0.02	0.02	0.13
Maximum	*S*	14.96	19.63	17.27	22.70	20.41	21.65	21.13
	LAA%	13.24	33.80	25.88	42.95	41.44	53.50	61.91
Coefficient of variation	*S*	65.16	54.84	55.89	55.14	51.80	39.32	27.26
	LAA%	129.63	177.92	131.96	112.51	114.81	80.31	53.80

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; *LAA*%, percent low attenuation areas.

TABLE 3

Univariate Regression Models for each of the Outcomes. Either *S* or *LAA*% Is Used in each Model

Outcome	Variable in Model	Adjusted R-Squared	Coeff. of Variation	Parameter Estimate	Standard Error	Pr > |t|
FEV_1	S	0.2382	34.08072	−0.09773	0.00222	<0.0001
	LAA%	0.2215	34.45309	−0.04721	0.00112	<0.0001
Six-minute walk	S	0.1004	26.24787	−8.19542	0.31094	<0.0001
	LAA%	0.0674	26.72477	−3.36491	0.15859	<0.0001
SGRQ	S	0.1138	80.33368	1.69611	0.05997	<0.0001
	LAA%	0.0993	80.99069	0.79356	0.03029	<0.0001

FEV_1, forced expiratory volume in 1 second; *LAA*%, percent low attenuation areas; SGRQ, St. George's Respiratory Questionnaire.

TABLE 4

Multivariate Regression Models for each of the Outcomes Controlling for Covariates

Outcome	Adjusted R-Squared	Coeff. of Variation	Variable	Parameter Estimate	Standard Error	Pr > |t|
FEV_1	0.5868	25.09844	S	−0.04202	0.0029	<0.0001
			LAA%	−0.02687	0.0014	<0.0001
Six-minute walk	0.3259	22.72081	S	−1.75754	0.5125	0.0006
			LAA%	−1.09679	0.2639	<0.0001
SGRQ	0.3491	68.85068	S	0.44639	0.09786	<0.0001
			LAA%	0.2555	0.05039	<0.0001

FEV_1, forced expiratory volume in 1 second; LAA%, percent low attenuation areas; SGRQ, St. George's Respiratory Questionnaire.