Automatic Emphysema Detection using Weakly Labeled HRCT Lung Images

Isabel Pino Peña
Department of Health Science and Technology, Aalborg University, Aalborg 9220, Denmark

Veronika Cheplygina
Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven 5600, The Netherlands
Biomedical Imaging Group Rotterdam, Erasmus Medical Center, Rotterdam 3015, The Netherlands

Sofia Paschaloudi
Department of Diagnostic Imaging, Vendsyssel Hospital, Fredrikshavn 9900, Denmark

Morten Vuust
Department of Diagnostic Imaging, Vendsyssel Hospital, Fredrikshavn 9900, Denmark

Jesper Carl
Department of Clinical Medicine, Aalborg University Hospital, Aalborg 9000, Denmark

Ulla Møller Weinreich
Department of Clinical Medicine, Aalborg University Hospital, Aalborg 9000, Denmark
Department of Pulmonary Medicine, Aalborg University Hospital, Aalborg 9000, Denmark

Lasse Riis Østergaard
Department of Health Science and Technology, Aalborg University, Aalborg 9220, Denmark

Marleen de Bruijne
Biomedical Imaging Group Rotterdam, Erasmus Medical Center, Rotterdam 3015, The Netherlands
Department of Computer Science, University of Copenhagen, Copenhagen 1165, Denmark

Purpose: A method for automatically quantifying emphysema regions using High-Resolution Computed Tomography (HRCT) scans of patients with chronic obstructive pulmonary disease (COPD) that does not require manually annotated scans for training is presented.

Methods: HRCT scans of controls and of COPD patients with diverse disease severity are acquired at two different centers. Textural features from co-occurrence matrices and Gaussian filter banks are used to characterize the lung parenchyma in the scans. Two robust versions of multiple instance learning (MIL) classifiers that can handle with weakly labeled data, miSVM and MILES, are investigated. Weak labels gives information relative to the emphysema without indicate
specifically the location of the lesions. The classifiers are trained with the weak labels extracted from the forced expiratory volume in one minute (FEV₁) and diffusing capacity of the lungs for carbon monoxide (DLCO). At test time, the classifiers output a patient label indicating overall COPD diagnosis and local labels indicating the presence of emphysema. The classifier performance is compared with manual annotations made by two radiologists, a classical density based method, and pulmonary function tests (PFTs).

Results: The miSVM classifier performed better than MILES on both patient and emphysema classification. The classifier has a stronger correlation with PFT than the density based method, the percentage of emphysema in the intersection of annotations from both radiologists, and the percentage of emphysema annotated by one of the radiologists. The correlation between the classifier and the PFT is only outperformed by the second radiologist.

Conclusions: The presented method uses MIL classifiers to automatically identify emphysema regions in HRCT scans. Furthermore, this approach has been demonstrated to correlate better with DLCO than a classical density based method or a radiologist, which is known to be affected in emphysema. Therefore, it is relevant to facilitate assessment of emphysema and to reduce inter-observer variability.

Keywords: COPD, multiple instance learning, weakly-supervised learning, texture analysis, chest HRCT.

I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the most important respiratory disease worldwide and one of the most important causes of death in high and middle-income countries[1,2]. COPD is described as a progressive and irreversible airflow limitation. Emphysema is one of the most common disease manifestations that causes this limitation due to the destruction of alveolar walls and loss of elasticity[3]. Emphysema can be identified visually in computed tomography (CT) scans as low attenuation areas (LAA). However, to enable the detection of lesions smaller than 5 mm, thin slice reconstructions, such as high-resolution computed tomography (HRCT) scans, are preferred.

The automatic identification and quantification of emphysema provides objectivity and more reliability to the clinical routine in the assessment of COPD. Currently, emphysema is assessed visually, which is time consuming, subjective and suffers from inter- and intra-observer variability[4]. Over the years, the most used methods for automatically quantifying emphysema have been density based[5–7]. These methods use a threshold based on percentile density or LAA, generally lower than -950 Hounsfield units (HU). However, these methods are very dependent on, among others, the inspiration level, scanner reconstruction kernel, exposure dose and scanners. Therefore, there is no consensus on the best threshold for quantifying emphysema[8,9]. Other quantification methods have been reported based on texture features, which collect information about the spatial relationship of the intensity values in the scan[10–12]. Machine learning methods based on texture
analysis extract information to learn normal and abnormal lung tissues, which facilitates the recognition of disease patterns and can therefore lead to a more reliable diagnosis\textsuperscript{13}. In general, machine learning methods use supervised classifiers that require annotated regions of interest (ROIs) or labeled patches based on manual annotations of emphysema performed by clinical experts\textsuperscript{13,14}. Manual annotations are even more time consuming than visual assessment of emphysema and also suffer from inter-observer variation\textsuperscript{15}.

Learning from weak labels, which assign a label to the entire image, is proposed in the literature as the less time-consuming alternative to the manual annotation of patches, and it is being increasingly used in different medical image analysis applications\textsuperscript{16,17}. Weak labels are easier to acquire than manual annotations because they can be obtained from basic quantification methods or complimentary data of the patient, such as pulmonary function tests (PFTs) or bio-markers. Classifiers which learn from weak labels are referred to as multiple instance learning (MIL) classifiers. All MIL classifiers can learn to label entire scans. For example, Sørensen et al.\textsuperscript{22} and Cheplygina et al.\textsuperscript{19} used spirometry results, which is the most common PFT to clinically assess COPD, to assign labels to scans from the Danish Lung Cancer Screening Trial, and trained different types of MIL classifiers to detect COPD in previously unseen scans from the same trial. However, a subset of MIL classifiers can also learn to classify individual patches, thus identifying regions with signs of COPD, including emphysema. Neither\textsuperscript{22} nor\textsuperscript{19} evaluated MIL classifiers for this purpose. For example, more than half of the classifiers studied in\textsuperscript{19} including the best performing classifier, could not provide individual patch labels.

In contrast with previous studies, this study aims to automatically identify emphysema regions in patients with COPD using HRCT scans without local annotations. Different texture-based methods and MIL classifiers are investigated. Furthermore, in this study, more robust versions of two MIL classifiers are proposed. The results from the classifiers are evaluated with manual annotations made by two radiologists.

II. MATERIALS AND METHODS

This study focuses on automatically distinguishing emphysema without using manual annotations to train the classifiers. For this purpose, different types of texture features are extracted to characterize emphysema, and two variations of MIL classifiers are investigated. Fig. 1 presents an overview of the method used.

II.A. Features

Two different types of texture features are computed: features from co-occurrence matrices and Gaussian derivative features. The co-occurrence matrix algorithm is used in 3D, and it aims to capture the spatial dependence of gray-level intensities through multiple slices. The co-occurrence of voxel pairs is evaluated in 13 directions and at five different distances. After obtaining the co-occurrence matrices, the spatial dependencies of gray-level values are described by 12 Haralick textural features: energy, entropy, correlation, contrast, homogeneity, variance, sum mean, inverse difference moment, inertia, cluster shade, cluster tendency and max probability\textsuperscript{23}.

Gaussian derivative features aim to capture the presence of structures such as edges and blobs. Each image is first convolved (using normalized convolution) with a Gaussian function: \( G(\mathbf{v}, \sigma) = \frac{1}{((2\pi)^{3/2}\sigma^3)^2} \exp \left(-\frac{||\mathbf{v}||^2}{2\sigma^2}\right) \), where \( \sigma \) represents the standard deviation of the Gaussian, or the scale at which the texture is examined, and \( \mathbf{v} = [x, y, z]^T \) is a voxel. Similar to\textsuperscript{22} eight filters are computed: smoothed image, gradient magnitude, Laplacian of Gaussian, three eigenvalues of the Hessian, Gaussian curvature, and
Fig. 1 Summary of the methodology. Texture features are extracted from the lung parenchyma. Two different MIL classifiers are trained and are tested on previously unseen scans. The results are evaluated against manual annotations performed by two radiologists, a density based analysis, and pulmonary function tests.

II. METHODS

II.A. Data Preprocessing

Eigen magnitude. The filters are computed at four different scales: 0.6mm, 1.2mm, 2.4mm, and 4.8mm. The filtered outputs are summarized using histograms with ten bins, where the bin sizes are determined by adaptive binning on an independent dataset prior to this study.

II.B. Classifiers

MIL is originally a binary classification problem, although multi-class extensions also exist. MIL classifiers are trained on labeled bags \( \{(B_i, y_i)\}_{i = 1,...,N} \), where \( i \) indicates the \( i \)-th out of total \( N \) subjects, and \( y_i \) is the label (\( y_i = +1 \) for COPD, or \( y_i = -1 \) for non-COPD) of the \( i \)-th subject. The bags are also referred to as positive or negative. Each bag \( B_i = \{x_{ij}\}_{j = 1,...,n_i} \subset \mathbb{R}^d \), is a set of \( n_i \) texture feature vectors or instances, where \( x_{ij} \) describes the \( j \)-th patch of the \( i \)-th subject.

In this study, the bags represent the entire scan of an individual subject, whereas the instances are randomly selected 3D patches from inside the lungs. The bags are related to the weak labels extracted from the pulmonary function tests, and the instance labels classify the lung parenchyma into emphysematous or healthy lung tissue. Typically, MIL classifiers assume that there are instance labels \( y_{ij} \) that relate to the bag labels as follows: a bag is positive if and only if it contains at least one positive or concept instance: \( y_i = \max_j y_{ij} \). Thus, a bag is classified as positive if at least one instance contains emphysematous tissue. In this study a less strict assumption is used, as described in Section II.C.

There are two main strategies that MIL classifiers follow. The instance-level strategy is to use the bag labels to infer an
instance classifier. To classify a previously unseen test bag, such classifiers classify its instances and then combine the instance labels into a bag label. The bag-level strategy is to represent the bags by some global characteristics and use supervised classifiers to classify the bags directly. Inferring the instance labels from the bag labels is not always possible in this case. In this study, the posterior probability that a classifier outputs for a bag is denoted as $f(B_i)$ and the posterior probability that a classifier outputs for an instance as $f(x_{ij})$.

Two popular and effective MIL classifiers are miSVM\textsuperscript{27} and MILES\textsuperscript{28}. The instance-level miSVM classifier extends the traditional support vector machine (SVM) by searching for an instance classifier that separates the instances as well as possible but such that the $\max_j \{y_{ij}\} = y_i$ condition still holds. In other words, the most positive (according to the classifier) instance in each bag is positive if the bag is positive and negative if the bag is negative. Similar to a supervised SVM, the miSVM can operate on polynomial or radial basis kernels between instances. A regularization parameter $C$ controls the trade-off between the margin, i.e., how well the instances are separated, and how many training bags are incorrectly classified with this margin. For a test bag, its instances are classified, and the most positive instance determines the label of the bag.

MILES is a bag-level approach that is able to infer instance labels. It assumes that positive and negative bags contain discriminative prototype instances. It represents each bag by a feature vector $s_i$ that contains its similarities to all instances in the training set, where the similarity is defined as $s(B_i, x) = \max_j k(x_{ij}, x)$, in which $k$ is a similarity function between instances, i.e., a polynomial or radial basis kernel. The maximum operator implies that the bag’s similarity to an instance is high if it contains a single similar instance. The MILES classifier then selects discriminative similarities, which correspond to discriminative prototype instances. A regularization parameter $C$ controls the trade-off between how many bags are incorrectly classified and how many discriminative prototypes are selected. For a test bag, the similarity to the discriminative prototypes determine whether the bag is positive (if it has instances sufficiently similar prototypes from positive bags).

II.C. Avoiding false positives

Because a single positive instance is sufficient to classify whether a bag is positive, miSVM and MILES may suffer from false positives. In this study, more robust formulations of miSVM and MILES are proposed, which use the quantile rather than the maximum operator to define the label of the bag. In the adapted version of the proposed miSVM, which is referred to in this study as miSVM-Q, the $\max_j \{y_{ij}\} = y_i$ is replaced by $\text{quantile}_j(\{y_{ij}\}, q) = y_i$, where $q$ is the desired quantile. For example, if $q = 0.5$, half of the instances must be positive for a bag to be positive.

In the adapted version of MILES proposed in this study, which is referred to as MILES-Q, the similarity function $s(B_i, x) = \text{quantile}_j(\{k(x_{ij}, x)\}, q)$ is adapted. This means that the bag must contain more similar instances to the prototype $x$ to be considered similar to it. For both miSVM-Q and MILES-Q, these adaptations mean that healthy subjects can still be considered healthy if they have a few emphysematous patches.

Furthermore, this study proposes an additional measure to evaluate a MIL classifier $f$, which is called Separability or $S$:

\[
S = \frac{1}{\sum_{y_i=+1} n_i} \sum_{y_i=+1} f(x_{ij}) - \frac{1}{\sum_{y_i=-1} n_i} \sum_{y_i=-1} f(x_{ij}).
\]
In other words, the Separability looks at the difference between the average posterior probabilities of instances in true positive training bags, and the average posterior probabilities of instances in true negative training bags. The intuition behind this is that true positive bags should have a larger proportion of positive instances, and therefore the average instance posterior probability should be higher than in negative bags. This allows reasoning about the classifier’s performance on instance-level, without having access to instance labels.

III. EXPERIMENTAL

III.A. Data

Two datasets are used in this study. Both datasets are named after the hospital where the HRCT scans were performed: Frederikshavn (Fre) and Aalborg (Aal). For both datasets, HRCT scans and pulmonary function tests (PFTs) are performed. The PFTs are spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO) and are acquired for each patient. Clinically a subject is defined as healthy if it has a DLCO value higher than 80% of the predicted value. PFTs and HRCT scans are performed with the patients in a steady state, i.e., no exacerbation within six weeks prior to the test, and HRCT scans are acquired with the patients in the supine position and with breath held. No contrast agents are used. Table I presents the details for the acquisition of scans.

Table II presents the clinical characteristics of both datasets. The Fre dataset contains COPD subjects and non-COPD subjects. The non-COPD subjects are referred from the out-patient clinic to have a HRCT scan due to different respiratory problems. Aal contains only subjects with COPD.

III.B. Experimental Setup

Two sets of experiments are performed, which differ in the ways that the positive and negative bags are defined. There are two ways to define the bag labels: by thresholding the COPD stratification (A-D = positive, otherwise = negative), and by thresholding the DLCO predicted value (<60% = low (positive), >60% = high (negative)). The value of 60% is chosen due to the small sample population of non-COPD subjects. Thus, patients with mild COPD are included in the high DLCO class.

To train and evaluate the classifiers, 50 patches with a size of $41 \times 41 \times 41$ pixels are randomly extracted from each HRCT scan. Previous studies have demonstrated that 50 patches is sufficient to classify an entire scan. The patches are selected inside the lung parenchyma using the lung masks.

In each patch, textural features extracted from co-occurrence matrices and Gaussian filter banks are computed. A total of 780 features are computed from co-occurrence matrices, and 320 features are obtained from Gaussian filter banks. High-dimensional feature representations are chosen because previous studies with MIL classifiers and similar feature representations showed good results in terms of bag-level performance. Furthermore, feature selection could increase the complexity of the classifiers and therefore the risk of overfitting on the training set.

III.B.1. Cross-validation

For each set of experiments, a 4-fold cross-validation is performed. Each fold is representative of all strata of the data. Thus, Fre and Aal datasets are combined and each fold contains non-COPD subjects, COPD subjects with high and low DLCO values, and COPD subjects with varying degrees of COPD severity.

The 4-fold cross validation uses 3 folds for
training and the fourth fold for evaluation. During training on the 3 folds, an internal 3-fold cross-validation is done to optimize the parameters. These parameters, which are selected only using the 3 folds of the training set, are then used to train a classifier on all the 3 training set folds. The classifier is evaluated on the fourth fold. This is repeated 4 times, so each of the folds is used once for evaluation.

MILES-Q and miSVM-Q classifiers are investigated, and the best parameters for each classifier are selected using the training set. The parameter ranges for both classifiers are as follows: polynomial kernel $p \in \{1, 2\}$, radial basis kernel $rbf \in \{8, 10, 12, 14, 16, 20\}$, regularization parameter $C \in \{0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1\}$, and quantile parameter $q \in \{0.25, 0.5, 0.75, 0.9, 1\}$.

### III.C. Evaluation

#### III.C.1. Classifier evaluation

During the 4-fold cross-validation, the best combination of parameters for each classifier is extracted on the three training folds. For the test results, the bag AUC is examined, as well as Separability (Eq. [1]). The bag AUC expresses the ability of the classifier to correctly classify a new HRCT scan. The Separability reflects the classifier’s ability to distinguish emphysema lesions and healthy lung tissue, without having access to such labels. Performance is considered good when the bag AUC is as high as possible and the Separability is as large as possible.

#### III.C.2. Clinical validation

In the clinical validation, the set of features and the classifier with the best performance in terms of bag AUC and Separability on the training sets are chosen for each of the test folds. The classifier is tested on 10 slices per HRCT scan. This number of slices is chosen to keep manual annotations by the radiologists feasible. The slices are spaced 25 slices apart in each HRCT scan, avoiding the slices belonging to the top and bottom parts of the lungs. In selected slices, the classifier classifies every 10th voxel in both directions in the slice, that is, inside the lung mask for that slice.

Two radiologists, expert 1 and expert 2, with 40 and ten years of experience, respectively, working with HRCT scans on a daily basis annotated all emphysema lesions in the same ten slices per scan in which the classifier is tested. The manual annotations

---

### Table I

Image acquisition details for both datasets. * Siemens SOMATON Definition Flash uses Quality reference mAs. ** GE Discovery CT750 HD uses Noise Index 40

| Dataset | Scanner            | Pixel Size (mm) | Voltage (kV) | Tube Current (mGycm) | Rotation (°) | Pitch | CTDIvol (mGycm) | Reconstruction |
|---------|-------------------|-----------------|--------------|----------------------|-------------|-------|----------------|----------------|
| Fre     | Siemens SOMATOM   | 0.58 × 0.58 × 0.6 | 120          | 72**                 | 0.5         | 1.2   | 7.96 L         | 170f very sharp |
| Aal     | GE Discovery      | 0.78 × 0.78 × 0.6 | 120          | 40**                 | 0.5         | 0.984 | 5.12 L         | B80s ultra sharp |

### Table II

Clinical characteristics of subjects belonging to both datasets. GOLD stratification reflects the classification of the COPD patients according to the \(^\text{GOLD combined risk stratification assessment}\).[^3]

| Dataset  | Gender (M/F) | Age [years] | Smoking | GOLD Stratification | FEV\(_1\) (%) | DLCO (%) |
|----------|--------------|-------------|----------|---------------------|----------------|----------|
| Fre      | 7/1          | 66 [48-77]  | 1        | A B C D             | 58 [36-91]     | 55 [32-90]|
| Aal      | 34/38        | 66 [32-83]  | 23       | 1 7 0 1 5 96 [63-137] | 74 [62-83]     | 62 [50-111]|

[^3]: GOLD combined risk stratification assessment
are performed using OsiriX imaging software (www.osirix-viewer.com) using a medical display (BARCO E-2621). The annotation process is blinded. Thus, the experts do not know the outlines of the other expert or the classification results. The amount of emphysema annotated by each expert, in percentage, is computed, as is the percentage of emphysema on which both experts agreed.

For local emphysema detection, the default threshold of $0.5$ is used to transform the posterior probabilities into emphysema or healthy category labels.

Spearman correlation analysis is performed, in which the emphysema percentages of the classifier are compared with the manual annotations, results from spirometry and DLCO, and a simple method based on the threshold of LAA. The threshold is set to $-950$ HU, which has been demonstrated to be an acceptable threshold for density based emphysema quantification. A comparison of correlations from independent samples using the Fisher $r$-to-$z$ transformation is computed to assess the significance of the differences between the results from the Spearman correlation.

IV. RESULTS

IV.A. Classifier performance

As shown in Table III, miSVM-Q has higher performance than MILES-Q on both bag AUC and Separability. For miSVM-Q, Gaussian features provide larger Separability and generally better bag classification than co-occurrence features. The combination of co-occurrence matrices and Gaussian features does not improve the results obtained with these features alone. In general, both classifiers can better distinguish obstructions given by low FEV$_1$ (ClassCOPD) than by low DLCO (ClassDLCO).

Additionally, lower-dimensional feature combinations are briefly investigated, such as orientation-invariant co-occurrence features (60 features) and using only a histogram of intensities (10 features); however, the results were worse than those obtained using the full co-occurrence or Gaussian features.

IV.B. Association with PFTs

Based on the classifier evaluation results, miSVM-Q and Gaussian features are selected for the clinical validation. The parameters of miSVM-Q for the different test folds are selected during cross-validation as before.

The default threshold of $0.5$ is chosen to convert the posterior probabilities into emphysema and healthy patch labels.

Table IV presents the percentage of emphysema detected by the different methods and their correlation with DLCO and FEV$_1$. The correlations are considered significant at the 0.05 level. Moreover, analysis using the Fisher $r$-to-$z$ transformation is computed which shows that there is not a significant difference between the correlation coefficients from the Spearman analysis.

IV.C. Association with manual annotations

The agreements of the annotations between the two radiologists and between the classifier and the radiologists are investigated. The corresponding scatter plots between the percentage of emphysema calculated by the classifiers and the average percentage of emphysema annotated by the two radiologists are shown in Fig. 2. Furthermore, Spearman correlation analysis are calculated between the percentage of emphysema computed from the manual annotations of the two experts (rho=0.756, $p=1.71 \times 10^{-14}$), and the percentage of emphysema computed from the classifiers and the average percentage of emphysema from the manual annotations (ClassDLCO: rho=0.561, $p=3.01 \times 10^{-7}$; ClassCOPD: rho=0.515, $p=4 \times 10^{-6}$). An example of the results from the classifiers, the
Table III miSVM-Q and MILES-Q results using both labels. ClassCOPD: results from classifier with COPD label; ClassDLCO: results classifier with DLCO label; S: separability; Feat: features; and Cooc: co-occurrence matrices. Results of overall bag AUC and $S \times 100$.

| Feat     | miSVM-Q | MILES-Q |
|----------|---------|---------|
|          | ClassDLCO | ClassCOPD | ClassDLCO | ClassCOPD |
|          | Bag S AUC | Bag S AUC | Bag S AUC | Bag S AUC |
| Cooc     | 74.0 4.87 100.0 45.67 | 62.7 0.55 | 93.7 4.91 |
| Gaussian | 81.6 21.67 | 100.0 61.06 | 59.8 4.0 | 80.6 27.88 |
| Cooc+Gaus| 62.4 6.78 | 97.5 33.49 | 69.1 2.20 | 89.0 7.30 |

Table IV Spearman correlation results with data from pulmonary tests. ClassCOPD: results from classifier with COPD label; ClassDLCO: results from classifier with DLCO label; Thr LAA: Threshold scan based on low attenuation areas; Agree Exp: area of agreement between the manual annotations of both experts; rho: correlation coefficient.

|          | ClassCOPD | ClassDLCO | Thr LAA | Agree Exp | Expert1 | Expert2 |
|----------|-----------|-----------|---------|-----------|---------|---------|
| DLCO val | rho -0.477 | -0.571 | -0.513 | -0.478 | -0.472 | -0.596 |
|          | p Value <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| FEV1     | rho -0.283 | -0.383 | -0.461 | -0.298 | -0.316 | -0.314 |
|          | p Value 0.016 | <0.0001 | 0.011 | 0.007 | 0.007 |

manual annotations from the experts, and the threshold using LAA is presented in Fig. 3. Although at instance level, the agreement between the classifier and the experts is not perfect, the emphysema quantification is consistent when using ClassDLCO. In contrast to ClassCOPD, ClassDLCO identifies small emphysema areas in the same patients in which the experts do not make annotations or the annotations are small, and it identifies larger emphysema areas where experts annotate large emphysema lesions.

V. DISCUSSION

In contrast with previous studies, this study uses an MIL approach to automatically identify emphysema regions in COPD patients without requiring manually annotated HRCT scans for training. Two robust versions of the MILES and miSVM classifiers are presented. Because good bag-level (patient classification) performance does not correspond to good instance-level (patch classification) performance and vice versa, both bag-level AUC and a measure of instance-level performance, called Separability, are taken into account. The best performing classifier is miSVM-Q. Other studies have shown that instance-level classifiers, such as miSVM, tend to have lower bag-level performance. In the present study, the bag-level performance of miSVM-Q is improved compared to the original miSVM by relaxing the condition that a bag should be classified as positive as soon as a single positive instance is detected.

The performance achieved at the bag-level is very high, with an AUC equal to 100% for the COPD class label. This result could be explained by the fact that half of the subjects in both datasets are in the severe and very severe stage of the GOLD stratification and, therefore, these stages are easier to identify by the classifier. In the same type of labels were used, however an AUC close to 75% was achieved. However, the dataset used was from a screening trial, and thus contained a much higher fraction of mild COPD subjects, which were difficult to classify correctly. Further, these studies did not investigate the agreement of
the classifier with manual instance-level annotations. Therefore, when making choices such as patch size, number of patches per scan, and so forth, the instance-level performance was not considered. Consequently, it would be worth investigating how the patch size and number of patches (which in this study are set to the same values as in [19, 22]) would affect the instance-level performance.

Features derived from Gaussian filters, using both classifiers and both labels, provide larger Separability than co-occurrence features or their combinations. All of these feature sets are high-dimensional compared to the size of the data. However, we observed that using lower-dimensional versions of these features reduced the performance, and high-dimensional features have been used with success in previous studies [19]. An interesting difference with respect to the relative dimensions is between the miSVM-Q and MILES-Q. Because miSVM-Q is an instance-level approach, its effective sample size is the total number of patches used, while the effective sample size of MILES is lower, i.e. the total number of subjects. This could explain why the performances of miSVM-Q are higher overall.

Spirometry has been widely used as an indicator of COPD severity due to the correlation between FEV<sub>1</sub>/FVC and airway obstruction. However, FEV<sub>1</sub> does not reflect structural changes in the lung parenchyma, and therefore, it is not a reliable indicator of emphysema lesions. In contrast, DLCO is a good indicator of the level of anatomic emphysema. In this study, a Spearman correlation analysis between the best classifier from the classifier evaluation, miSVM-Q, and the PFTs is computed. The results in the present study show, as presented in Table IV, that the classifier using both labels has a higher correlation with DLCO values than with FEV<sub>1</sub>. This result is comparable to the result in [34], where the emphysema segmentation using a texture-based approach had a better correlation with DLCO than with values from FEV<sub>1</sub>. This is explained because FEV<sub>1</sub> measures airflow obstruction; however, this is only partially reflected in emphysema lesions. The classifier that is trained on the COPD label based on FEV<sub>1</sub> values, likely detects mostly signs of emphysema and therefore, still correlates better with DLCO than with FEV<sub>1</sub>

The correlations from the classifier with the PFTs are also compared with the correlations between the PFTs and a density mask method that has been widely used to quantify emphysema lesions in CT scans. The results show that the density based method correlates moderately better with FEV<sub>1</sub> than both the classifiers and the expert evaluations, and the same behaviour can be observed in [35]. This may be explained by the inability of the density mask to discriminate between air trapping and emphysema due to the nature of their threshold [35]. However, other studies from the literature that aim to quantify emphy-
show a better correlation between FEV\textsubscript{1} with their proposed texture analysis methods than a traditional density based method.

This study uses the PFTs as the most reliable measurement to validate the results of the classifier despite manual annotations by two independent experts being available. This is due to the weak agreement between experts in the annotations of emphysema, as shown by the Spearman correlation results in section IV.C. This is in agreement with\textsuperscript{36} who showed a low inter-observer agreement in a task of quantifying emphysema in whole lungs. As shown in Fig. 2, ClassCOPD overestimates the amount of emphysema in comparison with the manual annotations. This results can be produced by the small dataset of non-COPD. However, ClassDLCO generally tends to agree with experts on the size of emphysema areas. The scatter plots show that ClassDLCO has a good agreement with the experts’ annotations in severe and very severe cases, but the agreement is fair in moderate patients and poor in mild patients. ClassDLCO overestimates the emphysema in these cases.

However, these findings in conjunction with the improved correlation with DLCO compared to manual annotations could indicate that ClassDLCO is more sensitive to early changes in the lung parenchyma and can detect emphysema even before these changes are able to be detected visually. To confirm this result, future studies should investigate the progression of emphysema in the areas where the classifier finds emphysema, but that were not assessed visually. This will also help to reduce inter-observer variability, which is a major limitation in visual assessment, as other studies have reported\textsuperscript{39,40}. Furthermore, the correlation results between the ClassDLCO and DLCO values show that quantitative assessment of emphysema with the presented method provides an important measurement of the reduction in the alveolar area. In addition, as suggested in\textsuperscript{35}, a better detection of emphysema in HRCT scans can also be used in refining the prediction of the 6 minute walking distance test.

A limitation of this study is the size and balance of the datasets. The Fre dataset is very small, and the Aal dataset does not contain any controls. Due to this unbalance, the DLCO threshold used is lowered to 60%; thus, patients diagnosed with mild COPD are included in the same class as the non-COPD patients. The texture features extracted from the non-COPD group could have a similar representation as the features extracted from COPD patients because different lung diseases could appear in CT scans as LAA as emphysema does, i.e. cystic lung disease. Therefore, it would be desirable to include scans without any pathology.

A related problem is the fact that the Fre and Aal datasets have different acquisition parameters, which can negatively affect classification performance\textsuperscript{39}. An improvement in performance will be expected if the appearance of healthy tissue could be learned from both datasets rather than only Fre. An alternative would be to use techniques such as intensity normalization or transfer learning classifiers to reduce the differences between datasets.

VI. CONCLUSION

This study presented two new versions of multiple instance classifiers which identify emphysema regions in patients suffering from COPD without requiring manual annotations. The proposed method showed a good correlation with the pulmonary function tests, particularly with DLCO, and was demonstrated to be superior in detecting emphysema than a density based method. Furthermore, it should be considered as a reliable tool to support radiologists in the assessment of emphysema to reduce the inter- and intra-observer variability.
VII. DISCLOSURE OF CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to disclose.

1C. Mathers and D. Loncar. Projections of global mortality and burden of disease from 2002 to 2030. PLOS Medicine, 3:1 – 20, 2006.
2WHO, the top 10 causes of death. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/ Accessed: June 2016.
3GOED. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. (January), 2015.
4S. B. Ginsburg, D. A. Lynch, R. P. Bowler, and J. D. Schroeder. Automated texture-based quantification of centrilobular nodularity and centrilobular emphysema in chest CT images. Academic Radiology, 10:1241 – 1251, 2012.
5S. Matsuoka, T. Yamashiro, GR. Washko, Y. Kurihara, Y. Nakajima, and H. Hatabu. Quantitative CT assessment of chronic obstructive pulmonary disease. Radiographics, 30:55 – 66, 2010.
6D. A. Lynch and J. D. Newell. Quantitative imaging of COPD. Journal of Thoracic Imaging, 3:189 – 194, 2009.
7Y. Nakano, S. Muro, H. Sakai, T. Hirai, K. Chin, M. Tsukino, K. Nishimura, H. Itoh, P. D Pare, J.C. Hogg, and M. Mishima. Computed tomographic measurements of airway dimensions and emphysema in smokers. correlation with lung function. American journal of respiratory and critical care medicine, 162:1102–8, 2000.
8K. Nishimura, K. Murata, M. Yamagishi, H. Itoh, A. Ikeda, M. Tsukino, H. Koyama, N. Sakai, M. Mishima, and T. Izumi. Comparison of different computed tomography scanning methods for quantifying emphysema. Journal of Thoracic Imaging, 13:193 – 198, 1998.
9O. M. Mets, P. A. Jong, B. Ginneken, H. A. Gietaema, and J. W. J Lamers. Quantitative computed tomography in COPD: Possibilities and limitations. Lung, 190:133 – 145, 2012.
10L. Sørensen, S. B. Shaker, and M. de Bruijne. Quantitative analysis of pulmonary emphysema using local binary patterns. IEEE Transactions on medical imaging, 29:559 – 569, 2010.
11J. Nagao, T. Aiguchi, K. Mori, Y. Suegaya, J. Toriwaki, M. Mori, and H. Natori. A cad system for quantifying COPD based on 3-D CT images. MICCAI, 2878:730 – 737, 2003.
12J. Yao, A. Dwyer, R. M. Summers, and D. J. Mollura. Computer-aided diagnosis of pulmonary infections using texture analysis and support vector machine classification. Academic Radiology, 18:396 – 314, 2011.
13U. Bagci, M. Bray, J. Caban, J. Yao, and D. J. Mollura. Computer-assisted detection of infectious lung diseases: A review. Computerized Medical Imaging and Graphics, 36:72 – 84, 2012.
14M. Prasad, A. Sowmya, and P. Wilson. Multi-level classification of emphysema in HRCT lung images. Pattern Analysis and Applications, 12:9 – 20, 2007.
15R. Uppaluri, E. A. Hoffman, M. Sonka, G. W. Hunninghake, and G. McLennan. Computer recognition of regional lung disease patterns. American Journal of Respiratory and Critical Care Medicine, pages 648 – 654, 199.
16Y. S. Park, J. B. Seo, N. Kim, E. J. Chae, Y. M. Oh, S. D. L. Lee, Y. Lee, and S. K. Kang. Texture-based quantification of pulmonary emphysema on high-resolution computed tomography: Comparison with density-based quantification and correlation with pulmonary function test. Investigative radiology, 43:395 – 402, 2008.
17N. Kim, J.B. Seo, Y. Lee, J. G. Lee, S. S. Kim, and S.H. Kang. Development of an automatic classification system for differentiation of obstructive lung disease using HRCT. Journal of Digital Imaging, 2:136 – 148, 2009.
18F. Chabat, G.Z. Yang, and D. M. Hansell. Obstructive lung diseases: Texture classification for differentiation at CT. Radiology, 228:871 – 877, 2003.
19V. Cheplygina, L. Sørensen, D.M.J. Tax, J.H. Pedersen, M. Loog, and M. de Bruijne. Classification of COPD with multiple instance learning. Proceedings International Conference on Pattern Recognition, pages 1508 – 1513, 2014.
20Jaime Melendrez, Bram van Ginneken, Pragnya Maduskar, Rick HHM Philipsen, Klaus Reither, Marianne Breuninger, Iedeyo MO Ade-tifa, Rahmatulai Maane, Helen Ayles, and Clara I Sánchez. A novel multiple-instance learning-based approach to computer-aided detection of tuberculosis on chest x-rays. IEEE Transactions on Medical Imaging, 34(1):179–192, 2015.
21Melih Kendemir and Fred A Hamprecht. Computer-aided diagnosis from weak supervision: A benchmarking study. Computerized Medical Imaging and Graphics, 42:44–50, 2015.
22L. Sørensen, M. Nielsen, Pechin Lo, H. Ashraf, J.H. Pedersen, and M. de Bruijne. Texture-based analysis of COPD: A data-driven approach. Medical Imaging, IEEE Transactions on, 31(1):70–78, 2012.
23F. Albrechtsen. Statistical texture measures computed from gray level cooccurrence matrices, 2008.
24T. Ojala, M. Pietikäinen, and D. Harwood. A comparative study of texture measures with classification based on featured distributions. Pattern recognition, 29(1):51–59, 1996.
25Z. H. Zhou and M. L. Zhang. Multi-instance multi-label learning with application to scene classification. In Advances in Neural Information Processing Systems, pages 1609–1616, 2006.
26 J. Amores. Multiple instance classification: Review, taxonomy and comparative study. *Artificial Intelligence*, 201:81–105, 2013.

27 S. Andrews, I. Tsochantaridis, and T. Hofmann. Support vector machines for multiple-instance learning. In *Advances in Neural Information Processing Systems*, pages 561–568, 2002.

28 Y. Chen, J. Bi, and J.Z. Wang. Miles: Multiple-instance learning via embedded instance selection. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 28(12):1931–1947, 2006.

29 L. Sørensen, L. Pechin, H. Ashraf, J. Sporring, M. Nielsen, and M. Bruijne. Learning COPD sensitive filters in pulmonary CT. *Lecture Notes in Computer Science*, 5762:699 – 706, 2009.

30 Z. Wang, S. Gu, J. K. Leader, S. Kundu, J.S. Tredow, F. C. Sciruba, D. Gur, J. M. Siegfried, and J. Pu. Optimal threshold in CT quantification of emphysema. *European Radiology*, pages 975 – 984, 2013.

31 V. Cheplygina, L. Sørensen, D. M. J. Tax, M. de Bruijne, and M. Loog. Label stability in multiple instance learning. In *Medical Image Computing and Computer-Assisted Interventions*. Springer, 2015.

32 V. Tragante do O, D. Fierens, and H. Blockeel. Instance-level accuracy versus bag-level accuracy in multi-instance learning. In *Benelux Conference on Artificial Intelligence*, 2011.

33 G. Vanwinckelen, V. Tragante do O, D. Fierens, and H. Blockeel. Instance-level accuracy versus bag-level accuracy in multi-instance learning. In *Benelux Conference on Artificial Intelligence*, 2011.

34 J. Tan, B. Zheng, X. Wang, D. Lederman, J. Pu, F. C. Sciruba, D. Gur, and J. K. Leader. Emphysema quantification in a multi-scanner HRCT cohort using local intensity distributions. In *Medical Imaging 2011: Biomedical Applications in Molecular, Structural, and Functional Imaging*, pages 1–7. SPIE, 2011.

35 N.F. Voelkel and W. MacNee. *Chronic Obstructive Lung Disease*. PMPH USA, Ltd., 2008.

36 M. Mascalchi, S. Diciotti, N. Sverzellati, G. Camiciottoli, C. Ciccotosto, F. Falschi, and M. Zompatori. Low agreement of visual rating for detailed quantification of pulmonary emphysema in whole-lung CT. *Acta Radiologica*, 53:53 – 60, 2012.

37 R. G. Barr, E. Berkowitz, F. Bigozzi, F. Bode, J. Bon, R. P. Bowler, C. Chiles, J. D. Crapo, G. J. Criner, J. L. Curtis, C. Dass, A. Dirksen, M. T. Dransfield, G. Edu, A. Erikkson, L. Friedlander, M. Galperin-Aizenberg, W. B. Geftner, D. S. Gierer, P. Grenier, J. Goldin, M. K. Han, N. Hanania, N. N. Hansel, F. L. Jacobson, H. Kauczor, V. L. Kinmula, D. Lipson, D. Lynch, W. MacNee, B. J. Make, J. Mamary, H. Mann, N. Marchetti, M. Mascalchi, G. McLennan, J. R. Murphy, D. Naidich, H. Nath, J. D. Newell, M. Pistoiesi, E. Regan, J. J. Reilly, R. Sandhaus, J. D. Schroeder, F. Sciruba, S. Shaker, A. Sharaakalleng, E. K. Silverman, R. M. Steiner, C. Strange, N. Sverzellati, J. H. Tashjian, E. J. R. van Beek, L. Washington, G. R. Washko, G. Westney, S. Wood, and P. G. Woodruff. A combined pulmonary-radiology workshop for visual evaluation of COPD: study design, chest CT findings and concordance with quantitative evaluation. *COPD*, 9:151 – 159, 2012.

38 A. A. Diaz, V. Pinto-Plata, C. Hernandez, J. Pea, C. Ramos, J. C. Diaz, J. Klaassen, C. M. Patino, F. Saldias, and O. Diaz. Emphysema and dico predict a clinically important difference for 6MWD decline in COPD. *Respiratory Medicine*, 109:882 – 889, 2015.

39 Marleen de Bruijne. Machine learning approaches in medical image analysis: from detection to diagnosis. *Medical Image Analysis, in press*, 2016.
Fig. 3 Example of results in randomly selected slices for the density based method, manual annotations from the experts, and classifier results using miSVM-Q and Gaussian features. From left to right: patients with mild, moderate, severe and very severe COPD.