Lobar Lung Density Embeddings with a Transformer encoder (LobTe) to predict emphysema progression in COPD

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Abstract. Emphysema is defined as an abnormal alveolar wall destruction exhibits varied extent and distribution within the lung, leading to heterogeneous spatial emphysema distribution. The progression of emphysema leads to decreased gas exchange, resulting in clinical worsening, and has been associated with higher mortality. Despite the ability to diagnose emphysema on CT scans there are no methods to predict its evolution. Our study aims to propose and validate a novel prognostic lobe-based transformer (LobTe) model capable of capturing the complexity and spatial variability of emphysema progression. This model predicts the evolution of emphysema based on %LAA-950 measurements, thereby enhancing our understanding of Chronic Obstructive Pulmonary Disease (COPD). LobTe is specifically tailored to address the spatial heterogeneity in lung destruction via a transformer encoder using lobe embedding fingerprints to maintain global attention according to lobes' positions. We trained and tested our model using data from 4,612 smokers, both with and without COPD, across all GOLD stages, who had complete baseline and 5-year follow-up data. Our findings from 1,830 COPDGene participants used for testing demonstrate the model's effectiveness in predicting lung density evolution based on %LAA-950, achieving a Root Mean Squared Error (RMSE) of 2.957%, a correlation coefficient (ρ) of 0.643 and a coefficient of determination (R^2) of 0.36. The model's capability to predict changes in lung density over five years from baseline CT scans highlights its potential in the early identification of patients at risk of emphysema progression. Our results suggest that image embeddings derived from baseline CT scans effectively forecast emphysema progression by quantifying lung tissue loss.

Keywords: Emphysema Progression · COPD · Transformers · ViT · Deep Learning.

1 Introduction

Emphysema, characterized by the abnormal destruction of alveolar walls, exhibits varied extents and distributions within the lung, leading to a heteroge-

neous spatial distribution of the condition [9,2,15]. This progression results in diminished gas exchange, clinical deterioration, and is associated with increased mortality. Affecting over two million people in the US, this destructive lung tissue process is a fundamental pathobiological aspect of chronic obstructive pulmonary disease (COPD), a leading cause of death worldwide [16,1]. While often linked to chronic tobacco smoke exposure, emphysema is also increasingly identified in non-smokers without clear risk factors. Furthermore, numerous studies have highlighted that individuals with emphysema face a heightened risk of death, even when considering broader population samples [10,6,8,14].

CT scans can objectify the evolution of lung density through the percentage of low-attenuation area below -950 Hounsfield Units (%LAA-950), providing a quantifiable measure of COPD and emphysema changes [7]. Despite the capacity to diagnose emphysema using simple threshold-based techniques [3] or advanced machine learning strategies, methods to predict its progression remain undeveloped. Our objective is to introduce a new transformer-based methodology capable of articulating the complexity of emphysema progression by forecasting lung density changes according to %LAA-950, thus enhancing our comprehension of COPD.

Convolutional Neural Networks (CNNs) and self-attention mechanisms [5,12] have significantly advanced COPD research through their ability to derive complex data-driven representations. For instance, a vanilla Vision Transformer (ViT) [5] was utilized to classify emphysema subtypes in CT images [18], while a ViT methodology identified COPD subjects by FEV1/FVC < 0.7 [13]. Moreover, a multimodal approach employing a cross-modal transformer was suggested to distinguish COPD stages according to the Global Initiative for Obstructive Lung Disease (GOLD) [19]. Building on our prior research on COPD [4], this study introduces and validates a novel prognostic transformer-based model, LobTe, for identifying COPD subjects at risk of emphysema progression by predicting the change in %LAA-950 over five years.

This work introduces three innovative aspects: (I) training includes learning the evolution of local emphysema progression and lung density without utilizing follow-up chest CT scans for inference; (II) a lobe embedding fingerprint is proposed to encapsulate the local disease evolution into five distinct prognostic lobe signatures; and (III) the introduction and validation of LobTe, a new prognostic transformer-based model designed to regress the evolution of emphysema based on %LAA-950 measurements (Δ%LAA-950). Our approach employs a transformer encoder on the lobe fingerprints to leverage a global self-attention mechanism to provide a prediction based on lobar tissue destruction.

2 Materials and Methods

A total of 4,612 smokers without and with COPD (across all severity stages) and with complete data at baseline and 5-year, including CT scans and accurate lobe segmentations, were selected from the COPDGene (Genetic epidemiology of

COPD) study [11]. This cohort was divided into training (n=2,782) and testing (n=1,830) groups to evaluate the proposed method.

Local Emphysema Progression (LEP) Definition and Ground Truth Generation: The method proposed was designed to locally learn the evolution of the lung density and local emphysema progression (LEP) according to the percentage of low-attenuation area (%LAA-950). We defined LEP as those pixels that change from lung tissue at baseline CT scan to air at 5-years follow-up after co-registration of the CT scans, i.e. the pixel density decays from a value of $>$ -950 HU at baseline to a value of $\leq$ -950 HU at 5-year follow-up co-registered CT scan. Figure 1 illustrates the LEP definition, with a region showing pixels transitioning from lung tissue (a) to air (b) highlighted in red, and a region without LEP in blue.

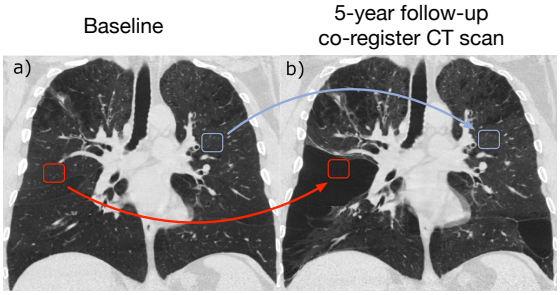

Fig. 1. Graphical definition of local emphysema progression, showcasing two 32 by 32 pixel regions over the CT scans to demonstrate areas with (red) and without (blue) LEP.

Methods

The method described in this section consists of three main components: (1) a local density model (Fig. 2 (a)) used to encode the local evolution of the lung density and emphysema progression at 5-year; (2) a lobe embedding strategy (Fig. 2(b-2)) used to summarize the local lung density embedding into five fingerprints corresponding to each lobe (left/right superior lobes, left/right inferior lobes and and right middle lobe); and (3) a transformer-based model, lobe Transformer (LobTe) (Fig. 2(b-3), designed to predict subject-specific changes in lung density at 5-year based on Δ%LAA-950.

Local Density Model: The local density model introduced in [4] incorporates a local attention mechanism via Convolutional Block Attention Modules [17]. This model, comprising a longitudinal encoder-decoder and a multilayer perceptron (MLP), is trained to both reconstruct a specific 32 by 32 pixel neighborhood at 5-year follow-up and predict the likelihood of emphysema progression. Initially,

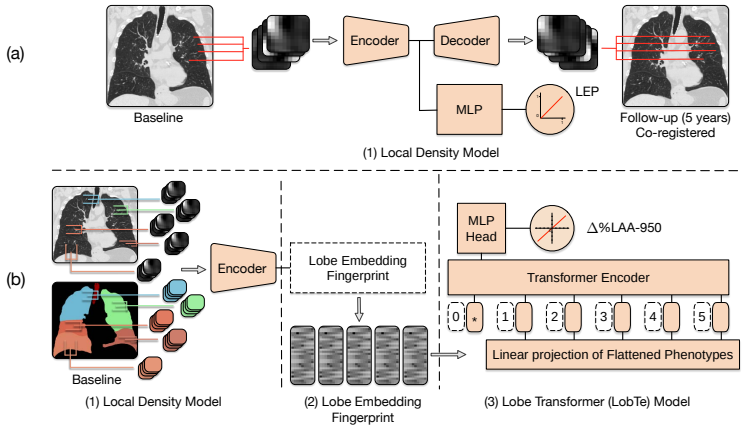

Fig. 2. (a) Local density model used to encode the local evolution of lung density and emphysema progression. (b-c) Proposed workflow to regress lung density change (Δ%LAA-950) using LSTM and Transformer.

the encoder-decoder is pre-trained separately for stability, followed by a combined training phase with the MLP under a conditional strategy that balances local reconstruction accuracy and emphysema progression encoding following this steps: (1) the MLP is fitted to regress the likelihood of the LEP using the encoded local patterns at 5-year; (2) the encoder is adjusted to maximize the likelihood of the LEP. In this stage the MLP model is frozen, no weight adjustments are made; and (3) the encoder-decoder is re-trained to keep a suitable local reconstruction.

Lobe Embedding Fingerprint: The local model encoder is applied on N local patches for each lobe extracted with stride of 4-pixels over the lobe region to derive $N \times 300$ embeddings that are aggregated into a fingerprint using the deciles of the embedding distribution resulting in a representation of 300 by 11 embedding percentiles (0%, 10%, ... 100%) per lung lobe as it can be seen in Fig.2 (b-2).

Lobe Transformer (LobTe) Model: A new lobe-based transformer (LobTe) model is proposed to regress the evolution of emphysema at 5-year according to Δ%LAA-950. The LobTe model employs a pure transformer encoder, substituting traditional ViT image patches with lobe embedding fingerprints to maintain global attention according to lobes' positions (see Fig. 2 (b-3)). This adaptation reduces the model size to under 141,700 parameters, addressing the challenge of ViT models' reliance on large datasets [5]. The transformer encoder features an 8 multi-head self-attention block layer, a 32-unit MLP with GELU non-linearity, and a 32-dimension global phenotype embedding representation. Lobe phenotypes are normalized using z-score standardization ($\mu = 0.0186$ and $\sigma = 2.868$).

Training: The local density model (Fig. 2 (a)) was trained on 6.8 million random co-registered patches extracted from the baseline and follow-up CT in 984 COPDGene participants randomly selected from the training set. The LobTe model (Fig. 2 (b-3)) was fitted with the remaining 2,226 COPDGene participants reserved for training. 1,670 were used to train the transformer and 556 subjects for internal validation and early stopping. The population reserved for training, including the validation dataset used for the early stop criteria, was randomly selected from our cohort to preserve as much as possible the GOLD distribution observed in the COPDGene cohort. The local density model was optimized as it was described in [4] while the LobTe model was optimized using a stochastic gradient descent (Adaptive Moment Estimation) with a learning schedule defined as follow:

$$\mathrm{lr} = \frac{1}{\sqrt{G}} \min\left(\frac{1}{\sqrt{i}}, i\frac{1}{\sqrt{\mathrm{w}^3}}\right),$$

where G corresponds to the dimension of the global lobe fingerprint (G=32) and i is the iteration step. The warm-up factor, w, was set to

$$\mathrm{w} = \left\lfloor \frac{N_e}{4} \right\rfloor \left\lfloor \frac{N}{\mathrm{bs}} \right\rfloor,$$

with the maximum number of epochs, N_e=1,000, the number of training samples, N=2,226, and the batch size used, bs=32.

3 Results

A total of 1,830 COPDGene participants with (n=712) and without (n=1,118) COPD from our cohort were reserved for testing our model. The model demonstrated good performance in predicting the evolution of %LAA-950, exhibiting a root mean squared error of RMSE=2.957 and slight bias (-0.24% and -0.06% for our testing dataset and COPD participants respectively) when compared to the measured values at 5-years (Fig. 3 Bland-Altman). Additionally, the model displayed good predictive capabilities for Δ%LAA-950 at 5 years with good correlation (Pearson's coefficient ρ=0.64) (Fig. 3 linear fit) and coefficient of determination of $R^2 = 0.36$. Table 1 presents model performance results stratified by disease stage defined as smokers without COPD (GOLD 0), mild disease (GOLD 1-2) and severe (GOLD 3-4).

Then, we studied the risk of emphysema progression (EP) according to distinct progression thresholds defined according to the 65th (Δ%LAA-950 $>$ 0.146%), 75th (Δ%LAA-950 $>$ 0.282%), 85th (Δ%LAA-950 $>$ 0.619%) and 95th percentiles (Δ%LAA-950 $>$ 1.835%) of the 5-year emphysema evolution of no-smokers controls (n=65). The model's performance to identify subjects at risk of EP was analyzed for each group by means of the sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), false rates (positive (FPR) and negative (FNR)), accuracy (ACC), balanced accuracy (BA), F1-score and Cohen's

	No COPD (GOLD 0)	Mild COPD (GOLD 1-2)	Severe COPD (GOLD 3-4)
RMSE	1.780	3.615	5.352
ρ	0.665	0.640	0.500
R^2	0.320	0.371	0.150

Table 1. Root mean squared error (RMSE), Pearson's correlation coefficient (ρ) and coefficient of determination (R^2) for predicting the evolution of %LAA-950 stratified by COPD severity.

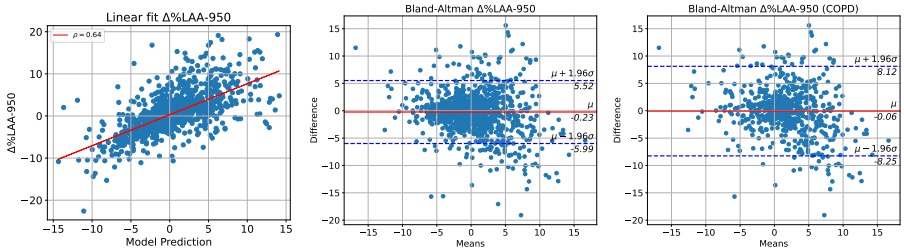

Fig. 3. Scatter plot, including a linear fit and the Pearson's correlation coefficient, and Bland-Altman plot between the model's prediction and Δ%LAA-950 measured at 5-year for the whole testing cohort (center) and testing subjects with COPD (right)

Kappa coefficient (K). Additionally, the 95% confidence interval was measured on 1000 bootstrap samples. The performance characteristics were computed for the whole testing cohort (n=1,830) and those with COPD (n=712).

The model's performance in detecting individuals at risk of EP, both in the overall testing cohort and specifically among COPD subjects, is summarized in Table 2. Across all risk groups, the model achieved good accuracy and F1 scores, particularly in COPD subjects, with mean values of ACC= 74.75%, Balanced ACC=73.41%, and F1=76.41%, alongside relatively low false rates (mean FPR=33.18% and FNR=19.99%). Cohen's Kappa coefficient indicated moderate agreement (mean K=47.38%), with the highest agreement observed in subjects with lung density decrement beyond the 75th percentile (K=50.3 and K=49.6). In contrast, groups with a density decrement lower than 0.3% (65th, and 75th percentiles) demonstrated lesser agreement (mean Kappa K=44.8%).

The entire testing population showed similar trends with good accuracy (mean ACC= 74.88%, Balanced ACC=71.47%), moderate agreement (mean K=43.33%), and low false rates (mean FPR=21.50% and FNR=35.55%), albeit with a reduced F1 score (mean F1=64%). Notably, agreement decreased by approximately 7.5% (mean K=37.35%) among subject groups with a lung tissue loss below 0.3%, predominantly comprising non-COPD participants. Subjects at mild (GOLD 1-2) and severe (GOLD 3-4) stages of COPD exhibited median (mean) Δ%LAA-950 values of 0.39% (0.87%) and 2.76% (3.4%), respectively.

Finally, we studied the distribution of LobTe predictions and Δ%LAA-950 stratified by disease severity. Statistical differences were found between the changes of %LAA-950 for these three groups, showing that the LobTe prediction could

be a useful tool to predict the evolution of Δ%LAA-950 across disease stages (Fig. 4). On the contrary, no statistical significant difference were found between Δ%LAA-950 at 5-year and the LobTe prediction with the exception of the control group (smokers GOLD 0) where a week difference was measured ($0.01 <$ p-value ≤ 0.05).

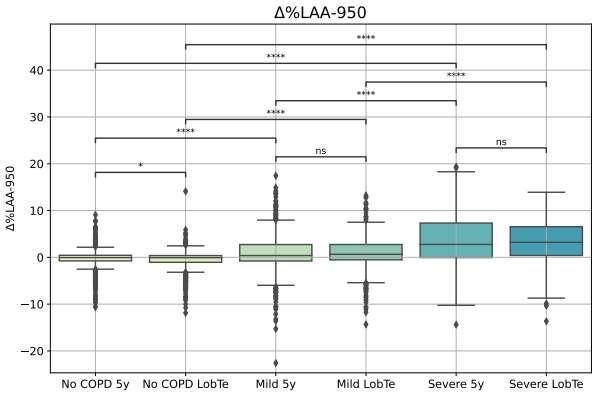

Fig. 4. Distribution of Δ%LAA-950 measured at 5-year an predicted (LobTe) stratified by disease stage defined as without COPD (GOLD 0), mild disease (GOLD 1-2) and severe (GOLD 3-4). ns: p-value ≥ 0.05 ; *: $0.01 <$ p-value ≤ 0.05; **: $0.001 <$ p-value ≤ 0.01; ***: $0.0001 <$ p-value ≤ 0.001; ****: p-value ≤ 0.000.

4 Discussion and conclusions

In this study, we have proposed and validated a novel prognostic transformer model based on local embeddings of the temporal evolution of lung density and designed to quantify the change in lung density at 5 years as measured by %LAA-950. This model's capability to accurately predict changes in lung density from baseline CT scans highlights its potential utility in the early identification of COPD patients at risk of emphysema progression.

To our knowledge, no current methodologies in the field of lung diseases, including COPD, have been able to predict changes in emphysema based on %LAA-950 or Perc15 (adjusted lung density). This unique aspect of our LobTe method sets it apart, as comparisons with existing methods are not feasible due to the novelty of our approach. Our analysis, grounded in data from a longitudinal study, lays a robust foundation for future research aimed at predicting lung density changes.

Our results indicate that the LobTe method can accurately predict the change in %LAA-950 over 5 years with a strong correlation and stability across disease severity and different values of progression. Furthermore, minimal discrepancy

Population		Δ%LAA-950			
		$> 0.146\%$	$> 0.282\%$	$> 0.619\%$	$> 1.835\%$
COPD (n=712)	Prev.	60.3 (57.2, 63.2)	58.0 (55.1, 61.1)	51.7 (48.6, 54.8)	39.7 (36.9, 42.6)
	Sens.	85.3 (82.7, 88.3)	82.1 (78.9, 85.2)	81.2 (77.9, 84.8)	71.4 (66.7, 76.0)
	Spec.	58.3 (53.3, 62.9)	61.5 (57.2, 66.1)	68.9 (64.7, 72.9)	78.6 (75.0, 81.8)
	PPV	75.6 (72.4, 78.8)	74.7 (71.4, 78.2)	73.6 (70.0, 77.1)	68.7 (64.4, 73.0)
	FPR	41.7 (37.1, 46.7)	38.5 (33.9, 42.8)	31.1 (27.1, 35.3)	21.4 (18.2, 25.0)
	FNR	14.7 (11.7, 17.3)	17.9 (14.8, 21.1)	18.8 (15.2, 22.1)	28.6 (24.0, 33.3)
	ACC	74.6 (71.9, 77.4)	73.5 (70.9, 76.3)	75.3 (72.7, 77.9)	75.7 (72.9, 78.4)
	BA	71.8 (69.0, 74.7)	71.8 (69.1, 74.7)	75.1 (72.5, 77.7)	75.0 (72.0, 77.8)
	F1	80.2 (77.8, 82.7)	78.2 (75.8, 80.8)	77.3 (74.6, 79.9)	70.0 (66.4, 73.5)
	K	45.1 (39.5, 50.9)	44.5 (39.0, 50.3)	50.3 (45.0, 55.6)	49.6 (43.7, 55.1)
All (n=1,830)	Prev.	45.0 (43.1, 46.9)	40.9 (39.0, 42.7)	32.8 (31.0, 34.7)	20.8 (19.2, 22.3)
	Sens.	69.8 (67.1, 72.3)	66.3 (63.4, 68.8)	63.8 (60.6, 67.0)	57.9 (53.7, 62.3)
	Spec.	66.6 (64.2, 69.0)	72.7 (70.5, 74.8)	82.8 (81.0, 84.7)	91.8 (90.7, 92.9)
	PPV	63.1 (60.5, 65.6)	62.7 (59.9, 65.5)	64.5 (61.2, 67.9)	65.0 (60.7, 69.3)
	FPR	33.4 (31.0, 35.8)	27.3 (25.2, 29.5)	17.2 (15.3, 19.0)	8.2 (7.1, 9.3)
	FNR	30.2 (27.7, 32.9)	33.7 (31.2, 36.6)	36.2 (33.0, 39.4)	42.1 (37.7, 46.3)
	ACC	68.0 (66.3, 69.8)	70.1 (68.3, 71.8)	76.6 (74.9, 78.3)	84.8 (83.5, 86.1)
	BA	68.2 (66.4, 69.9)	69.5 (67.7, 71.2)	73.3 (71.5, 75.2)	74.9 (72.7, 77.2)
	F1	66.2 (64.0, 68.4)	64.4 (62.1, 66.6)	64.1 (61.5, 66.8)	61.3 (57.6, 64.9)
	K	36.0 (32.5, 39.5)	38.7 (35.1, 42.0)	46.8 (43.1, 50.4)	51.8 (47.5, 55.9)

Table 2. Evaluation of the sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), false positive rate (FPR), false negative rate (FNR), accuracy (ACC), balanced accuracy (BA), F1-score and Cohen's Kappa coefficient (K) to identify subjects at risk of emphysema progression according to Δ%LAA-950. The observed value and 95% CI are expressed in percentage.

was observed between the predictions and the actual Δ%LAA-950 measurements stratified by disease severity. However, we observed a reduction in the model's performance among subjects exhibiting slight emphysema progression or no progression (Δ%LAA-950 $< 0.3\%$).

In conclusion, the LobTe method presents itself as a potentially invaluable tool for monitoring disease progression and guiding treatment strategies in COPD patients. Moreover, our study opens avenues for future research, emphasizing the need for validation in larger and more diverse cohorts and further exploration of the underlying biological mechanisms. Such efforts will not only reaffirm the significance of our findings but also advance personalized management and treatment strategies for COPD, leading to more efficient healthcare resource allocation.

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