CHEST Online Supplement

Machine Learning and Prediction of All-Cause Mortality in COPD

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CHEST 2020; 158(3):952-964

 DOI: 10.1016/j.chest.2020.02.079

e-Appendix 1.

eMethods

Study participants

Details regarding the designs of COPDGene and ECLIPSE studies have been published previously.[1,2]

Briefly, the COPDGene study enrolled 10,192 current and ex-smokers from 21 U.S. clinical centers; participants were non-Hispanic Whites or African Americans, 45 to 80 years of age. The ECLIPSE study was a 3-year longitudinal study to identify surrogate endpoints of 2746 subjects (2164 COPD cases) associated with disease progression and exacerbations in COPD. Participants were 40-75 years of age at enrollment. In both studies, all COPD subjects had 10 or more pack-years of cigarette smoking. Mortality in the ECLIPSE study has been previously described and was a pre-specified end point in the longitudinal study.[3]

In COPDGene, death was determined by searching the social security death index (SSDI) database; a central search was performed on October 14, 2016, and deaths were back-censored three months to account for lag time between death and appearance in the SSDI database. Nine sites performed local SSDI searches at varying dates, and deaths were also back-censored three months. Vital statuses of an additional 333 participants for whom an SSDI search could not be performed were determined by the COPDGene longitudinal follow-up program (LFU).

Study Design

To develop a mortality prediction model, we first applied random forests, a machine learning method that has excellent overall performance in a diverse set of datasets, which provides feature selection and feature importance,[4] and has an implementation suitable for survival analysis.[5] We also performed Cox regression, pruning features selected from the random forest model for collinearity. We employed both models because these methods can complement each other.[6] Random forest variable importance measures can be used to identify predictors of an outcome, give insight into relative variable importance, or identify a small number of features that offer good prediction of an outcome.[7] Cox regression has arguably greater interpretability and proportional hazards analyses lend insight into the clinical impact of individual features. Our primary goal was to develop a model with high predictive accuracy and generalizability.

We trained the RSF model by generating twenty thousand individual trees (each with 4 splits and 17 randomly selected features considered at each split), and ranked features by variable importance. For parsimony, the top 95% of features were then used to develop an RSF model for time-to-death.

We made predictions over the entire follow up time for participants in the testing samples, which included 1) a testing sample of COPDGene subjects, 2) an external testing sample of ECLIPSE subjects with 8-year follow up data. For Cox models, we constructed a Schoenfeld residual plot for each feature to ensure there was no violation of the Cox proportional hazards assumption.

To understand the contribution of RSF to our results, we also compared a range of feature selection methods and prediction models. Univariate screens were performed with a Student t-test, including only variables with p-value < 0.05. Stepwise logistic regression was performed using the MASS R package [8], and stepwise Cox regression was performed using the My.stepwise R package [9]. Lasso regression was performed using the glmnet R package [10,11]. We plotted calibration of models for predicting survival over 8 years using the pec R package [12], and tested for miscalibration using the Greenwood-Nam-D'Agostino (GND) test as detailed by Demler et al. [13].

For univariate associations with mortality, features were assessed for normality by visual inspection of histograms and Shapiro-Wilk tests. Results are shown as mean ± sd or median [interquartile range], as appropriate. Differences in continuous variables were assessed with Student t-tests and analysis of variance (ANOVA), or non-parametric Wilcoxon and Kruskal-Wallis tests. Categorical variables were compared by ANOVA or Kruskal-Wallis tests.

The R Shiny app was created for researchers and clinicians to explore the relationship between predictors and mortality in our model. This tool accepts user-defined values for each feature and based on the Cox model built from COPDGene subjects, a survival function is calculated. The survival function is then used to calculate the probability of survival over time, and this is plotted as a Kaplan-Meier curve with confidence intervals (ggfortify R package).[14] Our web-based tool additionally includes the option of estimating probability of survival using a set of clinical features exclusive of quantitative imaging.

Imaging feature harmonization

As imaging protocols differed between the COPDGene and ECLIPSE studies, we also performed a secondary analysis to determine whether harmonizing imaging features significantly changed our results. To assess the effects of imaging protocols, we matched COPDGene and ECLIPSE subjects based on FEV_1 (% predicted), FEV_1/FVC, age, sex, pack-years, and current smoking status. %LAA <-950 HU was log-transformed to allow for parametric testing. Visual display of imaging features in matched subjects can be found in Supplemental eFigure 1. To normalize imaging features for comparison between datasets, we transformed imaging data into z-scores. The means and standard deviations used for z-score calculation were derived from the matched subset of participants.

eResults

The MLMP-COPD model (trained on 75% of COPDGene subjects) outperformed updated BODE and ADO in subgroups of ECLIPSE subjects, including GOLD spirometry grade 3 or 4, and severe or frequent exacerbator phenotypes (supplementary eTable 8). Characteristics of subgroups are shown in supplementary eTable 9.

A Case Study

To illustrate how the MLMP-COPD could be used by clinicians and researchers, we present a hypothetical case of a COPD patient and examine her predicted survival using our online web application (available at

https://cdnm.shinyapps.io/cgmortalityapp/). This application allows the user to change the input variables for either the full model or clinical variables alone – we will be using the full model.

Our patient is a 62 year-old woman with 25 pack-years of smoking, an FEV_1 of 40 % of predicted, who had 1 exacerbation in the last 12 months requiring hospitalization (exacerbation frequency = 1, Severe exacerbations = Yes). She walks slower on the level than her same-aged peers (MMRC = 2), and her resting SpO2 is 90%. Her other measures are:

Variable	Hypothetical patient's value
6MWD	800 feet
FEV_1/FVC	45 %
FEF25-75	0.4 L
BMI	24 kg/m_2
Diabetes mellitus	No
PA:A ratio	0.9
Pi10	3.7
% LAA < -950 HU	8 %

Say, for example, we are interested in understanding how her predicted survival will change if she were to develop pulmonary vascular disease manifesting as an increased PA:A ratio. We simply input her clinical values into the online calculator and explore the change in predicted survival with changing PA:A ratio. Her baseline predicted survival over 8 years is 54.1% (supplementary eFigure 4A). If the patient were to develop worsening pulmonary vascular disease with a PA:A ratio increase from 0.9 to 1.2, her predicted survival would drop to 42.8% (supplementary eFigure 4B).

Competing Interests:

M.H.C. and E.K.S. have received grant funding from GlaxoSmithKline (GSK). E.K.S. has received honoraria from Novartis for Continuing Medical Education Seminars and travel support from GSK. M.H.C. has received consulting fees from Genentech, AstraZeneca, and speaking fees from Illumina.
G.R.W. has received grant support from Boehringer Ingelheim, BTG Interventional Medicine, and other support from Genentech, Quantitative Imaging Solutions, PulmonX, Regeneron, ModoSpira, Janssen Pharmaceuticals, Toshiba, and GSK.
J.M.W. has received research contracts from Bayer, GlaxoSmithKline, Mereo BioPharma, AstraZeneca and Gilead and advisory/consultancy fees from GSK, Boehringer Ingelheim, AstraZeneca, Mereo BioPharma, Mylan and Quintiles.
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G.M.H. reports personal fees from Genentech, Boehringer Ingelheim and the Gerson Lehrman Group.

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COPDGene Funding and Acknowledgements

Grant Support and Disclaimer

The project described was supported by Award Number U01 HL089897 and Award Number U01 HL089856 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

COPD Foundation Funding

The COPDGene® project is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer, Siemens and Sunovion.

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The **ECLIPSE** study (NCT00292552; GSK code SCO104960) was funded by GlaxoSmithKline.

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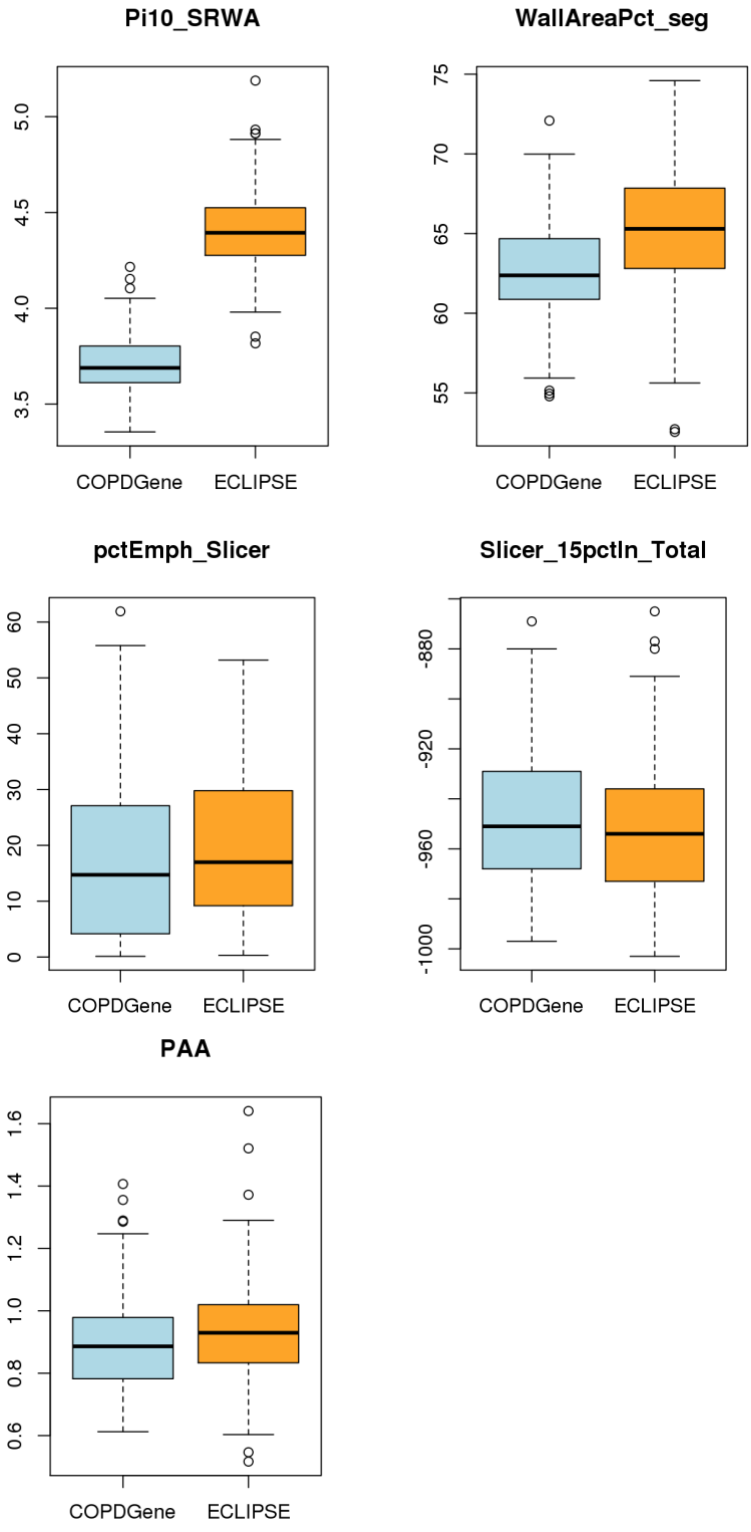
e-Figure 1: Comparison of quantitative imaging features in COPDGene and ECLIPSE. Boxplots are shown describing imaging features which included %LAA < -950 HU, Pi10, perc15, and % WA. Two-sample t-tests confirmed that the data were significantly different, despite matching.



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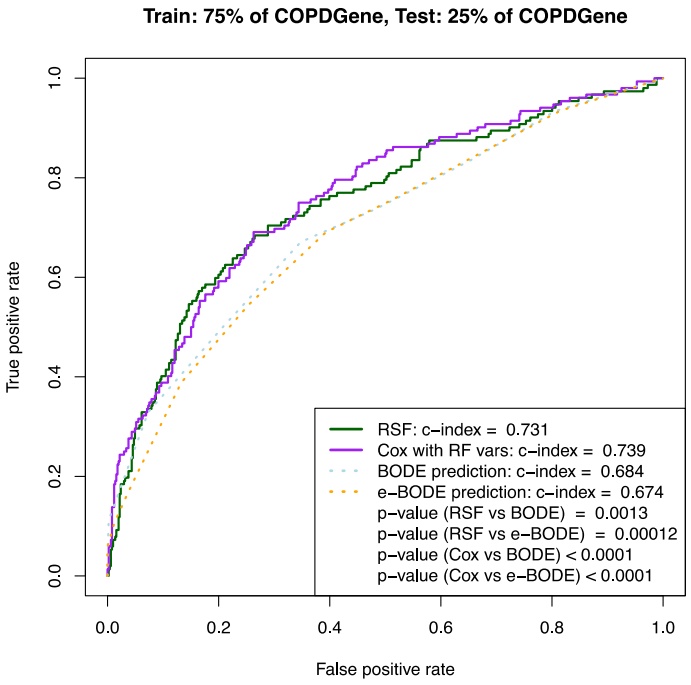
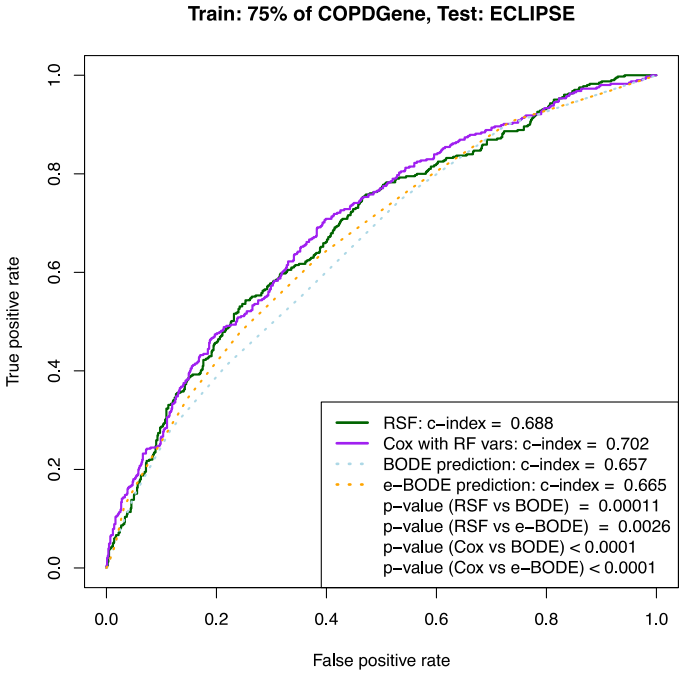
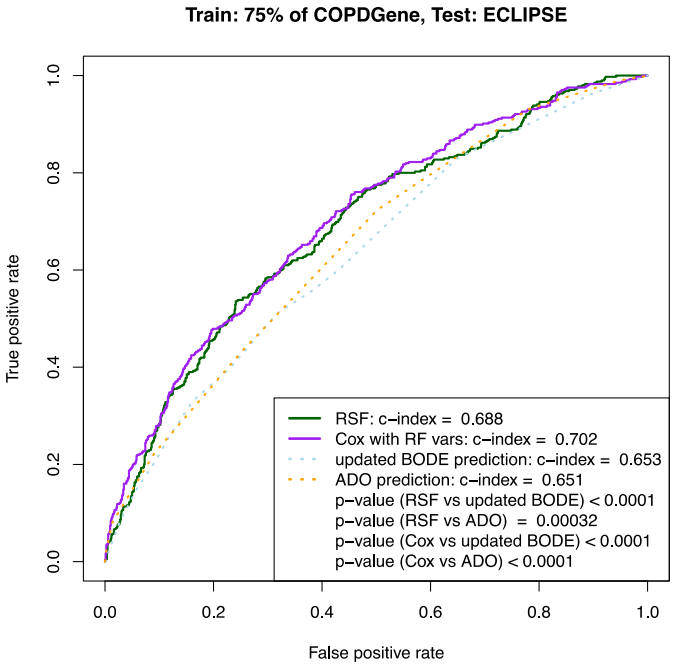
e-Figure 2A: Receiver operator characteristic (ROC) curve comparing the RSF-derived mortality prediction models to BODE and e-BODE tested within COPDGene. Models were trained and tested within the COPDGene sample.



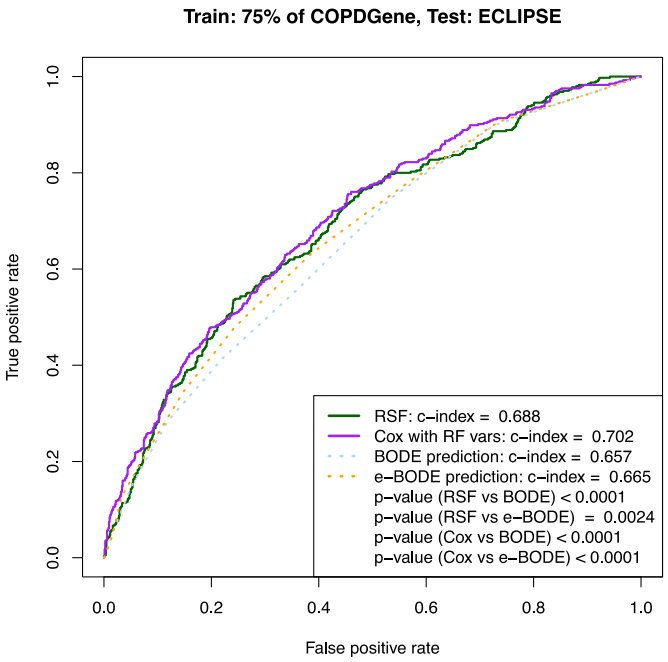
e-Figure 2B: Receiver operator characteristic (ROC) curve comparing the RSF-derived mortality prediction models to BODE and e-BODE tested on ECLIPSE. Models were trained in COPDGene and tested in ECLIPSE subjects.



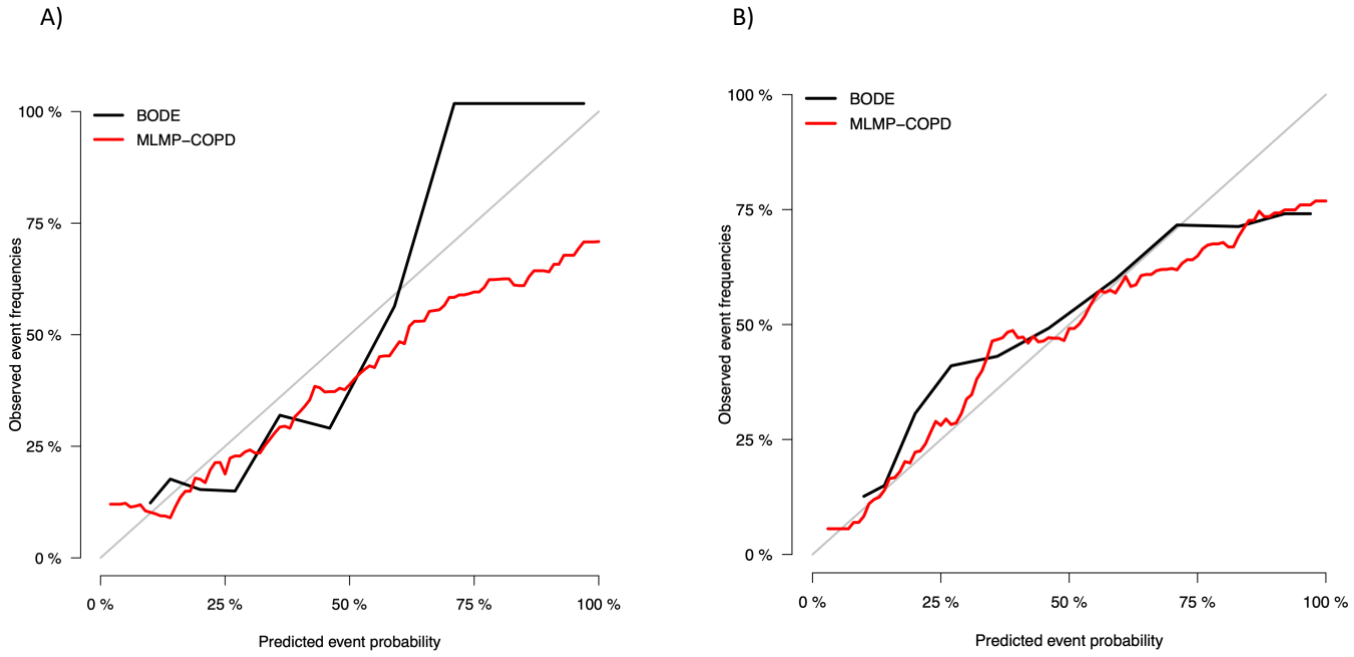
e-Figure 3A: ROC curve for MLMP-COPD model after data transformation using updated BODE and ADO for comparison. Both COPDGene and ECLIPSE dataset imaging features were transformed into Z-scores. RSF model was re-trained on the training set of COPDGene, and tested on both the testing sample of COPDGene and ECLIPSE. This figure shows the comparison of the performance of the RSF model and the Cox model with RSF-selected features to updated BODE and ADO.



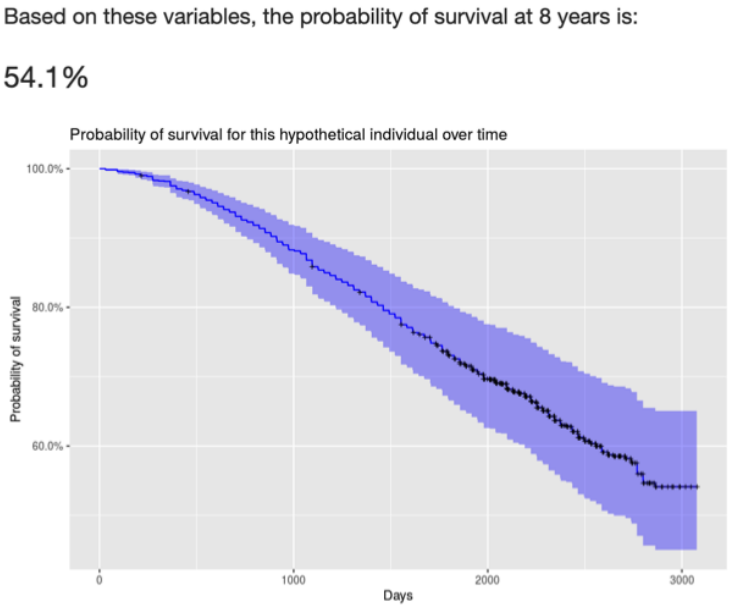
e-Figure 3B: ROC curve for MLMP-COPD model after data transformation using BODE and e-BODE for comparison. Both COPDGene and ECLIPSE dataset imaging features were transformed into Z-scores. RSF model was re-trained on the training set of COPDGene, and tested on both the testing sample of COPDGene and ECLIPSE. This figure shows the comparison of the performance of the RSF model and the Cox model with RSF-selected features to BODE and e-BODE.



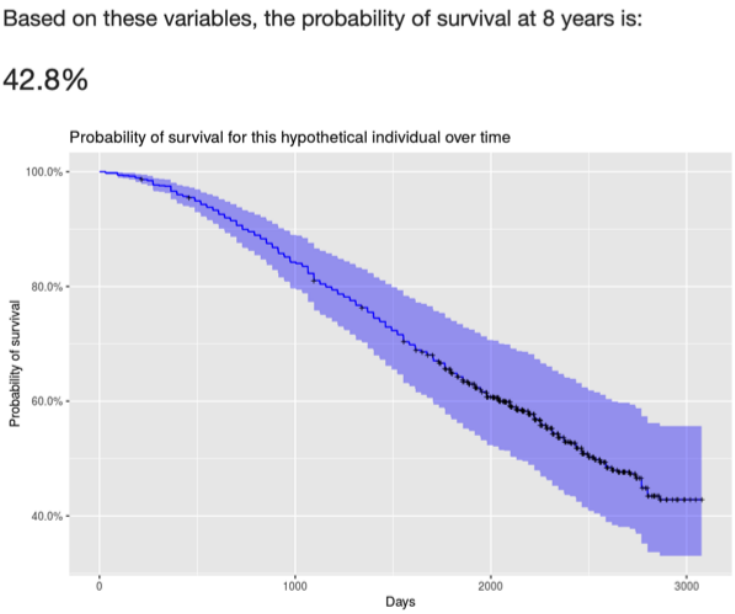
e-Figure 4: Calibration curves for BODE (*black*) and MLMP-COPD (*red*) models for predicting mortality over 8 years in A) the testing set of COPDGene, and B) ECLIPSE. The identity line (*gray*) represents an ideal, perfectly calibrated, model.



e-Figure 5A: COPDGene Mortality Risk Calculator (available at https://cdnm.shinyapps.io/cgmortalityapp/) outputs based on a hypothetical patient. The patient is a 62 year-old woman with 25 pack-years of smoking, an FEV_1 of 40 % of predicted, who had 1 exacerbation in the last 12 months requiring hospitalization. She walks slower on the level than her same-aged peers (MMRC = 2), and her resting SpO2 is 90%. See eResults section for other measures. Below shows the baseline predicted survival based on this patient's data.



e-Figure 5B: COPDGene Mortality Risk Calculator (available at https://cdnm.shinyapps.io/cgmortalityapp/) outputs based on a hypothetical patient. The patient is a 62 year-old woman with 25 pack-years of smoking, an FEV_1 of 40 % of predicted, who had 1 exacerbation in the last 12 months requiring hospitalization. She walks slower on the level than her same-aged peers (MMRC = 2), and her resting SpO2 is 90%. See eResults section for other measures. Below shows the Predicted survival after changing PA:A ratio from 0.9 to 1.2, holding all other variables constant.



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e-Table 1:

Characteristics of study participants. Full demographics of the COPDGene training and testing datasets, and ECLIPSE subjects included in the analysis:

	COPDGene Training Set	*COPDGene Testing Set*	*ECLIPSE*	*p-value*
n	1974	658	1268	
Sex (No. female, (%))	856 (43.4)	301 (45.7)	426 (33.6)	<0.001
Age in years (mean (sd))	63.54 (8.92)	63.69 (8.91)	63.51 (7.03)	0.890
Race (No. African American (%))	377 (19.1)	108 (16.4)	0 (0.0)	<0.001
FEV1 % predicted (median [IQR])	52.45 [37.20, 66.60]	50.50 [34.90, 66.00]	45.95 [35.00, 58.73]	<0.001
FVC % predicted (mean (sd))	77.35 (16.68)	76.62 (17.02)	79.16 (19.82)	0.003
FEV1/FVC ratio (median [IQR])	0.51 [0.39, 0.62]	0.49 [0.38, 0.60]	0.43 [0.35, 0.52]	<0.001
FEF25-75 in Liters (median [IQR])	0.49 [0.30, 0.80]	0.46 [0.29, 0.73]	0.40 [0.28, 0.57]	<0.001
Percent change in FEV1 post-bronchodilator (mean (sd))	8.62 (12.48)	9.84 (13.77)	11.35 (14.24)	<0.001
Percent change in FVC post-bronchodilator (mean (sd))	8.03 (14.46)	10.06 (21.83)	10.32 (14.75)	<0.001
GOLD Spirometry Grade (No. (%))				<0.001
2	1072 (54.3)	335 (50.9)	518 (40.9)	
3	616 (31.2)	203 (30.9)	568 (44.8)	
4	286 (14.5)	120 (18.2)	182 (14.4)	
Pack-years cigarette smoking (median [IQR])	47.60 [35.40, 67.50]	47.25 [36.85, 70.00]	45.00 [32.00, 60.00]	<0.001
Current Smoking (No. (%))	799 (40.5)	242 (36.8)	431 (34.0)	0.001
Dead at 3 years (No. (%))	164 (8.3)	57 (8.7)	121 (9.5)	0.477
Dead at 5 years (No. (%))	345 (17.5)	109 (16.6)	0 (NaN)	NaN
Dead at 8 years (No. (%))	479 (24.3)	152 (23.1)	0 (NaN)	NaN

Total Dead (No. (%))	479 (24.3)	152 (23.1)	405 (31.9)	<0.001
Days Followed (median [IQR])	2318.00 [2043.00, 2624.00]	2377.00 [2071.00, 2683.00]	2616.00 [1110.00, 2924.00]	<0.001
6-minute walk distance (ft) (mean (sd))	1208.06 (390.54)	1199.70 (397.70)	1190.36 (389.77)	0.453
BODE (median [IQR])	3.00 [1.00, 4.00]	3.00 [1.00, 5.00]	3.00 [2.00, 5.00]	<0.001
eBODE (median [IQR])	3.00 [1.00, 5.00]	3.00 [1.00, 5.00]	3.00 [2.00, 5.00]	<0.001
updated BODE (median [IQR])	3.00 [1.00, 7.00]	3.00 [1.00, 8.00]	3.00 [1.00, 7.00]	0.990
ADO (mean (sd))	4.58 (1.78)	4.67 (1.85)	3.84 (1.44)	<0.001
MMRC Dyspnea Score (No. (%))				<0.001
0	425 (21.5)	137 (20.8)	141 (11.1)	
1	275 (13.9)	92 (14.0)	424 (33.4)	
2	358 (18.1)	123 (18.7)	432 (34.1)	
3	584 (29.6)	175 (26.6)	210 (16.6)	
4	332 (16.8)	131 (19.9)	61 (4.8)	
BMI (kg/m^2) (mean (sd))	28.05 (6.16)	28.07 (5.96)	26.61 (5.48)	<0.001
Resting SaO2 (median [IQR])	95.00 [94.00, 97.00]	95.00 [93.00, 97.00]	95.00 [93.00, 96.00]	<0.001
Severe Exacerbations (No. (%))	394 (20.0)	156 (23.7)	271 (21.4)	0.117
Exacerbation Frequency (No./yr) (mean (sd))	0.70 (1.19)	0.82 (1.33)	0.78 (1.00)	0.027
PA:A Ratio (mean (sd))	0.89 (0.14)	0.90 (0.14)	0.93 (0.15)	<0.001
Pi10 (mean (sd))	3.72 (0.14)	3.72 (0.13)	4.41 (0.20)	<0.001
% WA (mean (sd))	62.73 (2.89)	62.83 (2.95)	65.62 (4.06)	<0.001
% LAA < -950 HU (median [IQR])	8.17 [2.56, 19.91]	10.05 [2.69, 21.74]	16.66 [8.92, 27.36]	<0.001
Perc 15 (mean (sd))	-938.05 (28.46)	-941.08 (27.89)	-956.78 (49.72)	<0.001
ILA (No. (%))	122 (6.2)	34 (5.2)	120 (9.5)	<0.001
Subpleural ILA (No. (%))	90 (4.6)	24 (3.6)	105 (8.3)	<0.001

Fibrotic ILA (No. (%))	24 (1.2)	4 (0.6)	23 (1.8)	0.076
Stroke (No. (%))	65 (3.3)	21 (3.2)	43 (3.4)	0.972
Hypertension (No. (%))	1003 (50.8)	333 (50.6)	485 (38.2)	<0.001
Diabetes (No. (%))	239 (12.1)	71 (10.8)	124 (9.8)	0.115
Chronic Bronchitis (No. (%))	552 (28.0)	183 (27.8)	436 (34.4)	<0.001

e-Table 2: The initial 30 features used as inputs into the RSF algorithm. Features included demographic and clinical, spirometric, radiographic, and cardiovascular features.

Demographic and clinical features	Spirometric features	Radiographic features	Cardiovascular comorbidities
Sex	FEV1 % predicted	PA:A Ratio	Stroke
Age	FVC % predicted	Pi10	Hypertension
Race	FEV1/FVC ratio	% WA	Diabetes
Pack-years cigarette smoking	FEF25-75 in Liters	% LAA < -950 HU	
Current Smoking	Percent change in FEV1 post-bronchodilator	Perc 15	
6-minute walk distance	Percent change in FVC post-bronchodilator	ILA	
MMRC Dyspnea Score	GOLD Spirometry Grade	Subpleural ILA	
BMI		Fibrotic ILA	
Resting SaO2			
Severe Exacerbations			
Exacerbation Frequency			
Chronic Bronchitis			

e-Table 3: Cox regression coefficients for RSF-selected features included in the final MLMP-COPD model.

Feature	*Coefficient*
6-minute walk distance (ft)	-0.00106
FEV1 % predicted	-0.0146
Age in years	0.0414
MMRC Dyspnea Score (No. (%))	0.138
FEV1/FVC ratio	-2.32
FEF25-75 in Liters	0.555
Resting SaO2	-0.0292
Exacerbation Frequency (No./yr)	0.0324
Pack-years cigarette smoking	0.00518
BMI (kg/m^2)	-0.03
Severe Exacerbations (No. (%))	0.282
PA:A Ratio	1.01
Pi10	0.484
Diabetes (No. (%))	0.279
% LAA < -950 HU	-0.00543

e-Table 4: Clinical interpretations of hazard ratios for the fully-adjusted Cox (MLMP-COPD) model. Interpretations are only provided for features that were significantly associated with mortality in the final model. Relevant changes in each feature are shown, with associated changes in predicted hazard (rate) of death, assuming all covariates are held constant. Note that the probabilities of survival will depend on the individual patient's baseline survival function, and be non-linear in relation to the reported changes in hazard rates.

Feature	*Change*	*Increase in hazard (rate) of death*
6-minute walk distance (ft)	Decrease 100 feet	11%
FEV1 % predicted	Decrease 10%	16%
Age in years	Increase 5 years	22%
MMRC Dyspnea Score (No. (%))	Increase 1 category	15%
FEV1/FVC ratio	Decrease by 0.1	26%
FEF25-75 in Liters	Increase by 100 mL	5.7%
Resting SaO2	Decrease by 1%	3%
Pack-years cigarette smoking	Increase by 10 pack years	10%
BMI (kg/m^2)	Decrease by 1 mg/kg^2	3.1%
Severe Exacerbations (No. (%))	Having 1 exacerbation requiring hospitalization	33%
PA:A Ratio	Increase by 0.1	11%
Diabetes (No. (%))	Presence of Diabetes	32%

e-Table 5: Evaluation of model calibrations in the COPDGene training, COPDGene testing, and ECLIPSE datasets. P-values for the Greenwood-Nam-D'Agostino (GND) test [13] are shown in the table. A p-value < 0.05 indicates significant miscalibration of the model.

Model	*COPDGene training set (n=1974, 479 deaths (24%))*	*COPDGene testing set (n=658, 152 deaths (23%))*	*ECLIPSE (n=1268, 405 deaths (32%))*
BODE	0.65	0.0023	7.50E-06
MLMP-COPD	0.42	0.056	0.09

e-Table 6: Cox regression coefficients for the clinical model without imaging features.

Feature	*Coefficient*
6-minute walk distance (ft)	-0.00109
FEV1pp	-0.0149
Age in years	0.0391
MMRC Dyspnea Score (No. (%))	0.13
FEV1/FVC ratio	-1.71
FEF25-75 in Liters	0.413
Resting SaO2	-0.0367
Exacerbation Frequency (No./yr)	0.0281
Pack-years cigarette smoking	0.00496
BMI (kg/m^2)	-0.0246
Severe Exacerbations (No. (%))	0.387
Diabetes (No. (%))	0.31

e-Table 7: Evaluation of impact of individual CT imaging features on predictive performance. Cox regression models adding individual quantitative imaging features compared to updated BODE and ADO. Models were trained in COPDGene and tested in ECLIPSE participants.

Model (BODE +)	*Model C-index*	*Updated BODE C-index*	*p-value*	*ADO C-index*	*p-value*
% LAA < -950 HU	0.659	0.653	0.4	0.651	0.5
Perc15	0.653	0.653	0.99	0.651	0.9
Pi10	0.653	0.653	0.98	0.651	0.9
WAP	0.661	0.653	0.2	0.651	0.3
PA:A ratio	0.663	0.653	0.2	0.651	0.3

e-Table 8: Predictive performance (C-indices) of combinations of features selection methods paired with prediction models. All models were compared to BODE, which had a C-index of 0.68 in the COPDGene testing set and 0.66 in the ECLIPSE dataset.

			COPDGene (set-aside test data)		*ECLIPSE (external validation)*	
Variable selection method	*Number of features selected*	*Prediction model*	*C index*	*p-value (vs. BODE)*	*C index*	*p-value (vs. BODE)*
Univariate screen	30	Cox	0.74	0.001	0.68	0.02
Stepwise logistic	20	Logistic	0.74	0.007	0.68	0.04
Stepwise Cox	19	Cox	0.73	0.01	0.68	0.05
Lasso	27	Cox	0.75	0.0006	0.69	0.007
Random survival forest	15	Random survival forest	0.73	0.001	0.69	0.00011
Random survival forest	15	Cox	0.74	< 0.0001	0.70	< 0.0001

e-Table 9: Subgroup analyses C-indices. The MLMP-COPD model was tested on subgroups of ECLIPSE, and c-indices are compared to updated BODE and ADO.

Subgroup	*Cox model*	*Updated BODE*	*p-value (updated BODE)*	*ADO*	*p-value (ADO)*
GOLD 2	0.699	0.659	0.05612	0.669	0.0561
GOLD 3	0.687	0.618	< 0.0001	0.616	< 0.0001
GOLD 4	0.638	0.554	0.0013655	0.554	0.00137
Frequent Exacerbators	0.71	0.655	0.0051689	0.634	0.00517
Severe Exacerbators	0.638	0.604	0.065322	0.59	0.0653

e-Table 10: Characteristics of ECLIPSE subgroups. MLMP-COPD performance was tested in subgroups of ECLIPSE participants, including GOLD spirometry grades 2-4, severe and frequent exacerbator phenotypes.

Variable	*GOLD 2*	*GOLD 3*	*GOLD 4*	*Severe Exacerbators*	*Frequent Exacerbators*
n	518	568	182	271	310
Sex (No. female, (%))	195 (37.6)	181 (31.9)	50 (27.5)	101 (37.3)	103 (33.2)
Age in years (mean (sd))	63.98 (7.18)	63.46 (6.91)	62.31 (6.83)	63.82 (7.05)	63.97 (7.03)
Race (No. Caucasian (%))	518 (100.0)	568 (100.0)	182 (100.0)	271 (100.0)	310 (100.0)
FEV1% predicted (mean (sd))	62.68 (8.33)	40.17 (5.79)	24.94 (3.42)	40.20 (13.94)	44.98 (15.53)
FVC % predicted (mean (sd))	90.77 (16.96)	75.10 (16.61)	58.76 (14.44)	74.25 (19.45)	78.13 (19.54)
FEV1/FVC ratio (mean (sd))	0.52 (0.08)	0.40 (0.09)	0.32 (0.07)	0.40 (0.10)	0.42 (0.11)
FEF25-75 in Liters (mean (sd))	0.65 (0.26)	0.37 (0.14)	0.24 (0.07)	0.36 (0.18)	0.43 (0.22)
Percent change in FEV1 post-bronchodilator (mean (sd))	12.05 (13.88)	11.55 (14.75)	8.77 (13.39)	11.61 (14.47)	11.84 (14.61)
Percent change in FVC post-bronchodilator (mean (sd))	8.81 (12.24)	10.74 (15.46)	13.35 (18.18)	11.08 (13.43)	10.03 (14.46)
Pack-years cigarette smoking (mean (sd))	48.74 (28.16)	49.59 (24.11)	50.91 (28.73)	47.21 (23.19)	48.49 (25.06)
Current Smoking (No. (%))	160 (30.9)	214 (37.7)	57 (31.3)	84 (31.0)	95 (30.6)
Total Dead (No. (%))	122 (23.6)	197 (34.7)	86 (47.3)	141 (52.0)	112 (36.1)
Days Followed (mean (sd))	2286.42 (866.98)	2072.00 (892.26)	1793.45 (894.03)	1907.58 (866.34)	2060.05 (867.92)
6-minute walk distance (ft) (mean (sd))	1302.83 (354.62)	1162.97 (390.91)	955.75 (362.82)	1059.29 (370.95)	1179.53 (360.90)
BODE (mean (sd))	1.70 (1.43)	3.98 (1.65)	5.66 (1.45)	4.50 (2.09)	3.57 (2.06)
MMRC Dyspnea Score (No. (%))					
0	92 (17.8)	46 (8.1)	3 (1.6)	12 (4.4)	29 (9.4)

1	211 (40.7)	183 (32.2)	30 (16.5)	54 (19.9)	86 (27.7)
2	149 (28.8)	204 (35.9)	79 (43.4)	112 (41.3)	114 (36.8)
3	49 (9.5)	107 (18.8)	54 (29.7)	59 (21.8)	63 (20.3)
4	17 (3.3)	28 (4.9)	16 (8.8)	34 (12.5)	18 (5.8)
BMI (kg/m^2) (mean (sd))	27.52 (5.46)	26.25 (5.37)	25.16 (5.45)	25.65 (5.36)	25.90 (5.48)
Resting SaO2 (mean (sd))	95.31 (2.13)	94.05 (3.23)	93.23 (3.43)	93.63 (3.59)	94.35 (2.79)
Severe Exacerbations (No. (%))	62 (12.0)	136 (23.9)	73 (40.1)	271 (100.0)	132 (42.6)
Exacerbation Frequency (No./yr) (mean (sd))	0.59 (0.89)	0.86 (1.05)	1.06 (1.04)	1.76 (0.82)	1.00 (0.00)
PA:A Ratio (mean (sd))	0.90 (0.14)	0.94 (0.16)	0.96 (0.15)	1.00 (0.16)	0.94 (0.15)
Pi10 (mean (sd))	4.40 (0.19)	4.42 (0.21)	4.40 (0.22)	4.40 (0.21)	4.41 (0.22)
% WA (mean (sd))	65.60 (4.09)	65.72 (4.09)	65.36 (3.90)	65.07 (4.23)	65.26 (4.28)
% LAA (mean (sd))	13.41 (9.83)	20.72 (11.69)	29.40 (12.76)	23.15 (12.93)	20.80 (13.37)
Perc 15 (mean (sd))	-937.45 (48.45)	-964.79 (48.17)	-986.81 (33.93)	-971.96 (45.82)	-959.68 (49.13)
ILA (No. (%))	55 (10.6)	60 (10.6)	5 (2.7)	25 (9.2)	31 (10.0)
Subpleural ILA (No. (%))	50 (9.7)	51 (9.0)	4 (2.2)	25 (9.2)	29 (9.4)
Fibrotic ILA (No. (%))	10 (1.9)	12 (2.1)	1 (0.5)	3 (1.1)	9 (2.9)
Stroke (No. (%))	21 (4.1)	17 (3.0)	5 (2.7)	10 (3.7)	11 (3.5)
Hypertension (No. (%))	221 (42.7)	207 (36.4)	57 (31.3)	86 (31.7)	114 (36.8)
Diabetes (No. (%))	59 (11.4)	43 (7.6)	22 (12.1)	22 (8.1)	22 (7.1)
Chronic Bronchitis (No. (%))	163 (31.5)	201 (35.4)	72 (39.6)	95 (35.1)	98 (31.6)

e-Table 11: Characteristics of BODE group (score 0-2) compared to equally-sized MLMP-COPD mortality risk group.

	BODE group	*MLMP-COPD group*	*p-value*
n	1726	1726	
Age in years (mean (sd))	63.54 (8.63)	60.60 (8.25)	<0.001
Race (No. African American (%))	221 (12.8)	252 (14.6)	0.138
Sex (No. female, (%))	680 (39.4)	751 (43.5)	0.016
Total Dead (No. (%))	256 (14.8)	199 (11.5)	0.005
Days Followed (median [IQR])	2499.00 [2158.25, 2864.00]	2499.00 [2196.00, 2834.00]	0.499
BODE (median [IQR])	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	<0.001
6-minute walk distance (ft) (mean (sd))	1412.65 (308.15)	1451.04 (298.37)	<0.001
FEV1 % predicted (median [IQR])	64.40 [54.70, 71.50]	63.25 [52.40, 71.27]	0.018
MMRC Dyspnea Score (No. (%))			<0.001
0	650 (37.7)	584 (33.8)	
1	627 (36.3)	463 (26.8)	
2	331 (19.2)	346 (20.0)	
3	118 (6.8)	244 (14.1)	
4	0 (0.0)	89 (5.2)	
FEV1/FVC ratio (median [IQR])	0.56 [0.48, 0.63]	0.57 [0.49, 0.64]	0.085
FEF25-75 in Liters (median [IQR])	0.67 [0.47, 0.93]	0.68 [0.47, 0.95]	0.342
Resting SaO2 (median [IQR])	96.00 [94.00, 97.00]	96.00 [95.00, 97.00]	0.002
Exacerbation Frequency (No./yr) (mean (sd))	0.42 (0.86)	0.42 (0.87)	0.906
Pack-years cigarette smoking (median [IQR])	44.50 [32.60, 60.58]	42.00 [30.92, 57.00]	<0.001
BMI (kg/m^2) (mean (sd))	27.97 (5.26)	28.43 (5.89)	0.014
Severe Exacerbations (No. (%))	186 (10.8)	141 (8.2)	0.011

PA:A Ratio (mean (sd))	0.88 (0.13)	0.87 (0.12)	0.006
Pi10 (mean (sd))	3.89 (0.36)	3.85 (0.33)	<0.001
Diabetes (No. (%))	175 (10.1)	145 (8.4)	0.089
% LAA < -950 HU (median [IQR])	6.30 [2.21, 14.66]	5.35 [1.89, 13.60]	0.012

e-Table 12: Characteristics of BODE group (score 3-4) compared to equally-sized MLMP-COPD mortality risk group.

	BODE group	*MLMP-COPD group*	*p-value*
n	1166	1166	
Age in years (mean (sd))	63.46 (8.28)	64.86 (7.87)	<0.001
Race (No. African American (%))	144 (12.3)	131 (11.2)	0.441
Sex (No. female, (%))	489 (41.9)	463 (39.7)	0.292
Total Dead (No. (%))	315 (27.0)	308 (26.4)	0.779
Days Followed (median [IQR])	2318.00 [1704.50, 2768.25]	2318.00 [1768.00, 2803.00]	0.436
BODE (median [IQR])	3.00 [3.00, 4.00]	3.00 [2.00, 4.00]	<0.001
6-minute walk distance (ft) (mean (sd))	1164.18 (325.39)	1150.99 (283.71)	0.297
FEV1 % predicted (median [IQR])	45.70 [37.80, 55.30]	45.25 [37.00, 56.60]	0.686
MMRC Dyspnea Score (No. (%))			<0.001
0	53 (4.5)	99 (8.5)	
1	144 (12.3)	263 (22.6)	
2	433 (37.1)	318 (27.3)	
3	410 (35.2)	341 (29.2)	
4	126 (10.8)	145 (12.4)	
FEV1/FVC ratio (median [IQR])	0.46 [0.38, 0.55]	0.45 [0.38, 0.54]	0.170
FEF25-75 in Liters (median [IQR])	0.40 [0.30, 0.58]	0.40 [0.29, 0.56]	0.345
Resting SaO2 (median [IQR])	95.00 [93.00, 97.00]	95.00 [93.00, 96.00]	0.545
Exacerbation Frequency (No./yr) (mean (sd))	0.84 (1.16)	0.83 (1.19)	0.874
Pack-years cigarette smoking (median [IQR])	47.05 [36.00, 66.00]	48.00 [38.00, 67.95]	0.111
BMI (kg/m^2) (mean (sd))	28.14 (6.26)	27.63 (5.93)	0.042

Severe Exacerbations (No. (%))	269 (23.1)	270 (23.2)	1.000
PA:A Ratio (mean (sd))	0.91 (0.14)	0.91 (0.14)	0.419
Pi10 (mean (sd))	3.97 (0.37)	4.00 (0.37)	0.113
Diabetes (No. (%))	160 (13.7)	143 (12.3)	0.324
% LAA < -950 HU (median [IQR])	13.15 [5.02, 23.75]	14.71 [6.36, 23.98]	0.021

e-Table 13: Characteristics of BODE group (score 5-6) compared to equally-sized MLMP-COPD mortality risk group.

	BODE group	*MLMP-COPD group*	*p-value*
n	824	824	
Age in years (mean (sd))	63.66 (8.05)	66.49 (7.25)	<0.001
Race (No. African American (%))	102 (12.4)	86 (10.4)	0.245
Sex (No. female, (%))	332 (40.3)	312 (37.9)	0.337
Total Dead (No. (%))	347 (42.1)	388 (47.1)	0.047
Days Followed (median [IQR])	2134.00 [1159.50, 2649.00]	2040.00 [1105.00, 2673.25]	0.162
BODE (median [IQR])	5.00 [5.00, 6.00]	5.00 [4.00, 6.00]	<0.001
6-minute walk distance (ft) (mean (sd))	941.64 (330.47)	883.23 (302.87)	<0.001
FEV1 % predicted (median [IQR])	31.60 [24.80, 38.70]	32.70 [25.37, 42.40]	0.004
MMRC Dyspnea Score (No. (%))			<0.001
0	0 (0.0)	20 (2.4)	
1	20 (2.4)	60 (7.3)	
2	130 (15.8)	217 (26.3)	
3	383 (46.5)	320 (38.8)	
4	291 (35.3)	207 (25.1)	
FEV1/FVC ratio (median [IQR])	0.36 [0.30, 0.43]	0.36 [0.30, 0.43]	0.879
FEF25-75 in Liters (median [IQR])	0.27 [0.20, 0.36]	0.27 [0.21, 0.36]	0.582
Resting SaO2 (median [IQR])	94.00 [92.00, 96.00]	94.00 [92.00, 96.00]	0.068
Exacerbation Frequency (No./yr) (mean (sd))	1.16 (1.44)	1.12 (1.30)	0.554
Pack-years cigarette smoking (median [IQR])	50.00 [38.00, 70.50]	50.30 [39.00, 72.00]	0.302
BMI (kg/m^2) (mean (sd))	26.84 (6.40)	26.22 (5.82)	0.040
Severe Exacerbations (No. (%))	280 (34.0)	315 (38.2)	0.081

PA:A Ratio (mean (sd))	0.93 (0.15)	0.95 (0.15)	0.005
Pi10 (mean (sd))	3.97 (0.35)	4.03 (0.37)	<0.001
Diabetes (No. (%))	79 (9.6)	108 (13.1)	0.030
% LAA < -950 HU (median [IQR])	21.74 [11.38, 33.19]	22.03 [12.92, 32.49]	0.591

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