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The Cardiovascular Phenotype of Chronic Obstructive Pulmonary Disease (COPD): Applying Machine Learning to the Prediction of Cardiovascular Comorbidities

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Corresponding Author:	Vasilis Nikolaou Guildford, UNITED KINGDOM
First Author:	Vasilis Nikolaou
Order of Authors:	Vasilis Nikolaou
	Sebastiano Massaro
	Wolfgang Garn
	Masoud Fakhimi
	Lampros Stergioulas
	David Price
Abstract:	Background Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous group of lung conditions that are challenging to diagnose and treat. As the presence of comorbidities often exacerbates this scenario, the characterization of patients with COPD and cardiovascular comorbidities may allow early intervention and improve disease management and care. Methods We analysed a 4-year observational cohort of 6,883 UK patients who were ultimately diagnosed with COPD and at least one cardiovascular comorbidity. The cohort was extracted from the UK Royal College of General Practitioners and Surveillance Centre database. The COPD phenotypes were identified prior to diagnosis and their reproducibility was assessed following COPD diagnosis. We then developed four classifiers for predicting cardiovascular comorbidities. Results Three subtypes of the COPD cardiovascular phenotype were identified prior to diagnosis. Phenotype A was characterised by a higher prevalence of severe COPD, emphysema, hypertension. Phenotype B was characterised by a larger male majority, a lower prevalence of hypertension, the highest prevalence of the other cardiovascular comorbidities, and diabetes. Finally, phenotype C was characterised by universal hypertension, a higher prevalence of mild COPD and the low prevalence of COPD exacerbations. These phenotypes were reproduced after diagnosis with 92% accuracy. The random forest model was highly accurate for predicting hypertension while ruling out less prevalent comorbidities. Conclusions This study identified three subtypes of the COPD cardiovascular phenotype that may generalize to other populations. Among the four models tested, the random forest classifier was the most accurate at predicting cardiovascular comorbidities in COPD patients with the cardiovascular phenotype.

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Vasilis Nikolaou, M.Sc. [1]; Sebastiano Massaro, Ph.D.[1,2]; Wolfgang Garn, Ph.D.[1]; Masoud Fakhimi, Ph.D.[1]; Lampros Stergioulas, Ph.D. [3]; David Price, FRCGP[4,5,6]

Affiliations:

[1] University of Surrey, Surrey Business School, Guildford GU2 7HX, United Kingdom.

[2] The Organizational Neuroscience Laboratory, London WC1N 3AX, United Kingdom.

[3] The Hague University of Applied Sciences, Johanna Westerdijkplein 75, 2521 EN Den Haag, Netherlands

[4] Optimum Patient Care, Cambridge, UK; [5]Observational and Pragmatic Research Institute, Singapore, Singapore; [6]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom

Corresponding author information:

Vasilis Nikolaou, M.Sc., University of Surrey, Surrey Business School, Alexander Fleming Rd, Guildford GU2 7XH, United Kingdom. E-mail: v.nikolaou@surrey.ac.uk; Telephone: 07799 363802.

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous group of lung conditions that are challenging to diagnose and treat. As the presence of comorbidities often exacerbates this scenario, the characterization of patients with COPD and cardiovascular comorbidities may allow early intervention and improve disease management and care.

Methods: We analysed a 4-year observational cohort of 6,883 UK patients who were ultimately diagnosed with COPD and at least one cardiovascular comorbidity. The cohort was extracted from the UK Royal College of General Practitioners and Surveillance Centre database. The COPD phenotypes were identified prior to diagnosis and their reproducibility was assessed following COPD diagnosis. We then developed four classifiers for predicting cardiovascular comorbidities.

Results: Three subtypes of the COPD cardiovascular phenotype were identified prior to diagnosis. Phenotype A was characterised by a higher prevalence of severe COPD, emphysema, hypertension. Phenotype B was characterised by a larger male majority, a lower prevalence of hypertension, the highest prevalence of the other cardiovascular comorbidities, and diabetes. Finally, phenotype C was characterised by universal hypertension, a higher prevalence of mild COPD and the low prevalence of COPD exacerbations. These phenotypes were reproduced after diagnosis with 92% accuracy. The random forest model was highly accurate for predicting hypertension while ruling out less prevalent comorbidities.

Conclusions: This study identified three subtypes of the COPD cardiovascular phenotype that may generalize to other populations. Among the four models tested, the random forest classifier was the most accurate at predicting cardiovascular comorbidities in COPD patients with the cardiovascular phenotype.

Key words: Cardiovascular subtypes, machine learning, cluster analysis, random forest

Abbreviations:

COPD: Chronic Obstructive Pulmonary Disease

FEV1: Forced Expiratory Volume in 1 second

FVC: Forced Vital Capacity

GP: General Practitioner

ICS: Inhaled Corticosteroids

LABA: Long-Acting Beta Agonist

LAMA: Long-Acting Anti-Muscarinic

MCA: Multiple Correspondence Analysis

MICE: Multivariate Imputation by Chained Equations

NPV: Negative Predictive Value

PPV: Positive Predictive Value

RF: Random Forest

RCGP: Royal College of General Practitioners

RSC: Research and Surveillance Centre

SAMA: Short-Acting Anti-Muscarinic

WHO: World Health Organisation

Introduction

Chronic Obstructive Pulmonary Disease (COPD) comprises a group of lung diseases, including asthma, emphysema and chronic bronchitis, that cause breathing difficulties due to inflammation of the lungs and narrowing of the airways.[1] According to the World Health Organisation (WHO), COPD is projected to become the third leading cause of death by 2030[2] because our ability to diagnose early and treat effectively has been relatively static. To better understand the heterogeneity of COPD, recent and ongoing research[3] is applying a wide range of machine learning methods, which can integrate patients' demographic and clinical characteristics to derive underlying disease traits that often occur together (i.e., COPD phenotypes). Among these, the cardiovascular phenotype remains one of the most relevant phenotypes to analyse, given that cardiovascular disease is the major contributor to morbidity and mortality in patients with COPD.[4] Unfortunately, however, this phenotype is highly complex and variegated being characterized by substantial differences in age, sex, and the hospital admission rate for acute exacerbations of COPD.[5-7] It thus remains both paramount and challenging to predict which COPD patients will develop cardiovascular comorbidities in the future.

This study aims to address this gap by characterising subtypes of the COPD cardiovascular phenotype. We derive three subtypes from a cohort of patients diagnosed with cardiovascular comorbidities before COPD and reproduce the subtypes in a cohort of patients after COPD diagnosis. Then, we train and test four classifiers to optimise the prediction of cardiovascular comorbidities in COPD patients.

Methods

Study design

This is a retrospective analysis of an observational cohort of patients with COPD in the UK. The data covers a 4-year period (2015–2018) and was extracted from the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database,[8,9] which includes more than 5 million patients, over 2 million records, and 500 million prescriptions (as of December 2017).[10] This project was approved by the University of Surrey's Institutional Review Board (353003-352994-40371074).

Study population

Figure 1 shows the inclusion and exclusion criteria, which yielded 6,883 patients.

[Figure 1 about here]

To be included, a patient needed to have a Read code[11] for COPD diagnosis, a diagnosis of at least one cardiovascular comorbidity, be older than 35 years of age, be a current or former smoker (i.e., ex-smoker), not have active asthma, have a Forced Expiratory Volume in 1 second to Forced Vital Capacity Ratio (FEV1/FVC ratio) of less than or equal to 0.7 (i.e., the threshold for COPD diagnosis[1]) and have follow-up FEV1 values recorded for 3 consecutive years. Recent

research confirms that a period of 3 years is an ideal timespan to account for clinically relevant FEV1 variations in COPD patients.[12]

We excluded patients who met one of the following: less than 35 years of age, never-smoker, active asthma, FEV1/FVC ratio greater than 0.7 and lacking 3 consecutive years of FEV1 tests.

Statistical analysis

We split our sample into two cohorts: a) the training cohort, consisting of patients who were registered with a GP before the COPD diagnosis, and b) the validation cohort, consisting of patients who were not registered until after their COPD diagnosis (Figure 2). Splitting the sample into two independent cohorts on the basis of such a clear-cut objective criterion (i.e., before and after COPD diagnosis), rather than randomly, allows the algorithms to unambiguously learn how to identify COPD phenotypes and classify patients into cardiovascular comorbidities at an early stage of the disease. In other terms, this is because the algorithms' learning step occurs among patients not yet diagnosed with COPD. We then used the training clusters (i.e., those clusters learned prior to diagnosis) to predict new clusters in the cohort of patients after COPD diagnosis, and assessed their agreement as described below in the "Cluster validation" section. Similarly, we used the classification of patients into four cardiovascular comorbidities learned by the algorithms in the training cohort to predict new classes of cardiovascular comorbities in the validation cohort. Finally, we assessed the validity of the predicted classes by cross-examining them with the pre-existing (i.e., observed) cardiovascular comorbidities.

[Figure 2 about here]

To perform these analyses, we used two types of machine learning approaches well suited to: a) identify clusters (i.e., subtypes) of the cardiovascular phenotype, and b) predict cardiovascular comorbidities in a new cohort of patients with COPD. For the first objective, we used unsupervised learning where we had no prior knowledge of the classification of patients into clusters. Indeed, these clusters are just inferred from the relationships within the data, and they are the algorithms which assign labels to the derived phenotypes (see the "Clustering" section below). To predict cardiovascular comorbidities, our second goal, we instead used supervised learning. Here, the classification of patients into cardiovascular comorbidities was already known a priori from the dataset, and our aim was to predict future classes (i.e., cardiovascular comorbidities) in a new (blind) cohort (i.e., the cohort after COPD diagnosis). The classification algorithms that we used for this task are further described in the "Predictive models" section of this paper.

Data reduction

We used multiple correspondence analysis (MCA)[13] to reduce the dimensionality of the training cohort from 19 variables (sex, body mass index, smoking, COPD severity, COPD exacerbations, emphysema, diabetes, hypertension, coronary artery disease, acute myocardial infarction, congestive cardiac failure, anxiety, depression and six types of treatment) into three uncorrelated components. We then applied k-means cluster analysis to the three components to identify the groups of patients with similar characteristics (i.e., subtypes of the COPD cardiovascular phenotype). We imputed missing values for body mass index and COPD severity with Multivariate Imputation by Chained Equations (MICE).[14]

Clustering

We used a hierarchical cluster analysis[15] to visually inspect—with a dendrogram—the optimal number of clusters (Figure 3). We then confirmed the number of clusters by performing the elbow[16] and silhouette[17] methods (Figure 4).

[Figure 3 about here]

[Figure 4 about here]

Figure 5 compares the silhouette plots of the clusters derived from two clustering methods: hierarchical (top plot) and k-means (bottom plot). Specifically, we compared a) the magnitude of the average silhouette width, and b) the sign (positive or negative) of the silhouette width. The average silhouette width was larger under the k-means algorithm than under the hierarchical algorithm. More subjects had a negative silhouette width under the hierarchical algorithm than under k-means clustering, especially for clusters 1 and 3. We concluded that k-means clustering generates more stable clusters than the hierarchical approach.

[Figure 5 about here]

Cluster validation

After establishing the three phenotype subtypes with k-means clustering, we developed our predictive model. The Random Forest (RF) model uses as independent variables (or predictors) the 19 categorical variables described above in the MCA step, with the addition of age and lung function (FEV1). First, we used what we called "the RF training dataset" (i.e., 70% of the full training dataset, randomly selected; n = 4,166), to train the RF model on the clusters identified by k-means clustering.[16] Then, we tested the RF model on an holdout group of the training dataset, the "RF test dataset" (i.e., the remaining 30% of the training dataset; n = 1,785) and achieved 99% accuracy.

Next, we trained the same model on the full training dataset (i.e., the RF training and test datasets combined, which is ultimately the training cohort pre-COPD diagnosis) and checked the

predicted cluster assignments against the entire validation dataset, which is the cohort of patients post- COPD diagnosis (whose clusters were also derived with k-means clustering). We used the Adjusted Rand index[18] and Jaccard index[19] to compare the clusters predicted by the RF model with those derived by k-means clustering, and we found 92% agreement.

Predictive models

With three highly robust COPD cardiovascular phenotype subtypes established, we proceeded to train four different classifiers to predict cardiovascular comorbidities from other components of the phenotype (i.e., demographics, COPD severity, and COPD treatments). Specifically, we trained a decision tree, multinomial logistic regression, RF and gradient boosting machine.[20] We were interested in predicting four cardiovascular comorbidities: hypertension, coronary artery disease, acute myocardial infarction and congestive cardiac failure. We trained each classifier on the RF training dataset and tested the optimised classifier on the RF test dataset. Once each model was finely tuned by using automated tuning within the R library 'caret',[21] we trained it on the whole training dataset and assessed its performance on the validation dataset.

All four models used cardiovascular comorbidities as the dependent variable and the following variables as predictors: age, sex, body mass index, smoking, COPD severity, COPD exacerbations, emphysema, lung function (FEV1), diabetes, anxiety, depression and type(s) of treatment (Inhaled Corticosteroids (ICS), ICS and Long-Acting Beta Agonist (LABA), Long-Acting Anti-Muscarinic (LAMA), LABA, Short-Acting Anti-Muscarinic (SAMA), mucolytics).

Moreover, in light of the class imbalance (i.e., a disparity in the distribution of patients with cardiovascular comorbidities), we re-trained the models with two sub-sampling methods: a) up-sampling, in which we randomly sampled (with replacement) the minority class until it was the same size as the majority class, and b) down-sampling, in which we randomly sampled (with replacement) the majority class until it was the same size as the minority class. The models were then evaluated on the blind validation dataset. All statistical analyses were implemented with the statistical software R.[22]

Results

Patient characteristics

Table 1 summarizes the descriptive baseline characteristics (Year 1) of patients who were registered with a GP before their COPD diagnosis and after diagnosis.

[Table 1 about here]

Prior to COPD diagnosis

Table 2 presents the baseline characteristics of the three subtypes of the COPD phenotype among patients with cardiovascular comorbidities who established care with a GP before their COPD diagnosis.

[Table 2 about here]

Phenotype A was characterized by the highest prevalence of severe COPD (as defined by the physician), substantial emphysema and nearly universal hypertension (though this was also true of phenotype C). Phenotype A was the most heavily medicated; almost all patients with this phenotype were treated with ICS and/or a combination of ICS and LABA; more than half were also treated with LAMA. Phenotype B was characterised by a large majority of male patients (whereas males comprised a small majority of the other phenotypes). Phenotype B had the lowest prevalence of hypertension but the highest prevalence of coronary artery disease, acute myocardial infarction, congestive cardiac failure, and diabetes. Just under half of the phenotype B patients were treated with LAMA; the next most common medications were ICS, followed by ICS with LABA. Phenotype C was characterised by universal hypertension (similar to phenotype A), though phenotype C had the lowest prevalence of severe COPD, the highest prevalence of mild COPD and the largest majority of patients with no exacerbations in the past year. Overall, patients with phenotype C were less medicated than the other phenotypes; the most common treatment was LAMA, though only about one-third of phenotype C patients used it. The most notable characteristics of each of the three phenotypes are summarized in Table 3.

[Table 3 about here]

Predicting cardiovascular comorbidities after COPD diagnosis

We tested the four trained classifiers on the validation dataset (i.e., post-COPD diagnosis), and we present the results in confusion matrices (Table 4). For each predictive model (i.e., each classifier), Table 4 compares the number of patients predicted to have each cardiovascular comorbidity with the actual number of diagnoses; it also reports the classifier's overall accuracy, sensitivity (i.e., the percentage of positive cases that were predicted to be positive), specificity (i.e., the percentage of negative cases that were predicted to be negative), positive predictive value (PPV, i.e., the percentage of positive predictions that were actually positive cases) and negative predictive value (NPV, i.e., the percentage of negative predictions that were actually negative cases).

[Table 4 about here]

As shown in Table 4, the RF classifier (even without sub-sampling) outperformed the other models. All models exhibited relatively high sensitivity and low specificity for hypertension, but the RF classifier had the highest sensitivity (87%) and PPV (98%, versus 34%–40% in the other models). All models exhibited relatively low sensitivity and high specificity for the other three cardiovascular comorbidities (coronary artery disease, acute myocardial infarction and congestive cardiac failure), but RF was the most accurate at ruling out these conditions (NPV: 99% for all three conditions, versus 74–85% in the other models).

Discussion

This study presents the use of machine learning toward acquiring a better characterization of the cardiovascular phenotype in patients with COPD and predicting specific cardiovascular comorbidities linked to these patients. Given the substantial contribution of cardiovascular disease to morbidity and mortality in COPD and the complexity of the cardiovascular phenotype we believe that our findings can offer several beneficial avenues to respiratory researchers and clinicians alike. For one example, by identifying subtypes of the cardiovascular phenotype and predicting future cardiovascular comorbidities early (i.e. prior to COPD diagnosis), it is possible to better understand of the disease's development, and consequently improve disease management, possibly prevent the development of cardiovascular disease, and thus lead to the application as well as development of targeted treatments.

Here, we specifically examined four cardiovascular comorbidities—hypertension, coronary artery disease, acute myocardial infarction and congestive cardiac failure—and used basic demographic information, COPD severity, and types of COPD treatments to predict a patient's phenotype. Two of the phenotypes (A and C) had almost universal hypertension but differed in COPD severity and treatment. Meanwhile, the third phenotype (B) had a lower prevalence of hypertension but a higher prevalence of coronary artery disease, acute myocardial infarction and congestive cardiac failure, as well as diabetes.

The large size of our training sample enabled the model to predict patients' phenotypes with high accuracy (92%). This encouraging result suggests that the three identified phenotypes may generalize to other datasets and populations of patients with COPD. Our use of statistical and machine learning tools went beyond a traditional summary of the demographic and clinical characteristics of patients with COPD, which offer little in the way of predictive diagnostics. We tested several algorithms, from a conventional multinomial logistic regression model to stronger classifiers such as the RF and gradient boosting machine, which are ensembles of weaker classifiers (i.e., classifiers with low predictive power such as decision trees are combined into classifiers with stronger predictive ability).

Moreover, we handled incomplete observations with multiple imputation, and we addressed class imbalance (i.e., unequal numbers of patients with each cardiovascular comorbidity) with additional sampling methods (namely, up- and down-sampling). We assessed the performance of our four candidate models by calculating the overall accuracy (86% for RF) as well as the sensitivity, specificity, PPV, and NPV for each comorbidity. The data showed that all four classifiers, and RF in particular, were highly sensitive in predicting hypertension (highly prevalent in phenotypes A and C) and highly specific in predicting the other three (less prevalent) cardiovascular comorbidities (coronary artery disease, acute myocardial infarction and congestive cardiac failure). These findings are of substantial clinical importance because these algorithms can be used as diagnostic tools for preventing cardiovascular disease. We indeed note that the information inputed in the models is readily acquirable during any medical visit, hence

offering the opportunity of rapid implementation of our framework in the clinical practice toward anticipatory diagnosis and improved medical predictions.

Finally, our findings suggest that patients clustered into three cardiovascular phenotypes also had different treatment patterns. Spefically, patients with less severe COPD (phenotype C) received less treatments; those with high prevalence of coronary artery disease, acute myocardial infarction and congestive cardiac failure and diabetes had an intermediate level of treatment (phenotype B); and, those with more severe COPD were the most-treated (phenotype A). These results are also clinically salient because they can assist clinicians to differentially treat these groups of patients, thus minimizing costs and adverse events of less-effective treatments. This categorization will also help future research toward the development of personalized therapies based on the patients' phenotype characteristics.

Limitations

We acknowledge four main limitations of this work that however represent important calls for future research. First, cluster analysis is a data-driven machine learning method; for this reason, the clusters (i.e., the phenotypes) derived bring no substansive meaning. They are formed by identifying groups of patients with similar characteristics (i.e., phenotype A, B or C); however the clinician still has to meaningfully interpret and label those clusters. While this interpretation remains a subjective task within the the medical encounter, our categorization here provides a blueprint toward a more refined and standardized understanding of the heterogenous nature of the disease. Future research is thus tasked to provide clinical consensus to the meaning of the phenotypes identified in this work to enable their implementations in the everyday medical practice. Second, we considered patients with at least three consecutive years of follow-up spirometry data because this allowed us to assess more reliable lung function measures and feed more complete lung function data into the predictive models. Including patients with different follow-up times - which often happens in real clinical practice - could have given us different results. Future research may test the robustness of our results by performing a sensitivity analysis by including those patients with less follow-up period of lung function recordings. Third, the RCGP database lacked data on relevant biomarkers, such as cytokines, that are well-known to be associated with coronary artery disease and myocardial infarction.[23] Should such biomarkers be available, our models would become even more accurate in predicting those less prevalent cardiovascular comorbidities and subsequently improve the sensitivity and PPV rates. Finally, the RCGP database covers a limited number of cardiovascular comorbidities, so the predictions are not exhaustive. All of these limitations could be addressed in the future by applying our models to other COPD datasets (e.g., the OPCRD database[24]).

Conclusions

To the best of our knowledge, this study is the first to implement machine learning to identify clinically meaningful phenotypes of cardiovascular comorbidities that develop after a COPD diagnosis, though we are not the first to apply machine learning to COPD in general.[3]

We used k-means clustering to identify three phenotypes prior to COPD diagnosis, and we trained an RF model to predict these phenotypes in a different blind dataset (i.e., after COPD diagnosis). We achieved a high level of agreement (92%) between the predicted cluster assignments and those derived by k-means clustering. Moreover, we trained and validated four different classifiers (of which RF performed the best) to predict cardiovascular comorbidities based on patients' demographics, COPD severity, and COPD treatments. This model represents a robust preliminary framework for predicting cardiovascular comorbidities in patients with a COPD diagnosis, though the model's predictive power likely could be improved with the inclusion of other risk factors such as biomarkers.

The insights presented in this paper may inform GPs' medical decision making for acute complaints (namely, acute myocardial infarction and congestive cardiac failure) as well as screening and prevention (for hypertension, coronary artery disease, and diabetes) in patients with a COPD diagnosis. Validation of our framework in non-UK populations may contribute to a more nuanced understanding of the COPD cardiovascular phenotypes, ultimately improving treatment for cardiovascular comorbidities in COPD patients and enabling their prevention at an earlier stage.

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Guarantor Statement:

Vasilis Nikolaou agrees to be accountable for all content and aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author Contributions:

Vasilis Nikolaou had full access to and analysis of the data. All authors were involved in the conception and design of the study, the interpretation, as well the critical revision of the manuscript. Vasilis Nikolaou and Sebastiano Massaro were responsible for drafting the manuscript. The study was supervised by Wolfgang Garn, Masoud Fakhimi and Lampros Stergioulas. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work.

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Table 1. Baseline (Year 1) demographic and clinical characteristics of patients with cardiovascular comorbidities who established care with a GP before and after COPD diagnosis

Variables	Prior to COPD diagnosis (n = 5,951)	After COPD diagnosis (n = 932)	Total (n = 6,883)
Age, mean (SD), years	72 (9)	72 (9)	72 (9)
Sex, Male, No. (%)	3,580 (60)	552 (59)	4,132 (60)
Body mass index, mean (SD), kg/m^2	28 (6)	27 (6)	28 (6)
Body mass index, No. (%) with data	5,937 (99)	925 (99)	6,862 (99)
Underweight	134 (2)	32 (3)	166 (2)
Normal weight	1,719 (29)	296 (32)	2,015 (29)
Overweight	2,220 (37)	315 (34)	2,535 (37)
Obese	1,864 (31)	282 (30)	2,146 (31)
Smoking status, No. (%)			
Active smoker	1,884 (32)	289 (31)	2,173 (32)
Former smoker	4,067 (68)	643 (69)	4,710 (68)
COPD severity, No. (%) with data	3,064 (51)	925 (52)	3,552 (52)
Mild	1,012 (33)	157 (32)	1,169 (33)
Moderate	1,532 (50)	244 (50)	1,776 (50)
Severe	477 (16)	82 (17)	559 (16)
Very severe	43 (1)	5 (1)	48 (1)
COPD exacerbations in the past year, mean (SD)	0.3 (0.9)	0.5 (1.0)	0.3 (1.0)
COPD exacerbations in the past year, No. (%)			
0	5065 (85)	728 (78)	5,793 (84)
1	509 (9)	104 (11)	613 (9)
2	225 (4)	40 (4)	265 (4)
> 2	152 (3)	60 (6)	212 (3)
FEV1, mean (SD), L	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)
Emphysema, No. (%)	320 (5)	106 (11)	426 (6)
Diabetes, No. (%)	1,322 (22)	208 (22)	1,530 (22)
Hypertension, No. (%)	5,317 (89)	823 (88)	6,140 (89)
Coronary artery disease, No. (%)	675 (11)	106 (11)	781 (11)
Acute myocardial infarction, No. (%)	822 (14)	144 (15)	966 (14)
Congestive cardiac failure, No. (%)	719 (12)	110 (12)	829 (12)
Anxiety, No. (%)	460 (8)	76 (8)	536 (8)
Depression, No. (%)	1,668 (28)	289 (31)	1,957 (28)
Treatment, No. (%)[a]			
ICS	2,675 (45)	527 (57)	3,202 (47)
ICS + LABA	2,341 (39)	481 (52)	2,822 (41)
LAMA	2,805 (47)	494 (53)	3,299 (48)
LABA	574 (10)	85 (9)	659 (10)
SAMA	335 (6)	54 (6)	389 (6)
Mucolytics	575 (10)	114 (12)	689 (10)

452 ICS: Inhaled Corticosteroids; LABA: Long-Acting Beta Agonist; LAMA: Long-Acting Anti-Muscarinic; SAMA:
453 Short-Acting Anti-Muscarinic

454

455 Table 2. Baseline (Year 1) phenotype characteristics prior to COPD diagnosis in patients with
456 cardiovascular comorbidities

	Phenotype		
Variables	**A (n = 2072)**	**B (n = 943)**	**C (n = 2936)**
Age, mean (SD), years	72 (8)	72 (9)	72 (9)
Sex, Male, No. (%)	1,199 (58)	732 (78)	1,649 (56)
Body mass index, mean (SD), kg/m^2	28 (6)	28 (5)	28 (6)
Body mass index, No. (%) with data	2,067 (99)	940 (100)	2,930 (99)
Underweight	56 (3)	16 (2)	62 (2)
Normal weight	595 (29)	269 (29)	855 (29)
Overweight	772 (37)	383 (41)	1,065 (36)
Obese	644 (31)	272 (29)	948 (32)
Smoking status, No. (%)			
Active smoker	586 (28)	297 (31)	1,001 (34)
Former smoker	1,486 (72)	646 (69)	1,935 (66)
COPD severity, No. (%) with data	1,196 (58)	493 (52)	1,375 (47)
Mild	288 (24)	154 (31)	570 (41)
Moderate	583 (49)	262 (53)	687 (50)
Severe	295 (25)	72 (15)	110 (8)
Very severe	30 (3)	5 (1)	8 (1)
COPD exacerbations in the past year, mean (SD)	0.5 (1)	0.2 (0.7)	0.1 (0.5)
COPD exacerbations in the past year, No. (%)			
0	1,584 (76)	815 (86)	2,666 (91)
1	239 (12)	77 (8)	193 (7)
2	128 (6)	33 (3)	64 (2)
>2	121 (6)	18 (2)	13 (1)
FEV1, mean (SD), L	0.7 (0.2)	0.7 (0.2)	0.8 (0.2)
Emphysema, No. (%)	145 (7)	54 (6)	121 (4)
Diabetes, No. (%)	444 (21)	249 (26)	629 (21)
Hypertension, No. (%)	2,055 (99)	326 (35)	2,936 (100)
Coronary artery disease, No. (%)	59 (3)	500 (53)	116 (4)
Acute myocardial infarction, No. (%)	93 (4)	617 (65)	112 (4)
Congestive cardiac failure, No. (%)	174 (8)	379 (40)	166 (6)
Anxiety, No. (%)	165 (8)	67 (7)	228 (8)
Depression, No. (%)	584 (28)	278 (29)	806 (27)
Treatment, No. (%)[a]			
ICS	2,054 (99)	402 (43)	219 (7)
ICS+LABA	1,981 (96)	353 (37)	7 (0.2)
LAMA	1,451 (70)	437 (46)	917 (31)
LABA	102 (5)	81 (9)	391 (13)
SAMA	114 (6)	50 (5)	171 (6)
Mucolytics	380 (18)	104 (11)	91 (3)

457 ICS: Inhaled Corticosteroids; LABA: Long-Acting Beta Agonist; LAMA: Long-Acting Anti-Muscarinic; SAMA:
458 Short-Acting Anti-Muscarinic

459 Table 3. Phenotype characteristics of patients with cardiovascular comorbidities prior to COPD diagnosis

Phenotype A	**Phenotype B**	**Phenotype C**
Highest prevalence of severe COPD	Larger majority of males	Lowest prevalence of severe COPD
Emphysema (more prevalent)	Highest prevalence of three cardiovascular comorbidities:	Zero COPD exacerbations (large majority)
Hypertension (almost all)	Coronary artery disease	Hypertension (all)
Most-treated overall	Acute myocardial infarction	Least-treated overall
ICS (nearly all)	Congestive cardiac failure	LAMA (one-third)
ICS+LABA (nearly all)	Highest prevalence of diabetes	
LAMA (large majority)	Intermediate level of treatment:	
Mucolytics	ICS (almost half)	
	ICS+LABA (one-third)	
	LAMA (almost half)	

460 ICS: Inhaled Corticosteroids; LABA: Long-Acting Beta Agonist; LAMA: Long-Acting Anti-Muscarinic; SAMA:
461 Short-Acting Anti-Muscarinic

462 Table 4. Confusion matrices of four models predicting cardiovascular comorbidities in patients with
463 COPD

Random Forest (no sampling)		**Observed**			
		Hypertension	**Coronary artery disease**	**Acute myocardial infraction**	**Congestive cardiac failure**
Predicted	**Hypertension**	3382	19	12	21
	Coronary artery disease	156	4	0	0
	Acute myocardial infraction	188	0	4	1
	Congestive cardiac failure	157	0	2	0
Statistics	**Accuracy (%) (95% CI)**	86 (85, 87)			
	Sensitivity (%)	87	17	22	0
	Specificity (%)	17	96	95	96
	PPV (%)	98	3	2	0
	NPV (%)	2	99	99	99
Decision Tree (up-sampling)		**Hypertension**	**Coronary artery disease**	**Acute myocardial infraction**	**Congestive cardiac failure**
Predicted	**Hypertension**	1193	752	738	751
	Coronary artery disease	64	53	19	24
	Acute myocardial infraction	53	47	40	53

	Congestive cardiac failure	42	34	34	49
Statistics	**Accuracy (%) (95% CI)**	34 (32, 35)			
	Sensitivity (%)	88	6	5	6
	Specificity (%)	14	97	95	96
	PPV (%)	35	33	21	31
	NPV (%)	69	78	79	78
Gradient boosting machine (up-sampling)		**Hypertension**	**Coronary artery disease**	**Acute myocardial infraction**	**Congestive cardiac failure**
Predicted	**Hypertension**	1367	895	549	623
	Coronary artery disease	46	66	21	29
	Acute myocardial infraction	57	49	42	45
	Congestive cardiac failure	51	40	20	48
Statistics	**Accuracy (%) (95% CI)**	39 (34, 40)			
	Sensitivity (%)	89	6	7	6
	Specificity (%)	15	97	95	96
	PPV (%)	40	40	22	30
	NPV (%)	70	74	84	82
Multinomial logistic regression (up-sampling)		**Hypertension**	**Coronary artery disease**	**Acute myocardial infraction**	**Congestive cardiac failure**
Predicted	**Hypertension**	1167	874	484	909
	Coronary artery disease	45	67	21	27
	Acute myocardial infraction	46	55	29	63
	Congestive cardiac failure	36	49	20	54
Statistics	**Accuracy (%) (95% CI)**	33 (32, 35)			
	Sensitivity (%)	90	6	5	5
	Specificity (%)	15	97	95	96
	PPV (%)	34	42	15	34
	NPV (%)	75	74	86	74

464 CI: Confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value

465

Figure 1. Flow chart of the study cohort

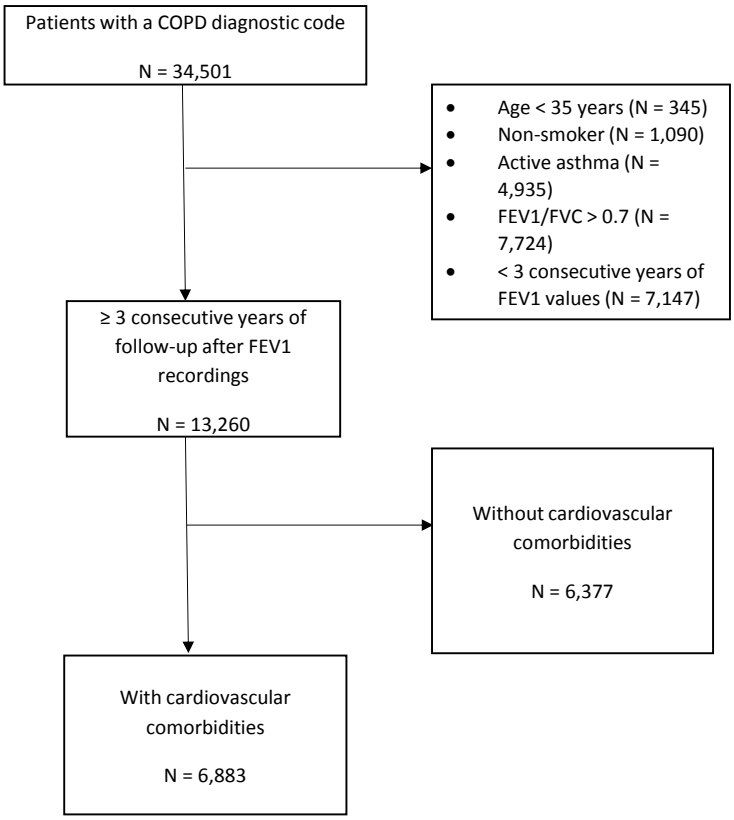

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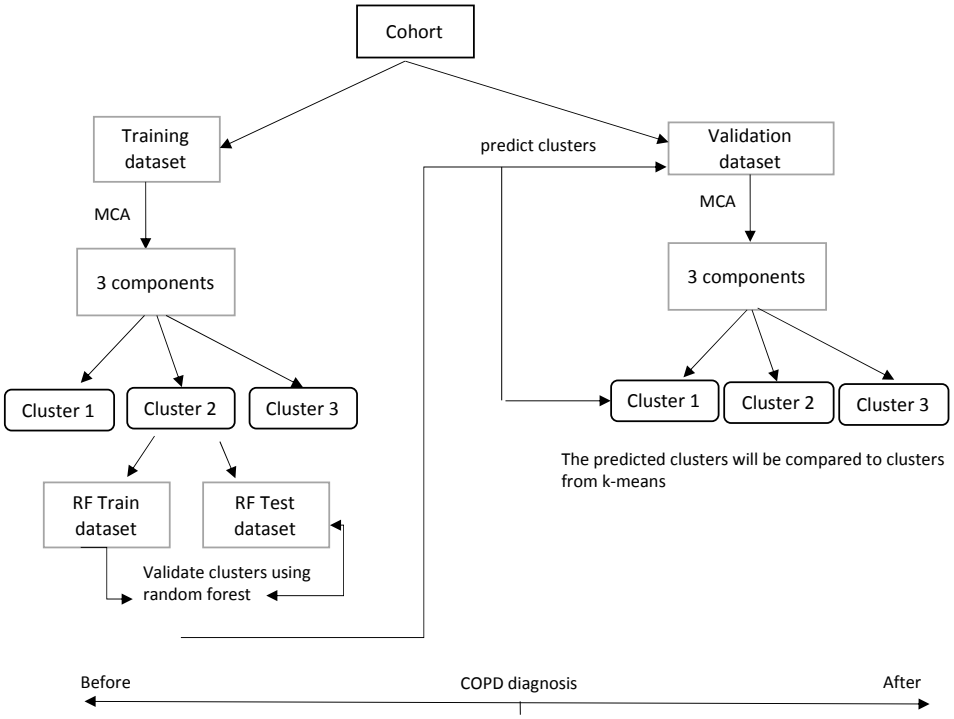
Figure 2. Main steps in phenotype identification before and after COPD diagnosis



467

Figure 3. Inspecting the number of clusters using hierarchical analysis in the training dataset

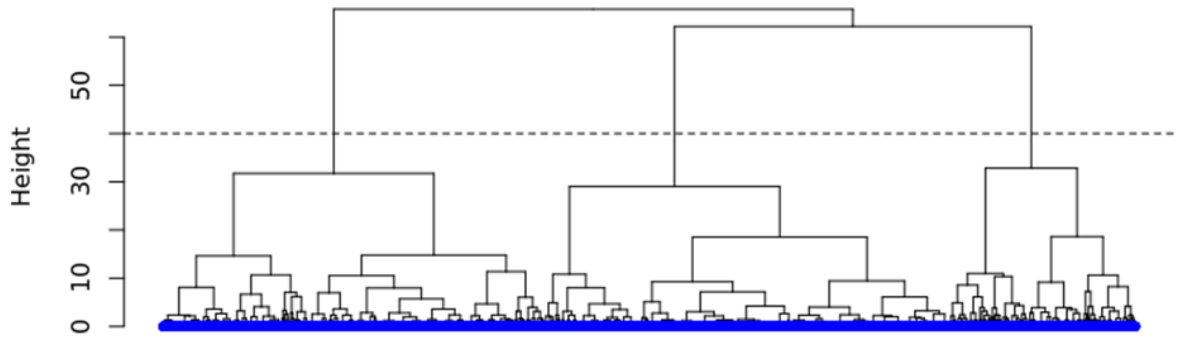


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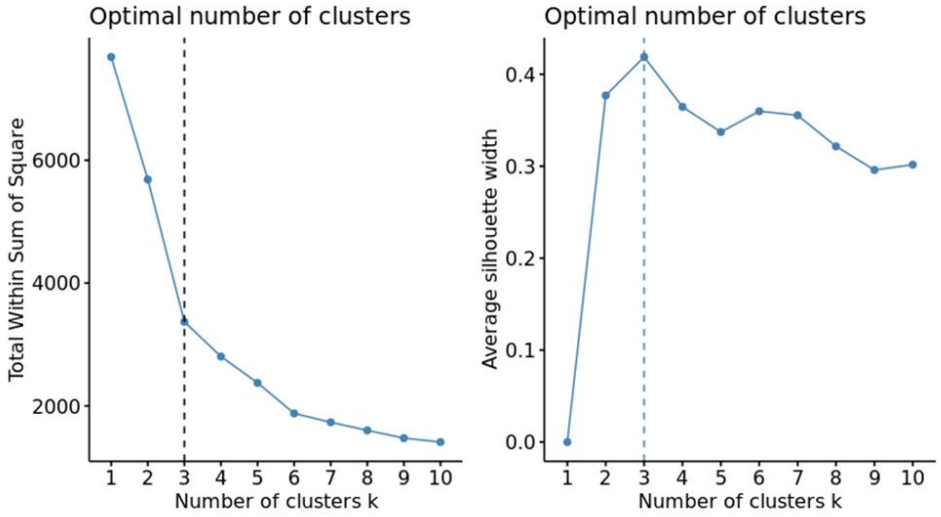
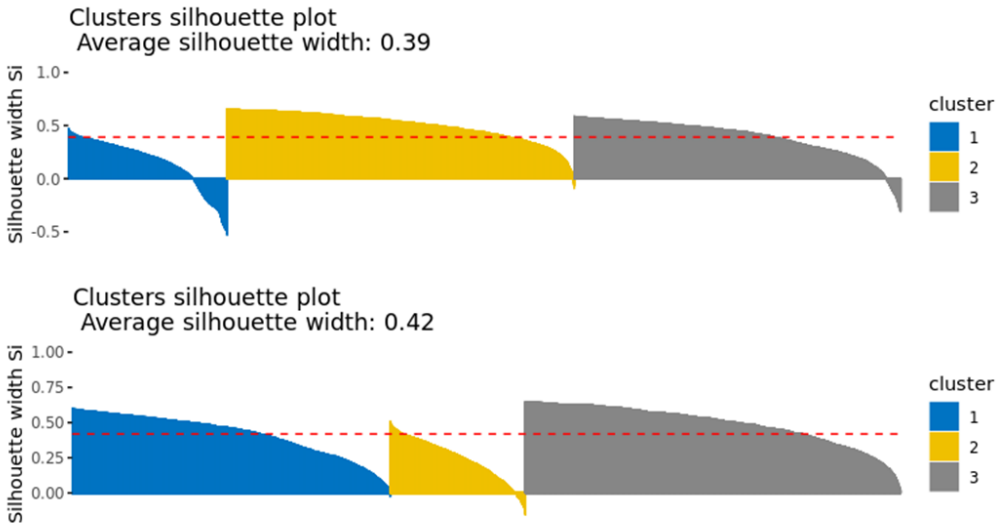
Figure 4. Determining the optimal number of clusters for the training dataset



470

Figure 5. Silhouette plots to determine the optimal clustering method – hierarchical (top) and k-means (bottom).



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Reviewer 1

Thank you for your attempt to group COPD patients' characteristics and relate them to CV comorbidities. It appears to be an interesting idea to then assess risk of issues such as CAD and CHF based on phenotypic properties of the COPD patients.

> *Thank you for your positive and constructive feedback. We are pleased to read that you valued our effort in associating COPD phenotypes with cardiovascular comorbidities (CV) toward better understanding the COPD cardiovascular phenotype and related issues.*

You have used machine learning in a population to assess these relationships, but how these were chosen were not clear. Recognize that most respiratory clinicians will not have the intimate knowledge of machine learning that you have.

> *Thank you for your request to further clarify our methodological selection. We appreciate that most respiratory clinicians might not have substantial expertise in machine learning. Thus, we added a 'lay' paragraph in the "Statistical analysis" section of the paper (page 2; lines 162-173) in which we describe in what ways the two main types of machine learning methods chosen (supervised and unsupervised) are well suited to address the specific objectives of this study. In sum, we used unsupervised learning, where we have no prior knowledge of the classification of patients into clusters, to group patients who share common characteristics with the use of hierarchical and k-means clustering. We also used supervised learning, where the classification of patients into CV comorbidities is known, to predict future CV comorbidities in a new dataset with the use of four classifiers (decision tree, multinomial logistic regression, random forest and gradient boosting machine).*

I think you may have been better to do the sampling and then first test it on a holdout group of the initial groups of patients before testing it on an outside cohort.

> *Thanks for raising this issue. We indeed first divided the sample in two cohorts, tested our models first on an 'holdout' subset of the training dataset (i.e., the RF test dataset) and then on the outside cohort (i.e., the entire validation dataset post-COPD diagnosis). We understand that the procedure, which is the norm in the machine learning literature, may appear a bit convoluted to the clinical readers, and that our initial framing was somewhat cumbersome, therefore we have now edited this passage to avoid any possible misunderstanding moving forward (Figure 2 and pages 3-4, lines 203-211 and 221-223).*

I am unclear, despite your discussion, on how this would be clinically useful. I think this needs to be expanded and much more clear

> *Thank you for raising our attention on the importance of highlighting further clinical implications. In the introduction and in the discussion sections, we have now expanded on the clinical relevance of our contribution (page 1, lines 111-116; page 6, lines 282-291). Moreover, we explained the usefulness of predicting the cardiovascular comorbidities with high degree of sensitivity (or specificity) toward preventing cardiovascular disease (page 6; lines 312-320), as*

well as the clinical importance of identifying different treatment patterns in patients with different phenotypes (page 7; lines 321-329). Finally, we highlight that the clinical interpretation of the derived phenotypes can be more generally beneficial in furthering knowledge on the heterogeneous nature of COPD (page 7; lines 332-340).

I believe that there is great potential for machine learning to discover relationships in patients and this premise is an excellent one. It just needs to be clarified better to the reader.

We share your enthusiasm on the use of machine learning to identify relationships in patient data; we are confident that our work can contribute to this emerging research trend moving forward. We appreciate that in some parts of our initial submission we were too technical, and this resulted at times in a somewhat convoluted narrative to the clinical reader. We therefore thank you for the valuable input that has allowed us to streamline our work and, we believe, to greatly improve its presentation.

Reviewer 2

In this manuscript Nikolaou and colleagues have evaluated the prediction of cardiovascular comorbidities in COPD patients with at least one cardiovascular comorbidity in a 4-year observational cohort of 6,883 UK patients. The study is overall interesting, yet some issues need to be clarified by the authors.

Thank you for your positive feedback and useful suggestions. We tackled your comments in our responses below.

Why did the authors decide to include patients with a diagnosis of COPD and at least one cardiovascular comorbidity?

The main aim of this work is to characterize COPD patients with cardiovascular (CV) comorbidities. The cardiovascular phenotype is one of the most clinically relevant phenotypes to analyse, given that cardiovascular disease is the major contributor to morbidity and mortality in patients with COPD[1]. As such, we included patients who satisfied two clear-cut inclusion criteria: a) having a COPD diagnosis, and b) at least one of the four cardiovascular comorbidities that were available in the dataset used. We selected at least one CV because within the burgeoning literature on COPD phenotypes some authors[2] have suggested that even one ischemic heart disease comorbidity alone could represent a self-standing COPD phenotype.

Was this a new diagnosis of a comorbidity or an existing one?

The CV diagnosis was pre-existing and provided in the dataset used. We clarify this aspect when describing our inclusion criteria at page 1, lines 136-137.

Were the additional CV comorbidities incident or pre-existing or both?

Pre-existing CV comorbidities are the observed ones, while additional CV comorbidities are those predicted by our models. We make this clearer in the statistical analysis section where we describe the cross validation used (page 2 lines 156-159).

A prediction model would be useful for newly diagnosed comorbidities.

Thanks for your remark. We fully agree with you and indeed we developed four prediction models—i.e., the 'classifiers'— (page 4, lines 215-234) able to forecast new CV comorbidities; these were cross validated against pre-existing comorbidities. Our research design also allowed us to assess the performance of each model (Table 4). We further explained this aspect of our contribution in the section "Predicting cardiovascular comorbidities after COPD diagnosis".

Why did the authors require FEV1 values for 3 consecutive years?

Thanks for raising this question. This is a longitudinal study of patients with COPD where the lung function is an important factor of patients' health. Thus, we reasoned that it would be both methodologically and clinically appropriate to include patients with complete (i.e., not missing) FEV1 values throughout the study period. This approach is also consisted with recently published works suggesting that a period of 3 years is an ideal timespan to account for clinically relevant FEV1 variations[3] in COPD patients.

Is this inclusion criterion for this study or part of another study? This is not likely to be relevant with the outcomes of interest in this study.

This is an inclusion criterion for this study. We agree that three consecutive years of lung function measures shall not be seen as an outcome variable here; indeed, assessing lung function is not the goal of this study. We however believe that lung function is an important contributing factor to improve the analytical performance of our models. Generally speaking, the more data available concerning a certain construct (i.e., longitudinal FEV1 data for COPD), the better the predictive ability of the models. In other words, the more COPD related data there are, the more accurate the models' output on the phenotypes is. We have added an explanation on this issue in the discussion section (page 7, lines 340-342).

What was the reason for the split in the training and validation cohorts based on the timing of registration with a GP prior or after a COPD diagnosis?

Thanks for your question. We divided the sample into two cohorts: patients registered with a GP prior to their COPD diagnosis and those registered after diagnosis. This was done as a straightforward, unbiased methodological device to allow the algorithms to learn patterns in the data (i.e., how to group patients into COPD phenotypes and classifying them into four cardiovascular comorbidities) at an early stage of the clinical development of the disease (i.e., prior to COPD diagnosis). In this way, we could ensure that the computations were able to truly predict such classifications in a new (blind) dataset after COPD diagnosis, without any possible researcher bias affecting the group selection a priori. We have added a relevant paragraph in the

"Statistical analysis" section (page 2; lines 148-159) to make our overall research strategy clearer.

Was the latter timing synchronous with the diagnosis of COPD?

Not necessarily. We used the COPD diagnosis as a reference threshold: as explained above, in line with the principles of machine learning, we consider those patients who were registered with a GP before and after diagnosis in order to generate two independent cohorts of patients (see "Statistical analysis" section). One cohort was used to train our models, and another one to test them. We also would like to specify that the potential lack of synchronicity does not affect – at least methodologically – the rationale for and the performance of the models used.

What is the potential explanation for the marked difference in the size of the two cohorts?

The majority of patients in our sample were registered with a GP prior to COPD diagnosis (n=5951) and the remaining ones (n=932) were registered after their COPD diagnosis. The different sample size between these two groups is just a feature of the available dataset used. This also guarantees once again avoidance of selection biases from the researchers.

In phenotype A, most patients were treated with ICS and/or ICS/LABA. How can the authors be confident of a COPD diagnosis in patients receiving mono-ICS treatment, without a LABA or LAMA?

Thanks for your comment. As explained above, the nature of the data is given by the database used. In other terms, the COPD patients, were patients already fully diagnosed with COPD, and we did not infer their COPD diagnosis by looking at the treatments. Methodologically, cluster analysis is a data-driven method: it is possible to group together patients who share different features, such as treatments with ICS and/or ICS/LABA. That is, we can have patients diagnosed with COPD receiving mono-ICS treatment only. It just happened that in the sample, there were patients receiving either LABA or LAMA along with mono-ICS treatment. In any case, there are studies[4,5] available in the literature that suggest that COPD patients can receive only mono-ICS treatment as well.

In closing we would like to thank you for your thought-provoking and constructive feedback that has helped us greatly to improve our contribution.

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Original research

Vasilis Nikolaou et al.

The Cardiovascular Phenotype of Chronic Obstructive Pulmonary Disease (COPD): Applying Machine Learning to the Prediction of Cardiovascular Comorbidities

Vasilis Nikolaou, M.Sc. [1]; Sebastiano Massaro, Ph.D.[1,2]; Wolfgang Garn, Ph.D.1; Masoud Fakhimi, Ph.D.[1]; Lampros Stergioulas, Ph.D. [3]; David Price FRCGP[4,5,6]

Affiliations:

[1] University of Surrey, Surrey Business School, Guildford GU2 7HX, United Kingdom.

[2] The Organizational Neuroscience Laboratory, London WC1N 3AX, United Kingdom.

[3] The Hague University of Applied Sciences, Johanna Westerdijkplein 75, 2521 EN Den Haag, Netherlands

[4] Optimum Patient Care, Cambridge, UK; [5]Observational and Pragmatic Research Institute, Singapore, Singapore; [6]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom

Highlights

- A large observational study that characterizes the COPD cardiovascular phenotype.
- Three phenotypes were identified and reproduced to another population.
- These phenotypes were characterized by different COPD severity and treatments.
- Random Forest was highly accurate at predicting cardiovascular comorbidities.

Credit Author Statement:

Vasilis Nikolaou agrees to be accountable for all content and aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author Contributions:

Vasilis Nikolaou had full access to and analysis of the data. All authors were involved in the conception and design of the study, the interpretation, as well the critical revision of the manuscript. Vasilis Nikolaou and Sebastiano Massaro were responsible for drafting the manuscript. The study was supervised by Wolfgang Garn, Masoud Fakhimi and Lampros Stergioulas. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work.