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Susceptibility to frequent exacerbation in COPD patients: impact of the exacerbations history, vaccinations and comorbidities?

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Abbreviation list:

COPD = Chronic Obstructive Pulmonary Disease; **CNIL** = Commission nationale de l'informatique et des libertés National (Data Protection and Privacy Commission); **CCTIRS** = Advisory Committee for Data Procession in Health Research; **FEV₁** = Forced Expiratory Volume in 1 second; **FVC** = Forced vital capacity; **RV** = Residual Volume; **TLC** = Total Lung Capacity; **EELV** = The end-expiratory lung volume; **VC** = Vital Capacity; **IC** = Inspiratory Capacity; **FRC** = Functional residual Capacity; **BMI** = Body Mass Index; **GOLD** = Global Initiative for Chronic Obstructive Lung Disease; **mMRC** = modified Medical Research Council; **CAT** = COPD Assessment Test; **ATS** = the American Thoracic Society; **ERS** = the European Respiratory Society; **PFT**= pulmonary function test; **LABA** = long-acting β -agonist; **LAMA** = long-acting muscarinic antagonist; **ICS** = inhaled corticosteroid; **SABA** = short-acting β -agonist; **RNIPP** = Répertoire national d'Identification des personnes physiques (National identification register of private individuals). **ROC** = receiver operating characteristic.

ABSTRACT

INTRODUCTION: Exacerbations are key events in the natural history of COPD, but our understanding of their longitudinal determinants remains unclear. We used data from a large observational study to test the hypothesis that vaccination status and comorbidities could be associated with the occurrence of exacerbations profile.

METHODS: Diagnosed COPD patients have been included by their pulmonologists, with up to 3 years of follow-up. Data were analyzed using the KmL method designed to cluster longitudinal data and receiver operating characteristic curve analysis to determine the best threshold to allocate patients to identified clusters.

RESULTS: 932 COPD patients were included since January 2014, 446 patients (65.68% males, 35.59% current smokers) were followed over a period of 3 years with complete data. 239(28.15%) patients reported two or more exacerbations in the year before enrolment (frequent exacerbations). Among them 142(16.68%) also had frequent exacerbations in the first year of the study, and 69(8.10%) who remained frequent exacerbators in the second year. Based on our hypothesis, we were able to determine four phenotypes: A (infrequent), B (frequent in underweight patients), C (transient), and D (frequent in obese patients). Frequent exacerbators had more airflow limitation and symptoms. Irrespective of cut-offs set to define the optimal number of clusters, a history of exacerbations OR: 3.72[2.53-5.49], presence of anxiety OR: 2.03[1.24-3.31] and absence of the annual influenza vaccination OR: 1.97[1.20-3.24] remained associated with the frequent exacerbator phenotypes.

CONCLUSIONS: The most important determinants of frequent exacerbations are a history of exacerbations, anxiety and unvaccinated against influenza.

KEY WORDS: COPD Phenotypes, Frequent Exacerbator, Cluster analysis, longitudinal analysis.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the airways characterized by an airflow limitation that is not fully reversible [1] and remains a highly prevalent [2] disease. Several phenotypes have been described with a focus on frequent exacerbator profile. Exacerbations become increasingly frequent and severe as COPD progresses [3], impacting lung function, morbidity, and mortality [4-7]. The causes of COPD exacerbations are not well known, and they can occur across all stages of airflow limitation.

Several models predicting exacerbations in COPD patients have been published reporting combinations of information from patient history, clinical characteristics and lung function. Though, it is still unclear which prediction model predicts exacerbations most accurately and applicable in daily practice.

Previous work on risk factors of COPD exacerbations confirms that a recent history of exacerbations is the strongest risk predictor of future exacerbations. However, this theory has not been adequately investigated because our current understanding of COPD exacerbations and their relationship to disease severity is based on large intervention studies or multiple smaller studies that have used varying definitions of exacerbation.

The ECLIPSE investigators suggested that individuals with two or more exacerbations in a given year represent a distinct frequent exacerbator phenotype [3]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guide [1] to COPD diagnosis and management uses a threshold of two or more acute exacerbations in the previous year, or at least one hospital admission related to an acute exacerbation, to identify individuals at high risk of future events (groups C and D). However, intra-subject variability of annual exacerbation frequency limits the ability of these criteria to predict the future risk of exacerbations at an individual level [3, 8].

The French cohort (Initiatives-BPCO) identified four phenotypes from which phenotype 1 was characterized by 4 exacerbations per year [9]. The SPIROMICS study reported a markedly lower proportion of stable frequent exacerbators over 3 years (2.00%) compared to the ECLIPSE cohort (12.00%) and the French cohort (EXACO) (7.00%) [3, 2, 10]. Some studies suggested a third intermediate phenotype called infrequent exacerbators, which includes patients with one exacerbation per year [3, 8, 11-13].

Most COPD patients with frequent exacerbations have comorbidities. A recent study demonstrates a salient influence of the cardiovascular comorbidities on the appearance of COPD-related respiratory exacerbations [14].

Psychiatric comorbidities such as anxiety and depression have a negative impact on exacerbation frequency [15]. A Chinese prospective cohort study report that the total number of exacerbations were higher in COPD patients with bronchiectasis [16]. The retrospective observational Korean study (KNHANES) showed that the metabolic syndrome increased the frequency of exacerbations in women with early COPD [17]. In addition, some comorbidities may mimic an exacerbation of COPD (e.g. ischemic heart disease) [15].

No definitive evidence exists about the impact of prevention of COPD exacerbations in reducing mortality, and current pharmacological treatments decrease exacerbations but do not abolish them [18-20]. Inhaled treatment aims to reduce exacerbation frequency in COPD but its impact is usually not taken into account in observational studies. Another aspect of management is vaccination status, recommended in clinical practice to reduce the number of exacerbations, however the impact of vaccinations on exacerbations rates in a real-life study is unknown: Two systematic Cochrane reviews showed a reduction in exacerbations in COPD patients for annual influenza and pneumococcal vaccinations versus control [21, 22]. The authors of a recent systematic review reported the acceptable safety profile of influenza vaccines in COPD patients [23]. Also Influenza vaccination has been shown to reduce the incidence of COPD exacerbations [24]. Descriptive population-based and cohort studies have shown that influenza vaccination significantly reduces hospitalizations and mortality in COPD patients [25-27]. Recently, Exacerbation rates were associated with influenza vaccination in the multicenter retrospective Turkish cohort [28].

We used data from a large observational study to test the hypothesis that vaccination status and comorbidities could be associated with the occurrence of exacerbations profile, taking into account inhaled treatment.

METHODS

Study design and population

The Palomb project is an ongoing, prospective, multicenter, observational cohort of COPD patients recruited in pulmonary clinics in South-West of France and followed up for 3 years. The study period started from 1st January 2014 (cohort entry date) and finished at 1st January 2018 (death, left practice or end of follow-up).

932 patients were enrolled and followed up by pulmonologists. Data was obtained using a web-site questionnaire filled by the pulmonologists on a secure platform and with specific agreement obtained for the storage of health data. The inclusion criterion was a diagnosis of COPD: The diagnosis was made by a pulmonologist based on symptoms, smoking history and confirmed by lung function, according to the ATS / ERS standards [1]:

spirometry with post-bronchodilator FEV₁/FVC<70.00%. A pulmonary function test (PFT) was performed for COPD patients by pulmonologists at a clinic visit.

The CNIL (National Data Protection and Privacy Commission) and the CCTIRS (Advisory Committee for Data Processing in Health Research) approved the study, and informed verbal consent was obtained before enrollment. The authors had asked the local ethics committee for feedback regarding the need for ethical clearance for such a retrospective analysis and were advised that this was not warranted.

Definition of outcomes

The online questionnaire included many fields such as demographic criteria, smoking habits, symptoms, severity of airflow obstruction [29], BMI, medications, and comorbidities.

The case definition of an exacerbation was based on the decision by the pulmonologist and defined by an increase of cough and/or phlegm and/or dyspnea lead to antibiotics and/or systemic corticosteroids. The exacerbations data in the year before enrolment was collected at the baseline visit and in the follow up visits. The frequency of exacerbations was classified as none, one, and two or more exacerbations.

Static hyperinflation was defined by a baseline RV/TLC >120.00% of the predicted value [30-32]. Twenty-three comorbidities were systematically recorded by the pulmonologist (see annex). Comorbidity diagnosis was confirmed by the patient's report, and reviewing their medication list (Data not shown). At the annual clinical visit, use of long-acting muscarinic antagonists (LAMAs), long-acting beta-2 agonists (LABAs), short-acting beta-2 agonists (SABAs) and inhaled corticosteroids (ICS) was collected, along with pneumococcal and influenza vaccinations.

On the 1st January 2018, vital status was obtained for each participant through the national database that annually records the deaths of all French citizens, living inside or outside the French Territory (National Identification Register of Private Individuals, Répertoire National d'Identification des Personnes Physiques (RNIPP)) [33]. The information obtained by the RNIPP database was compared to the data recorded in the civil registration and less than 1% of discrepancies were noted. All dates of death were obtained for participants who died during the follow-up. Authorizations to use these data were obtained in accordance with the French law (CNIL).

Data Analysis

The first analysis, done at inclusion, allowed us to describe and characterize frequent exacerbation patients (≥ 2). The second, called the extended analysis, was a confirmatory analysis using complete information on annual

exacerbations, during each of the 3 years of follow-up. We used KmL analysis, which is an implementation of a nonparametric algorithm designed to work specifically on longitudinal data [34]. It identified clusters of patients with similar evolution of exacerbation frequency over the 3 years. Five different indexes were used to choose the optimal number of clusters: The Calinski and Harabatz index (version 1, 2 and 3), the Ray and turi index, and the Davies and Bouldin index [34]. Receiver operating characteristic (ROC) curve analysis was performed to identify the best threshold to separate clusters.

Statistically significant differences between patients and differences between groups were examined using student's t-test, chi-squared (χ^2), or fisher's exact tests, as appropriate. Independent variables included in the model were those showing a $P < 0.05$ in bivariate analysis. A logistic regression multivariate model with a backward elimination procedure was computed to identify factors associated with the frequent exacerbations groups. The model included the studied comorbidities and was adjusted for treatments and other parameters. All analyses were performed with SAS software version 9.4 and R version 3.3.2. Data were analyzed using packages KmL, version 2.4.1, pROC, version 1.8, and dplyr version 0.5.0 [34, 35].

RESULTS

Characteristics of the Patients

932 patients with COPD were included in the PALOMB cohort (**Figure 1**) and their characteristics are summarized in **Table 1**. They were mostly men (64.91%) who were current smokers with symptomatic COPD and mild to very severe airflow obstruction associated with frequent comorbidities. 252 (27.04%) patients reported two or more exacerbations in the previous 12 months. 44.44% women had more than two exacerbations compared to 55.56% of men ($P = 0.0003$). 546 patients were considered to have higher dyspnea (defined by mMRC scale ≥ 2).

Factors Associated with Exacerbations

The frequent exacerbations (≥ 2) were higher in men with COPD, women with COPD, GOLD stage III, GOLD stage IV, chronic cough, chronic sputum, current smokers, higher dyspnea, and hyperinflation. FEV₁, RV, TLC and RV/TLC ratio were related to the frequent exacerbations ($P < 0.0001$).

Considering comorbidities, hypertension and anxiety were higher in symptomatic COPD patients whereas apnea syndrome was more frequent in mild and asymptomatic COPD. The frequent exacerbations were higher in patients with anxiety (23.81%), depression (25.00%), diabetes (15.48%), undernutrition (5.16%) and osteoporosis (3.97%) (See **Figure 2**). In our cohort, patients with the frequent exacerbations (two or more exacerbations), compared with those with infrequent exacerbations (zero or one exacerbation) were more

intensively treated with COPD medications (See the **Table 2**). Dead patients were older and exhibited more severe airflow limitation. Longitudinal analysis was performed in 446 patients with at least 3 years of follow-up and complete data (See **Figure 1**).

Multivariate analysis revealed that the presence of comorbidities such as anxiety, diabetes and depression was significantly different between the groups and strongly related to the frequent exacerbations group (**Table 3**).

Table 1. Baseline characteristics of the patients stratified by infrequent (<2/year) or frequent exacerbators (≥2/year).

Subjects characteristics,		All COPD, n=932	Infrequent exacerbators (<2), n=680 (72.96)	Frequent exacerbators (≥2), n= 252 (27.04)	P Value
Variable names					
Males, n (%)	605 (64.91)	465 (68.38)	140 (55.56)	0.0003	
Age, yrs. Mean (SD)	66.22 (10.25)	66.33 (10.17)	65.94 (10.47)	0.6105	
BMI, (kg/m ²), mean (SD)	27.14 (14.52)	26.94 (6.25)	27.69 (26.01)	0.4871	
<21 (underweight), n (%)	163 (17.49)	108 (15.88)	55 (21.83)	0.1344	
[21-26](normal), n (%)	303 (32.51)	220 (32.35)	83 (32.94)		
[26-29](overweight), n (%)	170 (18.24)	126 (18.53)	44 (17.46)		
≥29 (obese), n (%)	296 (31.76)	226 (33.24)	70 (27.78)		
FEV1, % pred, Mean (SD)	57.53 (20.73)	59.24 (19.36)	52.92 (23.46)	0.0002	
GOLD stage I, >80%, n (%)	130 (13.95)	104 (15.29)	26 (10.32)	0.0003	
GOLD stage II, 50-80%, n (%)	449 (48.18)	341 (50.15)	108 (42.86)		
GOLD stage III, 30-50%, n (%)	282 (30.26)	196 (28.82)	86 (34.13)		
GOLD stage IV, <30%, n (%)	71 (7.62)	39 (5.74)	32 (12.70)		
Chronic cough, n (%)	521 (55.90)	341 (50.15)	180 (71.43)	<0.0001	
Chronic sputum, n (%)	398 (42.70)	256 (37.65)	142 (56.35)	<0.0001	
Current smokers, n (%)	328 (36.12)	237 (35.85)	91 (36.84)	0.7828	
Dyspnea, 0-1 mMRC, n (%)	386 (41.42)	321 (47.21)	65 (25.79)	<0.0001	
Dyspnea, ≥ 2 mMRC, n (%)	546 (58.58)	359 (52.79)	187 (74.21)		
Pulmonary rehabilitation, n (%)	62 (6.65)	23 (3.38)	39 (15.48)	<0.0001	
Smoking cessation, n (%)	90 (9.66)	64 (9.41)	26 (10.32)	0.6776	
RV, Mean (SD)	147.27 (53.6)	142.02 (52.38)	161.44 (54.37)	<0.0001	
TLC, Mean (SD)	105.02 (20.70)	103.34 (20.82)	109.56 (19.70)	<0.0001	
RV/TLC, % pred, Mean (SD)	137.84 (33.00)	135.15 (33.07)	145.12 (31.73)	<0.0001	
Hyperinflation (RV/TLC≥120%), n (%)	659 (70.71)	465 (68.38)	194 (76.98)	0.0104	

COPD Treatment	All COPD, n=932	Infrequent exacerbators (<2), n=680 (72.96)	Frequent exacerbators (≥2), n= 252 (27.04)	P Value
SABA, n (%)	369 (39.59)	248 (36.47)	121 (48.02)	0.0014
LABA, n (%)	292 (31.33)	215 (31.62)	77 (30.56)	0.7562
LAMA, n (%)	494 (53.00)	341 (50.15)	153 (60.71)	0.0041
LABA or LAMA, n (%)	621 (66.63)	441 (64.85)	180 (71.43)	0.0586
LABA and LAMA, n (%)	165 (17.70)	115 (16.91)	50 (19.84)	0.2980
Inhaled corticosteroids, n (%)	54 (5.79)	27 (3.97)	27 (10.71)	<0.0001
Fixed combination (ICS + LABA), n (%)	264 (28.33)	174 (25.59)	90 (35.71)	0.0023
LABA and LAMA and ICS, n (%)	29 (3.11)	11 (1.62)	18 (7.14)	<0.0001
Annual influenza vaccination, n (%)	331 (35.52)	197 (28.97)	134 (53.17)	<0.0001
Pneumococcal vaccination, n (%)	406 (43.56)	255 (37.50)	151 (59.92)	<0.0001
Oxygen therapy, n (%)	88 (9.44)	46 (6.76)	42 (16.67)	<0.0001
Monotherapy				
SABA, n (%)	47 (5.04)	39 (5.74)	8 (3.17)	0.1126
LABA, n (%)	64 (6.87)	54 (7.94)	10 (3.97)	0.0332
LAMA, n (%)	64 (6.87)	47 (6.91)	17 (6.75)	0.9292
Inhaled corticosteroids, n (%)	2 (0.21)	2 (0.29)	0 (0.00)	0.3888
Dual Therapy				
SABA + LABA, n (%)	49 (5.26)	35 (5.15)	14 (5.56)	0.8040
SABA + LAMA, n (%)	152 (16.31)	100 (14.71)	52 (20.63)	0.0295
SABA + ICS, n (%)	7 (0.75)	3 (0.44)	4 (1.59)	0.0719
LABA + LAMA, n (%)	89 (9.55)	69 (10.15)	20 (7.94)	0.3078
LABA + ICS, n (%)	6 (0.64)	4 (0.59)	2 (0.79)	0.7276
Triple Therapy				
SABA + LABA + LAMA, n (%)	47 (5.04)	35 (5.15)	12 (4.76)	0.8114
SABA + LABA + ICS, n (%)	5 (0.54)	4 (0.59)	1 (0.40)	0.7224
SABA + LAMA + ICS, n (%)	5 (0.54)	3 (0.44)	2 (0.79)	0.5129
LABA + LAMA + ICS, n (%)	13 (1.39)	5 (0.74)	8 (3.17)	0.0048

Table 2. Medications used for treating the 932 COPD patients stratified by infrequent or frequent exacerbators.

Table 3. The determinants of frequent exacerbators (≥ 2 /year) at inclusion in the 932 COPD patients.

	Odds ratio (95% CI)
Pulmonary rehabilitation (Yes vs No)	3.68 [2.03 – 6.67]
Anxiety (Presence vs Absence)	2.12 [1.30 – 3.43]
Diabetes (Presence vs Absence)	1.93 [1.20 – 3.09]
Depression (Presence vs Absence)	1.90 [1.22 – 2.95]
Dyspnea (mMRC 0-1 Vs mMRC ≥ 2)	1.62 [1.14 – 2.29]
Chronic sputum (Presence vs Absence)	1.60 [1.07 – 2.39]
Chronic cough (Presence vs Absence)	1.59 [1.04 – 2.42]
Residual volume (RV \leq 140% Vs RV $>$ 140%)	1.53 [1.10 – 2.13]

Stability of the Frequent-Exacerbation Phenotype

Among patients with 3-year data, 3.13% had one exacerbation per year, 28.25% had no exacerbation per year and 3.13% had two or more exacerbations per year (See the **Figure 3**). Among the 121 patients with two or more exacerbations during the first year of the study, 27.27% and 11.57% persisted in having two or more exacerbations during the second and third years, respectively. Similarly, among the 121 patients with one exacerbation during the first year of the study, 28.92% and 11.57% still had one exacerbation during the second and third following years, respectively. Among the 204 patients with zero exacerbation during the first year of the study, 76.47% and 61.76% still had zero exacerbation during the second and third following years, respectively.

The Kml analysis was used in the sub group of 446 patients. According to all criteria, the optimal number of clusters to separate patients into groups with homogeneous numbers of exacerbations over time was four (See the **Figure 4.a**). The first cluster A consisted of 261 patients (58.52%) who experienced zero or one exacerbation (0.30 ± 0.46 exacerbations per patient per year), the second cluster B comprised 85 patients (19.05%) who experienced two or more exacerbations (2.68 ± 1.01 exacerbations per patient per year), the third cluster C consisted of 82 patients (18.38%) who experienced zero, one or two exacerbations (1.02 ± 0.83 exacerbations per patient per year) and the fourth cluster D consisted of 18 patients (4.03%) who experienced more than two exacerbations (3.55 ± 1.19 exacerbations per patient per year) over the 3 years of the study (See the **Figure 4.b**).

The ROC curve analysis found good accuracy, with multi-class area under the curve (AUC) of 0.88 (95% CI, 0.82-0.94) and a best threshold to maximize (sensitivity + specificity) of at least two exacerbations in the first year (sensitivity, 91%; specificity, 79%).

Factor associated with the Frequent Exacerbators phenotypes

Frequent exacerbators (cluster B and D) had more female patients. BMI proved to be significantly different between all the clusters. Noticeably, cluster B had the highest percentage of underweight ($<21 \text{ kg/m}^2$) patients while contrastingly obese ($\geq 29 \text{ kg/m}^2$) patients were higher in cluster D. Severe airflow limitation was seen in cluster D patients while cluster C (transient phenotype) encompassed the highest number of GOLD stage III patients. Chronic cough, sputum and dyspnea along with pulmonary rehabilitation were evidently higher in frequent exacerbators. These findings were further supported by higher functional measurement (RV/TLC ratio) in these phenotypes (See the **Table 4**). Determinants of frequent exacerbators (phenotype B or D) included higher levels of anxiety, chronic sputum, treatment with LABA, and unvaccinated against influenza (See the **Table 5**).

Table 4. Baseline characteristics of patients with 3-year follow-up separated into Clusters A, B, C and D.

Subjects characteristics,		A n =261 (58.50 %) Infrequent	B n =85 (19.05 %) Frequent	C n=82 (18.38 %) Transient	D n=18 (4.03 %) Frequent	P value
Variable names	COPD patients followed for 3 years, n=446					
Males, n (%)	302(67.71)	194(74.33)	47(55.29)	51(62.20)	10(55.56)	0.0035
Age, yrs. Mean (SD)	66.95 (10.04)	66.79 (9.98)	66.05 (10.22)	69.17 (9.86)	63.44 (9.70)	0.0866
BMI, (kg/m ²), mean (SD)	27.11(6.29)	27.84 (6.17)	25.94 (6.28)	25.91 (6.60)	27.47 (5.26)	0.0058
<21 (underweight), n (%)	76(17.04)	28(10.73)	23(27.06)	22(26.83)	3(16.67)	0.0033
[21-26](normal), n (%)	134(30.04)	77(29.50)	25(29.41)	27(32.93)	5(27.78)	
[26-29](overweight), n (%)	85(19.06)	61(23.37)	12(14.12)	10(12.20)	2(11.11)	
≥29 (obese), n (%)	151(33.86)	95(36.40)	25(29.41)	23(28.05)	8(44.44)	
FEV1, % pred, Mean (SD)	58.84 (19.98)	60.97 (19.36)	56.27 (21.28)	56.12 (19.43)	52.32 (22.18)	0.0399
GOLD stage I, >80%, n (%)	69(15.47)	43(16.48)	13(15.29)	10(12.20)	3(16.67)	0.038
GOLD stage II, 50-80%, n (%)	212 (47.53)	137(52.49)	34(40.00)	35(42.68)	6(33.33)	
GOLD stage III, 30-50%, n (%)	136 (30.49)	69(26.44)	30(35.29)	32(39.02)	5(27.78)	
GOLD stage IV, <30%, n (%)	29 (6.50)	12(4.60)	8(9.41)	5(6.10)	4(22.22)	
Chronic cough, n (%)	253(56.73)	133(50.96)	61(71.76)	47(57.32)	12(66.67)	0.007
Chronic sputum, n (%)	201(45.07)	101(38.70)	46(54.12)	44(53.66)	10(55.56)	0.0159
Current smokers, n (%)	153(34.30)	87(33.33)	32(37.65)	27(32.93)	7(38.89)	0.8572
Dyspnea, 0-1 mMRC, n (%)	189(42.38)	129(49.43)	23(27.06)	33(40.24)	4(22.22)	0.0008
Dyspnea, ≥ 2 mMRC, n (%)	257(57.62)	132(50.57)	62(72.94)	49(59.76)	14(77.78)	
Pulmonary rehabilitation, n (%)	32(7.17)	5(1.92)	14(16.47)	9(10.98)	4(22.22)	<0.0001
Smoking cessation, n (%)	48(10.76)	27(10.34)	10(11.76)	10(12.20)	1(5.56)	0.8448
RV, Mean (SD)	143.17 (54.01)	136.51 (53.15)	153.54 (54.21)	150.82 (55.11)	155.94 (50.03)	0.0045
TLC, Mean (SD)	103.98 (21.22)	101.57 (20.65)	107.16 (20.06)	107.82 (24.35)	106.5 (15.33)	0.0135
RV/TLC, % pred, Mean (SD)	135.28 (34.73)	132.16 (37.03)	140.9 (31.09)	137.12 (28.41)	145.58(39.26)	0.0153
Hyperinflation, n (%)	296 (66.37)	160(61.30)	63(74.12)	59(71.95)	14(77.78)	0.058

Table 5. Factors associated with the frequent exacerbator cluster (B) or (D) in 446 patients with full 3-year follow-up.

	Odds ratio (95% CI)
Anxiety (Presence vs Absence)	3.25 [1.67 - 6.32]
LABA (Presence vs Absence)	2.00 [1.22 - 3.28]
Annual influenza vaccination (Absence vs presence)	1.97 [1.20 - 3.24]
Chronic sputum (Presence vs Absence)	1.75 [1.08 - 2.82]
BMI (underweight, normal vs. overweight, obese)	1.67 [1.03 - 2.69]

DISCUSSION

We examined the frequency of exacerbations among 932 patients with mild, moderate, severe and very severe COPD. They were mostly men who were current smokers with symptomatic COPD associated with frequent comorbidities. 27.04% of the 932 patients reported two or more exacerbations in the previous 12 months. A range of variables showed an association with exacerbation frequency: GOLD stage III and IV, chronic cough, chronic sputum, current smokers, higher dyspnea and hyperinflation. The KmL method identified four clusters of patients based on longitudinal 3-year follow-up of exacerbation frequency. The multivariate analysis showed the determinants of frequent exacerbators (phenotype B or D): anxiety, chronic sputum, and unvaccinated against influenza.

At the end of our study, only 3.13% of COPD participants had two or more exacerbations compared with the 2.00% in SPIROMICS study, 12.00% in the ECLIPSE cohort and 7.00% in the French cohort (EXACO) [3, 8, 10]. We considered all stages of COPD severity, as opposed to the severe form in the above mentioned studies which accounts for the differences in the results.

Between years 1 and 2, 85.00% of patients changed from frequent exacerbators to infrequent exacerbators (0–1 exacerbation), while 30.00% changed from infrequent exacerbators to frequent exacerbators. This intra-subject variability of annual exacerbation frequency, limits the ability of these criteria to predict the future risk of

exacerbations, at an individual level. It is possible, that a period longer than 3 years of follow-up might reduce the captured variability of exacerbation rate over time, allowing for a better predictive efficacy by the model.

Most exacerbations are treated in an outpatient setting using SABA, LABA, LAMA, Inhaled and oral corticosteroids with or without antibiotics [1, 36]. Pneumococcal and annual influenza vaccinations are also often used to treat COPD exacerbations as influenza is a frequent cause of COPD exacerbations: A recent study showed that influenza viruses are detected in between 2.50% to 11.60% of COPD exacerbations [37], which is consistent with previously published reports documenting influenza detection in 5.00–22.00% of patients hospitalized with exacerbations [38 – 41]. Immunization against influenza is recommended for all patients with COPD by the World Health Organization (WHO), the US Centers for Disease Control and Prevention, the European Centre for Disease Control and Prevention (ECDC), numerous national agencies [42-44], and the Advisory Committee on Immunization Practices (ACIP) in USA [45]. Current guidelines recommend influenza and pneumococcal vaccination for COPD patients [1].

The originality of our study was to analyze the impact of annual influenza vaccination, pneumococcal vaccination status, and all prescribed COPD treatments on the longitudinal analysis of exacerbations frequency. We were able to show a strong association between unvaccinated against influenza and the frequent exacerbator phenotypes. Despite longstanding recommendations to vaccinate vulnerable high-risk groups against seasonal influenza, vaccination rates remain sub-optimal in this population.

Our study identified two stable frequent exacerbator phenotypes which differed on the basis of BMI. Phenotype D (frequent in obese patients) had a higher association with anxiety. Hence, in COPD patients with frequent exacerbations, adequate management of anxiety should be given due importance. Patient education about influenza vaccination might contribute towards decrease in exacerbations frequency.

Furthermore, studies have demonstrated an impact of pertussis vaccination in reducing frequency of exacerbations and could be an interesting consideration for future studies.

Strengths and Limitations

Our study has several strengths and limitations: 486 patients lost to follow-up were asymptomatic patients. There is a selection bias in our study but it is reflective of the complicated pathology of COPD. These results confirm that patients with COPD managed by pulmonologist are more severe than those managed in primary care. As more severe COPD patients were followed by pulmonologists, we cannot formally exclude selection bias with overestimation of frequent exacerbation phenotype.

We found four clusters with two frequent exacerbating phenotypes with a difference based on BMI. Adherence to COPD treatment was included in our analysis which has not been previously taken into account.

Comorbidities were recorded by pulmonologists, whereas in previous studies comorbidities remained underdiagnosed – reflective of real life. The recording of comorbidities might be a potential bias. However, this bias is limited, as we found a significant correlation between the reported comorbidities and compliance with their given treatment (data not shown).

Despite its limitations, this is one of the few studies that have investigated the association of frequent exacerbations and risk factors in COPD patients, taking into account therapeutic management: unvaccinated against influenza is an important determinant of frequent exacerbations and comorbidity of anxiety should be adequately treated.

CONCLUSIONS

Our study shows that the most important determinants of frequent exacerbations are: history of exacerbations, anxiety and unvaccinated against influenza. These analyses show the existence and clinical relevance of two frequent exacerbators' phenotypes of patients with COPD and the currently used threshold to define this phenotype.

Author contributions: All authors contributed to the acquisition of the data. CR-S and E-HO had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. CR-S, AB, CN-E, LF, FLG, LN, JMD, MS, MZ, MM and AO contributed to the conception and design of the study. All authors read and approved the final manuscript. CR-S is the guarantor. The corresponding author (E-HO) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Availability of data and materials: The data that support the findings of this study are available from INSERM U1219 Epicene Team, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of INSERM U1219 Epicene Team.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

The list of studied comorbidities: Hypertension, dyslipidemia, ischemic cardiopathy, apnea syndrome, anxiety, cancer, depression, diabetes, arrhythmia, asthma, left heart failure, bronchiectasis, atheroma, stroke, pulmonary arterial hypertension, lower limb arteriopathy, embolic thromboembolism, metabolic syndrome, undernutrition, osteoporosis, and sinus manifestation.

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Figures

Figure 1. Flow diagram of participants through each stage of the study.

Figure 2. Prevalence of the comorbidities in the frequent and in-frequent exacerbators.

Figure 3. Stability of the Frequent-Exacerbation Phenotype in the 446 COPD patients who completed the study.

**The bars at the left show the proportion of patients with no exacerbations, one exacerbation, or two or more exacerbations in year 1;

**The bars in the middle show the respective incidence of exacerbations for these patients in year 2;

**The bars at the right show the respective incidence in year 3;

**The percentages at right denote the proportions of all patients with no exacerbations, one exacerbation, or two or more exacerbations;

Figure 4. KmL clustering analysis of prospectively recorded annual exacerbation frequency.

a): Criteria applied to choose the optimal number of clusters including the first Calinski and Harabatz index (1, Blood red line), the second version of Calinski and Harabatz index (2, red line), the third version of Calinski and Harabatz index (3, green line), the Ray and Turi index (4, blue line), and the Davies and Bouldin index (5, sky blue line). These criteria are normalized to be mapped together using the KmL package in R. Scores range from 0 to 1 for each tested number of clusters ranging from 2 to 4. The highest score corresponds to the most appropriate number of clusters.

b): Individual trajectories of annual exacerbation frequency during each year of the study. Red corresponds to **cluster A (58.52% of patients)**, green corresponds to **cluster B (19.05% of patients)**, sky blue corresponds to **cluster C (18.38% of patients)** and purple corresponds to **cluster D (4.03% of patients)**. Thick lines labeled with the cluster letter represent the mean exacerbation frequency for each cluster.

PALOMB cohort
n=932 included patients

n=932 patients followed 1 year

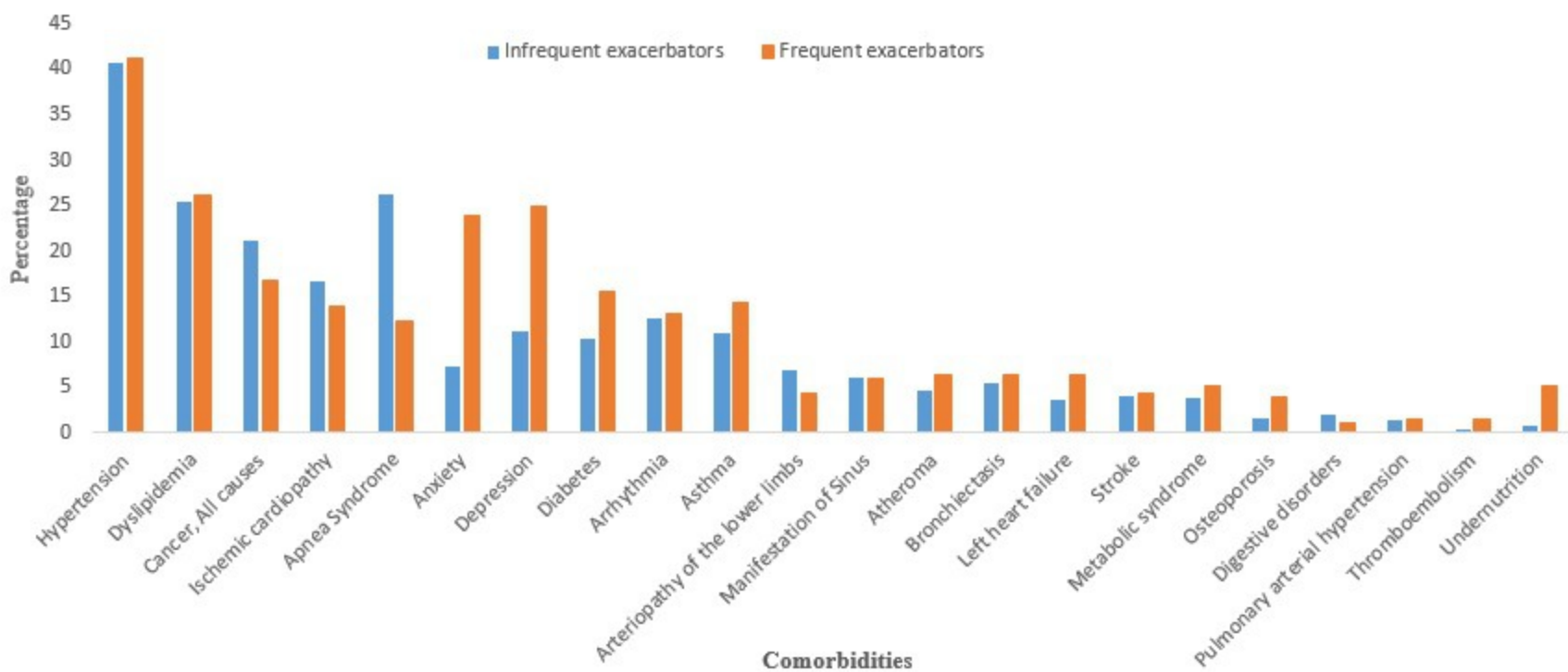
n=64 Lost to follow-up
n=15 Death

n=853 patients followed 2 year

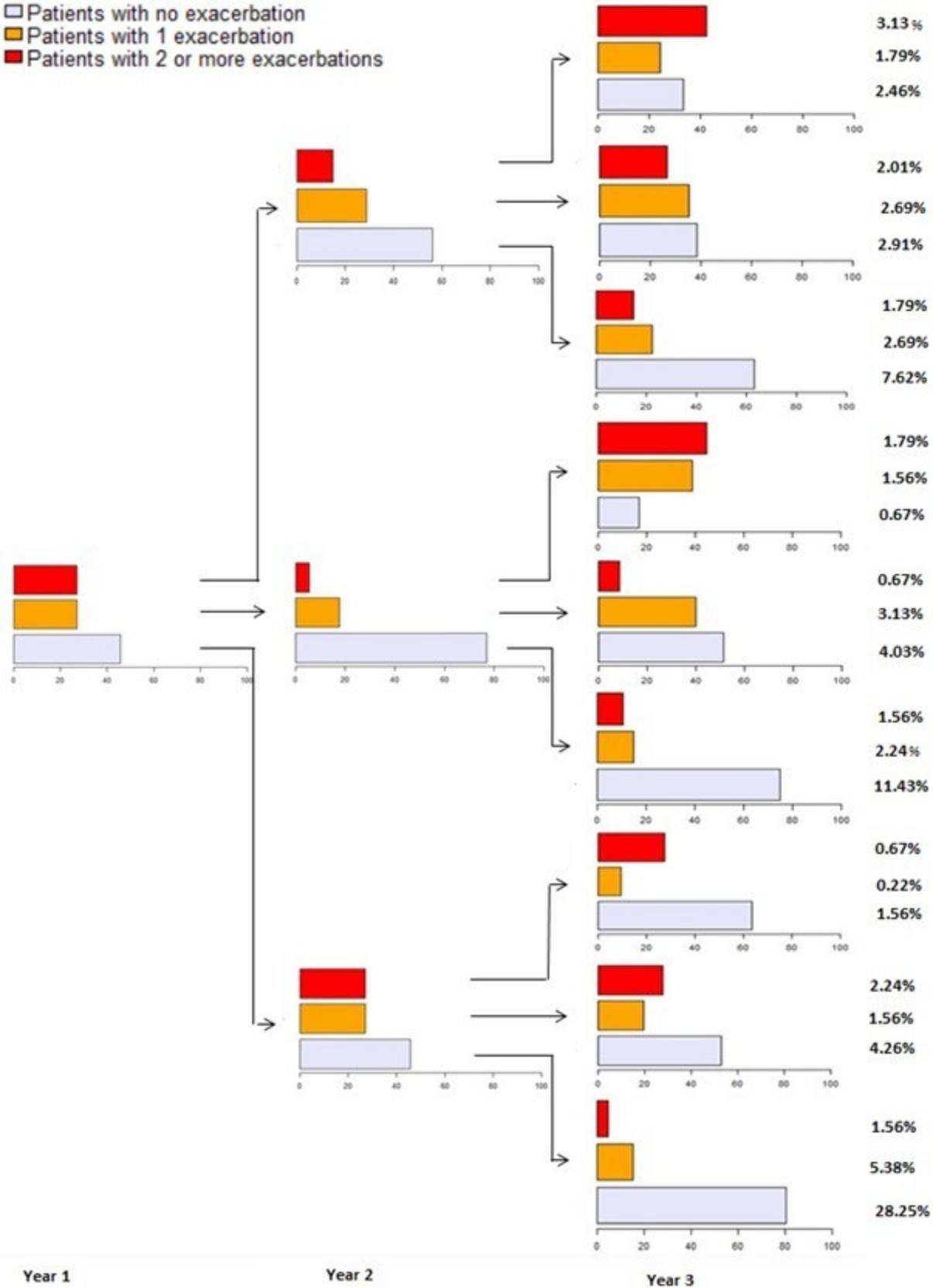
n=351 Lost to follow-up
n=40 Death
n=16 Data missing

n=446 patients followed 3 year

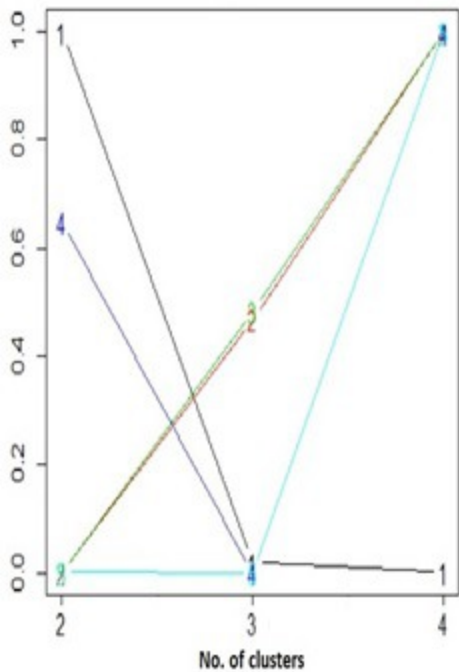
“Longitudinal analysis”
n=446 patients with at
least 3 year with full data



█ Patients with no exacerbation
█ Patients with 1 exacerbation
█ Patients with 2 or more exacerbations



a)



b)

