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CRediT authorship contribution statement

Spyridon Fortis: Formal analysis, Conceptualization, Funding acquisition, Writing - original draft, has full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, Study concept and design. **Emily S. Wan:** Funding acquisition, Formal analysis, Writing - original draft. **Ken Kunisaki:** Funding acquisition, Formal analysis, Writing - original draft. **Patrick Tel Eyck:** Funding acquisition, Formal analysis, Writing - original draft. **Zuhair K. Ballas:** Funding acquisition, Formal analysis, Writing - original draft. **Russell P. Bowler:** Funding acquisition, Formal analysis, Writing - original draft. **James D. Crapo:** Funding acquisition, Formal analysis, Writing - original draft. **John E. Hokanson:** Funding acquisition, Formal analysis, Writing - original draft. **Chris Wendt:** Funding acquisition, Formal analysis, Writing - original draft. **Edwin K. Silverman:** Funding acquisition, Formal analysis, Writing - original draft. **Alejandro P. Comellas:** Conceptualization, Funding acquisition, Formal analysis, Writing - original draft, Study concept and design, Funding acquisition, Formal analysis, Writing - original draft, Acquisition, analysis, or interpretation of data: All authors., Drafting of the manuscript: All authors, Critical revision of the manuscript for important intellectual content: All authors.

Declaration of competing interest

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Ethics approval

Clinical Center	Institution Title	Protocol Number
National Jewish Health	National Jewish IRB	HS-1883a
Brigham and Women's Hospital	Partners Human Research Committee	2007-P-000554/2; BWH
Baylor College of Medicine	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22209
Michael E. DeBakey VAMC	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22202
Columbia University Medical Center	Columbia University Medical Center IRB	IRB-AAAC9324
Duke University Medical Center	The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB)	Pro00004464
Johns Hopkins University	Johns Hopkins Medicine Institutional Review Boards (JHM IRB)	NA_00011524
Los Angeles Biomedical Research Institute	The John F. Wolf, MD Human Subjects Committee of Harbor-UCLA Medical Center	12756–01
Morehouse School of Medicine	Morehouse School of Medicine Institutional Review Board	07–1029
Temple University	Temple University Office for Human Subjects Protections Institutional Review Board	11369
University of Alabama at Birmingham	The University of Alabama at Birmingham Institutional Review Board for Human Use	FO70712014
University of California, San Diego	University of California, San Diego Human Research Protections Program	070876
University of Iowa	The University of Iowa Human Subjects Office	200710717
Ann Arbor VA	VA Ann Arbor Healthcare System IRB	PCC 2008-110732
University of Minnesota	University of Minnesota Research Subjects' Protection Programs (RSPP)	0801M24949
University of Pittsburgh	University of Pittsburgh Institutional Review Board	PRO07120059
University of Texas Health Sciences Center at San Antonio	UT Health Science Center San Antonio Institutional Review	HSC20070644H
Health Partners Research Foundation	Health Partners Research Foundation Institutional Review	07–127
University of Michigan	Medical School Institutional Review Board (IRBMED)	HUM00014973

Increased mortality associated with frequent exacerbations in COPD patients with mild-to-moderate lung function impairment, and smokers with normal spirometry

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Abstract

Background: The burden of frequent respiratory exacerbations in COPD patients with mild-to-moderate spirometric impairment and smokers with preserved lung function is unknown.

Methods: We categorized COPD participants in COPDGene with post-bronchodilator FEV1%predicted≥50% by the annual exacerbation frequency into three groups: i)frequent exacerbators (top 5%; n = 109), ii)exacerbators (>0 but less than frequent exacerbators; n = 1,009), and iii)No exacerbation (n = 981). Exacerbations were defined as respiratory episodes requiring

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Minneapolis VA Medical Center	Minneapolis VAMC IRB	4128-A
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Appendix A. Supplementary data
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antibiotics and/or systemic steroids. We performed a Cox proportional hazards regression analysis to examine the association with mortality. We repeated the same process in current/former smokers with preserved spirometry (FEV1≥80%predicted and FEV1/FVC≥0.7).

Results: Among 2,099 COPD participants, frequent exacerbators had ≥1.8 exacerbations/year and were responsible for 34.3% of the total exacerbations. There were 102 (10.4%) deaths in the group with no exacerbations, 119 (11.8%) in the exacerbator group, and 24 (22%) in the frequent exacerbators. Adjusted mortality in frequent exacerbators was higher relative to individuals with no exacerbations (hazard ratio (HR) = 1.98; 95%CI = 1.25–3.13). An increase in frequency of exacerbations by one exacerbation/year was associated with increased mortality (HR = 1.40,95%CI = 1.21–1.62). Among 3,143 participants with preserved spirometry, frequent exacerbators had ≥0.8 exacerbations/year and were responsible for more than half of the exacerbations. There were 93 (4.2%) deaths in the group with no exacerbations, 28 (3.8%) in the exacerbator group, and 14 (7.6%) in the frequent exacerbators. The adjusted mortality was increased in frequent exacerbators with preserved spirometry relative to those with no exacerbations (HR = 2.25; 95%CI = 1.26–4.01).

Conclusions: In COPD participants with mild-to-moderate spirometric impairment and smokers with preserved spirometry, the frequent exacerbator phenotype is responsible for a large proportion of total exacerbations and associated with high mortality.

Keywords

Chronic obstructive pulmonary disease; Exacerbations; Mortality

1. Introduction

Chronic obstructive pulmonary disease (COPD) patients experience exacerbations of the disease, defined as acute worsening of respiratory symptoms, that typically become more frequent as the disease progresses [1]. A major component of the burden of COPD is related to COPD exacerbations. Moderate and severe exacerbations are associated with a decline in lung function and health status, and substantial healthcare cost [2-5]. Severe COPD exacerbations require hospitalization and are responsible for more than 70% of the direct health-care cost of the disease [4,6]. In a cohort of COPD patients with moderate-to-severe lung function impairment, 13.6% of them were frequent exacerbators, defined as patients with at least 2 exacerbations every year [7], and were responsible for 50.6% of all hospitalizations [8]. Therefore, identifying COPD patients with frequent exacerbations is of major importance [9].

COPD-related hospitalizations are associated with increased short and long-term mortality [10-14]. As the frequency of COPD-related hospitalizations increases, the long-term mortality increases [15,16]. In a multicenter study using administrative data, COPD patients with at least 2 hospitalizations a year had increased mortality relative to those with no hospitalizations [17]. The long-term mortality among those with frequent exacerbations, not requiring hospitalizations, is under-studied. More recently, it has also been recognized that symptomatic smokers with normal spirometry also have respiratory exacerbations [18,19]. The burden of respiratory exacerbation including health-care utilization and mortality among

frequent exacerbators has predominantly been studied in COPD patients with significant lung function impairment [8,16] while the burden of the disease in patients with mild lung function impairment or preserved lung function remains unstudied. We hypothesized that the burden of disease in COPD with mild-to-moderate lung impairment, and smokers with preserved spirometry, with frequent exacerbations is high. To investigate our hypothesis we used data of COPD participants with post-bronchodilator FEV1% predicted≥ 50% predicted and smokers with normal spirometry from the COPDGene study with at least 3 years follow-up. We defined frequent exacerbators as those individuals at the top 5% in exacerbation frequency within their spirometric group. We assessed the burden of disease associated with frequent exacerbations, including mortality, and we identified factors associated with frequent exacerbators.

2. Methods

2.1. Data collection

We analyzed data from COPDGene, an ongoing study conducted at multiple clinical centers throughout the United States (http://www.copdgene.org/). Subjects were current and former smokers with ≥10 pack-years of smoking who self-identified as non-Hispanic whites (NHW) or African Americans (AA) and were between the ages of 45–80 years at enrollment. The institutional review boards at each participating center approved the study protocol, and written informed consent was obtained from all participants. Details of the study protocol have been published previously [20]. Briefly, participants completed a modified American Thoracic Society Respiratory Epidemiology questionnaire. Dyspnea was assessed using the modified Medical Research Council (mMRC) scale. Subjects performed pre- and post-bronchodilator spirometry according to American Thoracic Society–European Respiratory Society (ATS-ERS) guidelines [21] and a 6-min walk test (6-MWT) at the enrollment visit. Volumetric chest CT scans were obtained at total lung volume (TLV) (maximal inspiration) and at functional residual capacity (FRC) (end-tidal expiration) [20]. Percent emphysema and gas trapping were quantified using 3D Slicer software (www.airwayinspector.org) [20].

We included COPD participants with post-bronchodilator FEV1% predicted≥ 50% and participants with normal spirometry. Individuals with lung transplant or lung volume reduction surgery, and those with less than 3 years follow-up data were excluded. Respiratory exacerbation data were collected prospectively after enrollment. Subjects were contacted every 6 months after enrollment and completed a standardized questionnaire regarding respiratory exacerbations through the Longitudinal Follow-Up program. Vital status was also ascertained using information from the social security death index and the Longitudinal Follow-up program.

2.2. Definitions and outcomes

COPD was defined as post-bronchodilator FEV_1/FVC <0.7. Preserved spirometry was defined as post-bronchodilator FEV_1/FVC ≥0.7 and FEV1% predicted ≥80%. Exacerbations were defined as episodes of worsening respiratory symptoms requiring use of antibiotics and/or systemic steroids. Severe exacerbations were defined as those requiring

hospitalizations or emergency room visits. Other variable definitions have been previously described [20]. We defined frequent exacerbators as those at the top 5% in the average exacerbation frequency. Since the frequent exacerbator phenotype has not been investigated in COPD patients with mild-to-moderate lung function impairment and smokers with preserved spirometry, we did not use the typical 2 exacerbations/year definition [7]. In a sensitivity analysis, we defined frequent exacerbators as those with ≥2 exacerbations per year.

History of acute bronchitis or pneumonia was defined as self-reported history of bronchitis or pneumonia at study enrollment. Similarly, history of asthma, and obstructive sleep apnea were also self-reported. History of cancer was defined as self-reported history of lung, breast, prostate, colon, and/or bladder cancer. Bronchodilator response was defined as an increase in prebronchodilator FEV1 and/or FVC greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration [22].TLV was measured from volumetric inspiratory chest CT scans and is a surrogate of plethysmographic total lung capacity. TLV% predicted was calculated based on MESA predicted values [23]. Percent emphysema and gas trapping was calculated as previously [20].

2.3. Statistical analysis

We stratified COPD participants into 3 groups based on their annual rate of respiratory exacerbations: i) No-exacerbation, ii) exacerbators (>0 but less than frequent exacerbators), and iii) frequent exacerbators (top 5% in the rate of respiratory exacerbations). We compared the characteristics of participants between groups using ANOVA for continuous variables and chi-squared or fisher exact test for categorical variables.

In a univariate analysis, we identified variables associated with the frequent exacerbator group (frequent exacerbator vs the rest). Variables associated with the frequent exacerbator group with univariate p value < 0.10 were considered for a multivariable logistic regression model. Medication use and current smoking status were not considered for the model as participants with frequent exacerbations used more medications and were less likely to be current smokers (confounding by indication). Variables were selected for the final model using a stepwise backward variable elimination process to minimize the Akaike information criterion (AIC) [24]. We assessed for variable multicollinearity using correlation matrices and variance inflation factors [25]. We repeated the multivariable analysis after multiple imputations (5 datasets) by chained equations (MICE) to account for missing variables. We used the Multivariate Imputation by Chained Equations (MICE) package R software [26,27].

We used Cox proportional hazard regression models to examine the association between the groups with all-cause mortality (time-to-death analysis). We also used Cox proportional hazard regression models to examine the association between exacerbation frequency (exacerbation/year) and all-cause mortality. Models included the following covariates: age, gender, race, current smoking status, smoking pack-years, BMI, post-bronchodilator FEV1% predicted at enrollment, and history of obstructive sleep apnea. In a sensitivity analysis, we defined frequent exacerbators as those with 2 or more exacerbations per year, and we assessed the association of frequent exacerbations with mortality.

Similarly, we stratified current or former smokers with normal spirometry based on their annual rate of respiratory exacerbations, and we performed the same analysis as above. All statistical analyses were conducted using R statistical software (http://www.r-project.org/) using the following R software packages: 'car', 'dunn.test', 'ggplot2', 'survminer', 'tableone', 'mice', 'pscl', 'MASS', 'AER', 'survival', and 'DescTools'.

3. Results

Of 10,194 participants in COPDGene with at least 10 pack-years history of smoking, 2,713 have COPD with post-bronchodilator FEV1%predicted≥50% and 4,368 have normal spirometry (Supplement Fig. 1). Of 2,713 participants with COPD and post-bronchodilator FEV1%predicted≥50%, we excluded 1 that had lung transplant/lung volume reduction and 613 for whom we did not have exacerbation data for at least 3 years. Of 4,386 current or former smokers with preserved spirometry, we excluded one that had lung transplant/lung volume reduction and 1,242 for whom we did not have exacerbation data for at least 3 years. We analyzed data of 2,099 COPD participants with post-bronchodilator FEV1%predicted≥50% and 3,143 current or former smokers with preserved spirometry.

3.1. COPD participants with mild-to-moderate lung function impairment (n = 2,099)

In COPD participants with post-bronchodilator FEV1%predicted≥50%, the median duration of follow-up was 8 years (interquartile range = 6.6–8.9). The top 5% in exacerbation frequency (n = 109) had 1.8 or more exacerbations per year (frequent exacerbators), 1,009 had >0 exacerbation/year but less than 1.8 exacerbation a year (exacerbators), and 981 had no exacerbations. Table 1 shows the characteristics of the 3 groups. The count of respiratory exacerbations was 5,913 for all COPD participants, 3,886 (65.7%) for the exacerbators, and 2027 (34.3%) for the frequent exacerbators. The count of severe respiratory exacerbations was 1,919 for all COPD participants, 1,308 (68.2%) for the exacerbators, and 611 (31.8%) for the frequent exacerbators.

In frequent exacerbators during a median follow-up time of 7.4 years (interquartile range = 5.7–8.8), the median count of exacerbations was 18 with a range of 6–36 (interquartile range = 13–22) and median count of severe exacerbations was 4 with a range of 0–28 (interquartile range = 1–8).

Lung function (every 10% increase in FEV1%predicted with an odds ratio (OR) = 0.82; 95%CI = 0.68–0.99), 6-min walk distance (every 100 ft increase; OR = 0.94; 95%CI = 0.88–1.00),%emphysema (every 1%; OR = 1.05; 95%CI = 1.02–1.07), dyspnea (OR = 2.35; 95%CI = 1.41–4.00), chronic bronchitis (OR = 1.85; 95%CI = 1.17–2.90), history of asthma (OR = 2.13; 95%CI = 1.35–3.34), history of acute bronchitis and/or pneumonia (OR = 2.04; 95%CI = 1.17–3.77), and history of cancer (OR = 1.95; 95%CI = 1.05–3.45) were associated with the frequent exacerbator group (Supplement Table 1). Analysis after multiple imputations for missing values showed almost identical findings.

In the mortality analysis, there were 102 (10.4%) deaths in the group with no exacerbations, 119 (11.8%) in the exacerbator group, and 24 (22%) in the frequent exacerbator group (Fig. 1). After adjusting for age, sex, race, smoking pack-years, current smoking status, body

mass index, lung function, and history of obstructive sleep apnea, the frequent exacerbator phenotype was associated with increased mortality (hazard ratio (HR) = 1.98; 95%CI = 1.25–3.13, p = 0.004) (Table 2). When we defined frequent exacerbator phenotype as ≥2 exacerbation/years, we observed similar findings (Supplement Table 2). After adjusting for age, sex, race, smoking pack-years, current smoking status, body mass index, lung function, and history of obstructive sleep apnea, an increase in frequency of exacerbations by one exacerbation/year was associated with increased mortality (HR = 1.40, 95%CI = 1.21–1.62, p < 0.001).

3.2. Current or former smokers with normal spirometry (n = 3,143)

In current or former smokers with normal spirometry, the median duration of follow-up was 8.1 years (interquartile range = 6.9–8.9). The top 5% in exacerbation frequency (n = 185) had 0.8 or more exacerbations per year (frequent exacerbators), 743 had >0 exacerbations but less than 0.8 exacerbation a year (exacerbators), and 2,215 had no exacerbations. Table 3 shows the characteristics of the 3 groups. The count of total respiratory exacerbations was 3,548 for all participants with normal spirometry, 1620 (45.7%) for the exacerbators, and 1928 (54.3%) for the frequent exacerbators. The count of severe respiratory exacerbations was 1,086 for all participants with normal spirometry, 519 (44.8%) for the exacerbators, and 567 (55.2%) for the frequent exacerbators.

In frequent exacerbators during a median follow-up time of 8 years (interquartile range = 6.9–8.8), the median count of exacerbations was 8 with a range of 3–48 (interquartile range = 7–11) and median count of severe exacerbations was 2 with a range of 0–18 (interquartile range = 0–5).

Pack-years (every 10 with OR = 1.13; 95%CI = 1.05–1.21), dyspnea (OR = 2.10; 95%CI = 1.44–3.05), history of asthma (OR = 3.63; 95%CI = 2.52–5.20), history of acute bronchitis and/or pneumonia (OR = 2.16; 95%CI = 1.50–3.16), and history of obstructive sleep apnea (OR = 1.58; 95%CI = 1.04–2.34) were associated with the frequent exacerbator group (Supplement Table 3). We performed an additional analysis after multiple imputations accounting for missing values with almost identical findings.

In the mortality analysis, there were 93 (4.2%) deaths in the group with no exacerbations, 28 (3.8%) in the exacerbator group, and 14 (7.6%) in the frequent exacerbator group. After adjusting for age, sex, race, smoking pack-years, current smoking status, body mass index, lung function, and history of obstructive sleep apnea, the frequent exacerbator group was associated with increased mortality compared to that with no exacerbations (HR = 2.25; 95%CI = 1.26–4.01, p = 0.006) (Table 4). When we defined frequent exacerbator phenotype as ≥2 exacerbation/years, we observed similar findings (Supplement Table 4). After adjusting for age, sex, race, smoking pack-years, current smoking status, body mass index, lung function, and history of obstructive sleep apnea, an increase in frequency of exacerbations by one exacerbation/year was associated with increased mortality (HR = 1.66, 95%CI = 1.24–2.22, p < 0.001).

4. Discussion

Among COPD participants with mild-to-moderate spirometric impairment, we showed that the top 5% of patients with the most exacerbations (frequent exacerbators) are responsible for 34.3% and 31.8% of total and severe exacerbations, respectively. The mortality of COPD patients with frequent exacerbators is approximately double the mortality of the rest of the mild-to-moderate COPD participants in the study. Furthermore, in current or former smokers with normal spirometry, the frequent exacerbators are responsible for more than half of the total and severe exacerbations, respectively, and also have increased adjusted mortality relative to those with no exacerbations. An increase in frequency of exacerbations in COPD and current or former smokers with normal spirometry by one exacerbation a year was associated with increased mortality.

COPD patients with 2 or more exacerbations every year were defined as “frequent exacerbators” based on the landmark ECLIPSE study [7]. Since then, this cut-off has been used to identify high-risk COPD patients where escalation of treatment may be needed [1]. Using a hypothesis-free approach, Le Rouzic and colleagues found that frequent exacerbators have an average of 2.89 exacerbations/year as opposed to “infrequent exacerbators” who have an average of 0.71 exacerbations/year [28]. Two exacerbations in a given year is not a highly stable COPD exacerbation phenotype as exacerbations tend to occur in clusters. However, a patient with ≥2 exacerbations/year in the previous year has more than 46% chance to have at least 2 exacerbations in the subsequent year [29]. As the number of exacerbations increase, the probability of a subsequent exacerbation increases and the frequent exacerbator phenotype becomes more “stable” [17]. Suissa et al. showed that the median time to subsequent hospitalization is 5.4 years after the first hospitalization, 1.6 years after the second one, and 0.3 years after the seventh one [12]. In the current study, we found that the top 5% in exacerbation frequency among COPD patients with mild-to-moderate lung function impairment has ≥1.8 exacerbations/year which indicates that 2 exacerbation/year is likely the appropriate cut-off even among COPD patients with mild-to-moderate lung function impairment. Our findings also suggest that in current or former smokers with preserved spirometry, one exacerbation a year may indicate a “high-risk phenotype”.

In the ECLIPSE study, which included COPD participants with moderate or severe lung function impairment and an average FEV1% predicted of 48%, every year about a quarter of them had at least 2 exacerbations but they were not always the same individuals. Twelve percent of the entire cohort consistently had ≥2 exacerbations every year [7]. In the SPIROMICs cohort that includes COPD subjects across a wide spectrum of lung function with an average of FEV1%predicted of 63%, Han et al. found that every year 10–15% of the participants had 2 or more exacerbations but only 2.1% of them consistently had ≥2 exacerbations/year for 3 consecutive years [29]. The frequent exacerbator phenotype is relatively uncommon [30,31].

Nonetheless, the frequent exacerbator phenotype is associated with a high burden of disease. In a cohort of COPD patients with post-bronchodilator FEV1%predicted below 70%, Beeh et al. demonstrated that 13.6% of COPD participants classified as frequent exacerbators

were responsible for 50% of total hospitalizations [8]. Similarly, we found that among COPD participants with mild-to-moderate lung impairment, the top 5% in exacerbation frequency is responsible for approximately one third of all exacerbations. Moreover, we showed that the top 5% in exacerbation frequency among former or current smokers with normal spirometry is responsible for more than half of exacerbations.

COPD-related hospitalizations are associated with increased mortality [12,16,32] which increases further with each hospitalization [15]. In our study, frequent exacerbators (not necessarily with hospitalizations) have increased mortality after adjustment for demographics, smoking exposure, body mass index (BMI), and lung function relative to the mortality in individuals with no exacerbations. This association remains even when we defined frequent exacerbators as those with 2 or more exacerbations a year. An increase in frequency of exacerbations in COPD patients with mild-to-moderate lung impairment by one exacerbation a year is associated with 41% increase in mortality. This is the first study showing that frequent exacerbator phenotype is associated with increased mortality even among current or former smokers with preserved spirometry. An increase in frequency of exacerbations in smokers with normal spirometry by one exacerbation a year is associated with 62% increase in mortality.

History of asthma, gastroesophageal reflux disease, prior exacerbations, increased respiratory symptoms, poor health status, worsening lung function, increased fibrinogen and white blood cells, certain cytokines, and evidence of small airway disease in the chest CT have been reported as risk factors for frequent exacerbators [7,29,33]. Poor lung function and prior exacerbations are the most consistent risk factors. Chronic bronchitis is also associated with high risk for exacerbations [34] but the association between chronic bronchitis with frequent exacerbations is inconsistent [7]. In our analysis, poor lung function, poor exercise capacity, increased radiographic emphysema, dyspnea, chronic bronchitis, history of asthma, history of prior exacerbations and pneumonia, and history of cancer were risk factors for frequent exacerbators among COPD participants. Cancer may be related with immunodeficiencies [35], a known risk factor for COPD exacerbations [36]. Among current or former smokers with normal spirometry, smoking pack-years, dyspnea, history of asthma, history of prior exacerbation and pneumonia, and obstructive sleep apnea were associated with frequent exacerbations. Obstructive sleep apnea may be confounded by obesity hypoventilation syndrome [37]. Patients with obesity hypoventilation syndrome may be frequently hospitalized with acute respiratory failure and misdiagnosed with COPD [38]. For thar reason, in the mortality analysis obstructive sleep apnea was included in the models as a co-variate.

Our study has several limitations. First, we examined the average of exacerbations per year in a study period with a duration ≥3 years as opposed to annual exacerbations. Nevertheless, the definition of frequent exacerbation as 2 exacerbations a year for several consecutive years has limited clinical value as health care providers do not have the luxury of longitudinal data to decide the appropriate treatment plan. Secondly, our mortality analysis in the participants with preserved spirometry is limited by the low death rates and the relatively small sample size. Third, our mortality analysis is inherently biased as we selected patients with ≥3 years follow-up and therefore all the participants were alive for at

least 3 years. Another limitation is the variable participation in the Longitudinal Follow-Up program (exacerbations). In addition, we did not have data regarding plasma eosinophilic counts and carbon dioxide in arterial blood gases that may provide additional information regarding the exacerbation risk. Racial minorities other than black individuals did not participate in the study. The above do not undermine the strength of our study which are the wealth of our demographic and medical history data, and the stringent quality control of our questionnaires, spirometry and radiographic measurements. Moreover, the large number of women and black individuals in our study makes our findings more externally applicable.

The frequent exacerbator phenotype is potentially a clinically relevant phenotype as it may indicate specialized COPD treatments. e.g. COPD patients with chronic hypercapnic respiratory failure have a median of 5 exacerbations per year and one-year mortality of 33% [39,40] and benefit from domiciliary nocturnal non-invasive ventilation. Non-invasive ventilation in those patients can reduce exacerbations and mortality by one third. Another example is COPD patients with antibody deficiency syndrome that have a median rate of 4 exacerbations a year and their exacerbation rate drops to a median of 0.75 a year after treatment with immunoglobin replacement treatment and/or prophylactic antibiotics [36].

In conclusion, the top 5% with the most exacerbations in COPD participants with mild-to-moderate lung impairment is responsible for approximately one third of all exacerbations. Among current or former smokers with preserved spirometry, the top 5% of those with the most exacerbations is responsible for more than half of the exacerbations in the cohort. COPD participants and current or former individuals with preserved spirometry have increased mortality compared to those with no exacerbations. These findings demonstrate for the first time that even in the absence of severe lung function impairment, the frequent exacerbator phenotype is associated with increased mortality. An increase in frequency of exacerbations by one exacerbation a year is associated with increased mortality. Future studies should investigate disease mechanisms associated with frequent exacerbations with the goal to develop interventions with great impact on disease burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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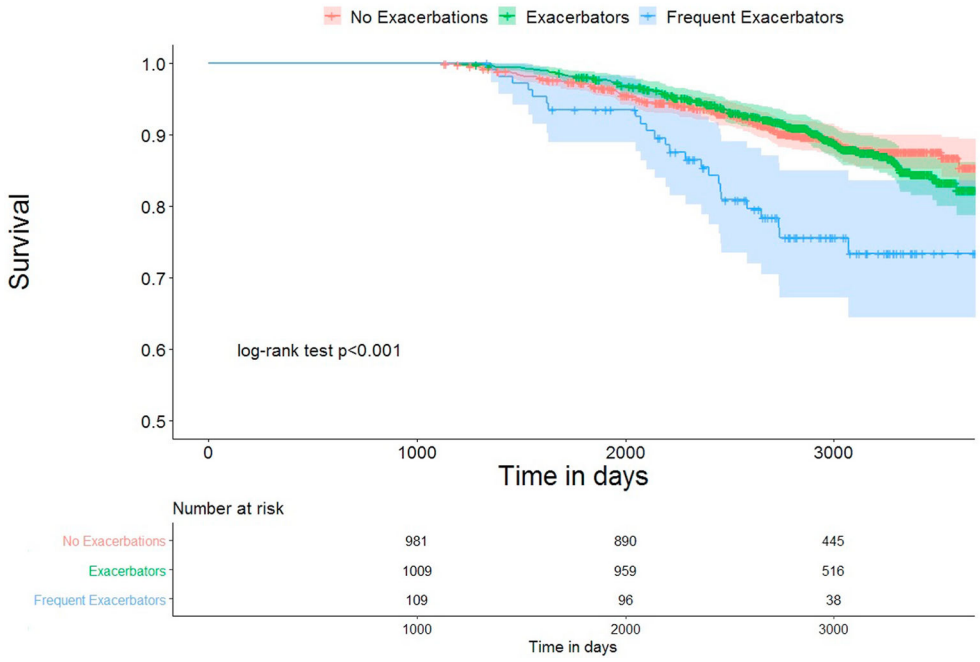

Fig. 1.

Crude survival in COPD participants with post-bronchodilator FEV1% predicted≥50% (n = 2,099) stratified by exacerbation group: i) No exacerbations (No exacerbation), ii)Exacerbations/year>0 and < 1.8 (Exacerbators), and iii) Exacerbation/year≥1.8 (Frequent Exacerbators).

Clinical Center	Institution Title	Protocol Number
National Jewish Health	National Jewish IRB	HS-1883a
Brigham and Women's Hospital	Partners Human Research Committee	2007-P-000554/2; BWH
Baylor College of Medicine	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22209
Michael E. DeBakey VAMC	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22202
Columbia University Medical Center	Columbia University Medical Center IRB	IRB-AAAC9324
Duke University Medical Center	The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB)	Pro00004464
Johns Hopkins University	Johns Hopkins Medicine Institutional Review Boards (JHM IRB)	NA_00011524
Los Angeles Biomedical Research Institute	The John F. Wolf, MD Human Subjects Committee of Harbor-UCLA Medical Center	12756–01
Morehouse School of Medicine	Morehouse School of Medicine Institutional Review Board	07–1029
Temple University	Temple University Office for Human Subjects Protections Institutional Review Board	11369
University of Alabama at Birmingham	The University of Alabama at Birmingham Institutional Review Board for Human Use	FO70712014
University of California, San Diego	University of California, San Diego Human Research Protections Program	070876
University of Iowa	The University of Iowa Human Subjects Office	200710717
Ann Arbor VA	VA Ann Arbor Healthcare System IRB	PCC 2008-110732
University of Minnesota	University of Minnesota Research Subjects' Protection Programs (RSPP)	0801M24949
University of Pittsburgh	University of Pittsburgh Institutional Review Board	PRO07120059
University of Texas Health Sciences Center at San Antonio	UT Health Science Center San Antonio Institutional Review	HSC20070644H
Health Partners Research Foundation	Health Partners Research Foundation Institutional Review	07–127
University of Michigan	Medical School Institutional Review Board (IRBMED)	HUM00014973
Minneapolis VA Medical Center	Minneapolis VAMC IRB	4128-A
Fallon Clinic	Institutional Review Board/Research Review Committee Saint Vincent Hospital – Fallon Clinic – Fallon Community Health Plan	1143

Table 1

Characteristics of COPD participants with post-bronchodilator FEV1%predicted≥50% and at least 3 years follow up (n = 2,099).

	No Exacerbation	Exacerbators	Frequent exacerbators	P value*
Exacerbations per year	0	>0 and <1.8	≥1.8	
n	981	1009	109	
Follow-up duration, y (IQR)	7.9 (6–8.8)	8.1 (7.1–9)	7.4 (5.7–8.8)	<0.001
Age, y ± SD	63.40 ± 8.47	63.47 ± 8.67	62.32 ± 8.62	0.411
Female, n (%)	399 (40.7%)	544 (53.9%)	56 (51.4%)	<0.001
African American, n (%)	199 (20.3%)	190 (18.8%)	17 (15.6%)	0.43
Active smokers, n (%)	460 (46.9%)	435 (43.1%)	35 (32.1%)	0.007
Pack-years smoking ± SD	48.21 ± 25.70	49.27 ± 25.41	55.58 ± 29.73	0.02
Body mass index, kg/m2 ± SD	27.76 ± 5.23	28.97 ± 6.34	29.02 ± 5.94	<0.001
History of Asthma, n (%)	147 (15.0%)	250 (24.8%)	40 (36.7%)	<0.001
History of acute bronchitis, n (%)	334 (34.0%)	588 (58.3%)	79 (72.5%)	<0.001
History of pneumonia, n (%)	324 (33.0%)	476 (47.2%)	74 (67.9%)	<0.001
Obstructive Sleep Apnea, n (%)	118 (12.0%)	199 (19.7%)	28 (25.7%)	<0.001
Gastroesophageal Reflux, n (%)	230 (23.5%)	354 (35.1%)	48 (44.0%)	<0.001
Diabetes Mellitus, n (%)	104 (10.6%)	117 (11.6%)	12 (11.0%)	0.78
History of Cancer, n (%)	72 (7.3%)	104 (10.3%)	19 (17.4%)	<0.001
Chronic bronchitis, n (%)	163 (16.6%)	258 (25.6%)	42 (38.5%)	<0.001
mMRC>2, n (%)	281 (28.7%)	463 (46.1%)	81 (74.3%)	<0.001
Post-FEV1% predicted ± SD	75.37 ± 14.77	70.63 ± 13.79	64.35 ± 11.65	<0.001
Post-FVC% predicted ± SD	93.58 ± 15.64	90.98 ± 15.93	88.67 ± 15.63	<0.001
Bronchodilator response, n (%)	281 (28.9%)	351 (34.9%)	46 (43.0%)	<0.001
6-min-walk-test distance, ft ± SD	1437.25 ± 357.68	1357.60 ± 352.82	1197.26 ± 339.28	<0.001
ICS/LABA, n (%)	141 (14.4%)	275 (27.3%)	61 (56.0%)	<0.001
LAMA, n (%)	105 (10.7%)	259 (25.7%)	50 (45.9%)	<0.001
ICS, n (%)	44 (4.5%)	84 (8.3%)	15 (13.8%)	<0.001
LABA, n (%)	32 (3.3%)	42 (4.2%)	8 (7.3%)	0.10
Total exacerbations per year ± SD	0.00 ± 0.00	0.50 ± 0.42	2.66 ± 0.80	<0.001
Severe exacerbations per year ± SD	0.00 ± 0.00	0.17 ± 0.24	0.81 ± 0.83	<0.001
Total exacerbations ± SD	0.00 ± 0.00	3.85 ± 3.27	18.60 ± 7.30	<0.001
Severe exacerbations ± SD	0.00 ± 0.00	1.30 ± 1.79	5.61 ± 5.77	<0.001
Emphysema, % ± SD	6.47 ± 6.70	7.37 ± 7.73	11.31 ± 10.23	<0.001
Gas trapping, % ± SD	23.44 ± 14.03	26.61 ± 14.48	33.94 ± 15.75	<0.001
TLV, L ± SD	5.95 ± 1.42	5.74 ± 1.33	5.92 ± 1.46	0.00401
TLV% predicted ± SD	109.14 ± 16.16	110.74 ± 17.08	113.10 ± 18.45	0.0176
Pi10, mm ± SD	3.65 ± 0.13	3.68 ± 0.13	3.69 ± 0.14	<0.001

*ANOVA for continuous and chi square of fisher exact test for categorical variables

Data regarding gastroesophageal reflex, mMRC, bronchodilator response, 6-min-walk-test distance, TLV, Pi10, gas trapping and emphysema were missing in 1,2,6,11,21,103,119,333, and 103 participants, respectively.

ICS = inhaled glucocorticosteroids; IQR = interquartile range; LABA = long acting beta-agonist; LAMA = long acting muscarinic antagonist; mMRC = modified Medical Research Council scale, post-FEV1% predicted = post-bronchodilator forced expiratory volume in 1 s %predicted; post-FVC% predicted = post-bronchodilator forced vital capacity %predicted, Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; TLV = total lung volume at maximum inspiratory volumes measure by chest CT.

Table 2

Association of exacerbation group with mortality in COPD participants with post-bronchodilator FEV1%predicted≥50% with at least 3 years follow up (n = 2,099).

	HR (95%CI)	P value
No Exacerbation (n = 981)	ref	ref
Exacerbators (n = 1,009)	0.91 (0.70, 1.20)	0.52
Frequent exacerbators (n = 109)	1.98 (1.25, 3.13)	0.004

Cox Proportional Hazards regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI), post-bronchodilator FEV1% predicted, and history of obstructive sleep apnea.

HR = hazard ratio.

Table 3

Characteristics of current and former smokers with normal spirometry with at least 3 years follow up (n = 3,143).

	No Exacerbation	Exacerbators	Frequent exacerbators	P value[a]
Exacerbations per year	0	>0 and <0.8	≥0.8	
n	2215	743	185	
Follow-up duration, y (IQR)	8 (6.5–8.8)	8.4 (7.5–9.1)	8 (6.9–8.8)	<0.001
Age, y ± SD	58.07 ± 8.60	58.38 ± 8.60	57.12 ± 8.45	0.2
Female, n (%)	1049 (47.4%)	463 (62.3%)	123 (66.5%)	<0.001
African American, n	699 (31.6%)	212 (28.5%)	67 (36.2%)	0.09
Active smokers, n (%)	1103 (49.8%)	349 (47.0%)	92 (49.7%)	0.41
Pack-years smoking ± SD	36.98 ± 20.57	35.72 ± 18.55	43.78 ± 25.54	<0.001
Body mass index, kg/m2 ± SD	28.70 ± 5.55	30.01 ± 6.09	30.91 ± 6.59	<0.001
History of Asthma, n (%)	179 (8.1%)	123 (16.6%)	73 (39.5%)	<0.001
History of acute bronchitis, n (%)	634 (28.6%)	364 (49.0%)	114 (61.6%)	<0.001
History of pneumonia, n (%)	565 (25.5%)	268 (36.1%)	88 (47.6%)	<0.001
Obstructive Sleep Apnea, n (%)	244 (11.0%)	126 (17.0%)	43 (23.2%)	<0.001
Gastroesophageal Reflux, n (%)	428 (19.3%)	236 (31.8%)	71 (38.4%)	<0.001
Diabetes Mellitus, n (%)	224 (10.1%)	102 (13.7%)	29 (15.7%)	0.004
History of Cancer, n (%)	115 (5.2%)	49 (6.6%)	12 (6.5%)	0.31
Chronic bronchitis, n (%)	197 (8.9%)	118 (15.9%)	42 (22.7%)	<0.001
mMRC>2, n (%)	374 (16.9%)	190 (25.6%)	88 (47.6%)	<0.001
Post-FEV1% predicted ± SD	97.76 ± 11.37	96.72 ± 11.60	94.38 ± 10.66	<0.001
Post-FVC% predicted ± SD	96.56 ± 11.56	95.58 ± 12.06	94.69 ± 10.85	0.026
Bronchodilator response, n (%)	214 (9.8%)	61 (8.4%)	25 (13.5%)	0.11
6-min-walk-test distance, ft ± SD	1534.40 ± 352.08	1484.22 ± 353.94	1366.52 ± 332.02	<0.001
ICS/LABA, n (%)	45 (2.0%)	49 (6.6%)	39 (21.1%)	<0.001
LAMA, n (%)	31 (1.4%)	19 (2.6%)	22 (11.9%)	<0.001
ICS, n (%)	23 (1.0%)	16 (2.2%)	15 (8.1%)	<0.001
LABA, n (%)	2 (0.1%)	5 (0.7%)	4 (2.2%)	<0.001
Total exacerbations per year ± SD	0.00 ± 0.00	0.27 ± 0.19	1.37 ± 0.76	<0.001
Severe exacerbations per year ± SD	0.00 ± 0.00	0.09 ± 0.14	0.41 ± 0.50	<0.001
Moderate-to-severe exacerbations, n (%)	0.00 ± 0.00	2.18 ± 1.50	10.42 ± 6.73	<0.001
Severe exacerbations, n (%)	0.00 ± 0.00	0.70 ± 1.10	3.06 ± 3.70	<0.001
Emphysema, % ± SD	2.36 ± 2.77	2.50 ± 3.13	2.36 ± 2.87	0.56
Gas trapping, % ± SD	10.72 ± 8.67	10.29 ± 8.05	10.58 ± 8.53	0.54
TLV, L ± SD	5.46 ± 1.32	5.20 ± 1.22	5.10 ± 1.18	<0.001
TLV% predicted ± SD	102.95 ± 15.56	103.06 ± 14.94	104.06 ± 14.54	0.66
Pi10, mm ± SD	3.63 ± 0.11	3.65 ± 0.11	3.67 ± 0.12	<0.001

Data regarding bronchodilator response, 6-min-walk-test distance, TLV, Pi10, gas trapping and emphysema were missing in 40,10,184,199,582, and 184 participants, respectively.

ICS = inhaled glucocorticosteroids; LABA = long acting beta-agonist; LAMA = long acting muscarinic antagonist; mMRC = modified Medical Research Council scale, post-FEV1% predicted = post-bronchodilator forced expiratory volume in 1 s %predicted; post-FVC% predicted = post-bronchodilator forced vital capacity %predicted, Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; TLV = total lung volume at maximum inspiratory volumes measure by chest CT.

[a]ANOVA for continuous and chi square of fisher exact test for categorical variables.

Table 4

Association of exacerbation group with mortality in current and former smokers with normal spirometry with at least 3 years of follow-up (n = 3,143).

	HR (95%CI)	P value
No Exacerbation (n = 2,215)	ref	ref
Exacerbators (n = 743)	1.02 (0.67, 1.57)	0.92
Frequent Exacerbators (n = 185)	2.25 (1.26, 4.01)	0.006

Cox Proportional Hazards regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI), post-bronchodilator FEV1% predicted, and history of obstructive sleep apnea.

95%CI = 95% Confidence interval; HR = hazard ratio.