Research Article

Risk Factors Associated with Severe Exacerbation in Non-Smoking COPD Patients in Primary Care: A Retrospective Observational Study

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide. While smoking is the main risk factor, a significant subset of COPD patients are non-smokers. The clinical features and exacerbation risk factors in this population remain understudied, especially in primary care.

Objective: To identify risk factors associated with severe exacerbations in non-smoking patients with COPD in a real-world primary care cohort.

Methods: We conducted a retrospective cohort study using anonymized data from 2,376 patients diagnosed with COPD in a Spanish primary care setting. Patients were classified according to their smoking status; only non-smokers (n=1,582) were included in the analysis. Severe exacerbation was defined as hospitalization or emergency department visits due to COPD worsening. We performed bivariate analyses and multivariate logistic regression to assess factors associated with exacerbations.

Results: Among non-smokers, 113 (7.1%) experienced a severe exacerbation. These patients were significantly older (median 77 *vs.* 74 years; p=0.003) and had worse lung function (median FEV1: 1.3[illegible] 1.70 L; p<0.001). Logistic regression identified atrial fibrillation (OR=2.04; 95% CI: 1.20-3.3[illegible] p=0.007) and bronchiectasis (OR=2.31; 95% CI: 1.42-3.68; p<0.001) as independent predictors of severe exacerbation.

Conclusion: Among non-smoking COPD patients, older age, atrial fibrillation and bronchiectasis are significant risk factors for severe exacerbations. These findings highlight the need for personalized management strategies in non-smoking COPD populations in primary care.

Keywords: COPD; Exacerbation; Non-Smoker; Primary Care; Atrial Fibrillation; Bronchiectasis

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is traditionally associated with cigarette smoking, which remains the leading modifiable risk factor worldwide [1]. However, a growing body of evidence reveals a substantial proportion of COPD patients who have never smoked, especially in low and middle income countries [2]. In Europe, non-smoking COPD may account for up to 25%-45% of all diagnosed cases and in some primary care settings, this figure can be even higher [3].

Non-smoking COPD represents a distinct clinical phenotype. Environmental exposures (e.g., biomass fuels, occupational agents), recurrent respiratory infections, poor lung development and genetic predispositions (e.g., alpha-1 antitrypsin deficiency) have been implicated as non-tobacco etiologies [4,5]. Compared to smokers with COPD, non-smokers often present with fewer emphysematous changes, more preserved lung function, higher prevalence of bronchiectasis and a predominance of female patients [6-8].

Despite its growing relevance, the clinical trajectory of non-smoking COPD remains underexplored. Exacerbations, defined as acute worsening of respiratory symptoms requiring additional therapy, are major drivers of morbidity, mortality and health care utilization in COPD [9]. Although several studies have investigated predictors of exacerbations in general COPD populations [10,11], few have focused on the non-smoking subgroup.

Moreover, common risk factors such as reduced Forced Expiratory Volume in 1 second (FEV1), prior exacerbation history, comorbidities (e.g., cardiovascular disease) and low Body Mass Index (BMI) may behave differently in non-smokers, who often have alternative pathophysiological mechanisms driving their disease [12-14]. There is also increasing interest in the role of comorbid atrial fibrillation and bronchiectasis, both

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of which are prevalent and potentially modifiable conditions in COPD patients [15,16].

To our knowledge, no prior study has assessed the specific risk factors associated with severe exacerbation in a well-characterized cohort of non-smoking COPD patients followed in primary care. Identifying such predictors is essential to developing targeted interventions and improving clinical outcomes (Figure 1).

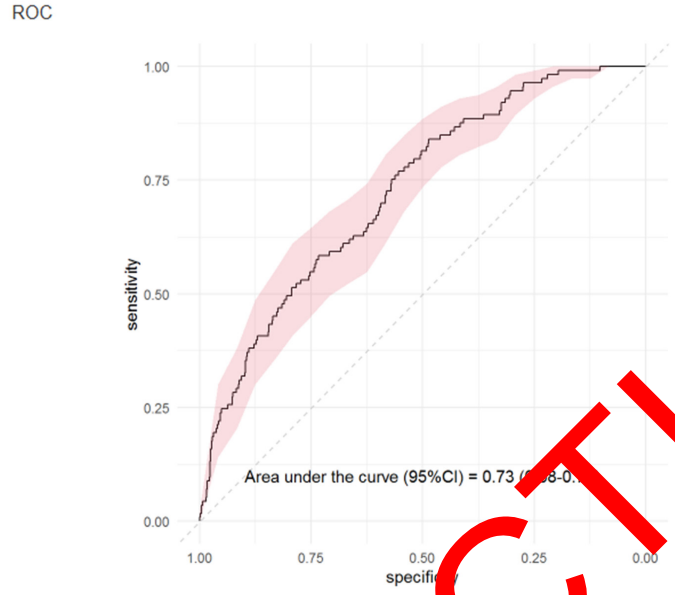

Figure 1. ROC curve of the predictive model for severe exacerbation among non-smoking COPD patients

Material and Methods

Study design and setting

This was a retrospective, observational cohort study using anonymized electronic health records from a large primary care database in Catalonia, Spain. The cohort included patients aged COPD according to GOLD criteria, who had at least one valid spirometry and were classified as non-smokers.

Participants

Inclusion criteria: Confirmed COPD diagnosis: Non-smoking status defined by physician report and EMR documentation. At least 12 months of follow-up data between 2019 and 2023 (a 5-year period).

Exclusion criteria: Current or former smokers. Incomplete spirometry or missing key variables.

Variables and Definitions: The primary outcome was severe exacerbation, defined as requiring emergency care, hospitalization, or systemic corticosteroids with antibiotics.

Predictor variables included: Demographics (age, sex, living alone).

Spirometric values: Forced Vital Capacity (FVC), FEV1, FEV1/FVC ratio. Comorbidities: atrial fibrillation, anemia, bronchiectasis, heart failure, Chronic Kidney Diseases (CKD), etc. Living in institutional care or requiring home oxygen.

Statistical analysis: Descriptive statistics were reported using medians and interquartile ranges or frequencies as appropriate. Differences between exacerbation and non-exacerbation groups were compared using chi-square and Mann-Whitney U tests. Logistic regression was used to identify independent predictors, adjusting for confounders. Statistical significance was set at $p<0.05$.

Results

Baseline Characteristics

Of 1,582 non-smoking COPD patients, 113 (7.1%) experienced at least one severe exacerbation during the study period. Patients with exacerbation were older (median age 77 *vs.* 74 years, p=0.003) and had significantly lower FVC (2.51 *vs.* 2.88 L, p<0.001) and FEV1 (1.37 *vs.* 1.70 L, p<0.001). The FEV1/FVC ratio was also significantly reduced in the exacerbation group (0.57 vs. 0.62, p<0.001).

Comorbidities

Atrial fibrillation (25.7% *vs.* 12.7%, p<0.001), bronchiectasis (26.5% *vs.* 12.9%, p<0.001), anemia (15.9% *vs.* 9.0%, p=0.024) and heart failure (14.2% *vs.* 6.8%, p=0.007) were more prevalent among exacerbators.

Multivariate analysis

In logistic regression (AUC=0.78), the following variables were independently associated with exacerbation:

- Bronchiectasis (OR 2.31, 95% CI 1.42-3.68, p<0.001)
- Atrial fibrillation (OR 2.04, 95% CI 1.20-3.39, p=0.007)
- Lower FEV1 (trend but not significant)
- Age was not an independent predictor after adjustment.

Discussion

This study identifies bronchiectasis and atrial fibrillation as key independent predictors of severe exacerbation in non-smoking COPD patients, highlighting the importance of comprehensive comorbidity assessment in this population.

Bronchiectasis is increasingly recognized as a frequent and underdiagnosed condition in COPD, especially in non-smokers and women [17,18]. Our findings are consistent with prior studies suggesting that the presence of bronchiectatic changes on imaging is associated with increased bacterial colonization, systemic inflammation and exacerbation risk [19]. The coexistence of COPD and bronchiectasis-termed the COPD-bronchiectasis overlap-has been linked to worse clinical outcomes and higher mortality [20].

Atrial fibrillation was another strong and independent risk factor. This supports existing literature that links cardiovascular comorbidities with adverse COPD outcomes [21]. Atrial fibrillation (AF) may worsen ventilation-perfusion mismatch and increase systemic inflammation, thereby predisposing to exacerbations [22]. Our data echo recent cohort studies from Korea and the UK that found similar associations [23,24].

Interestingly, female sex and anemia were not significant in multivariate models, despite showing unadjusted differences. Previous studies have been mixed regarding sex-specific

differences in COPD exacerbation risk, especially in non-smokers [25]. Similarly, the role of anemia remains unclear, with some suggesting protective effects due to reduced oxygen demand [26].

The lack of association between oxygen therapy and exacerbation likely reflects appropriate prescribing to more severe cases already under surveillance, introducing potential confounding.

Strengths and Limitations

This is one of the first studies to focus exclusively on non-smoking COPD in primary care. Strengths include a large, real-world cohort with confirmed spirometry and detailed comorbidity coding. Limitations include the retrospective design, possible residual confounding and the absence of radiological confirmation for bronchiectasis.

Conclusion

Non-smoking COPD patients are at measurable risk of severe exacerbations, especially those with bronchiectasis and atrial fibrillation. These findings suggest the need for routine screening for structural lung disease and cardiovascular comorbidities in this subgroup, even in the absence of a smoking history. Future prospective studies should validate these results and explore intervention strategies tailored to this emerging phenotype.

References

1. GOLD Report 2024. Global Initiative for Chronic Obstructive Lung Disease. 2024.
2. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009;374:733–743.
3. Lamprecht B, et al. COPD in never smokers: Results from the BOLD study. Eur Respir J. 2011;39(5):1057–1066.
4. Eisner MD, Balmes J, Katz PP, Trupin L, Yelin EH, et al. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. Environ Health. 2005;4:7.
5. Zeng G, Sun B, Zhong N. Non-smoking-related chronic obstructive pulmonary disease: A neglected entity?. Respirology. 2012;17(6):908-912.
6. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, et al. Chronic obstructive pulmonary disease phenotypes. Am J Respir Crit Care Med. 2010;182:598–604. [Crossref] [Google Scholar]
7. Çolak Y. COPD in never-smokers: risk factors and characteristics. Lancet Respir Med. 2020;8:782-790.
8. Martinez FJ. The clinical impact of non-smoking-related COPD. Chest. 2013;143(3):744-753.
9. Wedzicha JA, Seemungal TA. COPD exacerbations: Defining their cause and prevention. Lancet. 2007;370(9589):786-796.
10. Hurst JR, Vestbo J, Anzueto A, Locantore J, Müllerova H, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363(12):1128-1138.
11. Suissa S. Risk of death associated with exacerbations in COPD: A cohort study. Eur Respir J. 2012;40:988-995.
12. Celli BR. The BODE index in COPD. N Engl J Med. 2004;350:1005-1012.
13. López-Campos JL. COPD heterogeneity: Implications for diagnosis and treatment. Arch Bronconeumol. 2021;57(3):149-155.
14. Wheaton AG. Chronic obstructive pulmonary disease and smoking status-United States, 2017. JAMA. 2015;313(5):435-436.
15. Sin DD. The cardiovascular burden of COPD. Am J Med. 2005;118(2):94-100.
16. Martínez-García MA. Bronchiectasis as a comorbidity of COPD: Prevalence, clinical impact, and prognosis. Chest. 2011;140(5):1138-1143.
17. Kim YJ. Bronchiectasis in patients with COPD: A Korean cohort. Respir Res. 2021;22:71.
18. Gao YH. The impact of bronchiectasis on COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:543-550.
19. Chalmers JD. Bronchiectasis exacerbations and chronic infection. Lancet Respir Med. 2015;3(9):769-779.
20. Patel IS, Seemungal TA, Wilks M, Lloyd-Owen SJ, Donaldson GC, et al. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. Thorax. 2002;57(9):759-764.
21. Iqbal A. Cardiac arrhythmias in COPD: Cause or effect? J Thorac Dis. 2018;10(9):5760-5769.
22. Lip GYH. Atrial fibrillation in COPD: Mechanisms and management. Chest. 2021;159(5):1770-1781.
23. Lee H. Atrial fibrillation and risk of COPD exacerbations. Int J Chron Obstruct Pulmon Dis. 2022;17:199-210.
24. Quint JK. COPD and cardiovascular disease. Thorax. 2014;69(10):943-950.
25. de Torres JP. Gender differences in chronic obstructive pulmonary disease. Arch Bronconeumol. 2018;54(11):567-572.
26. John M, Hoernig S, Doehner W, Okonko DD, Witt C, et al. Anemia and systemic inflammation in COPD. Chest. 2005;127(3):825-829.]