Open Respiratory Archives 5 (2023) 100249

Sociedad Española de Neumología y Cirugía Torácica SEPAR

Open Respiratory Archives

www.elsevier.es/ora

Scientific letter

The Relevance of Comorbidities in the Persistence of Exacerbations in Patients With Chronic Obstructive Pulmonary Disease

Relevancia de la comorbilidad en la persistencia de agudizaciones en pacientes con enfermedad pulmonar obstructiva crónica

Dear Editor,

Up to 90% of patients with chronic obstructive pulmonary disease (COPD) have some associated comorbidity,[1,2] which impacts disease management and potentially contributes to a greater incidence of exacerbations.[3,4] Predicting future exacerbations has been the objective of many studies, with one of the most reliable predictors being a history of previous exacerbations[5]; but numerous patients follow inconsistent trajectories in this respect.[6] A study conducted by our group analyzed the incidence of severe COPD exacerbations before and after optimizing pharmacological treatment, describing four possible trajectories with different vital prognoses ("non-exacerbator", "converter to non-exacerbator", "converter to exacerbator" and "persistent exacerbator").[7] The subjects included in the latter two trajectories (i.e., those who continued to suffer exacerbations after optimizing treatment) had a greater comorbidity burden, which suggests that these comorbidities were relevant elements in the persistence of exacerbations. The objective of the current study is to analyze which comorbidities were significantly related to persistent exacerbations.

It is a retrospective observational study carried out in a specialized COPD clinic at a second-level hospital. Consecutive patients treated at that clinic between 2008 and 2020 were included in the study. The index date is that of the first clinic visit. The following variables were recorded: age, sex, BODEx index (body mass index, airflow obstruction, dyspnea and exacerbations), active smoking at index date, patients with an O2 saturation <90%, and the presence of the following comorbidities: arterial hypertension, atrial fibrillation, anxiety, ischemic heart disease, diabetes mellitus (DM), cerebrovascular disease, peripheral vascular disease, chronic hepatopathy, chronic kidney disease (CKD), leukemia or lymphoma and peptic ulcer. All variables were recorded dichotomously except for age and BODEx index value. A logistic regression analysis was carried out in which these were introduced as independent variables, with the dependent variable being the presence of severe COPD exacerbations (those that required hospitalization) after the index date. The variables included in the final model were selected using a backward stepwise regression method in which variables were introduced if their significance was $p < 0.05$ and eliminated if it was $p > 0.1$. The study was approved by the ethics committee of the Hospital Universitario Nuestra Señora de Candelaria. The study did not require informed consent.

A total of 1083 subjects were included. Mean age: 68.7 ± 9.6 years. In all, 862 (79.6%) were male. Mean FEV1%: 51.9 ± 17.0%. Two hundred forty-six (28%) were current smokers. Mean BODEx index value: 2.4 ± 1.8. Mean follow-up: 66.2 ± 36.8 months. A total of 187 subjects (17.3%) required hospitalization for a severe exacerbation after the index date. The only variables retained in the regression model were BODEx index (odds ratio [OR]: 2.06, 95% CI: 1.57–2.69, $p < 0.001$), a diagnosis of DM (OR: 3.42, 95% CI: 1.36–8.62, $p = 0.009$) and chronic kidney disease (OR: 5.21, 95% CI: 1.24–21.83, $p = 0.02$).

The results of the study suggest that DM and CKD are especially relevant comorbidities in COPD with respect to the risk of persistent severe exacerbations. DM is a very frequent and relevant comorbidity in patients with COPD.[8] Studies conducted in the ECLIPSE cohort showed that a diagnosis of DM is associated with a greater degree of dyspnea and lower effort capacity in subjects with COPD.[9] Furthermore, DM could plausibly increase the risk of exacerbation. Patients with DM and worse glucose control have a greater risk of suffering infections.[10] In subjects with COPD, higher glucose levels in respiratory samples are correlated with a greater probability of isolating potentially pathogenic microorganisms during an exacerbation,[11] and elevated glycosylated hemoglobin concentrations during a severe COPD exacerbation are associated with a greater risk of suffering another exacerbation in the next 12 months, regardless of previously being diagnosed with DM.[12] Our results are compatible with these studies suggesting that DM has an impact on persistent exacerbations.

CKD is another disease to take into account in COPD, and it has been associated with worse symptom control, a shorter distance in the 6-min walk test, worse quality of life and shorter expected survival.[13] Subjects with CKD have a greater risk of malnutrition, myopathy, anemia, osteoporosis and cardiovascular disease.[14] All of this influences symptom burden, the risk of mortality and potentially the risk of suffering more severe COPD exacerbations. Our results are consistent with this.

The aforementioned comorbidities were significantly associated with these events regardless of BODEx index, which is established in the multidimensional assessment of COPD, and following assessment at a clinic specializing in pulmonology at which treatment of COPD would have plausibly been optimized. This points toward the need to pay attention to comorbidities with the intention of preventing future exacerbations. DM and CKD were outlined in this analysis as the most relevant in the persistence of these events. We did not find a significant association between the persistence of exacerbations and other comorbidities like cardiovascular disease or psychiatric disease, which other studies did associate with these episodes,[15] although this is not a universal finding. In a study by Ouaalaya et al.[15] in just over 900 patients, an independent association between cardiovascular comorbidities and the persistence of exacerbations was not found, with anxiety

https://doi.org/10.1016/j.opresp.2023.100249

being the main pathology involved. However, these authors did not specifically focus on severe exacerbations.

There are limitations to our study related to the retrospective design, such as the fact that not all pharmacological treatments were recorded. It is possible that, within the context of a COPD clinic, there is more thorough management of cardiovascular diseases (traditionally identified as a particularly relevant pathology in the disease) than of a cardiovascular risk factor like DM, whose influence on exacerbations would be less evident. Obesity, a sedentary lifestyle and the pharmacological treatment used in COPD both in stable phases and during exacerbations, among others, are some of the factors that could influence correct glucose control and thus lead to an increase in risk of infection. Due to the setting for the study (in a single center and a highly selective environment – a specialized clinic in a pulmonology department –), results must be interpreted with caution, although it opens a debate on the need to identify which comorbidities are related to a trajectory of persistent exacerbations. On the other hand, the study has some strengths, such as its sample size and the definition of exacerbations established in other studies, as well as the fact that it has little susceptibility to reporting bias since reliable information about hospitalizations was obtained from the electronic medical record.

To summarize, some comorbidities seem to be significantly and independently related to the persistence of COPD exacerbations, and it is thus important to study and control them when establishing a personalized therapeutic plan for the disease.

Funding

No financial support has been received for conducting the study or drafting the manuscript.

Authors' contributions

JMFG and RG performed the conception and manuscript design; data collection; data analysis and interpretation; and drafting, revising and approval of the manuscript. IVT did data collection and drafting, revising and approval of the manuscript. All authors approved the final version.

Conflicts of interest

The authors declare not to have any direct or indirect conflict of interest related to the manuscript contents.

References

1. García-Olmos L, Alberquilla A, Ayala V, García-Sagredo P, Morales L, Carmona M, et al. Comorbidity in patients with chronic obstructive pulmonary disease in family practice: a cross sectional study. BMC Fam Pract. 2013;14:11.
2. Van Manen JG, Bindels PJ, IJzermans CJ, Van der Zee JS, Bottema BJ, Schadé E. Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. J Clin Epidemiol. 2001;54:287–93.
3. Figueira Gonçalves JM, Martín Martínez MD, Pérez Méndez LI, García Bello MÁ, García-Talavera I, Hernández SG, et al. Health status in patients with COPD according to GOLD 2017 classification: use of the COMCOLD score in routine clinical practice. COPD. 2018;15:326–33.
4. Divo M, Cote C, De Torres JP, Casanova C, Marín JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186:155–61.
5. Whittaker H, Rubino A, Müllerová H, Morris T, Varghese P, Xu Y, et al. Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. Int J Chron Obstruct Pulmon Dis. 2022;17:427–37.
6. Sadatsafavi M, McCormack J, Petkau J, Lynd LD, Lee TY, Sin DD. Should the number of acute exacerbations in the previous year be used to guide treatments in COPD? Eur Respir J. 2021;57:2002122.
7. Golpe R, Figueira-Gonçalves JM, Amado-Diago CA, Expósito-Marrero A, González-Ramos L, Dacal-Rivas D, et al. Trajectories of severe exacerbations of chronic obstructive pulmonary disease and their relationship with mortality risk. Lung. 2022;200:601–7.
8. Santos NCD, Miravitlles M, Camelier AA, Almeida VDC, Maciel RRBT, Camelier FWR. Prevalence and impact of comorbidities in individuals with chronic obstructive pulmonary disease: a systematic review. Tuberc Respir Dis (Seoul). 2022;85:205–20.
9. Miller J, Edwards LD, Agustí A, Bakke P, Calverley PM, Celli B, et al. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. Respir Med. 2013;107:1376–84.
10. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. Diabetes Care. 2018;41:2127–35.
11. Mallia P, Webber J, Gill SK, Trujillo-Torralbo MB, Calderazzo MA, Finney L, et al. Role of airway glucose in bacterial infections in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2018;142:815–23, e6.
12. Chen G, Lin Q, Zhuo D, Cui J. Elevated blood glucose is associated with severe exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2022;17:2453–9.
13. Trudzinski FC, Alqudrah M, Omlor A, Zewinger S, Fliser D, Speer T, et al., German COSYCONET consortium. Consequences of chronic kidney disease in chronic obstructive pulmonary disease. Respir Res. 2019;20:151.
14. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet. 2017;389:1238–52.
15. Ouaalaya EH, Falque L, Dupis JM, Sabatini M, Bernady A, Nguyen L, et al. Susceptibility to frequent exacerbation in COPD patients: impact of the exacerbations history, vaccinations and comorbidities? Respir Med. 2020;169:106018.

Juan Marco Figueira-Gonçalves [a,b,*], Rafael Golpe [c], Iria Veiga-Teijeiro [c]

[a] *Pneumology and Thoracic Surgery Service, Unit for Patients with Highly Complex COPD, University Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain*
[b] *University Institute of Tropical Disease and Public Health of the Canary Islands, University of La Laguna, Santa Cruz de Tenerife, Spain*
[c] *Pneumology Service, University Hospital Lucus Augusti, Lugo, Spain*

[*] Corresponding author at: Corresponding author.
E-mail address: juanmarcofigueira@gmail.com
(J.M. Figueira-Gonçalves).