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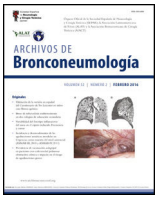

Scientific Letter

Relationship Between the Summation of GesEPOC High-Risk Factors and the Presence of Cardiovascular Disease☆

To the Director,

Comorbidities are a fundamental part of managing patients with chronic obstructive pulmonary disease (COPD).[1–3] The 2021 GesEPOC guide proposes classifying patients with COPD as low risk (LR) or high risk (HR) based on the degree of airflow obstruction, degree of dyspnea measured using the modified Medical Research Council (mMRC) scale and the history of exacerbations in the previous year.[2] If we consider that each of these factors has been separately related to the existence of cardiovascular disease,[4–8] it stands to reason that the sum of these increases the possibility of this type of comorbidity coexisting, which can impact the management of these patients. The aim of this study was to find the relationship between the summation of risk factors that make up the GesEPOC HR group and the coexistence of cardiovascular disease (CVD).

A cross-sectional, multicenter study was performed involving four historical cohorts of outpatients with COPD. These cohorts have been presented in previous studies.[9] The following inclusion criteria were applied: (1) patient attending follow-up at an outpatient pneumology service; (2) age > 40 years; (3) active or former smoker with a pack-year index (PYI) ≥ 10 or exposure to another known risk factor; (4) forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio < 70% upon administration of 400 μg of salbutamol. Chronic respiratory diseases other than COPD were considered an exclusion criterion except a history of asthma. Clinical data extraction was authorized by the corresponding ethics committee (Ethics Committee for Clinical Research of the University Hospital Nuestra Señora de Candelaria, registry number CHUNSC_2021_41).

Variables included were age, gender, body mass index (BMI [kg/m^2]), pack-year index (PYI), dyspnea (mMRC scale) and the number of severe exacerbations requiring hospital stays during the year prior to the first visit as an outpatient. The comorbidities arterial hypertension (AHT), type 2 diabetes mellitus (DM2), dyslipidemia (DLP), obesity (defined as BMI ≥ 30 kg/m^2), atrial fibrillation (AF), ischemic heart disease (IHD), chronic heart failure (CHF), cerebrovascular accidents (CVA), neoplasia (solid tumors, lymphoma, leukemia), osteoporosis, and mood disorders were obtained. Each associated morbidity was confirmed by a comprehensive review of the electronic medical records, data from diagnostic procedures, and disease-specific therapies. For the analysis, cardiovascular disease was defined as the presence of AF, IHD, CHF and/or CVA. The non age-adjusted Charlson comorbidity index (CCI) score[10] and the BODEx[11] index were determined for each patient. Forced spirometry data following bronchodilation was recorded. Patients were also classified as LR vs HR patients.[2]

For continuous normal variables, bivariate comparisons between independent samples were made using Student's *t* test. The Mann–Whitney *U* test was used for continuous non-normal variables. Qualitative variables were tested using Chi-square.

To study the association between the coexistence of CVD and the summation of the 3 risk factors, a multivariate logistic regression was performed with two models: model 1, which was adjusted for age, sex, BMI and PYI, and model 2 which, in addition to the previous adjustments, was adjusted for the existence of AHT, DM2 and dyslipidemia. In addition, the multiplicative effect of the combination of more than one risk factor including the interaction between risk factors and their main factors was evaluated; no interactions were significant. The model was not included in the results since it did not contribute to the interpretation of the simpler model. A *p*-value < 0.05 was considered statistically significant. Analyses were performed using SPSS v.21 software.

The baseline characteristics of the 877 patients comprising the study population have been presented in previous studies[9] (70% were classified HR). The subjects with cardiovascular disease are described in Table 1. In the multivariate analysis (model 1), patients with dyspnea mMRC ≥ 2 and those with a history of severe exacerbations in the previous year had a greater probability of coexisting cardiovascular disease (OR = 1.62; $CI_{95\%}$ 1.06–2.47; $p = 0.025$ and OR = 2.72; $CI_{95\%}$ 1.24–5.94; $p = 0.012$, respectively). The combination of these risk factors in a single patient independently increased the OR to 4.09 ($CI_{95\%}$ 1.83; 9.17; $p = 0.001$). 65% ($CI_{95\%}$ 47.5–80%) of patients with both risk factors had CVD compared to 27% ($CI_{95\%}$ 21.8–32.2%) of those without any risk factors. FEV_1 was not significant when present on its own or in combination with the other risk factors. Age and BMI were associated with a greater likelihood of having cardiovascular disease (OR = 1.08; $CI_{95\%}$ 1.07–1.11; $p < 0.001$ and OR = 1.03; $CI_{95\%}$ 1.01–1.07; $p = 0.017$, respectively), Table 2.

Similarly to model 1, after adjusting for the existence of AHT, DLP and DM2 (model 2), the risk of CVD coexistence was greater in those patients with a combination of a greater degree of dyspnea and a history of severe exacerbations, compared to the risk obtained with each of the GesEPOC risk factors separately. Subjects with a high degree of dyspnea showed an elevated risk of coexisting CVD, although it was not statistically significant, Table 2.

CVD is especially relevant, producing great morbidity and mortality.[12–17] The GesEPOC risk classification was designed to guide the pharmacological treatment of COPD, but two of the classifying elements (dyspnea and exacerbations) can be conditioned by the existence of CVD.[4,17] Therefore, using these elements just to decide on specific COPD therapies (e.g.: bronchodilators, steroids) may not be enough to improve patients' quality of life and progno-

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Table 1
Characteristics of patients with chronic obstructive pulmonary disease based on the presence of cardiovascular disease.

	Without cardiovascular disease $n = 568$	With cardiovascular disease $n = 309$	p-Value
Clinical data			
Mean age, years (SD)	65.40 (10.31)	73.38 (8.38)	**<0.001**
Female, *n* (%)	135 (23.8)	41 (13.3)	**<0.001**
Mean pack-year index (SD)	47.34 (27.63)	47.55 (27.31)	0.914
Active smoker, *n* (%)	277 (48.8)	117 (37.9)	**0.002**
Mean BMI (SD)	26.91 (5.51)	28.13 (4.93)	**0.001**
Median severe exacerbations in the previous year (IQR)	0 (0)	0 (0)	**0.001**
Mean severe exacerbations in the previous year, (SD)	**0.18 (0.50)**	**0.31 (0.64)**	0.002
≥1 severe exacerbation in the previous year, *n* (%)	78 (13.7)	69 (22.3)	**0.002**
mMRC score ≥ 2, *n* (%)	257 (45.2)	188 (60.8)	**<0.001**
Median BODEx index (IQR)	2 (2)	2 (2)	**0.005**
Mean BODEx index, (SD)	**1.9 (1.67)**	**2.16 (1.57)**	0.025
Mucus hypersecretion, *n* (%)	238 (41.9)	156 (50.5)	**0.015**
High risk, *n* (%)	377 (66.4)	243 (78.6)	**<0.001**
Functional parameters			
Mean FEV1/FVC, (SD)	55.54 (11.36)	57.30 (10.34)	**0.024**
Mean FEV1 (%), (SD)	58.4 (20.2)	57.1 (17.9)	0.335
Mean FVC (%), (SD)	83.81 (22.09)	74.26 (20.13)	**<0.001**
$FEV_1 \geq 50\%$, *n* (%)	353 (62.1)	196 (63.4)	0.708
Mean baseline SpO_2, % (SD)	95.42 (2.09)	95.04 (1.96)	**0.01**
Comorbidities, n (%)			
Arterial hypertension	293 (51.6)	229 (74.1)	**<0.001**
Type 2 diabetes mellitus	126 (22.2)	148 (47.9)	**<0.001**
Dyslipidemia	284 (50.0)	192 (62.1)	**0.001**
Obesity	137 (24.2)	100 (32.4)	0.009
Mood disorder	46 (8.1)	11 (3.6)	**0.009**
Osteoporosis	11 (1.9)	6 (1.9)	0.996
Bronchial asthma	74 (13)	37 (12)	0.654
Neoplasm	71 (12.5)	55 (17.8)	0.033
CCI	1.7 (1.3)	3.2 (1.7)	**<0.001**
Charlson ≥ 3	109 (19.2)	183 (59.4)	**<0.001**

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; CCI, Charlson comorbidity index score, not age-adjusted; mMRC, modified Medical Research Council scale; IQR, interquartile range.

Table 2
Multivariate analysis of risk of coexistence of cardiovascular disease and summation of GesEPOC risk factors.

	Multivariate model without AHT, DLP, DM2 adjustment				Multivariate model with AHT, DLP, DM2 adjustment			
	Beta	Wald test	p-Value	OR (CI 95%)	Beta	Wald test	p-Value	OR (CI 95%)
Age	0.08	89.09	<0.001	1.09 (1.07; 1.11)	0.08	67.81	<0.001	1.08 (1.06; 1.11)
Sex	−0.34	2.41	0.121	0.71 (0.46; 1.09)	−0.24	1.16	0.282	0.79 (0.51; 1.22)
PYI	0	0.23	0.629	1.00 (0.99; 1)	−0.001	0.06	0.808	1.00 (0.99; 1.01)
BMI	0.04	5.69	0.017	1.04 (1.01; 1.07)	0.02	1	0.318	1.02 (0.99; 1.01)
AHT	–	–	–		0.47	6.18	0.013	1.59 (1.10; 2.30)
DM2	–	–	–		0.68	14.92	<0.001	1.97 (1.40; 2.78)
DLP	–	–	–		0.15	0.72	0.397	1.16 (0.82; 1.63)
mMRC score ≥ 2	0.48	5.02	0.025	1.62 (1.06; 2.47)	0.30	1.84	0.175	1.35 (0.87; 2.10)
≥1 severe exacerbation in the previous year	1	6.28	0.012	2.72 (1.24; 5.94)	0.91	5.04	0.025	2.50 (1.12; 5.45)
FEV < 50%	−0.05	0.03	0.855	0.95 (0.53; 1.7)	−0.16	0.03	0.607	0.85 (0.47; 1.56)
mMRC score ≥2 + ≥1 severe exacerbation in the previous year	1.41	11.72	0.001	4.09 (1.83; 9.17)	1.23	8.51	0.004	3.43 (1.50; 7.85)
mMRC score ≥2 + ≥1 severe exacerbation in the previous year + FEV1 < 50%	0.28	0.74	0.391	1.33 (0.69; 2.54)	0.09	0.07	0.796	1.10 (0.56; 2.13)
mMRC score ≥2 + FEV1 < 50%	0.35	2.32	0.128	1.41 (0.91; 2.21)	0.29	1.6	0.206	1.34 (0.85; 2.11)
≥1 severe exacerbation in the previous year + FEV1 < 50%	−0.30	0.20	0.657	0.74 (0.2; 2.77)	−0.21	0.1	0.756	0.81 (0.21; 3.10)
Constant	−7.56	89.25	<0.001	–	−7.56	73.34	<0.001	–

Abbreviations: AHT, arterial hypertension; BMI, body mass index; DLP, dyslipidemia; FEV1, forced expiratory volume in 1 s; mMRC, modified Medical Research Council scale; IQR, interquartile range. PYI, pack-year index; DM2, type 2 diabetes mellitus.

sis. Our hypothesis was that the presence of GesEPOC risk factors, particularly the sum of several of them, would be related to a greater prevalence of CVD. The results of the study confirm said hypothesis and show that the combination of a higher degree of dyspnea and a history of severe exacerbations is associated with a significantly higher prevalence of established CVD, even when adjusting for the classic cardiovascular risk factors. The practical implications of these results are clear: in patients classified as HR according to GesEPOC, and particularly those in which the two mentioned factors coincide, special attention must be paid to actively looking for CVD if we want to achieve the aim of optimal clinical control and reducing future risk.

It must be noted that we did not find any significant relationship between worse lung function and a greater prevalence

of CVD. In this respect, there are conflicting previous results and although some studies agree with ours,[18,6] others find an association between worse lung function and an increased risk of suffering these comorbidities.[19]

This study has several strengths, such as its multicentric nature and sample size. Its limitations include a potential information bias due to obtaining the study variables from the patients' medical records, the cross-sectional nature of the study and the fact that the number of exacerbations treated on an outpatient basis was not recorded. Furthermore, the study population includes patients from pneumology clinics (70% HR) which partly limits the extrapolation of these results to other settings such as Primary Care clinics. On the other hand, given the characteristics of the study, we cannot rule out the existence of undiagnosed CVD that could influence our results, especially in those subjects with greater dyspnea and cardiovascular risk factors like DM2 or AHT, which would justify the results obtained in these subjects in model 2 of the multivariate analysis.

To conclude, high-risk patients according to GesEPOC must be carefully evaluated in order to rule out CVD if we want to achieve the objective of optimal clinical control and reducing future risk.

Authors' contribution

All authors have made substantial contributions to the intellectual content and manuscript design and drafting.

Approval

All authors gave their approval to the final version of the manuscript and declare to have met the requirements for authorship.

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Conflict of interest

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

References

1. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2022 report. [Accessed October 1, 2022]. Available from: https://goldcopd.org/2022-gold-reports-2/.
2. Miravitlles M, Calle M, Molina J, Almagro P, Gómez JT, Trigueros JA, et al. Spanish COPD guidelines (GesEPOC) 2021 updated pharmacological treatment of stable COPD. Arch Bronconeumol. 2022;58:69–81.
3. Soler-Cataluña JJ, Almagro P, Huerta A, González-Segura D, Cosío BG, CLAVE study Investigators. Clinical control criteria to determine disease control in patients with severe COPD: the CLAVE study. Int J Chron Obstruct Pulmon Dis. 2021;16:137–46.
4. Kunisaki KM, Dransfield MT, Anderson JA, Brook RD, Calverley PMA, Celli BR, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the SUMMIT randomized clinical trial. Am J Respir Crit Care Med. 2018;198:51–7.
5. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. Chest. 2010;137:1091–7.
6. 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.
7. Speizer FE, Fay ME, Dockery DW, Ferris BG Jr. Chronic obstructive pulmonary disease mortality in six U.S. cities. Am Rev Respir Dis. 1989;140 Pt 2:S49–55.
8. Silvestre OM, Nadruz W Jr, Querejeta Roca G, Claggett B, Solomon SD, Mirabelli MC, et al. Declining lung function and cardiovascular risk: the ARIC study. J Am Coll Cardiol. 2018;72:1109–22.
9. Figueira-Gonçalves JM, Hernández-Pérez JM, Cabrera-López C, Wangüemert-Pérez AL, García-Talavera I, Ramallo-Fariña Y, et al. Characteristics of patients referred to Canary Island pneumology outpatient services for chronic obstructive pulmonary disease: the EPOCan study. BMC Res Notes. 2022;15:36.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83.
11. Soler-Cataluña JJ, Martínez-García MA, Sánchez LS, Tordera MP, Sánchez PR. Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. Respir Med. 2009;103:692–9.
12. Houben-Wilke S, Triest FJJ, Franssen FME, Janssen DJA, Wouters EFM, Vanfleteren LEGW. Revealing methodological challenges in chronic obstructive pulmonary disease studies assessing comorbidities: a narrative review. Chronic Obstr Pulm Dis. 2019;6:166–77.
13. 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.
14. 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.
15. 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.
16. Figueira Gonçalves JM, Martín Martínez MD, Pérez Méndez LI, García Bello MÁ, Garcia-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.
17. Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? Eur Respir Rev. 2018;27:180057.
18. Greulich T, Weist BJD, Koczulla AR, Janciauskiene S, Klemmer A, Lux W, et al. Prevalence of comorbidities in COPD patients by disease severity in a German population. Respir Med. 2017;132:132–8.
19. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J. 2003;21:1012–6.

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