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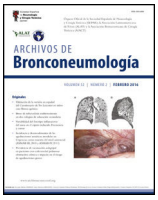

Scientific Letters

Can the COPD-comorbidome Be Applied to All Outpatients With Chronic Obstructive Pulmonary Disease? A Single-center Analysis

¿El comorbidoma de COPD se puede aplicar a todos los pacientes ambulatorios con enfermedad pulmonar obstructiva crónica? Un estudio unicéntrico

Dear Editor:

Cardiovascular diseases, lung cancer, diabetes mellitus, osteoporosis, anxiety, and depression are among the most prevalent comorbidities in patients with chronic obstructive pulmonary disease (COPD)[1,2] and have a negative impact in both their quality of life as well as their survival.[3,4] Divo et al.[4] developed the COTE (COPD Specific Comorbidity Test) index after evaluating 1664 patients with COPD. Cancers of the lung, esophagus, breast, and pancreas, liver cirrhosis, atrial fibrillation or flutter, coronary heart disease, diabetes-associated neuropathy, pulmonary fibrosis, congestive heart failure, gastroduodenal ulcer, and anxiety were the pathologies with the greatest impact on the vital prognosis. Based on these findings, the group designed a bubble chart (mimicking the solar system) of the prevalence of these pathologies and their association with mortality and named it a "comorbidome". However, distributions within this chart seem to be alterable and depend on the study population (in hospital vs outpatients).[4,5] Therefore, we wondered whether the distribution of the comorbidome described by Divo et al. could vary even among different outpatient populations with COPD.

Our group has recently outlined that comorbidities, particularly the cardiovascular and psychiatric ones, impact the quality of life of patients with COPD (measured through the COMCOLD index), especially in the more symptomatic sub-groups according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2017 classification.[6] In the present work, we performed a sub-analysis of the same population, aimed at reproducing the comorbidome depicted by Divo et al.,[4] and evaluated (1) the impact of a panel of comorbidities on the survival of our outpatients with COPD and (2) their distribution within that comorbidome chart.

Briefly, retrospective observational study was performed on follow-up outpatients with COPD. Inclusion criteria were: age ≥40 years, current or former smoker with a pack-year index (PYI) ≥10 and a forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) ratio <0.70 past salbutamol administration. Exclusion criteria were chronic airflow obstruction and a PYI < 10 or any pathology different from COPD. Patients were stratified according to the GOLD 2017 document. Information on the following comorbidities, included in the Charlson comorbidity index, was collected: myocardial infarction, angina, cardiovascular disease, cerebrovascular disease, dementia, COPD, connective tissue disease, gastrointestinal disease, mild or severe liver disease, complicated or uncomplicated diabetes mellitus, stroke, kidney failure, cancer, leukemia, lymphoma, secondary metastasis, and AIDS. Additionally evaluated pathologies were: arterial hypertension, dyslipidemia, cardiac arrhythmia, peripheral arterial disease, asthma, anxiety, and depression.

Qualitative variables were expressed as absolute values and percentages, while quantitative variables were summarized as means ± SD. Cox logistic regression and Kaplan–Meier statistics were applied for time-dependent variables. The study was approved by the Clinical Research Ethics Committee of the University Hospital Nuestra Señora de la Candelaria (Spain). The comorbidome was plotted according to the original design of Divo et al.,[4] where the circle diameter expressed the prevalence of the distinct comorbidities in percent and the distance of the circles to the center the risk of death based on the numerical value of the hazard ratio. The comorbidome represents comorbidities with a prevalence of more than 5% in the entire cohort.

A total of 439 patients were included in the study. The cohort characteristics had been described in a previous work.[6] The patients' mean age was 70; most of them were males with a predicted FEV_1% of 55 ± 20; 35% of them were current smokers. According to the GOLD 2017 categories, 142 (32%) were classified as GOLD A, 207 (48%) as GOLD B, 10 (2%) as GOLD C, and 80 (18%) as GOLD D. The mean Charlson index was 2.5 ± 1.5.

During the follow-up period of 53 months, 131 patients (30%) died. Surviving patients were followed up for at least 41 months and a maximum of 88.5 months. The prevalence of comorbidities in both survivors and deceased patients is shown in Table 1. The following pathologies had the greatest impact on the vital prognosis of our patients: cardiac arrhythmia, chronic kidney disease (CKD), heart failure (HF), osteoporosis, and cancer (Table 1, Fig. 1).

As shown in Fig. 1/Table 1, the impact of comorbidities on the survival of our outpatients diverges from that published by Divo et al.,[4] thus reflecting differences between both comorbidomes. In contrast to the BODE cohort, CKD and osteoporosis did show a significant relationship with mortality. We need to stress that the latter, together with HF, had the greatest impact on survival. In our cohort, ischemic heart disease and neuropsychiatric pathologies were not related to the vital prognosis of the patients.

A number of works describe the negative impact of HF and CKD on COPD patients' survival.[4,7] The prevalence is even higher in overweight and obese subjects,[8,9] and these account for up to 72% of our cohort. A study published by Verberne et al.[8] shows that, in contrast to subjects with normal weight, obese COPD patients have an increased risk of diabetes (OR 3.79, $CI_{95\%}$ 3.04–4.71), hypertension (OR 2.46, $CI_{95\%}$ 2.07–2.93), and HF (OR 2.32, $CI_{95\%}$ 1.55–3.46). The authors also detected significant inverse associations between patients' survival and anxiety disorders (OR 0.49, CI 95% 0.28–0.86) and osteoporosis (OR 0.51, $CI_{95\%}$ 0.37–0.71). The latter comorbidity

Table 1
Comorbidities of COPD and their association with risk of death.

Comorbidities	Prevalence in non-deceased patients ($n = 308$)	Prevalence in deceased patients ($n = 131$)	Hazard ratio[a] (95% confidence interval)		P
Osteoporosis, *n* (%)	7 (2.3)	9 (6.9)	2.00	1.02–3.95	.045
HF, *n* (%)	30 (9.7)	33 (25.2)	1.84	1.23–2.75	.003
CKD, *n* (%)	28 (9.1)	28 (21.5)	1.66	1.08–2.56	.020
Neoplasia, *n* (%)	24 (7.8)	24 (18.3)	1.57	1.00–2.44	.049
Arrhythmia, *n* (%)	48 (15.6)	41 (31.3)	1.51	1.03–2.21	.033
Asthma, *n* (%)	66 (21.4)	33 (25.2)	1.43	0.96–2.13	.078
Peripheral arterial disease, *n* (%)	31 (10.1)	18 (13.7)	1.12	0.68–1.85	.650
Anxiety, *n* (%)	24 (7.8)	9 (6.9)	1.11	0.56–2.19	.763
CVA, *n* (%)	21 (6.8)	11 (8.4)	1.10	0.59–2.05	.757
IHD, *n* (%)	45 (14.6)	26 (19.8)	1.07	0.70–1.65	.757
Diabetes mellitus, *n* (%)	93 (30.2)	50 (38.2)	0.98	0.69–1.41	.926
SA, *n* (%)	72 (23.4)	33 (25.2)	0.95	0.64–1.41	.798
Liver disease, *n* (%)	27 (8.8)	9 (6.9)	0.91	0.46–1.80	.792
Obesity, *n* (%)	97 (31.5)	41 (31.3)	0.82	0.56–1.11	.285
Depression, *n* (%)	42 (13.6)	13 (9.9)	0.77	0.43–1.37	.372
Arterial hypertension, *n* (%)	110 (35.7)	39 (29.8)	0.76	0.51–1.12	.170
Dyslipidemia, *n* (%)	99 (32.1)	45 (34.4)	0.74	0.52–1.07	.112

Abbreviations: HF: heart failure. CKD: chronic kidney disease. IHD: ischemic heart disease. CVA: cerebrovascular accidents. SA: sleep apnea.
[a] All the HR are estimated adjusted by age of patients.

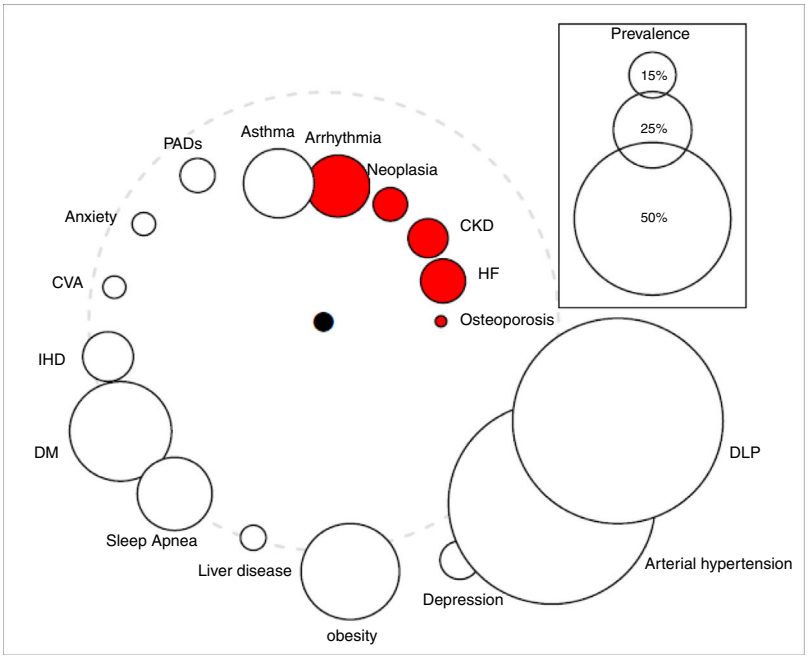

Fig. 1. The "comorbidome" is a graphic expression of comorbities with more than 5% prevalence in the entire cohort. The area of the circles relates to the prevalence of the disease. The proximity to the center (mortality) express the strength of the association between the disease and the risk of death. This was scaled from the inverse of the HR (1/HR). The dotted line represents HR = 1. Beyond the line, HR are less than 1. The red bubble represents statistical significance association (HR > 1; $P < .05$). *Abbreviations*: HF: heart failure. CKD: chronic kidney disease. IHD: ischemic heart disease. CVA: cerebrovascular accidents. DM: diabetes mellitus. DLP: dyslipidemia. PADs: peripheral arterial disease.

is classically described for patients with an emphysema phenotype, usually characterized by low weight, considerable air trapping, and a worse vital prognosis than the other phenotypes.[10]

We may not ignore the limitations of our study, i.e., the sample size, methodology—this is an observational study—and the fact that some of the comorbidities in the article by Divo et al.[4] were not analyzed in our cohort. In contrast to the BODE cohort, patients with relevant comorbidities that prevented them from performing the 6-minute walk test were not excluded from our study. In addition, minimum follow-up was slightly longer in our study. In this sense, our work may better represent the patients with COPD that we find in healthcare practice. This prompted us to reflect on a general applicability of the COTE index (COPD specific comorbidity test) based on the comorbidome of Divo et al.,[4] thinking that it should be substantiated in different patient populations. In summary, our study suggests that distributions within the comorbidome may vary according to the analyzed outpatient population.

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Hemangiopericitoma pulmonar primario

Primary Pulmonary Hemangiopericytoma

Estimado Director:

La elevada prevalencia del cáncer de pulmón de origen epitelial convierte a las neoplasias broncopulmonares de estirpe mesenquimal en rarezas que se observan muy ocasionalmente en la práctica clínica habitual. Presentamos el caso de una paciente remitida a las consultas de neumología para estudio por episodios recidivantes de expectoración hemoptoica autolimitada.

Se trata de una paciente mujer de 56 años de edad, natural de Venezuela, que acudió por presentar episodios autolimitados y repetidos de expulsión de sangre con la tos, sin repercusión hemodinámica, oximétrica o hematimétrica. Había sido diagnosticada 4 años antes en su país natal de una tumoración sólida prevertebral por TC, etiquetada como angioma torácico mediante toracotomía y tratada mediante radioterapia (dosis total desconocida). Herniorrafia inguinal izquierda, histerectomía y doble anexectomía como otros antecedentes quirúrgicos. La exploración física fue anodina, y tanto los valores analíticos del hemograma como los de la bioquímica se encontraban dentro de los valores de referencia. En la radiografía torácica se observó la presencia de una lesión subcarinal redondeada. La tomografía computarizada confirmó la presencia de una masa que realzaba su contenido con la introducción de contraste, de unos 8,5 × 4,5 cm de diámetro, localizada inmediatamente dorsal a la arteria pulmonar derecha y acompañada de adenopatías paraaórticas y retroperitoneales.

La fibrobroncoscopia (fig. 1) objetivó la presencia de una tumoración violácea de superficie polilobulada asentada en la carina principal y que ocluía casi en su totalidad la entrada del bronquio principal izquierdo, pero sin impedir el paso del broncoscopio. El aspecto de la lesión endobronquial y el antecedente de una lesión vascular intratorácica hicieron aconsejable no realizar biopsias endoscópicas. Días más tarde, bajo anestesia general, se realizó broncoscopia rígida con toma de biopsias, ocurriendo como complicación un sangrado severo que se controló con diatermia, y posterior arteriografía con embolización de ramas nutricias provenientes de la arteria bronquial derecha. Las muestras biópsicas demostraron la presencia de numerosos vasos endotelizados con pared fibrosa y una proliferación densa constituida por células de núcleos alargados dispuestos en haces de variable disposición espacial, sin observarse necrosis ni mitosis, siendo positiva para marcadores CD34 y CD31, Ki-67 en menos de 5% y negativa para marcadores epiteliales y musculares; hallazgos compatibles con un hemangiopericitoma pulmonar.

Entre el 2 y el 6% de todos los tumores primarios del mediastino son de estirpe mesenquimal. De entre ellos, el hemangiopericitoma es, a su vez, una rareza: se origina a partir de los pericitos de Zimmerman, que forman parte de la capa externa alrededor del endotelio de los capilares y se clasifica en la actualidad como tumor perivascular. Supone menos del 2% de todos los sarcomas de tejidos blandos[1] y aproximadamente el 1% de todos los tumores de origen vascular[2]. Las localizaciones principales suelen ser el tejido muscular de las extremidades, el tejido subcutáneo y el retroperitoneo. La localización primaria torácica (habitualmente mediastínica) es extremadamente infrecuente entre los hemangiopericitomas, como atestigua la literatura revisada, con muy pocos casos descritos[3]. A nivel pulmonar, los casos que se han publicado han comenzado en su mayoría como nódulos pulmonares solitarios, siendo este el primer caso en nuestro conocimiento con expresión endobronquial evidenciada por broncoscopia.

Este tipo de tumores suele comenzar con una gran variedad de sintomatología, en la que destaca la hemoptisis[4]. Las pruebas de imagen, sobre todo la tomografía computarizada (TC) con y sin contraste y la resonancia magnética (RM)[1,2], ayudan a visualizar la

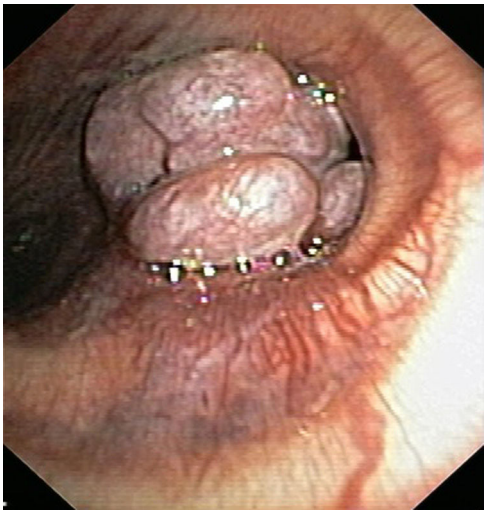

Figura 1. Imagen obtenida durante la broncoscopia donde destaca la presencia de una tumoración polilobulada a la entrada del bronquio principal izquierdo.