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COPD patients with and without metabolic syndrome: clinical and functional differences

Jesús Díez-Manglano · José Barquero-Romero · Pedro Almagro · Francisco Javier Cabrera · Francisco López García · Lorena Montero · Joan Baptiste Soriano · Working Group on COPD; Spanish Society of Internal Medicine

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Abstract Chronic obstructive pulmonary disease (COPD) and the metabolic syndrome (MetS) are considered public health challenges of the 21st century. The coexistence of MetS in COPD patients and any clinical differences between COPD patients with and without MetS have not been extensively studied. We aimed to describe the clinical characteristics of patients with MetS and COPD. An observational, multicenter study of 375 patients hospitalized for a COPD exacerbation with spirometric confirmation was performed. We measured the components of the MetS and collected comorbidity information using the Charlson index and other conditions. Dyspnea, use of steroids, exacerbations, and hospitalizations were also investigated. The overall prevalence of MetS in COPD patients was 42.9 %, was more frequent in women (59.5 %) than men (40.8 %), $p = 0.02$, but with no differences in age and smoking history. COPD patients with MetS had greater % predicted FEV_1, more dyspnea, and more comorbidity and used more inhaled steroids (all $p < 0.05$). Diabetes, osteoporosis, coronary artery disease, and heart failure were more frequent in patients with MetS. They had been hospitalized more frequently for any cause but not for COPD. In multivariate analysis, the presence of MetS was independently associated with greater FEV_1, inhaled steroids use, osteoporosis, diabetes, and heart failure. MetS is a frequent condition in COPD patients, and it is associated with greater FEV_1, more dyspnea, and more comorbidities.

Keywords COPD · Metabolic syndrome · Comorbidity

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with significant extrapulmonary effects and associated comorbidities that may

J. Díez-Manglano (✉)
Internal Medicine Service, Hospital Royo Villanova, Avda San Gregorio no 30, 50015 Saragossa, Spain
e-mail: jdiez@aragon.es

J. Barquero-Romero
Internal Medicine Service, Hospital Tierra de Barros, Almendralejo, Badajoz, Spain
e-mail: pepebarquero@gmail.com

P. Almagro
Internal Medicine Service, Hospital Universitario Mutua de Terrasa, Terrassa, Barcelona, Spain
e-mail: 19908pam@comb.cat

F. J. Cabrera
Internal Medicine Service, Hospital General Universitario Gregorio Marañón, Madrid, Spain
e-mail: fjcabrera51@yahoo.es

F. López García
Internal Medicine Service, Hospital Vega Baja, Orihuela, Alicante, Spain
e-mail: F.LOPEZGARCIA@terra.es

L. Montero
Internal Medicine Service, Hospital de la Axarquia, Vélez-Málaga, Málaga, Spain
e-mail: lmonteror77@hotmail.com

J. B. Soriano
Programa de Epidemiología e Investigación Clínica, Fundación Caubet-CIMERA, Centro Internacional de Medicina Respiratoria Avanzada, Baleares, Spain
e-mail: jbsoriano@caubet-cimera.es

contribute to its severity in individual patients [1]. In 2005 it was the fourth leading cause of death [2] and is associated with cardiovascular disease [3].

Obesity is one of the greatest public health challenges of the twenty-first century, and its prevalence has tripled in many European countries in the past 30 years [4]. In addition, obesity is responsible for 2–8 % of health costs and 10–13 % of deaths. The metabolic syndrome (MetS) is a complex of interrelated medical disorders that increase the risk of developing type-2 diabetes and cardiovascular disease [5]. Approximately 34 % of American adults older 20 years of age and over [6, 7] and 25–30 % of European adults [8] have MetS. The prevalence increases with age and is strongly correlated with high body mass index [6]. The MetS is associated with an increase of cardiovascular disease and mortality [9, 10]. It has a rising prevalence worldwide that relates to increasing obesity and sedentary lifestyles.

In patients with COPD, the frequencies of obesity and MetS are on average 18 and 47 %, respectively [12]. The MetS is more prevalent in younger patients and in earlier stages of COPD, and it is suggested that these patients may constitute a specific COPD phenotype [12].

The aim of the present study was to determine the relationship between the clinical characteristics and the MetS in COPD patients.

Methods

Study design

ECCO is the acronym in Spanish of "EPOC Con COmorbilidad", that is, "COPD with comorbidity study". It is an observational, cross-sectional, multicenter study, participated by 26 hospital centers throughout Spain (see "Appendix"). Detailed features of the study have been reported elsewhere [13, 14]. Each researcher included the patients admitted with a COPD exacerbation that were attended consecutively between January 1, 2007, and December 31, 2008. COPD was diagnosed with spirometry in stable condition, preceding admission, according to GOLD guidelines [1]). All participating patients were GOLD II or higher (predicted FEV_1 <80 % and postbronchodilator FEV_1/FVC <0.7). The primary objective was to determine the prevalence of MetS in COPD patients, and secondary objectives were to establish the clinical and lung function differences between COPD patients with and without MetS.

Evaluation of MetS

The diagnosis of MetS was established using the following criteria: body mass index >30 kg/m^2, fasting glucose ≥100 mg/dL or drug treatment for elevated glucose, systolic ≥130 or diastolic ≥85 mmHg blood pressure or antihypertensive drug treatment in a patient with history of hypertension, triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides, high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men or <50 mg/dL in women, or drug treatment for reduced HDL-C. The presence of any three of the five criteria constitutes a diagnosis of the MetS [5].

Procedures

A comprehensive questionnaire with demographic and relevant clinical data was administered to patients upon admission, and a detailed physical examination was also undertaken. Data registered included age, gender, smoking history, total number of admissions for COPD or other causes and number of acute COPD exacerbations in the previous 12 months. To assess associated comorbidities we used the Charlson index [15] as well as other conditions not included in this index that are prevalent in COPD [16], namely osteoporosis, anemia, hypertension, dyslipidemia, and alcoholism. Baseline dyspnoea prior to admission was assessed with the modified (5-point) Medical Research Council (mMRC) dyspnoea scale. Body mass index was calculated as weight/height squared, and it was expressed in kg/m^2. Fasting venous blood was collected and plasma glucose, HDL-C, and triglycerides were measured.

The study was approved by the Clinical Investigation Ethics Committee of the coordinating center, Hospital de la Vega Baja in Orihuela, Alicante, and all patients signed informed, written consent form.

Statistical analysis

Reported prevalence of MetS in American and European adults is within 20–34 % [6–8]. Assuming a 5 % type I error and a 5 % precision, a sample size of 323 patients was calculated.

Quantitative data are presented as mean ± SD. Comparison of variables between the two groups was performed using the ANOVA test.

Qualitative data are presented as absolute frequencies and percentages. Comparison between two groups was performed using χ^2 and Fisher exact tests. Comparison among three or more groups was performed using χ^2 test for trend.

A logistic regression model was constructed using the variables with statistical significance in the univariate analysis. In all analysis p values <0.05 were considered statistically significant.

Statistical analysis was performed using the software G-Stat 2.0 (www.e-biometria.com).

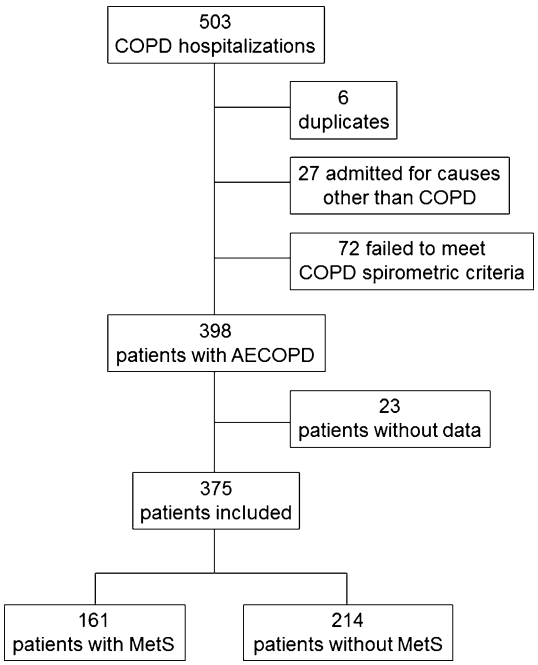

Fig. 1 Flow chart CONSORT of patients considered in the study. *AECOPD* acute exacerbation of COPD, *MetS* metabolic syndrome

Results

The flow chart of study participants is presented in Fig. 1. Finally we included 375 patients, 333 men and 42 women, with a mean (SD) age of 73.7 (8.9) years. The characteristics of patients are given in Table 1.

Prevalence of MetS and its components

One hundred and sixty-one (42.9 %) patients had MetS. The prevalence of MetS in COPD patients was more frequent in women (59.5 %) than in men (40.8 %), $p = 0.02$, but with no differences in age or smoking history, either by current status or in pack-years. Hyperglycemia and high blood pressure were the most frequent components of MetS (Fig. 2). Women met more components of MetS [2.74 (0.96) vs. 2.25 (1.10); $p = 0.006$] and had more frequent hyperglycemia (92.9 vs. 78.1 %; $p = 0.02$) than men. In COPD patients with MetS, there was no difference in the number of components by gender.

MetS and lung function

Patients with MetS had less airflow obstruction, either expressed by FEV_1 and FEV_1/FVC ratio compared with patients without MetS ($p < 0.01$). They presented less severe GOLD stages, but had more elevated grade of dyspnoea measured with mMRC scale and used more inhaled steroids (Table 1). Further, they had neither more exacerbations in the

Table 1 Demographic and clinical characteristics of COPD participants with and without MetS

	MetS ($n = 161$)	No MetS ($n = 214$)	p
Age[a]	73.7 (8.3)	73.8 (9.4)	0.94
Men	136 (84.5)	197 (92.1)	0.02
Women	25 (15.5)	17 (7.9)	
Smoking			
Smoker	25 (15.5)	39 (18.2)	
Ex-smoker	112 (69.6)	158 (73.8)	0.09
Non-smoker	24 (14.9)	17 (7.9)	
Pack-year	54.7 (25.8)	57.5 (26.6)	0.36
Height (cm)	165.6 (7.9)	167.0 (9.1)	0.12
Weight (kg)	81.5 (15.1)	69.5 (11.0)	<0.0001
FEV_1 (% predicted)	45.5 (12.1)	41.8 (12.4)	0.004
FVC (% predicted)	59.9 (14.0)	62.6 (17.1)	0.22
FEV_1/FVC	0.55 (0.10)	0.51 (0.10)	0.006
GOLD stage			
Moderate	65 (40.4)	62 (29.0)	
Severe	84 (52.2)	117 (54.7)	0.009
Very severe	12 (7.4)	35 (16.4)	
mMRC dyspnea			
0	1 (0.9)	2 (0.6)	
1	12 (7.4)	31 (14.5)	
2	45 (27.9)	65 (30.4)	0.03
3	57 (35.4)	81 (37.8)	
4	46 (28.6)	35 (16.4)	
Components of MetS			
Body mass index (kg/m^2)	29.8 (5.6)	24.9 (3.7)	<0.001
SBP (mmHg)	143 (22)	131 (21)	<0.001
DBP (mmHg)	77 (14)	76 (45)	0.84
Fasting glucose (mg/dL)	148 (58)	121 (52)	<0.001
Triglycerides (mg/dL)	157 (53)	124 (33)	<0.001
HDL Cholesterol (mg/dL)	43 (13)	52 (12)	<0.001
Charlson index[a]	2.88 (1.61)	2.45 (1.83)	0.02
Comorbidities			
Osteoporosis	25 (15.5)	11 (5.1)	<0.001
Moderate kidney failure	15 (9.3)	11 (5.1)	0.11
Dementia	6 (3.7)	9 (4.2)	0.81
Alcoholism	23 (14.3)	32 (14.9)	0.85
Coronary arterial disease	37 (23.0)	30 (14.0)	0.02
Heart failure	59 (36.6)	45 (21.0)	<0.001
Diabetes	70 (43.5)	44 (20.6)	<0.001
Long term steroid therapy			
Inhaled	46 (28.6)	40 (18.7)	0.02
Oral	20 (12.4)	21 (9.8)	0.42
Statins use	14 (8.7)	19 (8.9)	0.95
Long term oxygen therapy	61 (37.9)	77 (36.0)	0.70
Total number of exacerbations in the previous 12 months[a]	2,55 (2.19)	2.50 (1.88)	0.80
Total number of admissions for COPD[a]	3.35 (3.10)	3.16 (2.83)	0.54
Total number of admissions for any cause[a]	5.34 (4.61)	4.03 (3.34)	0.002

SBP systolic blood pressure, *DBP* diastolic blood pressure

[a] Values are given as No (%) or mean (SD)

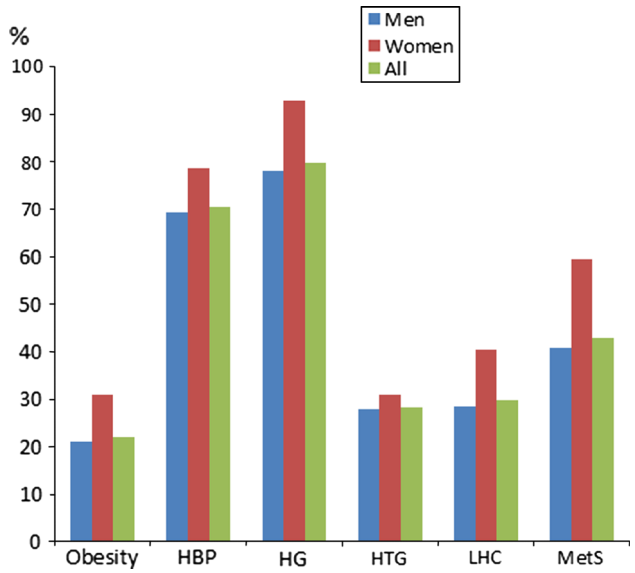

Fig. 2 Metabolic syndrome and its components by gender. *HBP* high blood pressure, *HG* hyperglycemia, *HTG* hypertrygliceridemia, *LHC* low HDL-cholesterol, *MetS* metabolic syndrome

Table 2 MetS and its components by GOLD COPD spirometric classification

	GOLD stage II	GOLD stage III	GOLD stage IV	p^a
Obesity	34 (26.8)	41 (20.4)	8 (17.0)	0.11
High blood pressure	97 (76.4)	142 (70.6)	25 (53.2)	0.006
Hyperglycemia	99 (77.9)	160 (79.6)	40 (85.1)	0.34
Hypertriglyceridemia	41 (32.3)	53 (26.4)	12 (25.5)	0.26
Low HDL cholesterol	40 (31.5)	63 (31.3)	9 (19.1)	0.21
Metabolic syndrome	65 (51.2)	84 (41.2)	12 (25.5)	0.003
	127 (100)	201 (100)	47 (100)	

[a] χ^2 for trend

Data are presented as *N* (%)

previous year nor more admissions for COPD, although they were hospitalized more frequently for any cause. Interestingly, there was an inverse association of MetS with greater GOLD COPD severity, the frequencies of MetS being 51.2, 41.8, and 25.5 % in patients with GOLD stages II, III, and IV, respectively (χ^2 for trend $p = 0{,}003$). A lower proportion of patients in GOLD stage IV had high blood pressure (Table 2). Patients in more severe GOLD stages significantly used more inhaled steroids (18.9, 22.4, 36.2 % in stages II, III, and IV, respectively, χ^2 for trend $p = 0.03$) but not more systemic steroids (7.9, 12.4, 12.8 % in stages II, III, and IV, respectively, χ^2 for trend $p = 0.22$).

In addition, patients treated with inhaled corticosteroids had lower FEV_1 than others [40.9 (13.5) vs. 44.1 % (12.0); $p = 0.03$].

MetS and comorbidities

Patients with MetS had more comorbidities (Table 1). They had a higher Charlson score compared with patients without MetS [2.88 (1.61) vs. 2.45 (1.83), $p = 0.02$). Diabetes, coronary artery disease, heart failure, and osteoporosis were also more frequently present in COPD patients with MetS ($p < 0.05$).

Factors associated with the presence of MetS

In a multivariate logistic analysis, the presence of MetS was independently associated with FEV_1, inhaled steroids, osteoporosis, diabetes, and heart failure (Table 3).

MetS and mortality

Fifteen (4.0 %) patients died during admission. In-hospital mortality was higher in patients with MetS (5.7 vs. 1.9 %; $p = 0.07$), but this difference was not statistically significant.

Discussion

The main findings of our study were that more than 40 % of COPD patients had MetS, and although MetS was associated with less impaired lung function and actually it had an inverse association with GOLD COPD severity, these patients had more hospital admissions and burden: they had more osteoporosis and heart failure. In addition, COPD patients with MetS had a less obstructive pattern.

The prevalence of MetS in our study is higher than in previous studies in the general population, but it is similar to others in European elderly populations. Hildrum et al. [8], report a prevalence of MetS of 45 % in men and of 60 % in women aged 70–79 years. The presence of MetS in COPD patients depends both on the study inclusion criteria and the criteria used to diagnose MetS. In Germany, using the International Diabetes Foundation criteria, the prevalence was estimated at 47.5 % [11]; by contrast, in Greece, using the criteria of Adult Treatment Panel III criteria and excluding patients with diabetes, known history of cardiovascular disease and other comorbidities, it was found to be 21 % [12]. Other studies conducted in China and Japan report that 22.6 and 23 % of COPD patients have MetS, respectively [17, 18]. Other studies with smaller populations report prevalences of 28 and 47 % [19, 20]. To label MetS we have used the unified criteria that do not require waist circumference as an obligatory component [5]. To our knowledge, there are no existing reports that have used these criteria. This could explain why the prevalence we find is higher than the one in other studies.

Table 3 Crude and adjusted factors associated with MetS in COPD patients

	Crude OR (95 % IC)	*p*	Adjusted OR (95 % CI)	*p*
Age	0.99 (0.98–1.02)	0.94	0.99 (0.96–1.01)	0.45
Women	2.13 (1.11–4.09)	0.02	1.29 (0.61–2.71)	0.50
$pFEV_1$	1.02 (1.01–1.04)	0.004	1.03 (1.01–1.05)	<0.001
Inhaled steroids	1.74 (1.07–2.82)	0.00	3.30 (1.33–3.98)	0.003
Osteoporosis	3.39 (1.62–7.12)	0.001	2.80 (1.24–6.32)	0.01
Heart failure	2.17 (1.37–3.44)	<0.001	1.98 (1.20–3.28)	0.007
Coronary artery disease	1.83 (1.07–3.12)	0.02	1.67 (0.93–3.01)	0.09
Diabetes	2.97 (1.89–4.68)	<0.001	3.54 (2.14–5.86)	<0.001

Reference categories in the logistic regression were male, no use of inhaled steroids, and absence of comorbidities

Metabolic syndrome (MetS) tends to be less frequent in patients with very severe COPD. This initially surprising finding is in line with other reports. The frequencies of the MetS in patients with GOLD stages II, III, and IV are 53, 37, and 44 %, respectively, in the study of Watz et al. [11]. In the study of Marquis et al. [12] the overall frequency of MetS in patients with COPD is 21 %, and the frequency decreases to about 10 % at GOLD stages III and IV. The weight loss that frequently occurs in patients who are in the more severe stages of COPD may be the cause of these observations. As in heart failure, we think that the obesity paradox is present in COPD patients, that is, the greater FEV_1 values were found in COPD with MetS.

In contrast with the general population findings, hyperglycemia is the component of MetS more frequently observed in COPD patients. This finding can be explained because all our patients were in moderate or higher GOLD stages of COPD, and the use of steroids is high in these patients. In the study of Watz et al. [11], the use of both inhaled and systemic steroids is higher in patients in GOLD stages III and IV without increase of presence of MetS. Also elevated blood pressure was a frequent component in our patients (70 %) as it was reported in other studies [11].

An interesting observation was that patients with MetS had less impaired predicted FEV_1 and more dyspnoea compared with those without MetS. This is consistent with the findings of recent studies in overweight and obese patients with COPD [21]. We think that the presence of comorbidities, particularly heart failure, could partly explain this observation. Further, osteoporosis can modify respiratory mechanics and contribute to more breathlessness. More and more severe comorbidities also could explain why COPD patients with MetS have more hospitalizations by any cause without an increase neither of admissions for COPD nor of exacerbations in the previous year. This observation is consistent with recent reports on subtypes of COPD [22]. But contrary to this finding, a prospective study with 106 patients observes that the presence of MetS is associated with an increase of acute exacerbations of COPD [23].

In a multivariate analysis, greater FEV_1 and comorbidities were independently associated with MetS. As stated previously, weight loss associated with severity of COPD could explain the association between MetS and greater spirometric values. Osteoporosis and heart failure are conditions that limit the capacity for physical activity and lead to sedentary life styles. These factors predispose to weight gain and, therefore, contribute to having MetS. In addition, physical inactivity increases the levels of inflammatory biomarkers as CRP and interleukin-6, which are high in obese individuals [24, 25].

Recent studies in older patients observe that the association of MetS with bone mineral density is reversed after adjusting for BMI such that MetS is associated with lower bone mineral density [26]. This could explain the association of MetS and osteoporosis that we observed, and that is not in line with previous reports that demonstrate a close relationship between low BMI and osteoporosis in COPD.

To our knowledge this is the first study of MetS in COPD patients with any mortality data. We have observed that mortality during admission was 5.7 % in patients with MetS and 1.9 % in patients without MetS. The difference is clinically relevant but not statistically significant. Our study was not powered to find this difference, but it might be interesting if new short- and long-term studies evaluate mortality in COPD patients with MetS.

Our study has some limitations. First, it is a cross-sectional analysis of patients admitted to Internal Medicine departments. In Spain 37–53 % of COPD patients are admitted to these departments [27, 28]. They are older and have more comorbidities than those admitted to Pulmonology departments [27]. However, the observed prevalence of MetS is similar to those reported in studies conducted in Pulmonology or Rehabilitation departments [11, 20]. Second, about 90 % our patients are men. The small number of women included is similar to that of other studies performed in Spain, where women were exposed to active smoking only after the 1960s. Third, patients recruited had an acute exacerbation. It is possible that patients with MetS have more or less frequent acute exacerbations, and this element could produce some bias in the data. Fourth, we have used the body mass index to diagnose obesity instead of waist circumference. Our patients were recruited during

admission for an acute exacerbation of COPD and the variables were collected when the patients were in a clinically stable situation. However, it is known that waist circumferences vary by posture, site of measure, respiratory phase, and time since last meal [29]. To avoid this variability and to increase the accuracy of measure we decided to use the body mass index although it could influence the observed prevalence of abdominal obesity and MetS.

Finally, we suggest that perhaps COPD, MetS, heart failure, and osteoporosis constitute a cluster of diseases that define a disease in some association with physical inactivity and systemic inflammation [30–34].

In summary, our study concludes that MetS is frequent in COPD patients and not only associated with greater FEV_1 and milder GOLD COPD severity, but also with more elevated degree of dyspnea and more comorbidities.

Conflict of interest None.

Appendix

Investigators of the ECCO Study, Working Group on COPD of the Spanish Society of Internal Medicine: Santiago Mola Caballero de Rodas, Francisco López García, Jose Antonio Carratalá Torregrosa, Gemma Penadés Cervera, Juan Custardoy Olavarrieta (Hospital Vega Baja-Orihuela, Alicante); Alberto Muela Molinero, Juan Carlos Borrego Galán, (Hospital General de León); Rocío Llanos Llanos, María del Carmen García Orenes (Hospital Morales Meseguer, Murcia); Juan Manuel Quiroga Iturralde, Gabriel Zubillaga Garmendia, Elena Zubillaga Azpiroz (Hospital de Donostia, San Sebastián); Mario Fernández Ruiz (Hospital General Universitario 12 de Octubre, Madrid); Jesús Recio Iglesias (Hospital General Universitario Vall d'Hebron, Barcelona); María del Carmen Martínez Velasco (Hospital San Juan de Dios, Pamplona); María Paz Pérez Gutiérrez (Hospital Clínico Universitario, Valladolid); Francisco Javier Cabrera Aguilar, Pablo Ryan Murua (Hospital General Universitario Gregorio Marañón, Madrid), Juan Antonio Oriz Minuesa, Manuel Montero Pérez-Barquero (Hospital General Universitario Reina Sofía, Córdoba); Jesús Castiella Herrero, Francisco José Sanjuan Portugal (Fundación Hospital Calahorra, La Rioja); Juan Lucio Ramos Salado, José Barquero Romero (Complejo Universitario Infanta Cristina, Badajoz); Fernando Javier Sánchez Lora (Hospital de Antequera, Málaga); Angel Hortal Tavira (Hospital Virgen de Las Nieves, Granada); Jerónimo Nieto López Guerrero (Hospital de Cantoblanco, Madrid); María Cruz Almendros Rivas (Hospital de Palamos, Madrid); Fernando de la Iglesia Martinez (Hospital Juan Canalejo, A Coruña); Carlos Dueñas Gutiérrez (Hospital General Yagüe, Burgos); José Luis Lozano Polo (Hospital General Marqués de Valdecilla, Santander); Dámaso Escribano Sevillano (Hospital de Jove, Gijón); Luis Quiroga Prado (Hospital de León); Carmen Mella Pérez (Hospital Vilagarcia de Arousa, Pontevedra); Ramón Cigüenza Gabriel (Hospital Clínico San Carlos, Madrid); José Portillo Sánchez (Hospital General de Ciudad Real); Ramon Boixeda i Viu (Hospital de Mataró, Barcelona); Lorena Montero Rivas, Carlos M San Román Terán (Hospital Comarcal Axarquía. Vélez Málaga, Málaga); Joan Carles Trullas Vila (Hospital San Jaume Olot, Gerona); Bernardino Roca Villanueva (Hospital General de Castellón); Julio Montes Santiago (Hospital Do Meixoeiro, Vigo); José Manuel Varela (Hospital Virgen del Rocío, Sevilla); David Morchón, Juan Carlos Martín Escudero (Hospital Universitario Rio Hortega, Valladolid); Jesús Díez Manglano (Hospital Royo Villanova, Zaragoza); Elena Güell i Farré (Consorci Sanitari Integral, Barcelona); Olga Araújo Loperena (Hospital Xarxa Tecla, Tarragona); Nuria Galofré Alvaro (Hospital de Badalona); Beatriz Sobrino Diaz (Hospital General Universitario Carlos Haya, Málaga); Ana Belen Mecina Gutiérrez, María del Carmen Romero Pérez (Hospital de Leganés, Madrid); Patricia Crecente Otero, Laura Madrigal Cortés, Rubén Díez Bandera, Verónica Alvarez Alamo (Hospital Clínico Universitario, Salamanca); PedroAlmagro Mena (Hospital Mutua de Terrassa, Barcelona); Pablo Espejo Salamanca (Fundación Hospital de Manacor, Mallorca); Vicente Giner Galvan (Hospital de Alcoy, Alicante); Rafael Castillo Rubio (Hospital La Malvarrosa, Valencia).

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