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ORIGINAL RESEARCH

Burden of Disease Among Exacerbating Patients with COPD Treated with Triple Therapy in Spain

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Background: The cost of chronic obstructive pulmonary disease (COPD) in Spain has been studied from different perspectives, but parameters such as the patient's phenotype have seldom been considered. Our aim was to describe the disease burden of COPD patients with frequent exacerbator phenotype, treated with triple therapy.

Methods: An observational, multicenter study was carried out from December 2017 to November 2018 in pulmonology services among patients ≥40 years with COPD confirmed diagnosis receiving triple therapy (ICS/LAMA/LABA) and history of ≥2 moderate or ≥1 severe exacerbation in the 12 months prior to the inclusion visit. COPD-related healthcare resources were collected over a 12-months period prior to the inclusion visit: pharmacological and non-pharmacological treatments, medical and ER visits, hospitalizations, tests and productivity loss. Costs were updated to €2019. Patients were classified according to blood eosinophil levels: <150 cells/μL and ≥150 cells/μL.

Results: A total of 306 patients were included (77.1% men), with mean age of 69.9 years. Mean COPD exacerbation rate was 2.5/patient/year and 51.3% of patients had ≥150 cells/μL eosinophil level. On average, for the total population, COPD-related visits/patients/year were 6.2. Resource use in moderate exacerbation was higher in patients with eosinophils ≥150 cells/μL, whereas in severe exacerbation was higher in patients with eosinophils <150cells/μL. According to eosinophil levels, total annual mean (SD) costs/patient accounted for €8382 (9863) and €5144 (5444) for patients with eosinophils <150 cells/μL and ≥150 cells/μL, respectively.

Conclusion: The impact of exacerbating COPD patients treated with triple therapy in Spain is large, especially among those with eosinophils <150 cells/μL.

Keywords: frequent exacerbation, triple therapy, cost, eosinophil, health care resources, COPD

Introduction

Chronic obstructive pulmonary disease (COPD) remains a major health problem in Spain and worldwide. The prevalence keeps growing and is expected to be the third leading cause of death in 2020.[1] The results of the EPI-SCAN II study[2] indicates that 11.8% of the Spanish population aged > 40 years has COPD.

COPD entails a high economic burden associated with a consumption of health resources and a loss of health-related quality of life.[3–6] COPD exacerbations make up a large part of this economic burden and have also a significant impact on patients and their environment. In addition, they are associated with a higher likelihood of future exacerbations, more rapid functional impairment and increased mortality.[7,8]

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Therefore, identification of biomarkers for the diagnosis and prognosis of COPD could help establishing more accurate therapeutic strategies and improving health outcomes. Blood eosinophils count have been suggested as a useful biomarker for response to therapy in COPD. Studies show that COPD patients with elevated eosinophil levels (≥150 cells/μL) have a greater reduction in the rate of exacerbations when treated with inhaled corticosteroids (ICS).[9,10] Some studies suggest that blood eosinophil levels could also be used to direct systemic corticosteroid therapy during exacerbations.[11,12] Moreover, it has been noted that blood eosinophil levels in COPD patients might be considered as a possible prognostic biomarker.[13] However, the use of blood eosinophil counts as a predictor of the risk of exacerbations is less clear, and some studies suggest that it is not useful in populations at low risk of exacerbations.[14,15]

In Spain, the cost of COPD has been studied from different perspectives,[4,5,16,17] but parameters such as the patient phenotype have not been taken into account. To remedy this lack of information, this observational study was designed to more specifically describe the disease burden and health resource use of patients with exacerbating COPD treated with triple therapy and a different eosinophilic profile.

Methods

Study Design

An epidemiological, observational, retrospective, multicenter study was carried out in pulmonology services from 20 Spanish hospitals to estimate the burden of exacerbating COPD in Spain. Patients with COPD who attended a follow-up visit and met all selection criteria were consecutively invited to participate in the study until the required number of patients was fulfilled. Only one visit per patient was required and no follow-up visits were made. The study was approved by the Clinical Research and Ethics Committee of Hospital Universitari Vall d'Hebron (Barcelona, Spain) and all patients provided signed informed consent to participate in the study. It was carried out in accordance with the principles of Declaration of Helsinki and complied with the standards of Good Clinical Practice[18] as well as following the guidelines for Good Epidemiological Practice.[19]

The study did not impede normal diagnostic or therapeutic action in usual clinical practice, which are based on national/international recommendations and guidelines. The economic assessment was carried out from the social perspective. The study period was December 2017 to November 2018. The time horizon of the analysis was 12 months before the inclusion visit.

Study Population

Patients with the following criteria were included: (1) age ≥ 40 years; (2) previous COPD diagnosis with a post-bronchodilator FEV_1/FVC <70% recorded at any time in the medical record; (3) current or past smoking with a cumulative exposure ≥ 10 pack-years; (4) blood eosinophil test recorded in the 3 months before the inclusion visit; (5) treatment with triple inhaled maintenance therapy at inclusion (ICS/ long-acting beta-2 agonist (LABA)/ long-acting muscarinic antagonist (LAMA)) without more than 30 days of separation between prescriptions; (6) ≥2 moderate or ≥1 severe exacerbations in the 12 months before the inclusion visit; and (7) signed the patient's written informed consent form. Exclusion criteria were: (1) patients without a qualifying peripheral blood eosinophil count recorded in the 3 months prior to the inclusion visit and who refuse to perform the test during the inclusion visit; (2) patients treated with oral corticosteroids on an ongoing basis during the 12 months before the inclusion visit; (3) diagnosis of eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis or other conditions resulting in increased eosinophil levels independent of COPD; (4) patients with oncological disease under treatment or in advanced stages with no possibility of remission, terminal states and/or receiving palliative care; (5) cognitively impaired patients; and (6) participation in an interventional clinical trial during the 12 months prior.

Patients were stratified into two groups according to blood eosinophil levels: <150 cells/ μL and ≥150 cells/μL.

Data Collection

Sociodemographic characteristics and clinical variables such as body mass index (BMI), smoking history, concomitant diseases and COPD characteristics such as time from COPD diagnosis, modified dyspnoea scale (mMRC),[20] spirometry and blood biochemical data were collected.

Main Outcomes

Moderate exacerbation was defined as an acute increase in respiratory symptoms requiring a prescription for antibiotics and/or oral corticosteroids or an emergency visit <24

hours, while a severe exacerbation was defined as that requiring hospitalization or emergency visit for ≥24 hours.

Resource use in the stable phase, including primary care (PC) and secondary care (SC) medical visits, outpatient tests, pharmacological and non-pharmacological treatments, and related to the moderate and/or severe exacerbations (hospitalizations, pharmacologic treatments, emergency visits, PC and SC visits) were collected. The days of lost work attributable to COPD, the impact of COPD on patients measured by the COPD Assessment Test (CAT) questionnaire[21] and health-related quality of life (HRQoL) using the Spanish version of the self-administered EuroQoL 5 Dimensions (EQ-5D-5L)[22] were also collected. Utilities were calculated based on the results of the EQ-5D-5L questionnaire. The health states were converted into a weighted index score that ranges from 0 to 1, with 0 being the reference value assigned to death and 1 being perfect health. Spanish weighting for each dimension was applied according to the individual responses, resulting in the tariff applied.[23]

For pharmacological treatments, the total dose was calculated for each of the active substances during the last 12 months in the stable phase and for the duration of the exacerbations. The dose was multiplied by the time on treatment. In cases where the dosing schedule was on demand, the minimum dose according to the data sheet was assigned.

Costs

To estimate the economic impact from the social perspective, direct health care costs due to resource use in the stable phase and to moderate and severe COPD exacerbations; and indirect costs due to working days lost, were included.

The unit costs of resource use were obtained from ESALUD, (database of reported Spanish healthcare costs)[24] (Supplementary Table A-1) and the costs of pharmacological treatments were obtained from the website of the General Council of Official Colleges of Pharmacists[25] plus value added tax without applying the deduction of Royal Decree-Law 8/2010.[26] Working days lost were measured using the latest data published by the National Statistical Institute in the 2016 survey of the salary structure[27] (Supplementary Table A-1). All costs were expressed in 2019 euros.

Direct Healthcare Costs

Direct healthcare costs included resource use in the stable phase: medical visits, outpatient tests, pharmacological and non-pharmacological treatments; and resource use due to exacerbations: hospitalizations, intensive care unit (ICU), emergency/PC/SC visits and pharmacological treatment. The costs of emergency, PC and SC visits, outpatient tests and non-pharmacological treatments were calculated by multiplying the natural units of the resources used by the unit cost. The cost of hospitalizations was obtained by multiplying the days of stay by the corresponding unit cost.

The costs of each pharmacological treatment were obtained by multiplying the total dose each patient received during the stable phase and during exacerbations by the unit cost of each treatment.

Indirect Costs

The costs of lost working days attributable to COPD were included as indirect costs. The calculation was made according to the human capital method, considering that the salary reflects the worker's productivity. Therefore, the days that the patient was unable to work due to COPD were multiplied by the most up-to-date salary cost.

Statistical Analysis

A descriptive analysis of the study variables was made. Quantitative variables were described using means and standard deviation (SD) or, in the case of time from diagnosis, median and interquartile range (IQR). Qualitative variables were analysed at absolute and relative frequencies. For comparisons between patients with eosinophils <150 cells/μL and ≥150 cells/μL, the Mann Whitney *U*-test was used for continuous variables and the exact Fisher test and the χ^2 test for categorical variables, depending on the nature of the comparative variable. The analysis was made using the R statistical package (version 3.5.1).

Sample Size

To obtain a representative sample of patients with severe exacerbating COPD treated with triple therapy, the necessary number of patients was calculated according to the estimated prevalence of Spanish patients with severe COPD (5.2% according to the EPI-SCAN study)[28] and the mean proportion of these with eosinophils ≥ 150 cells/μL (estimated at between 40% and 60%).[29,30] Given this data and a 95% confidence interval, a 2% precision, and a reposition percentage of 10%, an estimate of 250 patients with ≥150 cells/μL was needed. Similarly, the adequate number of patients with <150 cell/μL needed to evaluate secondary objectives was 104, considering

the prevalence of patients with severe COPD in Spain already cited and an estimated proportion of patients with these eosinophil values of approximately 40%. Thus, the number of patients considered necessary was 354.

Results

The initial cohort included 341 patients with exacerbating COPD treated with triple therapy, of whom 306 were valid for the analysis and 51.3% of them had blood eosinophil levels of ≥150 cells/µL. Reasons for exclusion are described in Figure 1.

Of the 306 patients, 77.1% were male and the mean age (SD) was 69.9 (9.2) years. Former smokers accounted for 79.4% of patients, with a mean number (SD) of pack-year of 54.8 (31.7). Similar results were observed in sociodemographic and clinical characteristics by stratifying patients according to eosinophil levels. The mean (SD) post-bronchodilator FEV_1 was 44.5% (16.4) for the total population and 42.7% (15.6) and 46.3% (17.0) for patients with eosinophils <150 cells/µL and ≥150 cells/µL, respectively (Table 1). In 68.5% of patients, eosinophil levels were collected in the stable phase (53.0% and 83.3% in patients with eosinophils <150 cells/µL and ≥150 cells/µL, respectively).

For the total population, 21 patients had ≥1 sick leave in the last 12 months (mean (SD):8.6 (51.2) days/patient). According to eosinophil levels, 8.1% and 5.7% of patients with eosinophils <150 cells/µL and ≥150 cells/µL, respectively had ≥1 sick leave in the last 12 months. The mean (SD) working days lost due to COPD in this period was 14.3 (66.5) and 3.2 (29.5) days/patient, in patients with eosinophils <150 cells/µL and ≥150 cells/µL, respectively. No significant differences in working days lost according to eosinophil levels were observed.

According to the CAT questionnaire results, COPD had a high (27.0%) or very high impact (9.2%) on symptoms. In the EQ-5D-5L questionnaire, the mean utilities score (SD) was 0.6 (0.3) for the total population. No significant differences between the two groups of patients were observed either in CAT or in EQ-5D-5L scores (Table 1).

Resource Use

Two hundred and five of the 306 patients included, had ≥1 moderate exacerbation and 194 had ≥1 severe exacerbation. The mean number (SD) of exacerbations (moderate and/or severe) was 2.5 (1.4) (Table 1).

Of patients with eosinophils <150 cells/µL, 59.1% had ≥1 moderate exacerbation (mean [SD]: 1.2 [1.4] exacerbations/patient), while 75.8% had ≥1 severe exacerbation (mean [SD]: 1.3 [1.2] exacerbations/patient). Of patients with eosinophils ≥150 cells/µL, 74.5% had ≥1 moderate exacerbation (mean (SD): 1.7 (1.5) exacerbations/patient),

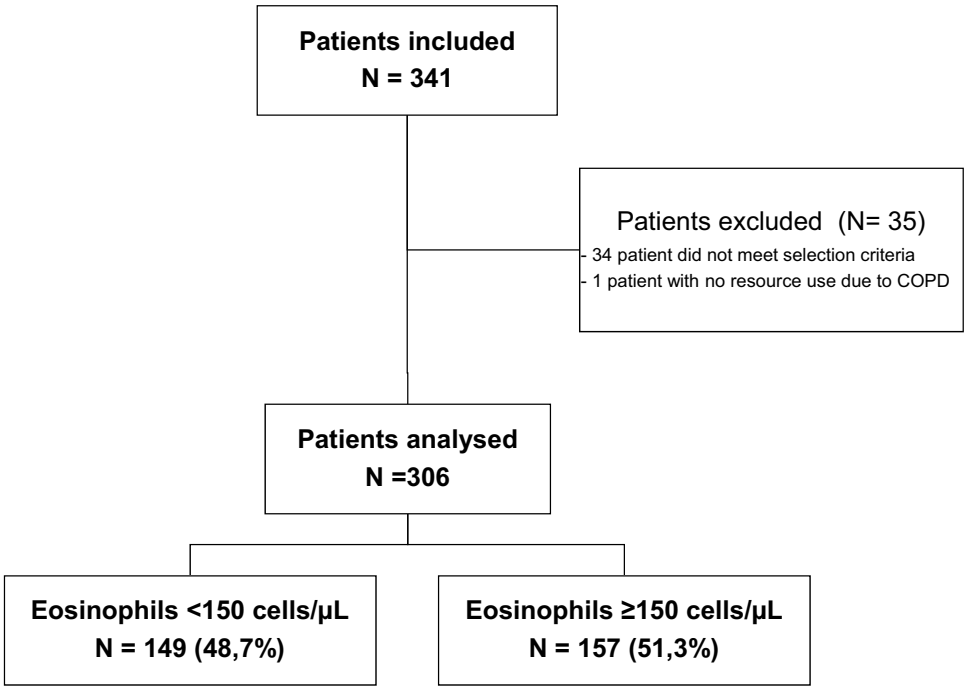

Figure 1 Patient flow according to STROBE guide.
Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 1 Sociodemographic and Clinical Variables of COPD and Impact on the Quality of Life of Patients with Exacerbating COPD Treated with Triple Therapy

Variables	Total Sample N=306 (100.0%)	Eosinophils <150 Cells/μL N=149 (48.7%)	Eosinophils ≥ 150 Cells/μL N=157 (51.3%)	P-value[a]
Sociodemographic variables				
Age (years)				
Mean (SD)	69.9 (9.2)	70.5 (9.0)	69.3 (9.4)	0.310
Sex - n (%)				
Male	236 (77.1%)	114 (76.5%)	122 (77.7%)	0.910
Clinical features				
BMI (kg/m^2)				
Mean (SD)	27.5 (5.5)	27.4 (5.9)	27.6 (5.0)	0.465
Smoking – n (%)				
Former smoker[b]	243 (79.4%)	115 (77.2%)	128 (81.5%)	0.424
Current smoker	63 (20.6%)	34 (22.8%)	29 (18.5%)	
Number of packs-year				
Mean (SD)	54.8 (31.7)	54.6 (32.1)	55.0 (31.3)	0.936
Comorbidities – n (%)				
Diabetes without target organ involvement	51 (16.7%)	20 (13.4%)	31 (19.7%)	0.184
Congestive heart failure	41 (13.4%)	21 (14.1%)	20 (12.7%)	0.857
Myocardial infarction	39 (12.7%)	18 (12.1%)	21 (13.4%)	0.866
Malignancies	28 (9.1%)	15 (10.1%)	13 (8.3%)	0.731
Kidney disease	27 (8.8%)	8 (5.4%)	19 (12.1%)	0.061
Peripheral vascular disease	23 (7.5%)	10 (6.7%)	13 (8.3%)	0.762
Other[c]	74 (24.2%)	41 (27.5%)	33 (21.0%)	0.185
COPD features				
Time from diagnosis (years)[d]				
Median (IQR)	8.0 [5.0–12.0]	8.0 [5.0–13.0]	8.0 [5.0–11.0]	0.565
Modified dyspnoea scale score (mMRC) - n (%)				
Grade 0	8 (2.6%)	2 (1.3%)	6 (3.8%)	0.036
Grade 1	61 (19.9%)	21 (14.1%)	40 (25.5%)	
Grade 2	124 (40.5%)	65 (43.6%)	59 (37.6%)	
Grade 3	85 (27.8%)	43 (28.9%)	42 (26.7%)	
Grade 4	28 (9.2%)	18 (12.1%)	10 (6.4%)	
Post-bronchodilator FEV_1(% predicted)				
Mean (SD)	44.5 (16.4)	42.7 (15.6)	46.3 (17.0)	0.098
Post-bronchodilator FEV_1/FVC (%)				
Mean (SD)	46.9 (12.1)	45.6 (11.2)	48.2 (12.9)	0.055
Eosinophils (cells/μL)				
Mean (SD)	217.9 (384.9)	61.3 (51.5)	366.6 (491.4)	<0.001
Impact of COPD on quality of life				
Total CAT score				
Mean (SD)	17.4 (8.5)	17.7 (8.3)	17.1 (8.7)	0.512

(*Continued*)

Table 1 (Continued).

Variables	Total Sample N=306 (100.0%)	Eosinophils <150 Cells/µL N=149 (48.7%)	Eosinophils ≥ 150 Cells/µL N=157 (51.3%)	P-value[a]
Low impact (CAT score ≤10)– n (%)	73 (24.0%)	30 (20.3%)	43 (27.6%)	0.328
Moderate impact (CAT score >10 and ≤20)– n (%)	121 (39.8%)	66 (44.6%)	55 (35.3%)	
High impact (CAT score >20 and ≤30)– n (%)	82 (27.0%)	39 (26.3%)	43 (27.6%)	
Very high impact (CAT score ≥30)– n (%)	28 (9.2%)	13 (8.8%)	15 (9.6%)	
Utilities (EQ-5D-5L) Mean (SD)	0.6 (0.3)	0.6 (0.3)	0.7 (0.3)	0.270
Number of exacerbations (patient/year)				
Total exacerbations Mean (SD)	2.5 (1.4)	2.5 (1.6)	2.5 (1.3)	0.421
Moderate exacerbations Mean (SD)	1.5 (1.4)	1.2 (1.4)	1.7 (1.5)	0.001
Severe exacerbations Mean (SD)	1.0 (1.1)	1.3 (1.2)	0.8 (0.9)	<0.001

Notes: [a] P-value between patients with eosinophils <150 cells/µL vs ≥ 150cells/µL. The chi-square test was used for dichotomous variables and the Mann–Whitney *U*-test for quantitative variables. [b] Ex-smoker: Former smoker who has not smoked for at least the last 6 months. [c] Others in the global population: Peptic ulcer (n-16), rheumatological disease (n-15), mild liver disease (n-14), cerebrovascular disease (n-10), diabetes with target organ involvement (n-7), acquired immunodeficiency syndrome (n- 4), moderate or severe liver disease (n- 3), hemiplegia or paraplegia (n-3), dementia (n-1), metastasis of solid tumours (n-1). [d] Until the inclusion visit.
Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second;SD, standard deviation; IQR, interquartile range.

while 51.6% had ≥1 severe exacerbation (mean (SD): 0.8 (0.9) exacerbations/patient) (Table 1).

Figure 2 shows resource use due to moderate and severe exacerbations. The mean hospital stay (SD) was 11.6 (10.9) days for the total study population and 13.1 (12.7) and 9.5 (7.3) days for patients with eosinophils <150 cells/µL and ≥150 cells/µL, respectively. No significant differences in the number of visits, the number of hospital admissions or the mean hospital length of stay were observed according to eosinophil levels.

Table 2 shows the use of resources during stable phase. Significant differences were only observed in number of PC visits, blood analysis and bronchodilators tests, which were more frequent in patients with ≥150 eosinophils/µL (Table 2).

Costs

Table 3 and Figure 3 show the costs due to COPD during the last 12 months for the total population and according to blood eosinophil levels. For the total population, the annual mean cost (SD) per patient was €155.8 (€240.9) for moderate and €3117.9 (€4372.5) for severe exacerbations. Annual mean cost (SD) per patient during the stable phase was €2427.5 (€1377.3) (Table 3). Pharmacological treatments accounted for more than 40% of the cost in the stable phase (Figure 3). Annual indirect mean cost (SD) per patient due to COPD was €1019.5 (€6066.1) (Table 3).

The total annual mean direct health costs (SD) per patient was €5701.3 (€4733.0). Adding indirect costs gave a total mean cost (SD) of €6720.7 (€8061.3). According to eosinophil levels, the total annual mean cost (SD) was €8381.7 (€9862.5) and €5144.4 (€5443.9) for patients with eosinophils <150 cells/µL and ≥150 cells/ µL, respectively (Table 3).

Discussion

This study assessed the impact of exacerbating COPD patients treated with triple therapy in Spain through the analysis of direct and indirect costs and their quality of life, providing information about the economic burden of the disease and patients' self-perception of their health status. These patients with a phenotype of frequent and/or severe exacerbations have a higher risk of hospitalization and an increased risk of death.[31]

The annual cost of a patient with exacerbating COPD treated with triple therapy in Spain from the social

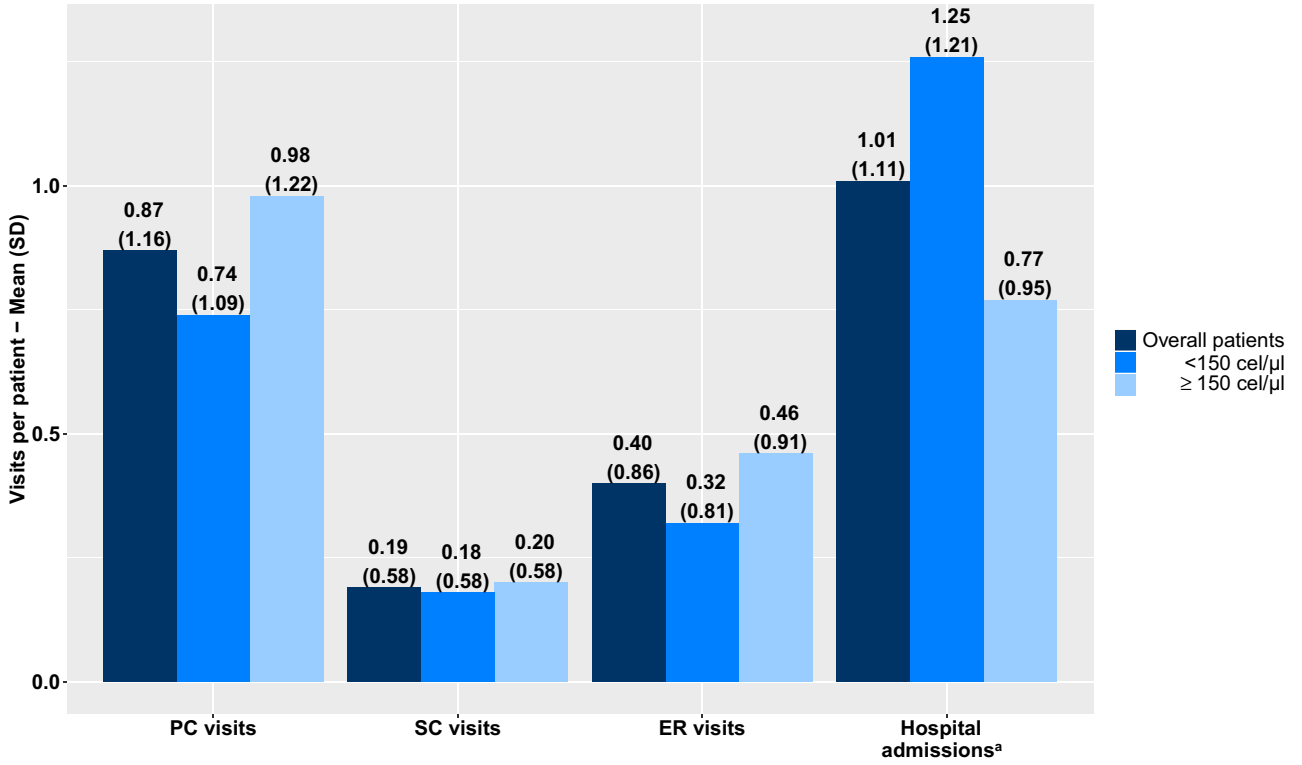

Figure 2 Use of resources for COPD exacerbations (per patient) in patients with exacerbating COPD treated with triple therapy: total population and according to blood eosinophil levels (<150 cells/µL, ≥ 150 cells/µL).
Notes: [a] Statistical difference in hospital admission according to blood eosinophil levels (<150cells/µL, ≥ 150 cells/µL).
Abbreviations: COPD, chronic obstructive pulmonary disease; PC, primary care; SC, secondary care, ER, emergency room; SD, standard deviation.

perspective was €6721 (84.8% direct costs and 15.2% indirect costs). To the best of our knowledge, this is the first Spanish multicenter study of costs in patients with exacerbating COPD who receive the maximum possible inhaled treatment; therefore, we cannot compare our data with similar studies. However, our results can be compared with cost analysis developed using different designs or performed in different populations. In this regard, the costs obtained in our study were higher than those reported in other Spanish studies, which showed an annual direct cost of COPD between €890 and €3085 per patient.[3,4,17,32] The 2018 study by Merino et al,[4] estimated the annual cost of COPD at €3757/patient (82.1% direct costs and 17.9% indirect costs). The total costs in our study were almost twice as high. In addition to the subtle differences in resource use accounting, the main reason for the higher cost is probably that our study only included patients with exacerbating COPD.

According to the eosinophil level, the mean annual cost was €8382 and €5144 for patients with eosinophils <150 cells/µL and ≥150 cells/µL, respectively. Although the total number of exacerbations was not significantly different between both groups of patients, those with low eosinophils had a higher frequency of hospital admissions, which accounted for the significantly increased costs compared with patients with high eosinophils. The relationship between blood eosinophil counts and frequency of exacerbations remains controversial. Some studies have found a significant increase in severe exacerbations in patients with higher eosinophils,[13,33] while others have not found any relationship in populations of patients at low risk of exacerbations.[14,15] In general, our results support the lack of association of blood eosinophil counts and frequency of exacerbations, at least in patients receiving triple therapy.

The benefits of triple therapy have been extensively studied, and there is a greater effect on lung function and a decrease in exacerbations and hospitalizations in severe patients compared to other alternatives of treatment, in particular in patients with high blood eosinophil counts.[34] However, some high-risk patients may still not have good disease control despite receiving triple therapy, as seen in the results of this and previous studies.[35–37] All this reflects that there are still unmet needs in treatment of patients with COPD.

Table 2 Use of Resources Due to Stable-Phase COPD (per Patient) in Patients with Exacerbating COPD Treated with Triple Therapy

Variables	Total Sample N=306 (100.0%)	Eosinophils <150 Cells/μL N=149 (48.7%)	Eosinophils ≥ 150 Cells/μL N=157 (51.3%)	P-value[a]
Visits				
Number of total visits Mean (SD)	6.2 (4.2)	5.8 (3.8)	6.6 (4.5)	0.125
Number of PHC physician visits Mean (SD)	3.7 (3.8)	3.3 (3.5)	4.1 (3.9)	0.037
Number of specialized medical visits [b] Mean (SD)	2.5 (1.7)	2.5 (1.5)	2.5 (1.9)	0.492
Outpatient tests[c]				
Spirometries Mean (SD)	1.3 (0.7)	1.3 (0.7)	1.4 (0.8)	0.348
Blood analyses Mean (SD)	2.8 (3.8)	2.6 (3.4)	3.1 (4.2)	0.030
Chest X-rays Mean (SD)	1.5 (1.8)	1.4 (1.5)	1.6 (2.1)	0.809
Bronchodilator tests Mean (SD)	0.8 (0.8)	0.7 (0.7)	0.9 (0.8)	0.035
Arterial blood gases Mean (SD)	1.0 (1.6)	1.0 (1.7)	0.9 (1.5)	0.188
Lung volumes and/or DLCO Mean (SD)	0.02 (0.1)	0.03 (0.2)	0.01 (0.1)	0.374
6-minute walk test Mean (SD)	0.3 (0.5)	0.2 (0.4)	0.3 (0.5)	0.535
Chest CT Mean (SD)	0.2 (0.5)	0.3 (0.5)	0.2 (0.5)	0.875
FE_{NO} measurements Mean (SD)	0.1 (0.4)	0.1 (0.4)	0.2 (0.5)	0.531
Non-pharmacological treatment				
Influenza vaccination – n (%)	249 (81.4%)	119 (79.9%)	130 (82.8%)	0.608
Pneumococcal vaccination - n (%)	197 (64.4%)	94 (63.1%)	103 (65.6%)	0.734
Home oxygen – n (%)	102 (33.3%)	55 (36.9%)	47 (29.9%)	0.241
Respiratory rehabilitation – n (%)	22 (7.2%)	12 (8.0%)	10 (6.4%)	0.727
Non-invasive home ventilation - n (%)	20 (6.5%)	13 (8.7%)	7 (4.5%)	0.201
Drug treatment[d,e]				
LAMA – n (%)	217 (70.9%)	108 (72.5%)	109 (69.4%)	0.556
LABA/ICS – n (%)	214 (69.9%)	108 (72.5%)	106 (67.5%)	0.344
SABA – n (%)	122 (39.9%)	58 (38.9%)	64 (40.8%)	0.743
ICS – n (%)	94 (30.7%)	43 (28.9%)	51 (32.5%)	0.492

(*Continued*)

Table 2 (Continued).

Variables	Total Sample N=306 (100.0%)	Eosinophils <150 Cells/µL N=149 (48.7%)	Eosinophils ≥ 150 Cells/µL N=157 (51.3%)	P-value[a]
LABA/LAMA – n (%)	92 (30.1%)	42 (28.2%)	50 (31.8%)	0.485
Other airway agents – n (%)	43 (14.0%)	21 (14.1%)	22 (14.0%)	0.984

Notes: [a]P-value between patients with eosinophils <150 cells/µL vs ≥ 150 cells/µL. The chi-square test was used for dichotomous variables and the Mann–Whitney *U*-test for quantitative variables. [b]Not including inclusion visit. [c]Outpatient tests required by <5% of patients not shown. [d]Treatment prescribed in <10% of patients not shown. [e]Categories mutually non-exclusive.

Abbreviations: COPD, chronic obstructive pulmonary disease; PHC, primary healthcare; DLCO, lung diffusion capacity; CT, computed tomography; FE_{NO}, exhaled nitric oxide; SABA, short-acting inhaled adrenergic; LABA, long-acting β agonists; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroids; SD, standard deviation; IQR, interquartile range.

Table 3 Total Costs per Patient Due to COPD During the Last 12 Months in Patients with Exacerbating COPD Treated with Triple Therapy[a]

Variables	Total Sample N= 306 (100.0%)	Eosinophils <150 Cells/µL N= 149 (48.7%)	Eosinophils ≥ 150 Cells/µL N= 157 (51.3%)	P-value[b]
Direct health costs due to exacerbations				
Cost of resource use in exacerbations (moderate and severe)	3273.8 (4353.6)	4324.2 (5080.2)	2276.9 (3243.2)	<0.001
Cost of resource use in moderate exacerbations	155.8 (240.9)	120.8 (171.6)	189.1 (288.5)	0.005
Pharmacological cost	42.9 (152.9)	25.4 (37.8)	59.6 (209.3)	0.001
Cost of PC visits	28.2 (37.9)	24.3 (35.6)	32.0 (39.7)	0.060
Cost of SC visits	16.7 (50.6)	15.7 (50.5)	17.7 (50.8)	0.811
Cost of emergency visits	68.0 (148.3)	55.4 (138.8)	79.9 (156.3)	0.096
Cost of resource use in severe exacerbations	3117.9 (4372.5)	4203.4 (5100.6)	2087.7 (3240.8)	<0.001
Pharmacological cost	526.2 (1071.4)	663.6 (1131.3)	395.8 (997.4)	<0.001
Cost of hospital admissions	2491.7 (3489.1)	3360.8 (4189.3)	1667.0 (2397.0)	<0.001
Cost of ICU stay	99.9 (659.9)	179.0 (884.7)	24.9 (311.5)	0.015
Fixed health costs in stable phase				
Total annual cost of resource use	2427.5 (1377.3)	2378.7 (1378.6)	2473.8 (1378.8)	0.312
Annual pharmacological cost	1037.7 (627.9)	965.2 (489.7)	1106.5 (730.5)	0.036
Annual cost of total visits	336.9 (195.6)	321.0 (172.4)	352.0 (214.8)	0.431
Annual cost of PC visits	121.2 (122.7)	107.9 (115.6)	133.8 (128.2)	0.037
Annual cost of SC visits	215.8 (146.9)	213.1 (128.6)	218.3 (162.8)	0.492
Annual cost of outpatient tests	522.9 (433.8)	493.9 (408.0)	550.3 (456.6)	0.153
Annual cost of spirometry	67.9 (37.7)	65.1 (36.9)	70.5 (38.4)	0.348
Annual cost of blood analyses	179.6 (243.2)	162.3 (218.4)	196.0 (264.4)	0.030
Annual cost of chest X-ray	39.9 (48.1)	37.3 (40.3)	42.3 (54.6)	0.809
Annual cost of bronchodilator testing	46.9 (45.1)	40.5 (39.8)	52.9 (48.9)	0.035
Annual cost of arterial blood gases	42.0 (70.8)	45.0 (74.8)	39.1 (66.9)	0.188
Annual cost of complete functional testing	53.7 (86.6)	53.0 (85.9)	54.3 (87.5)	0.889
Annual cost of 6-minute walk test	15.3 (27.3)	13.9 (25.2)	16.6 (29.1)	0.535
Annual cost of chest CT	46.0 (97.5)	48.5 (104.1)	43.6 (91.1)	0.875
Annual cost of FE_{NO} measurements	15.0 (44.8)	12.1 (36.6)	17.8 (51.3)	0.531
Annual cost of other tests	16.6 (61.1)	16.0 (53.4)	17.1 (67.7)	0.885
Annual cost of non-pharmacological treatment	530.0 (1020.0)	598.5 (1130.8)	465.0 (901.2)	0.544
Annual cost of home oxygen	289.9 (499.4)	310.4 (511.5)	270.5 (488.4)	0.322
Annual cost vaccinations	31.3 (20.2)	30.7 (20.5)	31.9 (19.8)	0.611
Annual cost respiratory rehabilitation	12.7 (70.1)	17.8 (92.9)	7.75 (36.9)	0.550
Annual cost of non-invasive home ventilation	156.2 (680.3)	196.4 (756.7)	118.1 (598.8)	0.199
Annual cost of other treatments	39.8 (193.0)	43.1 (206.9)	36.73 (179.4)	0.899

(*Continued*)

Table 3 (Continued).

Variables	Total Sample N= 306 (100.0%)	Eosinophils <150 Cells/μL N= 149 (48.7%)	Eosinophils ≥ 150 Cells/μL N= 157 (51.3%)	P-value[b]
Total cost				
Total annual cost	6720.7 (8061.3)	8381.7 (9862.5)	5144.4 (5443.9)	<0.001
Total direct health costs (exacerbations + stable phase)	5701.3 (4733.0)	6702.9 (5388.4)	4750.7 (3792.7)	<0.001
Total indirect costs	1019.5 (6066.1)	1678.9 (7820.5)	393.7 (3620.9)	0.369

Notes: [a]Costs in euros 2019. Mean (SD). [b]P-value between patients with eosinophils <150 cells/μL vs ≥ 150 cells/μL. The Mann–Whitney *U*-test was used.
Abbreviations: COPD, chronic obstructive pulmonary disease; PC, primary care; SC, secondary care; ICU, intensive care unit; CT, computed axial tomography; FE_{NO}, exhaled nitric oxide test; SD, standard deviation.

The association between high eosinophil levels and the response to corticosteroids, both during exacerbations and in the stable phase of COPD,[9,10,12] has led to questions about the role of eosinophils in lung diseases. In recent years, interest in blood eosinophil levels in COPD patients as a possible prognostic biomarker has increased.[38–40] The IMPACT clinical trial, in a population of patients with COPD with similar characteristics to that of our study, showed that the annual rate of moderate or severe exacerbations was lower with triple therapy compared with LABA/LAMA, and a greater reduction in the exacerbation rate was observed in patients with eosinophil levels above 150 cells/μL.[41]

COPD has a great impact on the quality of life. Our results show a remarkable difference between the mean utility of the study population (0.65 (SD: 0.29)) compared with the mean utility of the Spanish general population (0.91 (SD: 0.18)),[42] and the mean utility of COPD in general (0.73 (SD: 0.29)).[22,43]

This study had some limitations. Firstly, it was recommended that blood eosinophil levels were collected in the stable phase; however, this was not possible in all patients. Quantifying blood eosinophils during an exacerbation may result in lower values due to the use of systemic corticosteroids. Secondly, the setting selected and the retrospective design of the study may underestimate the economic impact of exacerbating COPD, since visits to other hospitals or specialists were not collected, as well as we did not consider non-healthcare direct costs relevant to COPD, such as formal and informal cares. These costs may amount up to 38% of the total cost of COPD.[4,44] In addition, the indirect costs included only those associated with lost workdays attributable to COPD. Finally, 305 patients in our study were treated with open-triple therapy. Currently, there are devices on the market that allow single-inhaler triple therapy, which might reduce the real cost by improving adherence and outcomes.[45] This study might not be representative of the management in other Spanish hospitals. Therefore, generalization of the results may be limited and should be interpreted with caution. In summary, the high economic impact of COPD and its

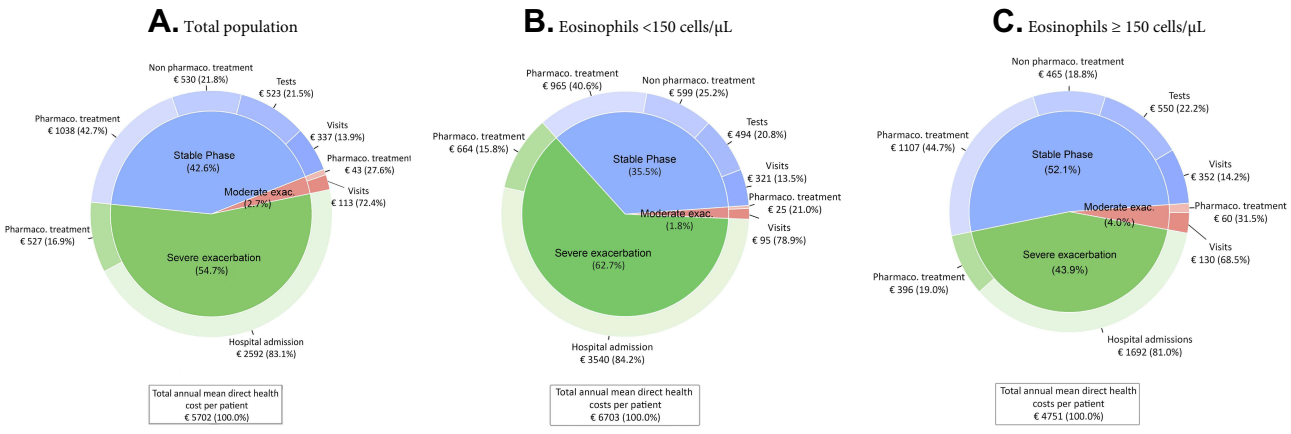

Figure 3 Distribution of total direct health costs per COPD patient in the last 12 months.

exacerbations in Spain is evident. In addition, we found that patients may not achieve optimal disease control despite medication. The results of this study suggest that further studies of new targeted therapies and new biomarkers are needed to guide and improve treatment. Additionally, studies that include a cost-effectiveness analysis may be beneficial, given the high cost of these therapies, to support their use when appropriate.[46]

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