



## Early View

Original research article

# Real-life burden of hospitalizations due to COPD exacerbations in Spain

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## REAL-LIFE BURDEN OF HOSPITALIZATIONS DUE TO COPD EXACERBATIONS IN SPAIN

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## **ABSTRACT**

Patients with chronic obstructive pulmonary disease (COPD) often suffer episodes of exacerbation of symptoms (ECOPD) that may eventually require hospitalization due to several, often overlapping, causes.

We aimed to analyse the characteristics of patients hospitalized because of ECOPD in a real-life setting using a big-data approach.

The study population included all patients older than 40 years with a diagnosis of COPD (n=69.359; prevalence 3.72%) registered since January 1<sup>st</sup>, 2011 until March 1, 2020 in the database of the public healthcare service (SESCAM) of Castilla-La Mancha (Spain) (n=1.863.759 subjects). We used natural language processing (Savana Manager v3.0) to identify those who were hospitalized during this period for any cause, including ECOPD.

During the study 26.453 COPD patients (38.1%) were hospitalized (at least once). Main diagnoses at discharge were respiratory infection (51%), heart failure (38%) or pneumonia (19%). ECOPD was the main diagnosis at discharge (or hospital death) in 8.331 of them (12.0% of the entire COPD population and 31.5% of those hospitalized). In-hospital ECOPD-related mortality rate was 3.1%. These patients were hospitalized 2.36 times per patient, with a mean hospital stay of 6.1 days. Heart failure (HF), the most frequent comorbidity in patients hospitalized because of ECOPD (52.6%).

This analysis shows that, in a real-life setting, ECOPD hospitalizations are prevalent, complex (particularly in relation to HF), repetitive and associated with significant in-hospital mortality.

**Abstract word count:** 223 words (<250 words)

## **INTRODUCTION**

Chronic Obstructive Pulmonary Disease (COPD) is a prevalent and complex disease, associated with significant morbi-mortality (1). During the course of their disease, COPD patients often present episodes of symptom worsening, known as exacerbations (ECOPD), that sometimes require hospitalization (2-5). These ECOPD episodes are in themselves heterogeneous and can be mimicked and/or aggravated by co-existing multimorbidity (6-8). As a result, it is difficult to ascertain from standard hospital registries (and discharge diagnoses) the burden of hospitalizations due to ECOPD and the characteristics of these patients in a real life-setting. On the other hand, information available from randomized clinical trials (RCTs) is not generalizable because RCTs study highly selected populations (9). In particular, the diagnostic role of biomarkers such as circulating leukocytes or eosinophils, and C-reactive protein (CRP), fibrinogen and brain-natriuretic peptide (BNP) levels in a real-life setting in relation to ECOPD and associated multi-morbidity is unknown.

New technologies, such as natural language processing (NLP), big-data analysis and different artificial intelligence techniques, allow the analysis of very large populations of patients in real-life. Savana Manager is a platform able to analyse free text (FT) and interpret the content of electronic medical records (EMRs), regardless of the specific clinical information system used in each hospital (10). Based on our previous experience using NLP (11-13), in this study we sought to describe the characteristics of COPD patients requiring hospitalization for any acute condition (including but not limited to ECOPD in order to have a wider perspective) and/or ECOPD (as a specific discharge diagnosis or cause of death in hospital) identified by the Savana Manager platform over the past decade in our community.

## **METHODS**

### **Study design and Ethics**

This retrospective, observational, non-interventional study used the Savana Manager v 3.0 platform to capture data from FT in the EMRs registered in the public healthcare system (SESCAM) of Castilla-La Mancha (Spain) from January 1, 2011, until March 1, 2020. After this date, hospital admissions were significantly affected by the COVID19 pandemic, so we decided to censor the analysis then. To avoid missing data from COPD patients hospitalized for ECOPD but coded with a different diagnosis, we first included in the analysis all patients older than 40 years of age with a diagnosis of COPD in the SESCAM database who required acute hospitalization for any cause during the study period; thereafter, we compared these results with those observed in patients hospitalized because of the specific diagnosis of ECOPD. The SESCAM database includes information on specialized care institutions (hospitalization, emergency care and outpatient consultations) and primary care clinics in the entire community of Castilla-La Mancha (Spain). This study follows the STROBE guidelines for observational studies (14) and was approved by the Guadalajara regional Research Ethics Committee.

### **Data analysis**

Savana Manager is a data extraction system based on artificial intelligence (NLP) and bigdata techniques (10). This system can extract unstructured clinical information from natural language or free text in EMRs and transform it into usable information for research, while maintaining patient anonymity. Besides, using computational linguistic techniques, the clinical context is detected and scientifically validated with the SNOMED CT tool (15).

### *Data management and protection*

The information services of each hospital were responsible for data processing and anonymization, which was subsequently sent to Savana, so the latter never received identifiable data. Furthermore, an algorithm was used during data extraction that randomly introduced confounding information per patient, while at the same time only retrieving part of the individual information. The end-result of this methodology is an anonymous database, completely dissociated for EMRs. Results, therefore, relate only to aggregated data, not being possible to identify either patients or physicians. According to the European Data Protection Authority, once an anonymous clinical record is separated from personal data, the EU General Data Protection Regulation does not longer apply.

### *Evaluation of the quantity and quality of the extracted information*

Using EHRead technology, the free text contained in the EMR was analysed and processed with natural language processing (NLP) techniques (10). To evaluate the performance and accuracy of the Savana system to identify records that mention the main study variables, a gold standard “annotated corpus” of clinical documents (n=560) was developed where these variables were manually curated by three clinical experts. Using this corpus as the gold standard, we could then calculate the Precision (P), Recall (R) and F-measure of Savana’s performance, as follows (16):

Precision (P) =  $\frac{tp}{tp + fp}$ , which indicates the reliability of the system to retrieve information.

Recall (R) =  $\frac{tp}{tp + fn}$ , which indicates the amount of information that the system retrieves.

F-measure =  $\frac{2 \times \text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}}$ , which indicates the overall data retrieval performance.

Where a true positive (*tp*) corresponds to a correctly identified record, a false positive (*fp*) to an incorrectly identified record, and a false negative (*fn*) to a record that should have been identified but was not.

### **Statistical analysis**

Qualitative variables are presented as absolute frequency and percentage, and quantitative variables as mean, 95% confidence interval and standard deviation.

The most common diagnoses in our study population (patients with COPD over 40 years old) are determined by the total number of patients who have been diagnosed with that specific pathology during their clinical course. The prevalence is calculated based on the total study population. Furthermore, the degree of association between the most common diagnosis and COPD was analysed by Savana Manager v 3.0 platform by a chi-square test, using a correlation matrix adjusted by age and sex. Those with a significant correlation ( $p < 0.05$ ) are presented.

### **RESULTS**

Figure 1 shows the consort diagram of this analysis. From January 1, 2011, until March 1, 2020, the SESCAM database included 1.863.759 subjects older than 40 years with a total of 24.316.255 clinical documents. Among these subjects, 69.359 (3.72%) were diagnosed and treated for COPD at different healthcare levels of SESCAM. The Precision, Recall and F-measure of a diagnosis of COPD were 0.93, 0.90 and 0.91, respectively, indicating that the diagnosis of COPD was accurately detected in our population. F values of other terms included in this analysis, such as comorbidities, ranged between 0.92 and 0.97. Table 1 presents the main demographic and clinical characteristics of these 69.359 COPD patients. Mean age was 72.9 years (95%CI 72.8-73.0), and 77.1% were males. Cardiovascular and



metabolic comorbidities were often present, and most patients were prescribed inhaled therapies in different combinations (Table 1).

### **Acute hospitalizations due to any cause**

Among the 69,359 COPD patients identified in the SESCAM database, 26,453 of them (38.1%) were hospitalized (at least once) during the study period (10 years) because of an acute condition, as identified by the discharge diagnosis in the database (Table 2). Hospitalized COPD patients were slightly older (76.2 vs. 72.9 years) with a higher prevalence of males (85.1 vs. 77.1%) than in the total population (Table 1). Yet, the prevalence of comorbidities was similar to that seen in the population of COPD patients at large. Interestingly, the proportion of patients receiving chronic inhaled therapies was nominally lower in hospitalized patients (Table 1). Their mean hospital stay was 5.7 days. In total, these patients generated 56,972 hospitalization events during the study period (2.15 per patient), with a mortality rate of 4.7% per hospital admission. Table 2 shows that the two most frequent diagnoses at discharge in this population were respiratory infection (51.7%) and heart failure (38.1%). Finally, Table 3 shows that most of these patients (47.8%) were hospitalized in general medicine wards, 20.1% in pulmonology wards and 11.5% in geriatric wards. Patients admitted to the pulmonology ward tended to be younger and suffer heart failure less often (Table 3).

### **Hospitalizations due to ECOPD**

ECOPD was identified as the main diagnosis at hospital discharge or as a cause of death during hospitalization in 8,331 patients (31.5% of all COPD patients hospitalized during the study period). Age, gender and comorbidities distribution were similar in the two hospitalized COPD patient groups, except for a higher prevalence of heart failure in patients hospitalized because of ECOPD (52.6% vs. 38.0%, respectively). Of note too, these latter patients

received inhaled treatment more frequently than the former (Table 1). Patients hospitalized because of ECOPD generated a total of 19.674 hospitalization events (mean 2.36 admissions per patient), with a mean hospital stay of 6.1 days and a hospital mortality rate of 3.11% per hospital admission. Table 2 shows that the main diagnoses (besides ECOPD) in this population.

## **DISCUSSION**

The three main observations of this big-data (n=69.359 COPD patients), real-life analysis that spans over a decade in the community of Castilla-La Mancha in Spain are that: (1) the prevalence of diagnosed and treated COPD in the community was very low (3.72%), and diagnosed patients are old (72.9 years) predominantly males (77.1%); (2) hospitalization events for acute conditions (including ECOPD) in this population are frequent (38.1%), recurrent (2.15/patient) and associated with significant in-hospital mortality (4.7% per hospital admission). Of note, hospitalized patients appear undertreated before hospitalization, as compared to the population of COPD patients at large. Further, only a few hospitalized patients (20.1%) are treated by pulmonary specialists; and (3) the prevalence of heart failure is particularly high in patients hospitalized because of ECOPD (52.6%).

### **Previous studies**

Hospitalized ECOPD episodes worsen the health status and prognosis of COPD patients and generate a high economic burden for healthcare systems (17). Because ECOPD are heterogeneous and can be mimicked and/or aggravated by coexisting comorbidities (8), their characteristics and true impact on health care systems is not precisely defined (18-20). A previous study in another region of our country (Catalunya), based on diagnosis at discharge, showed that 23% of patients hospitalized for the first time because ECOPD died

within a year after hospital discharge, and that in the remaining patients, all-cause mortality was related to the number of re-hospitalizations, particularly early (<30 days) readmissions (21). To our knowledge, the current study is the first to have investigated hospitalizations in COPD using artificial intelligence and natural language processing techniques (10).

### **Interpretation of novel findings**

Using such a big-data approach, we found that the prevalence of COPD in our community was 3.72%. This figure is much lower than that reported recently in an epidemiological study in the Spanish general population older than 40 years of age (11.8 %) (22). Yet, this same epidemiological study reported an underdiagnosis of COPD of 74.7% and, in fact, applying this proportion of infra-diagnosis to our community, we would expect to find a prevalence of COPD in our community of 3.99%, which is actually quite close to the observed figure. Hence, this real-life, big-data analysis confirms that underdiagnosis of COPD in Spain (and likely elsewhere) is very high. Similarly, we observed that diagnosed patients are quite old (72.9 years) and predominantly males (77.1%). This supports recent calls to diagnose and treat younger patients, both males and females, with COPD (23,24).

Our results also show that the episodes of hospitalization for any cause (including ECOPD) in COPD patients in our community are frequent (38.1%), recurrent (2.15/patient) and associated with significant in-hospital mortality (4.7% per hospital admission). This illustrates the associated disease burden and impact of COPD on the health-care system. Of note, we also observed that, compared to the population of diagnosed COPD patients at large, those hospitalized for any cause appear undertreated before hospitalization (Table 1). Further, only a few hospitalized patients (20.1%) are treated by pulmonary specialists. These two observations open a window of opportunity to improve the care of these patients, both before and during hospitalization (25).

Heart failure was the most frequent diagnosis in patients hospitalized because of ECOPD (52.6%). These observations support previous studies showing the clinical relevance of concomitant heart failure (HF) in patients hospitalized because of ECOPD (26-35).

Finally, in 26% of patients hospitalized because of ECOPD, pneumonia was also diagnosed. Whether this should be considered a different event from an ECOPD or included in the same concept is arguable (32,36).

### **Strengths and potential limitations**

The size of the population studied, and the use of novel big data analysis methodologies, are clear strength of this study. Further, the fact that this is a real-life study and that it expands a decade are novel aspects. Yet, such a big size of the study population limits a more granular analysis of some clinical variables of potential interest, such as the specific type of respiratory infection that may have triggered the ECOPD event or the impact of treatments received during hospitalization. Likewise, we acknowledge that our analysis is based on diagnostic codes and not on spirometric measurements, which may underestimate the true prevalence of the disease in the population.

### **Conclusions**

This study in a large population studied in a real-life setting shows that: (1) there is a huge underdiagnosis of COPD in our Community; (2) COPD is diagnosed too late and rarely in females; (3) hospitalization events for acute conditions (including ECOPD) in this population are frequent, recurrent and associated with significant in-hospital mortality; and, (4) heart failure is particularly prevalent in patients hospitalized because of ECOPD.

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**Table 1.** Demographics and main clinical characteristics of the total population of COPD patients identified in the study, those acutely hospitalized because of any medical condition (including ECOPD) and those with a main hospital discharge diagnosis of ECOPD.

	<b>Total COPD population</b> (n=69.359)	<b>All-cause acute hospitalization of COPD patients</b> (n=26.453)	<b>Acute hospitalizations due to ECOPD</b> (n=8.331)
<b>Demographics</b>			
Age, years (95%CI)	72.9 (72.8-73.0)	76.2 (76.1–76.5)	77.8 (77.6-78.0)
Males (%)	77.1	85.1	88.4
<b>Comorbidities</b>			
Arterial hypertension (%)	70.2	70.9	73.5
Dyslipidaemia (%)	48.5	40.7	42.3
Heart failure (%)	38.8	38.0	52.6
Diabetes (%)	37.4	36.2	39.2
Obesity (%)	25.4	17.0	20.4
Atrial fibrillation (%)	18.7	17.1	19.9
Sleep Apnoea (%)	17.8	14.5	16.5
Depression (%)	13.6	11.4	13.0
Hiatal hernia (%)	13.3	9.9	10.5
Ischemic cardiopathy	12.8	12.3	13.3
Pulmonary embolism (%)	4.3	4.7	5.7
<b>Respiratory treatments</b>			
LAMA (%)	81.1	55.0	84.6
LABA-ICS (%)	62.5	45.1	72.7
LABA-LAMA (%)	37.6	19.2	20.3

LAMA: long-acting anti-muscarinic; LABA: long-acting  $\beta$ 2 adrenergic; ICS: inhaled corticosteroids. The percentages of inhaled treatments can add up to more than 100% due to changes in the treatment of some patients during the follow-up period. Most LAMA were administered in association with LABA/ICS (triple therapy).

**Table 2.** Diagnoses (%) (at discharge or death) in COPD patients hospitalized because of any cause or ECOPD.

<b>Any cause</b>	<b>Prevalence</b>
Respiratory infection (%)	51.7
Heart failure (%)	38.0
Pneumonia (%)	19.0
Anaemia (%)	17.9
Atrial fibrillation (%)	17.1
Obesity (%)	17.0
Bronchial hyperreactivity (%)	15.5
Urinary tract infection (%)	13.2
Acute renal failure (%)	11.3
<b>ECOPD</b>	
Heart failure (%)	52.6
Pneumonia (%)	26.0
Chronic respiratory failure (%)	23.2
Bronchial hyperreactivity (%)	21.8
Obesity (%)	20.4
Atrial fibrillation (%)	19.9
Anaemia (%)	18.9
Urinary tract infection (%)	14.1
Respiratory acidosis (%)	13.3
Acute renal failure (%)	13

**Table 3.** Demographics and main diagnosis at discharge of COPD patients requiring acute hospitalization during the study period due to any cause, by hospital service attending them. Other 5.446 (20.6%) patients were hospitalized in other departments due to diseases unrelated to COPD (not shown in the Table due to the very long list of potential diagnosis).

	<b>Pulmonology</b> N=5.319 (20.1%)	<b>Internal Medicine</b> N=12.637 (47.8%)	<b>Geriatrics</b> N=3.051 (11.5%)
Age, years (95%CI)	72.2 (71.9 – 72.5)	78.1 (77.9-78.3)	87.4 (87.3-87.6)
Males (%)	88.8	86.8	82.7
Respiratory infection (%)	48.1	59.1	49.6
Heart failure (%)	21.0	45.5	53.4
Pneumonia (%)	23.1	19.9	28.3
Anaemia (%)	5.9	17.6	21.6
Atrial fibrillation (%)	8.5	17.4	20.9
Chronic respiratory failure (%)	20.6	13.2	12.6

# Figure Legends

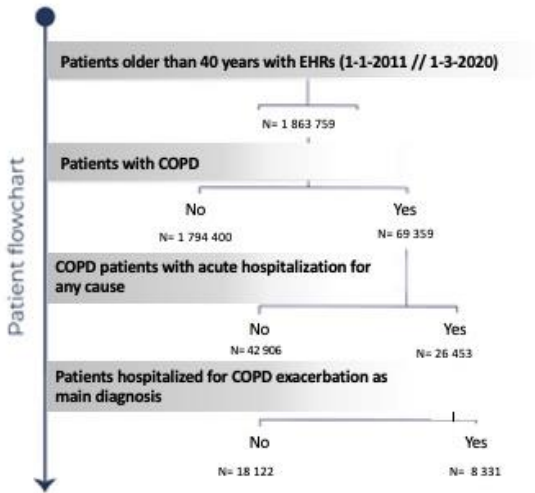


Figure 1

Figure 1 Flow chart of the study