Clinical Profile of Patients with Chronic Obstructive Pulmonary Disease from a Portuguese Integrated Health Care Unit: A Real-World Study

Caracterização Clínica de Doentes com DPOC Numa Unidade Local de Saúde Portuguesa: Um Estudo do Mundo Real

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Abstract:

Introduction: Clinical characteristics of patients with chronic obstructive pulmonary disease (COPD) in Portugal were mainly examined in studies with small sample sizes from either primary or secondary care. The integrated analysis of primary and secondary care data reflecting daily clinical practice has yet to be explored.

We aimed to comprehensively describe the clinical characteristics of patients with COPD within an unselected population of a Portuguese Integrated Health Care Unit across two periods.

Methods: This is a real-world, retrospective, observational study that used healthcare data of the Local Health Unit of Matosinhos. Two COPD cohorts were analysed: an incident cohort, from January 1, 2013, to December 31, 2018; and a prevalent cohort, established as of December 31, 2021. Individuals ≥40 years, diagnosed with COPD and with 1 year of history prior to diagnosis were identified. Data regarding age, sex, exacerbations, comorbidities and COPD medication were analysed. Moderate exacerbations were defined as COPD-related outpatient visits requiring respiratory antibiotics, and/or oral systemic corticosteroids within a 7 days window, while severe exacerbations included emergency room visits or hospitalizations. COPD medications were categorized based on the Anatomical Therapeutic Chemical Classification System.

Results: In the incident analysis (2013–2018), 5,696 COPD cases were identified (median age 68.0 [IQR 18.0] years; 68% male), while the 2021 prevalent cohort included 3,457 patients (median age 71.0 [IQR 17.0] years; 69.3% male). More than half of the patients experienced at least one moderate or severe exacerbation (2013-2018 59.7%, 2021 76.7%) and more than one-third (2013-2018 36.9%, 2021 49.6%) had severe exacerbations. The combination of long-acting β-2 agonists (LABA) or long-acting anticholinergics (LAMA) plus inhaled corticosteroids (ICS) (2013-2018 23.2%, 2021 36.1%) were the most common inhaler prescriptions. Triple combination therapy (ICS+LABA+LAMA) in free combinations was prescribed to around 10% of patients (2013-2018 9.1%; 2021 10.0%), while in fixed-dose combination was marginally prescribed (2013-2018 0.1%, 2021 1.7%). Almost half of the 2013-2018 incident cohort (49.6%) and a quarter of the 2021 prevalent cohort (24.7%) received no inhaled medication.

Conclusion: Our findings offer valuable insights into the clinical profile of patients with COPD, their exacerbation history, and treatment patterns. These findings underscore the need for comprehensive, targeted and integrated interventions for this population.

Keywords: Pulmonary Disease, Chronic Obstructive/epidemiology; Pulmonary Disease, Chronic Obstructive/drug therapy.

Resumo:

Introdução: As características clínicas dos doentes com doença pulmonar obstrutiva crónica (DPOC) em Portugal foram exploradas principalmente por meio de estudos com amostras pequenas, provenientes dos cuidados primários ou hospitalares. A análise conjunta de dados de cuidados primários e hospitalares que refletem a prática clínica diária permanece por explorar.

Este estudo teve como objetivo descrever de forma abrangente as características clínicas de doentes com DPOC da Unidade Local de Saúde (ULS) em 2 períodos.

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Métodos: Estudo observacional retrospetivo, baseado em registos eletrónicos de saúde da ULS de Matosinhos. Foram analisadas duas coortes: uma coorte incidente, de 01-01-2013 a 31-12-2018; e uma coorte prevalente, a 31-12-2021. Foram incluídos indivíduos ≥40 anos, com diagnóstico de DPOC e com um ano de histórico pré-diagnóstico. Dados como idade, sexo, agudizações, comorbilidades e medicação foram analisados. Agudizações moderadas foram definidas como consultas em ambulatório com prescrição de antibióticos respiratórios e/ou corticosteroides sistémicos orais (dentro de 7 dias); agudizações graves incluíram atendimentos de urgência ou hospitalizações. Os medicamentos foram categorizados com base na Classificação ATC (*Anatomic Therapeutic Chemical*).

Resultados: Na análise incidente (2013–2018), foram identificados 5.696 doentes (mediana 68,0[IQR 18,0] anos; 68,0% homens), enquanto a coorte prevalente de 2021 incluiu 3.457 doentes (mediana 71,0[IQR 17,0] anos; 69,3% homens). Mais de metade dos doentes experienciou pelo menos uma agudização moderada ou grave (2013-2018 59,7%; 2021 76,7%) e mais de um terço (2013-2018 36,9%; 2021 49,6%) teve agudizações graves. A combinação de agonistas β-2 de longa duração (LABA) ou anticolinérgicos de longa duração (LAMA) com corticosteroides inalados (ICS) (2013-2018 23,2%; 2021 36,1%) foram as prescrições mais comuns. A terapêutica tripla (ICS+LABA+LAMA) em combinações livres foi prescrita a cerca de 10% dos doentes (2013-2018 9,1%; 2021 10,0%), no entanto, em combinação fixa foi marginalmente prescrita (2013-2018 0,1%; 2021 1,7%). Quase metade da coorte incidente de 2013-2018 (49,6%) e um quarto da coorte prevalente de 2021 (24,7%) não tinham prescrita medicação inalada.

Conclusão: Os resultados deste estudo fornecem informações sobre o perfil clínico, história de agudizações e padrões terapêuticos dos doentes com DPOC, destacando a necessidade de intervenções integradas, direcionadas e abrangentes para esta população.

Palavras-chave: Doença Pulmonar Obstrutiva Crónica/epidemiologia; Doença Pulmonar Obstrutiva Crónica/tratamento farmacológico.

Introduction

Chronic obstructive pulmonary disease (COPD) is defined "as a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation".[1] The most common respiratory symptoms of this heterogeneous disease are dyspnoea, cough and sputum production, often associated with functional decline and significantly impacting patients' quality of life. Exacerbations and concomitant chronic diseases, such as cardiovascular diseases, skeletal muscle dysfunction, metabolic syndrome, diabetes, osteoporosis, anxiety, depression and lung cancer, are also part of the natural history of COPD, being a major source of morbidity, mortality and consumption of healthcare resources.[1] Worldwide, COPD is the third most common cause of death and it is among the top ten causes of disability-adjusted-life-years, constituting a major current and future health burden.[2,3]

The trajectory of COPD and its associated outcomes can vary markedly across geographic region.[4] Factors such as age, socioeconomic status, sex, geography, and ethnicity significantly influence disparities in access to care and health outcomes.[5] Thus, local epidemiological studies are essential for informing policy decisions and resource allocation for the prevention and management of COPD.

In Portugal, COPD prevalence is estimated to be 14.2% in the population aged 40 years and over.[6] Despite this significant prevalence, there remains a palpable gap in knowledge regarding the disease within the Portuguese population. Existing studies that characterize patients with COPD, their exacerbation histories, and associated comorbidities are generally based on small sample sizes (n=280 to 339),[7–10] limiting the generalizability of their findings. Furthermore, the potential of secondary data analysis of multiple dimensions, namely of longitudinal data from primary and secondary care and medical prescriptions, as performed in other countries, is still to be explored.

Therefore, this study aimed to comprehensively describe the clinical characteristics of patients with COPD within an unselected population of a Portuguese Integrated Health Care Unit across two time periods.

Methods

STUDY DESIGN

A real-world, retrospective, observational, and longitudinal study was conducted using electronic health records (EHR) of adults from the Local Health Unit of Matosinhos (Unidade Local de Saúde de Matosinhos; ULSM). This is a real-world study as it uses real-world data relating to patient health status and the delivery of health care routinely collected in clinical practice.[11] The analysis included two COPD cohorts across two different periods: an incident cohort, comprising data collected from January 1, 2013, to December 31, 2018; and a prevalent cohort, established as of December 31, 2021. The ULSM database included clinical information coded using standardized classifications such as the International Classification of Diseases, Tenth Revision (ICD-10), the International Classification of Diseases, Ninth Revision (ICD-9), Anatomical Therapeutic Chemical (ATC) codes, and the International Classification of Primary Care, Second edition (ICPC-2).

All methods were performed in accordance with the ethical guidelines for human participants. The study received approval by the Ethical Committee and Data Protection Officer of the ULSM (approval code 107/CE/JAS of 16-07-2021 and 23/CLPSI/2021 of 15-10-2021). Patient consent was waived due to the retrospective nature of the study. This study was reported according to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.[12]

STUDY POPULATION

For the incident cohort, the index date was defined as the first recorded COPD diagnosis/code between January 1, 2013, and December 31, 2018. For the prevalent cohort, the index date was December 31, 2021. The pre-index period was set at a minimum of 12 months prior to the index date, though data extending up to 3 calendar years pre-index could be processed. Patients were included in both cohorts if at index date they were alive, were at least 40 years old and fulfilled at least one of the following criteria:

a) A relevant diagnosis code based on the International Classification of Diseases, Ninth and Tenth Revisions, and the International Classification of Primary Care, 2nd edition (relevant codes: ICD-10 J44, ICD-9 496 or ICPC-2 R95);
b) A spirometry report with confirmation of the presence of persistent airflow limitation by a post-bronchodilator forced expiratory volume in the first second [FEV1]/forced vital capacity [FVC] < 0.7 (according to GOLD criteria).[1]
c) One of the following text expressions in the spirometry report: DPOC | COPD | copd | dpoc | obstr.*sem.*resp.*broncodil*.

Patients were excluded if no information about age or sex was found in the EHR and if patients had a prescription of either leukotriene receptor antagonists or inhaled corticosteroids (ICS) alone.

VARIABLES

Data regarding age, sex, tobacco consumption, weight, height, lung function, exacerbations, COPD diagnosis, comorbidities and COPD medication were analysed. The patient's age and sex were determined from the administrative record available in the EHR. The presence of other health conditions was defined using the most comprehensive and granular records available, which included: i) visit and diagnosis data, which were coded using ICPC-2, ICD-9, and ICD-10 codes; ii) laboratory and clinical measurements, coded using ad-hoc vocabularies that were standardized to the systematized nomenclature of medicine clinical terms (SNOMED CT); iii) prescribed medications, coded using the ATC Classification System; and iv) free-text clinical notes from both primary and secondary care. A detailed definition of these variables is shown in Supplementary Table S1.

LUNG FUNCTION

When spirometry detailed reports were available, pre and post bronchodilator FEV1 and FEV1/FVC were analysed. When structured numeric values were not available, we asserted the presence of COPD based on the spirometry report conclusions using regular expression matching rules, derived from predefined text templates used by the spirometry technicians at ULSM.

EXACERBATIONS

Exacerbations were defined as the occurrence of hospitalizations, emergency room (ER) visits, claims for courses of oral corticosteroids and/or respiratory antibiotics. If more than one of these occurred within a 2-week window, this was calculated as one exacerbation. A moderate exacerbation was defined as a COPD-related office/outpatient visit with a prescription for respiratory antibiotics (ATC code J01AA, J01CA, J01CR, J01FA, J01MA) and/or systemic corticosteroids (oral) used within a 7-day window.[13,14] A severe exacerbation was defined as hospitalization (ICD-10-CM code J44 as primary diagnosis or J44.0/J44.[1] as secondary diagnosis) or ER visits (ICD-10-CM code J44.0/J44.[1] in outpatient hospital care).[13,14] Patients were grouped in 5 categories: 0 exacerbations; 1 moderate exacerbation; ≥ 2 moderate exacerbations; 1 severe exacerbation; and ≥ 2 exacerbations, but 1 severe.

COMORBIDITIES

Respiratory (asthma, influenza and pneumonia, other lower respiratory tract infections, lung cancer), cardiovascular (coronary heart disease, atrial fibrillation, heart failure, hypertension), psychiatric (dementia, depression and/or anxiety), and bone (osteoporosis, bone fracture) comorbidities, among others (chronic kidney disease, microvascular disease, obesity, obstructive sleep apnoea, type 2 diabetes), were classified by the ICD-9 and 10 codes.

COPD MEDICATIONS

Medications prescribed at index date and pre-index period (up to 3 calendar years prior to index date) were analysed according to the ATC Classification System. Treatment groups for inhaled medication were mutually exclusive. Patients were assigned to the first applicable treatment option from the following ordered list: ICS + long-acting β-2 agonists (LABA) + long-acting anticholinergics (LAMA) free combinations; ICS + LABA + LAMA fixed combinations; ICS + LABA or ICS + LAMA combinations; LABA + LAMA combination; LABA or LAMA monotherapy; short-acting beta agonists (SABA), short-acting muscarinic antagonist (SAMA) monotherapy. Oral corticosteroids were also registered.

DATA PROCESSING

Data were stored and processed exclusively within the ULSM infrastructure. Researchers had no direct access to the data source. The ULSM maintains a data lakehouse that contains a complete copy of all EHR records structurally formatted according to Observational Medical Outcomes Partnership - Common Data Model (OMOP-CDM).[15] OMOP-CDM is an open-source data standard that enables efficient analysis and reliable evidence using Observational Health Data Sciences and Informatics (OHDSI) standardized vocabularies. Following an 'algorithm-to-data' approach, all processing steps were planned and encapsulated in a study package developed via the SIGIL Scientific Enterprises Vero Framework. This package was compiled for the ULSM infrastructure (Apache Trino, v466) and executed locally. Only

anonymized, aggregated tabular results were exported for researcher analysis, ensuring strict adherence to data privacy protocols.

STATISTICAL ANALYSES

Study variables were summarized for each COPD cohort. Within the 2013–2018 incident cohort, a sub-analysis was conducted to characterize medication patterns stratified by exacerbation frequency. Categorical variables were presented using absolute and relative frequencies. Numerical variables were presented as medians with interquartile ranges (IQR), as the median provides a more representative profile of the patient population. Unlike the mean, the median is robust against outliers and data recording anomalies common in real-world datasets. Due to the descriptive nature of the study's aim, no formal hypothesis testing was employed. Statistical analysis was performed using Apache Spark version 3.2.1 and R version 4.0.

Results

COPD COHORTS

In the incident analysis (2013-2018), a total of 6418 patients fulfilled all inclusion criteria, of whom 722 met at least one exclusion criterion. Therefore, a total of 5696 patients were included in the incident cohort. Patients in the incident cohort had a median age at index of 68 [IQR 18] years, more than two-thirds (68.0%) were male and about one quarter (25.3%) were current smokers (Table 1).

In the 2021 prevalent cohort, a total of 4572 patients fulfilled all inclusion criteria, of whom 1115 met at least one exclusion criterion. Therefore, a total of 3,457 patients were included in

Table 1: Characteristics of patients with chronic obstructive pulmonary disease (COPD) in the 2013-2018 incident cohort (n=5696) and in the 2021 prevalent cohort (n=3457).

	2013-2018 Incident cohort (n=5696)		2021 Prevalent cohort (n=3457)	
Demographic				
Male at index date, n (%)	3871	(68.0%)	2396	(69.3%)
Age at index date, Median (IQR), years	68.0	(18.0)	71.0	(17.0)
BMI closest to index date, Median (IQR), kg/m^2	26.7	(6.8)	26.2	(6.8)
Smoking status closest to index datea, n (%)				
Never smoker	1441	(25.3%)	1715	(49.6%)
Current smoker	1441	(25.3%)	1170	(33.8%)
Former smoker	249	(4.4%)	468	(13.5%)
Unknown	2565	(45.0%)	104	(3.0%)
Lung function closest to index date[b]				
FEV1 pre-bronchodilation L, Median (IQR)	1.8	(0.9)	1.7	(1.0)
FEV1 post-bronchodilation L, Median (IQR)	1.9	(0.9)	1.8	(1.0)
FEV1/FVC pre-bronchodilation % predicted, Median (IQR)	66.9	(12.8)	67.6	(16.3)
FEV1/FVC post-bronchodilation % predicted, Median (IQR)	67.7	(12.6)	67.0	(14.7)
Comorbidities at index date and pre-index period, n (%)				
Asthma	183	(3.2%)	427	(12.4%)
Atrial fibrillation	581	(10.2%)	543	(15.7%)
Bone fracture	58	(1.0%)	102	(3.0%)
CKD	1011	(17.8%)	816	(23.6%)
Dementia	185	(3.3%)	234	(6.8%)
Depression and/or anxiety	1461	(25.7%)	2232	(64.6%)
Heart failure	277	(4.9%)	464	(13.4%)
Hypertension	3079	(54.1%)	2684	(77.6%)
Influenza and pneumonia	224	(3.9%)	568	(16.4%)
Coronary heart disease	201	(3.5%)	359	(10.4%)
Lung cancer	103	(1.8%)	200	(5.8%)
Microvascular disease	207	(3.6%)	365	(10.6%)
Obesity	961	(16.9%)	803	(23.2%)
Osteoporosis	66	(1.2%)	130	(3.8%)
Other lower respiratory infections	262	(4.6%)	500	(14.5%)
Obstructive sleep apnoea	151	(2.7%)	291	(8.4%)
Type 2 diabetes	1816	(31.9%)	1812	(52.4%)

a, missing data for 45.0% of 2013-2018 incident cohort and for 3.0% of 2021 prevalent cohort; b, missing data for 95.9% of 2013-2018 incident cohort and for 87.0% of 2021 prevalent cohort. Abbreviations: BMI, body mass index; CKD, chronic kidney disease; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; IQR, Interquartile range.

the prevalent cohort, with a median age at index of 71 [IQR 17] years. More than two-thirds (69.3%) were male and about one-third (33.8%) were current smokers (Table 1).

COMORBIDITIES

Hypertension (54.1% and 77.6%), type 2 diabetes (31.2% and 52.4%) and depression and/or anxiety (25.7% and 64.6%) were the three most common comorbidities in both the incident and prevalent cohorts, respectively (Table 1). Other relevant comorbidities identified in both cohorts included CKD (17.8% and 23.6%) and obesity (16.9% and 23.2%) (Table 1).

EXACERBATION HISTORY

Exacerbation history in both cohorts is presented in Fig. 1. In the 2013-2018 incident cohort, 59.7% of patients experienced at least one moderate or severe exacerbation in the 365-days before index date: 16.4% had experienced one moderate exacerbation, 6.4% two or more moderate exacerbations (but no severe), 31.8% one severe exacerbation and 5.1% two or more exacerbations, but at least one severe (Fig. 1).

In the 2021 prevalent cohort, 76.7% of patients experienced at least one moderate or severe exacerbation in the 365-days before the index date. Of these, 16.6% had experienced two or more exacerbations, with at least one being severe (Fig. 1).

MEDICATION

Table 2 presents the medication prescribed at the index date and the pre-index period for both analysed COPD cohorts. A total of 50.4% in the 2013-2018 incident cohort and 75.3% in the 2021 prevalent cohort were treated with at least one inhaled medication (Table 2). ICS with LABA or LAMA was the most frequent treatment option, prescribed to 23.2% of the incident cohort and 36.1% of the prevalent cohort. Triple combination therapy (both free and fixed combinations) was prescribed to 9.2% of the 2013-2018 incident cohort and 11.7% of the 2021 prevalent cohort (Table 2).

A sub-analysis of the 2013-2018 incident cohort demonstrated an association between exacerbation severity/frequency and medication complexity (Fig. 2). In patients with 2+ moderate exacerbations and 2+ exacerbations (including 1 severe), triple therapy reached 25.1% and 15.8%, while oral corticosteroids use reached 54.0% and 80.1%, respectively, surpassing the rates seen in other groups. Conversely, patients with no exacerbations were more often on simpler therapies, including monotherapy (18.5% *vs* 8.0%-15.3% in the other exacerbation cohorts; Fig. 2).

Discussion

This study provides a comprehensive characterization of patients with COPD in a Portuguese Integrated Health Care Unit over two periods, leveraging large, unselected cohorts. Our findings offer valuable insights into the clinical profile of patients with COPD, their exacerbation history, comorbidities, and treatment patterns.

A large proportion of patients experienced at least one moderate or severe exacerbation in the year prior to index date

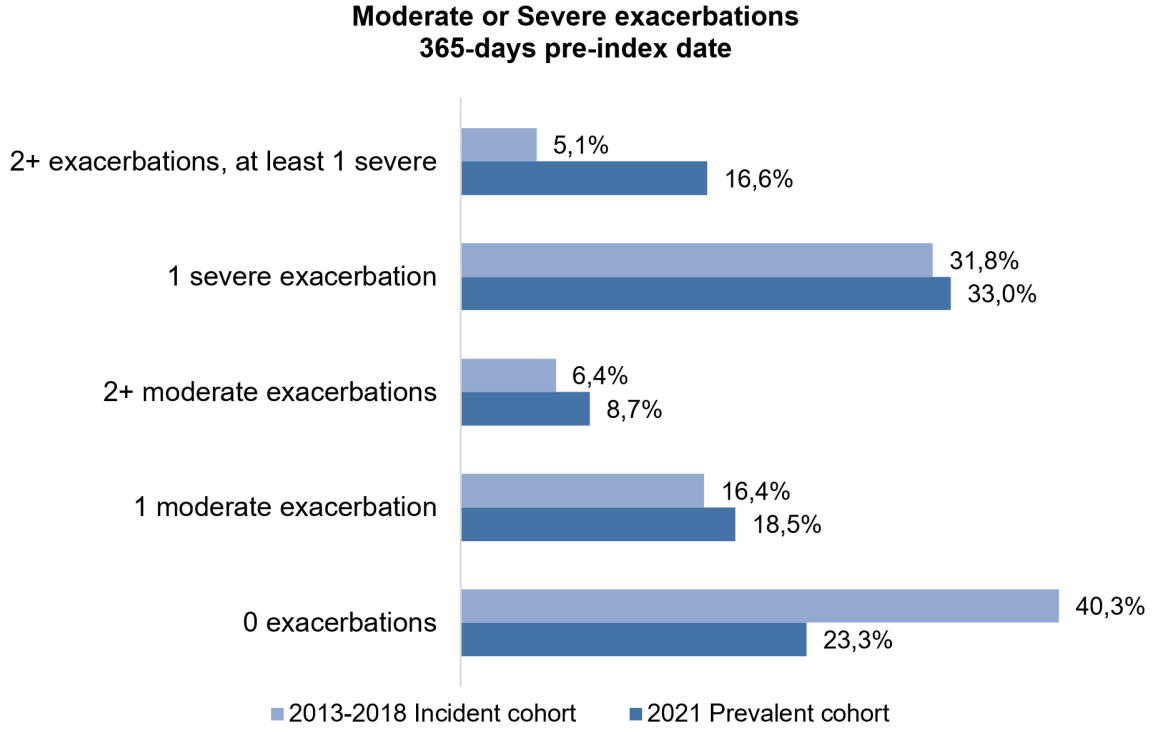

Figure 1: Frequency of moderate or severe exacerbations 365-days pre-index date. Data are presented for the chronic obstructive pulmonary disease (COPD) incident cohort (2013–2018; n=5696) and the 2021 prevalent cohort (n=3457).

Table 2: Chronic obstructive pulmonary disease (COPD) medication at index date and pre-index period in the 2013-2018 incident cohort (n=5696) and in the 2021 prevalent cohort (n=3457).

	2013-2018 Incident cohort (n=5696)		2021 Prevalent cohort (n=3457)	
COPD Medication at index date and pre-index period (up to 3 calendar years prior to index date)*, n (%)				
Any COPD Inhaled Medication	2871	(50.4%)	2602	(75.3%)
ICS + LABA + LAMA free combinations	520	(9.1%)	346	(10.0%)
ICS + LABA + LAMA fixed combinations	7	(0.1%)	60	(1.7%)
ICS + LABA or ICS + LAMA combinations	1324	(23.2%)	1248	(36.1%)
LABA + LAMA combination	176	(3.1%)	291	(8.4%)
LABA or LAMA monotherapy	787	(13.8%)	604	(17.5%)
SABA or SAMA monotherapy	57	(1.0%)	53	(1.5%)
OCS	690	(12.1%)	1718	(49.7%)

Abbreviations: ICS, Inhaled corticosteroids; LABA, Long-acting β-2 agonists; LAMA, Long-acting anticholinergics; SABA, Short-acting beta agonists; SAMA, Short-acting muscarinic antagonists; OCS, Oral corticosteroids systemic. *Treatment groups for inhaled medication were mutually exclusive. Patients were assigned to the first applicable treatment option from the following ordered list: ICS + LABA + LAMA free combinations; ICS + LABA + LAMA fixed combinations; ICS + LABA or ICS + LAMA combinations; LABA + LAMA combination; LABA or LAMA monotherapy; SABA or SAMA monotherapy.

(2013-2018 incident cohort 59.7% and 2021 prevalent cohort 76.7%) and more than one third (2013-2018 incident cohort 36.9% and 2021 prevalent cohort 49.6%) had severe exacerbations. This high exacerbation rate is higher than findings from international cohorts[13,16] and highlights the significant disease burden in this population. The group of patients with severe exacerbations may represent a high-risk phenotype requiring targeted interventions to reduce hospitalizations and mortality.

Almost half of the 2013-2018 incident cohort and a quarter of the 2021 prevalent cohort received no inhaled medication. This underscores a critical gap in disease management within the Portuguese healthcare system, suggesting potential

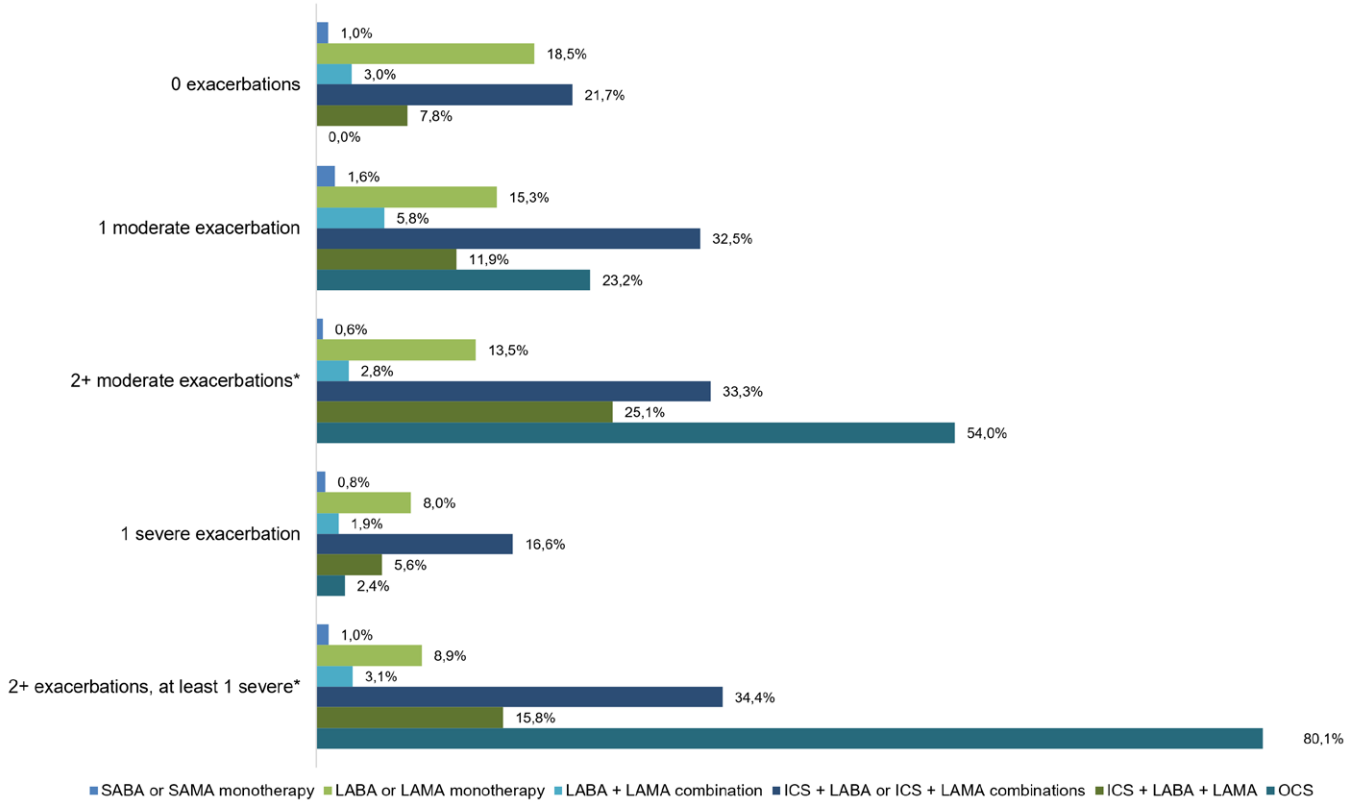

Figure 2: Distribution of chronic obstructive pulmonary disease (COPD) medication at index date and pre-index period. Data stratified by exacerbation severity groups for the w2013–2018 incident cohort (n=5696).

Abbreviations: ICS, Inhaled corticosteroids; LABA, Long-acting β-2 agonists; LAMA, Long-acting anticholinergics; SABA, Short-acting beta agonists; SAMA, Short-acting muscarinic antagonists; OCS, Oral corticosteroids systemic).

lack of adherence to guideline-directed therapy.[1] Part of this finding may also reflect coding bias, as some patients included in the sample may have been incorrectly coded as having COPD. COPD-specific training programs should be implemented for healthcare providers across primary and secondary care, not only on early pharmacological intervention aligned with current guidelines but also on the accurate coding of diagnoses in EHR. The trends in COPD treatment choices have changed significantly over the last decade, as several important randomized controlled trials were published, showing beneficial effects of a combination of medication, such as LABA +/- ICS and LAMA on symptoms and exacerbation rates.[17–20] After the FLAME trial, we have assisted a change towards a preferred indication for LAMA+LABA over LABA+ICS and a decreased suggestion for initial ICS usage because of the increased pneumonia risk addressed in some studies.[19] In our cohorts, the combination of LABA or LAMA plus ICS (2013-2018, 23.2%, 2021 36.1%) was the most common inhaler combination.[21] In a Canadian retrospective study using administrative health databases, ICS was the most commonly used inhaled medication (49.9%), but this high frequency may be related to the higher time period analysed (1997–2015).[22] GOLD guidelines now advocate for a stepwise approach to therapy based on the level of symptoms and risk of exacerbations, escalating from single-agent inhalers (e.g., LABA) to combination therapies (e.g., LABA+LAMA) and eventually to triple therapy (ICS+LABA+LAMA) for the most complex and severe cases (predominant symptoms, multiple comorbidities, persistent exacerbations).[1] Triple therapy in free combinations was prescribed to around 10% of patients. Fixed triple therapy was marginally prescribed (2013-2018 0.1%, 2021 1.7%) as expected, as fixed triple therapy was only available in Portugal from 2019 onwards. This result may evolve as more evidence is gathered to demonstrate the real-world impact of fixed options on patients' adherence and inhaler use.[23] Furthermore, as expected, the history of exacerbations was linked with the treatment escalation in COPD. Our sub-analysis across the exacerbation groups of the 2013-2018 incident cohort showed that more complex regimens, including triple therapy (both free and fixed) or oral corticosteroids, were prescribed with greater frequency to patients experiencing more frequent and severe exacerbations. This finding aligns with established clinical guidelines that advocate for treatment escalation in individuals with a higher exacerbation burden.[1]

Our results suggest that some patients may be experiencing undertreatment, highlighting an important opportunity to further optimize management strategies and improve outcomes. The need for robust disease control in patients with recurrent exacerbations underscores the importance of more aggressive therapeutic strategies to prevent future events and improve their quality of life. This link between treatment complexity and exacerbation history emphasizes the critical role of personalized and dynamic therapeutic approaches, tailored to the severity of the disease and the patient's risk profile. In addition to medication prescribed, it would also be interesting to evaluate in future research access to non-pharmacological treatments, such as smoking cessation, vaccination, or pulmonary rehabilitation, as they may also impact the rate of exacerbations.

Regarding comorbidities, more than half of our patients were affected by hypertension which is in concordance with the epidemiology of hypertension.[24,25] Patients with COPD also presented a high prevalence of other cardiovascular diseases, such as diabetes and chronic kidney disease.[13,24] A slight higher prevalence of depression and anxiety was demonstrated in our cohorts, when compared with international data,[13,24] but aligned with previous national estimates.[9] These findings are consistent with other studies, and further highlight the multi-systemic nature of the comorbidity burden of COPD and the need for comprehensive and integrated management approaches addressing both physical and psychological health. We observed a higher frequency of comorbidities, such as depression/anxiety and influenza/pneumonia, within the incident cohort. These differences likely stem from both methodological and temporal factors. Specifically, while the incident cohort characterizes patients at the time of diagnosis, the prevalent cohort includes individuals under longitudinal follow-up. This greater cumulative exposure to healthcare services naturally increases the probability of capturing additional diagnoses over time. Furthermore, as clinical guidelines have increasingly emphasized the multimorbid nature of COPD, the higher frequency noted in our more recent 2021 cohort likely reflects temporal improvements in disease codification and diagnostic capture within EHR.

Our study confirms that COPD is more frequent in men (2013-2018 68.0%, 2021 69.3%) and in older patients (2013-2018 median 68 years; 2021 median 71 years).[26] Notably, almost one third (2013-2018 25.3%, 2021 33.8%) were current smokers, suggesting persistent tobacco exposure despite COPD diagnosis. This underscores the need for reinforced smoking cessation interventions in clinical practice, as smoking remains a key modifiable risk factor for disease progression. One unexpected finding of our analysis was the low percentage of former smokers (2013-2018 4.4%, 2021 13.5%).[27,28] The low percentage of former smokers may be partly linked with the underreporting of smoking status in EHR or to our processing methodology. Since our analysis relied solely on standardized, structured codes, it did not capture smoking habits if they were reported in free-text fields. This suggests that the actual percentage of smokers in the cohort may be higher than recorded.[29] Future real-world studies should integrate both standardized codes and free-text search to enhance data capture and improve the completeness of clinical risk factor assessment. Nevertheless our data may also demonstrate that, besides smoking, other factors, for example genetic susceptibility, impaired lung growth, respiratory infections and environmental exposures including occupational exposures and (outdoor and indoor) air pollution may contribute to the development of this disease.[26]

STRENGTHS AND LIMITATIONS

Our study included two periods of patient real-world data and was driven from a health unit that integrates both primary and secondary care, thus being closer to the representativeness of the COPD population than previous datasets from only one of those settings. COPD clinical characteristics found in our population may be considered representative of the North region, but caution needs to be taken before extrapolating the results nationwide. The ULSM population is predominantly urban and benefits from extensive primary healthcare coverage, factors that may differ significantly in other Portuguese regions with distinct demographic and healthcare delivery profiles. The decision not to rely solely on spirometry results to identify patients with COPD can be viewed as a strength, reflecting the realities of clinical practice data. A strict spirometry-based inclusion criterion would have led to a limited sample size due to missing values, severely compromising the representativeness of the COPD population within the ULSM database. The low availability of spirometry data was expected, primarily reflecting the absence of dedicated fields for recording spirometry data. This challenge is not unique to our context, as two reviews found that fewer than 13% of studies utilized spirometry findings to identify COPD in health systems.[30,31] We recognized that relying solely on ICD-10 J44 (and its equivalents, ICD-9 496 and ICPC-2 R95) could potentially lead to missed patients with COPD, as related conditions (e.g., J41, J42, J43; ICD-9 codes 491, 492) also capture relevant cases.[30,31] Nevertheless, the multi-faceted approach, which combined disease codes with spirometry results and/or their textual interpretation to identify incident cases, along with exclusion criteria to avoid the wrongful inclusion of asthma, reduced misclassification and potential biases. This approach aligns with previous research suggesting that combining multiple criteria improves COPD patient detection.[30] Despite knowing that even mild exacerbations impact patients' health, we focused on moderate and severe exacerbations due to the inherent difficulty in identifying mild events from EHR. These mild episodes are often self-managed and under-reported.[32,33] Future research in this cohort can also address questions such as characterization of patient journey in this real-world setting and specifically the impact of exacerbations in the risk of future events (exacerbations, cardiovascular events, death). The high proportion of oral corticosteroids systemic treatment reported in our cohorts likely overestimates the rate of chronic or maintenance oral corticosteroids systemic use as it includes short-course pulses given during exacerbations. This potential overestimate must be considered when interpreting our findings on oral corticosteroid systemic exposure.

Conclusion

This real-world study provides a comprehensive characterization of patients with COPD in a Portuguese integrated care setting, revealing critical insights into disease burden, treatment patterns, and comorbidities. The high exacerbation rate, particularly severe exacerbations, underscores the need for targeted interventions. The striking finding that at least a quarter of patients received no inhaled medication highlights gaps in guideline-adherent care, calling for improved clinician education and multidisciplinary collaboration. The predominance of cardiovascular and mental health comorbidities further reinforces the necessity of integrated care models that address COPD as part of a multimorbid disease spectrum. ■

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Conflicts of interest

MP, JM, IE, HM, CA and F.B. are employees of Astrazeneca Portugal.
ALF: Acknowledges the participation on Data Safety Monitoring/Advisory Boards from GSK, Recordati; support for attending meetings and/or travel from Astrazeneca, Boehringer Ingelheim, Vivisol, Dar Saúde, GSK, Gasoxmed; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Astrazeneca, GSK, Boehringer Ingelheim, Sanofi, Recordati and Medinfar; and payment for expert testimony from GSK, Astrazeneca and Boehringer Ingelheim. C.P. reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events; and support for attending meetings and/or travel by Astrazeneca. M.B. reports support for attending meetings and/or travel from Astrazeneca; Bial and Nestle. The remaining authors have no conflicts of interest to declare.

Contributorship Statement

PS, ALF, CP, DSS, MB, MP, FB - Study conception and design, interpretation of data, critical revision of the manuscript
JM, IE, CA, HM - Interpretation of data, critical revision of the manuscript for important intellectual content
RA, RL - Developed the analytical code, interpretation of data, and critical revision of the manuscript for important intellectual content
CJ - Wrote the first draft, interpretation of data, and critical revision of the manuscript for important intellectual content
All authors contributed to the interpretation of data, to the critical revision of the manuscript for important intellectual content; all approved the final version for submission; and all attests that listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaração de Contribuição

PS, ALF, CP, DSS, MB, MP, FB – Conceção e desenho do estudo, interpretação dos dados e revisão crítica do manuscrito.
JM, IE, CA, HM – Interpretação dos dados e revisão crítica do manuscrito quanto ao seu conteúdo científico relevante.
RA, RL – Desenvolvimento do código analítico, interpretação dos dados e revisão crítica do manuscrito quanto ao seu conteúdo científico relevante.
CJ – Redação da primeira versão do manuscrito, interpretação dos dados e revisão crítica do manuscrito quanto ao seu conteúdo científico relevante.
Todos os autores contribuíram para a interpretação dos dados e para a revisão crítica do manuscrito quanto ao seu conteúdo científico relevante;

todos aprovaram a versão final para submissão; e todos atestam que os autores listados cumprem os critérios de autoria e que nenhum outro que cumpra esses critérios foi omitido.

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REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2025. [accessed March 19 2025] Available at: https://goldcopd.org/2025-gold-report/
2. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392: 1859–922.
3. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020; 396: 1204–22. doi: 10.1016/S0140-6736(20)30925-9.
4. Robichaux C, Aron J, Wendt CH, Berman JD, Rau A, Bangerter A, et al. Sociodemographic and Geographic Risk Factors for All-Cause Mortality in Patients with COPD. Int J Chron Obstruct Pulmon Dis. 2023;18:1587-93. doi: 10.2147/COPD.S406899.
5. Shatto JA, Stickland MK, Soril LJJ. Variations in COPD health care access and outcomes: A rapid review. Int J Chron Obstruct Pulmon Dis. 2024; 11: 229–46. doi: 10.15326/jcopdf.2023.0441.
6. Bárbara C, Rodrigues F, Dias H, Cardoso J, Almeida J, Matos MJ, et al. Chronic obstructive pulmonary disease prevalence in Lisbon, Portugal: the burden of obstructive lung disease study. Rev Port Pneumol. 2013;19:96-105. doi: 10.1016/j.rppneu.2012.11.004. .
7. Marote Correia L, Chaves S, Pestana A, et al. Exacerbações de Doença Pulmonar Obstrutiva Crónica num Serviço de Medicina Interna: Caracterização e Preditores de Prognóstico. Med Interna. 2017;24:182-90. doi: 10.24950/rspmi/216/2017.
8. Silva L, Mota Â, Lemos L, Santos M, Cunha H, Maricoto T, et al. Characterisation of Patients With Chronic Obstructive Pulmonary Disease (COPD) From an Urban Municipality in the Northern Region of Portugal: A Cross-Sectional Study. Cureus. 2024;16:e59262. doi: 10.7759/cureus.59262.
9. Jácome C, Marques A, Gabriel R, Cruz J, Figueiredo D. Anxiety and depression in Portuguese patients with chronic obstructive pulmonary disease: a multicentre cross-sectional study. Rev Port Med Geral Fam. 2015; 31: 24–32.
10. Duarte-de-Araújo A, Teixeira P, Hespanhol V, Correia-de-Sousa J. COPD: Analysing factors associated with a successful treatment. Pulmonology. 2020; 26: 66–72. doi: 10.1016/j.pulmoe.2019.05.012.
11. Liu F, Panagiotakos D. Real-world data: a brief review of the methods, applications, challenges and opportunities. BMC Med Res Methodol. 2022; 22: 287. doi: 10.1186/s12874-022-01768-6.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007; 335: 806–8. doi: 10.1136/bmj.39335.541782.AD.
13. Vogelmeier CF, Diesing J, Kossack N, Pignot M, Friedrich FW. COPD Exacerbation History and Impact on Future Exacerbations - 8-Year Retrospective Observational Database Cohort Study from Germany. Int J Chron Obstruct Pulmon Dis. 2021;16:2407-17. doi: 10.2147/COPD.S322036
14. Vogelmeier CF, Friedrich FW, Timpel P, Kossack N, Diesing J, Pignot M, et al. Impact of COPD on mortality: An 8-year observational retrospective healthcare claims database cohort study. Respir Med. 2024;222:107506. doi: 10.1016/j.rmed.2023.107506.
15. OMOP Common Data Model, OMOP CDM v5.4, [accessed December 6, 2023] Available at: https://ohdsi.github.io/CommonDataModel/cdm54.html
16. Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. Lancet Respir Med. 2017;5:619-26. doi: 10.1016/S2213-2600(17)30207-2.
17. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775-89. doi: 10.1056/NEJMoa063070.
18. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Mölken MP, Beeh KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364:1093-103. doi: 10.1056/NEJMoa1008378.
19. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016;374:2222-34. doi: 10.1056/NEJMoa1516385.
20. Roche N, Aguilaniu B, Zhi Li P, Hess D; COLIBRI collaborators. Trends over time in COPD treatment choices by respiratory physicians: An analysis from the COLIBRI-COPD French cohort. Respir Med. 2019;156:8-14. doi: 10.1016/j.rmed.2019.07.023 .
21. Park HJ, Lee JU, Jeon S, Lee HS, Kim BY, Chae YJ, et al. Prescription patterns and effectiveness of medications for chronic obstructive pulmonary disease: A retrospective study of real-world settings. PLoS One. 2024;19:e0304362. doi: 10.1371/journal.pone.0304362.
22. Bahremand T, Etminan M, Roshan-Moniri N, De Vera MA, Tavakoli H, Sadatsafavi M. Are COPD Prescription Patterns Aligned with Guidelines? Evidence from a Canadian Population-Based Study. Int J Chron Obstruct Pulmon Dis. 2021;16:751-9. doi: 10.2147/COPD.S290805.
23. Richeldi L, Schino P, Bargagli E, Ricci A, Rocca A, Marchesani F, et al. TRI-TRIAL: The Impact of Fixed Triple Therapy with Beclometasone/Formoterol/Glycopyrronium on Health Status and Adherence in Chronic Obstructive Pulmonary Disease in an Italian Context of Real Life. Int J Chron Obstruct Pulmon Dis. 2024;19:475-87. doi: 10.2147/COPD.S445858.
24. Greulich T, Weist BJ, Koczulla AR, Janciauskiene S, Klemmer A, Lux W, et al. Prevalence of comorbidities in COPD patients by disease severity in a German population. Respir Med. 2017;132:132-8. doi: 10.1016/j.rmed.2017.10.007.
25. Rodrigues AP, Gaio V, Kislaya I, Graff-Iversen S, Cordeiro E, Silva AC, et al. Sociodemographic disparities in hypertension prevalence: Results from the first Portuguese National Health Examination Survey. Rev Port Cardiol. 2019;38:547-55. doi: 10.1016/j.repc.2018.10.012.
26. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al. Global

and regional estimates of COPD prevalence: Systematic review and meta-analysis. J Glob Health. 2015;5:020415. doi: 10.7189/jogh.05.020415..
27. Terzikhan N, Verhamme KM, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. Eur J Epidemiol. 2016;31:785-92. doi: 10.1007/s10654-016-0132-z.
28. Tan WC, Sin DD, Bourbeau J, Hernandez P, Chapman KR, Cowie R, et al. Characteristics of COPD in never-smokers and ever-smokers in the general population: results from the CanCOLD study. Thorax. 2015;70:822-9. doi: 10.1136/thoraxjnl-2015-206938.
29. Polubriaginof F, Salmasian H, Albert DA, Vawdrey DK. Challenges with Collecting Smoking Status in Electronic Health Records. AMIA Annu Symp Proc. 2018;2017:1392-400.
30. Gothe H, Rajsic S, Vukicevic D, Schoenfelder T, Jahn B, Geiger-Gritsch S, et al. Algorithms to identify COPD in health systems with and without access to ICD coding: a systematic review. BMC Health Serv Res 2019; 19: 737. doi: 10.1186/s12913-019-4574-3.
31. Sivakumaran S, Alsallakh MA, Lyons RA, Quint JK, Davies GA. Identifying COPD in routinely collected electronic health records: a systematic scoping review. ERJ Open Res 2021; 7: 00167–02021. doi: 10.1183/23120541.00167-2021.
32. Langsetmo L, Platt RW, Ernst P, Bourbeau J. Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort. Am J Respir Crit Care Med 2008; 177: 396–401. doi: 10.1164/rccm.200708-1290OC.
33. Jones PW, Lamarca R, Chuecos F, Singh D, Agustí A, Bateman ED, et al. Characterisation and impact of reported and unreported exacerbations: results from ATTAIN. Eur Respir J. 2014; 44: 1156–65. doi: 10.1183/09031936.00038814.

Supplementary Material

Table S1: Study variable definitions.

Age	Ad-hoc vocabulary
Antileukotrienes	ATC Code R03DC (including children codes)
Arteriosclerotic disease	Meeting criteria for either "Unstable Angina", "Myocardial Infarction", "Ischemic Stroke" or "Peripheral Artery Disease"
Asthma	ICD-9 code 493 ICD-10 code J45 ICPC-2 code R96
Atrial fibrillation	ICD-9 code 427.3 ICD-10 code I48 ICPC-2 code K78
BMI	Weight/Height^2, ad-hoc vocabulary Unit kg/m2
Bone comorbidities	Presence of Osteoporosis and/or Bone Fracture
Bone fracture	ICD-9 codes 733.14, 733.96, 820 ICD-10 code S72.00
Bronchiectasis	ICD-9 code 494 ICD-10 code J47
CV death	Having one of the following diagnosis codes: ICD-9 codes 41, 43 ICD-10 code I AND having been discharged to morgue
CV comorbidities	Presence of at least one of the following conditions: Atrial Fibrillation, CKD, Heart Failure, Hypercholesterolemia, Microvascular Disease, Hypertension, Myocardial Infarction, Coronary Heart Disease, Stroke, Angina Unstable, Peripheral Artery Disease, Obesity, Type 2 Diabetes Mellitus, Peripheral Artery Disease
CKD	Having at least one of the following codes in the EHR: ICD-9 codes 583.81, 250.4, 585 ICD-10 codes E10.2, E11.2, E12.2, E13.2, E14.2, I12.0, I12.9, I13.1, I13.2, N00, N01, N02, N03, N04, N05, N06, N07, N08, N10, N11, N12, N13, N14, N15, N16, N17, N18, N19, Z49, Z99.2 AND/OR Having at least one of the following laboratory measurements: - Estimated Glomerular Filtration Rate equal or inferior to 60 mL/min/1.73m^2 Urine Albumin-Creatinine Ratio equal or superior to 30 mg/g
Coronary heart disease	Defined as the presence of codes for either Unstable Angina or Myocardial Infarction: ICD-9 codes 410, 411 ICD-10 codes I20.0, I21, I22, I25.2, I25.6 ICPC-2 codes K74, K75
Crohn disease	ICD-9 code 555 ICD-10 code K50
CV disease	ICD-9 codes 41, 43 ICD-10 code I
Cystic fibrosis	ICD-9 code 277.0 ICD-10 code E84
Death	Having a Date of Death within study period.
Dementia	ICD-9 codes 331.0, 290, 291.2, 292.82, 294.1, 294.2, 331.1 ICD-10 codes G30, F00, F01, F02, F03 ICPC-2 code P70
Depression and anxiety (Major psychiatric disorder)	ICD-9 codes 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 30, 31 ICD-10 codes F0, F1, F2, F3, F4, F5, F6, F7, F8, F9 ICPC-2 codes p70, p71, p73, p74, p75, p76, p77, p78, p79, p80, p81, p83, p84, p85, p86, p87, p88, p89, p90, p91, p93, p94, p95, p96, p97, p98, p99
Emphysema	ICD-9 code 492 ICD-10 code J43

ATC, Anatomical Therapeutic Chemical; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; EHR, electronic health record; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; ICS, inhaled corticosteroids; LABA, long-acting β 2-agonist; LAMA, long-acting muscarinic antagonist; MACE, major adverse cardiovascular event; SABA, short-acting β 2-agonist; SAMA, short-acting muscarinic antagonist.

Age	Ad-hoc vocabulary
Heart failure	Having at least one of the following codes in the EHR: ICD-9 code 404.03, 404.13, 404.93, 428 ICD-10 code I11.0, I13.0, I13.2, I50 ICPC-2 code K77 AND/OR Having Heart failure with reduced ejection fraction or with no reduced ejection fraction, defined as: **Heart failure with reduced ejection fraction:** Left ventricular ejection fraction < 40% and either: • N-terminal pro-B-type natriuretic peptide ≥ 400 pg/mL (≥ 600 pg/mL if atrial fibrillation) • B-type natriuretic peptide ≥ 100 pg/mL (≥ 125 pg/mL if atrial fibrillation) **Heart failure with no reduced ejection fraction:** Left ventricular ejection fraction ≥ 40% + at least 1 structural cardiac abnormality and either: • N-terminal pro-B-type natriuretic peptide ≥200 pg/mL (≥ 600 pg/mL if atrial fibrillation /flutter) • B-type natriuretic peptide ≥ 100 pg/mL (≥125 pg/mL if atrial fibrillation /flutter)
Hemorrhagic stroke	ICD-9 codes 430, 431, 432 ICD-10 codes I60, I61, I62
Hypercholesterolemia	Total cholesterol > 190 mg/dL, ad-hoc vocabulary
Hypertension	ICPC-2 codes K86, K87 AND/OR Having 2 Systolic Blood Pressure observations equal or above 140 mmHg registered at least 7 days apart AND/OR Having 2 Diastolic Blood Pressure observations equal or above 90 mmHg registered at least 7 days apart
ICS + LABA + LAMA fixed combinations	Triple therapy in a fixed-dose combination in a single inhalation device at pre-index period and index date
ICS + LABA + LAMA free combinations	Triple therapy in a free-dose combination (using distinct inhalation devices, prescribed within a 90-day period) at pre-index period and index date
Influenza	ICD-9 codes 487, 488 ICD-10 codes J09, J10, J11 ICPC-2 code R80
ICS	ATC Codes (including children codes): R03BA01 R03BA02 R03BA03 R03BA04 R03BA05 R03BA06 R03BA07 R03BA08 R03BA09
Ischemic stroke	ICD-9 codes 433, 434, 435, 436, 437, 438 ICD-10 codes I63, I65, I66
LAMA	ATC Codes (including children codes): R03BB01 R03BB04 R03BB05 R03BB06 R03BB07
LABA	ATC Codes (including children codes): R03AC12 R03AC13 R03AC18 R03AC19
Lung cancer	ICD-9 codes 162, V101, V101.1 ICD-10 code C34 ICPC-2 code R84, R85
Median Tiffeneau index (FEV1/FVC)	Ad-hoc vocabulary Information available closest to index date
Microvascular disease	ICD-9 codes 250.4, 250.5, 250.7, 352, 354, 355, 357.2, 362.07, 365.44, 366.41, 583.81, 713.5 ICD-10 codes E10.2, E10.3, E10.4, E10.5, E11.2, E11.3, E11.4, E11.5, E11.6, E12.2, E12.3, E12.4, E12.5, E13.2, E13.3, E13.4, E13.5, E14.2, E14.3, E14.4, E14.5, G59, G60, G99.0, H35.0, H35.1, H36, L98.4, M14.2, M14.6, M90.8, N08.3
Moderate exacerbation	A moderate exacerbation is defined as a claim of oral systemic corticosteroids (ATC code H02AB) or respiratory antibiotics (ATC codes J01AA, J01CA)
Myocardial infarction	ICD-9 codes 410 ICD-10 codes I21, I22, I25.2, I25.6 ICPC-2 code K75
Obesity	BMI equal or superior to 30
Obstructive sleep apnea	ICD-9 code 327.23 ICD-10 code G47.33
Oral systemic corticosteroids	ATC Codes (including children codes): H02AB
Osteoporosis	ICD-9 codes 733.0, 733.96 ICD-10 codes M80, M81 ICPC-2 code L95
Other respiratory tract infections / Respiratory infection	ICD-9 codes 466.0, 482.84 ICD-10 codes J20, J22 ICPC-2 code R83
Peripheral artery disease	ICD-9 codes 440, 441, 444 ICD-10 codes I70.2, I73.9, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9 ICPC-2 code K92
Pneumonia	ICD-9 codes 487, 488 ICD-10 codes J10.0, J11.0, J12, J13, J14, J15, J16, J17, J18, J85.1 ICPC-2 code R81
Polymyalgia rheumatica	ICD-9 code 725 ICD-10 code M35.3
Psychiatric comorbidities	Presence of major psychiatric disorder and/or dementia
Respiratory comorbidities	At least one of the following conditions: asthma, bronchiectasis, emphysema, influenza, pneumonia, lung cancer, other respiratory tract infections and/or obstructive sleep apnea.
Respiratory infection	ICPC-2 codes R75 or R83 recorded more than once within a 365-day period

ATC, Anatomical Therapeutic Chemical; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; EHR, electronic health record; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; ICS, inhaled corticosteroids; LABA, long-acting β 2-agonist; LAMA, long-acting muscarinic antagonist; MACE, major adverse cardiovascular event; SABA, short-acting β 2-agonist; SAMA, short-acting muscarinic antagonist.

Age	Ad-hoc vocabulary
Rheumatoid arthritis	ICD-9 code 714.0 ICD-10 code M05
Risk factor for malignancy	ICPC-2 code A21
Severe exacerbation	A severe exacerbation is defined as an hospitalization with NICD-10 code J44 as primary diagnosis or J44.0/J44.1 as secondary diagnosis or an emergency visit (ICD-10-CM code J44.0/J44.1 in outpatient hospital care)
Sex	Ad-hoc vocabulary
SAMA	ATC Codes (including children codes): R03BB01
SABA	ATC Codes (including children codes): R03AC02 R03AC03 R03AC04
Smoking status	Ad-hoc vocabulary and/or ICPC-2 code P17
Stable angina	ICD-9 codes 413, 414.0 ICD-10 codes I20.1, I20.8, I20.9, I25.1, I25.5 ICPC-2 code K76

Age	Ad-hoc vocabulary
Stroke	Meeting criteria for either “Ischemic Stroke” or “Hemorrhagic Stroke”
Transient ischemic attack	ICD-9 code 435 ICD-10 codes G45 ICPC-2 code K89
Type 2 diabetes	Not having a code for Type 1 Diabetes Mellitus in the EHR and Having at least one of the following laboratory measurements: - Glycated hemoglobin equal or superior to 6.5% - Glucose superior to 200mg/dL AND/OR Having a prescription for a glucose lowering drug excluding Biguanides
Ulcerative colitis	ICD-9 code 556 ICD-10 code K51
Unstable angina	ICD-9 code 411 ICD-10 code I20.0 ICPC-2 code K74
(3-Point) MACE	Composite outcome of myocardial infarction, stroke and peripheral artery disease

ATC, Anatomical Therapeutic Chemical; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; EHR, electronic health record; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; ICS, inhaled corticosteroids; LABA, long-acting β 2-agonist; LAMA, long-acting muscarinic antagonist; MACE, major adverse cardiovascular event; SABA, short-acting β 2-agonist; SAMA, short-acting muscarinic antagonist.

LOCAL HEALTH UNIT OF MATOSINHOS CONSTITUTION

Local Health Unit of Matosinhos (ULSM) provides primary, differentiated and continuous healthcare. Its area of influence corresponds to the municipalities of Matosinhos, Vila do Conde and Póvoa de Varzim.

ULSM UNITS

- **Pedro Hispano Hospital**
- **Health Care Center Leça da Palmeira**
  - Family Health Unit Leça
  - Family Health Unit Maresia
  - Family Health Unit Dunas
  - Family Health Unit Progresso
  - Primary Care Unit Santa Cruz
  - Continuity Care Unit Leça
- **Health Care Center Matosinhos**
  - Family Health Unit Horizonte
  - Family Health Unit Oceanos
  - Primary Care Unit Matosinhos
  - Continuity Care Unit Matosinhos
- **Health Care Center Senhora da Hora**
  - Family Health Unit Caravela
  - Family Health Unit Lagoa
  - Family Health Unit Custóias
  - Continuity Care Unit Senhora da Hora
- **Health Care Center S. Mamede de Infesta**
  - Family Health Unit Infesta
  - Family Health Unit Porta do Sol
  - Primary Care Unit S. Mamede
  - Continuity Care Unit S. Mamede