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ORIGINAL RESEARCH

Economic Burden of Uncontrolled COPD Under Triple Therapy: A Population-Based Study

Nicolas Molinari[1], Nicolas Roche[2], Anne-Lise Vataire[3], Stanislas Perrier[3], Nicolas Pagès[4], Arnaud Panes[4], Aurélie Schmidt[4], Arnaud Bourdin[5,6], Laurence Watier[7]

[1]IDESP, INSERM, PreMEdical INRIA, Univ Montpellier, CHU Montpellier, Montpellier, France; [2]Department of Respiratory Medicine; APHP Centre, Institut Cochin (UMR 1016), Assistance Publique-Hôpitaux de Paris, Cochin Hospital, University Paris Cité, Paris, France; [3]HEOR, Sanofi, Paris, France; [4]Department of Epidemiology, HEVA, Lyon, France; [5]Department of Respiratory Diseases, Phymedexp, INSERM, CNRS, CHU de Montpellier, Université de Montpellier, Montpellier, France; [6]Département of Pneumology and Addictology; CHU de Montpellier-Hôpital Arnaud de Villeneuve, Montpellier, France; [7]Epidemiology and Modelling of Bacterial Escape to Antimicrobials, Institut Pasteur, Paris, France

Correspondence: Stanislas Perrier, Email stanislas.perrier@sanofi.com

Objective: This study aimed to provide real-life data on COPD healthcare resource utilization (HCRU)-related costs in patients receiving triple therapy and to quantify the economic burden of uncontrolled COPD patients (ie, ≥1 severe or 2 moderate exacerbations within 12 months before inclusion and at least one exacerbation under treatment) versus controlled COPD patients and the general population.

Methods: Patients aged over 40 years receiving triple therapy in 2015 (ie, long-acting ß2-agonist, long-acting anticholinergic and inhaled corticosteroids) for at least 90 continuous days were included. The index date was defined as the 91st day of triple therapy exposure. Patients were followed for up to 5 years. HCRU-costs were computed by calendar year in controlled and uncontrolled COPD patients and in the general population. The association between costs and COPD has been estimated, for each calendar year, using GEE with a negative binomial distribution.

Results: Among the 186,963 patients included, 21.2% (N= 39,647) of patients were identified as uncontrolled. Among these, the average cost related to HCRU per patient was around 12,000€ by year. Hospitalizations, drugs and medical devices represented approximately 2/3 of expenses. Costs were in average 1.25 higher than in controlled COPD treated patients and 2.7 higher than the general population. Attributable costs to COPD in uncontrolled patients were estimated at approximately €7,600 per patient each year.

Conclusion: This study offers a robust representation of health care resource consumption and related costs of COPD patients receiving triple therapy in France over several years with a focus on uncontrolled patients.

Keywords: COPD, economic burden, population-based study

Introduction

Chronic obstructive pulmonary disease (COPD) is a devastating respiratory illness characterized by chronic respiratory failure, limitations in daily life activities and handicap, worsened by dreadful episodes of acute exacerbations. Several comorbidities including cardiovascular diseases, cancers, osteoporosis, depression/anxiety, and others can strongly affect the trajectory of the disease. This chronic disease is highly prevalent worldwide and represents a substantial socio-economic burden for individuals and healthcare systems. Its prevalence has been estimated to be as high as 10.6% of the worldwide adult population globally, corresponding to 480 million cases in 2020.[1] As described in the recent global burden of disease study 2021, COPD was the third leading cause of death and the sixth cause of disease burden worldwide in 2022.[2,3] Projections predict a major burden in the coming years with an increase of 23% in the number of cases of COPD (approaching 600 million in 2050) and an estimation of the 20-year discounted direct medical costs attributable to COPD of $800.90 billion (95% [CI]565.29 billion-1,081.29 billion) in the United states from 2019 to 2038.[4]

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Previous studies focusing on the assessment of health care direct and indirect costs related to COPD pointed out a major impact on countries' health budget.[5] Three main economic cost drivers were identified: disease severity, comorbidities and the presence of frequent and/or severe exacerbations. Indeed, frequent COPD exacerbations (ECOPDs) are a key driver of health care resource utilization (HCRU) due to more frequent interactions with the health care system (visits to the emergency department, hospitalizations and admissions to intensive care unit, …). In this context, optimal management of COPD is crucial to slow disease progression but also to reduce symptoms burden and the risk of ECOPDs. Beside non-pharmacologic interventions, pharmacological treatment is tailored according to the severity of symptoms and the presence of ECOPDs.[6,7] In France, the 2021 French Society of Pulmonology (SPLF) guidelines recommend the use of triple therapy for patients with moderate to severe exacerbations or persistent dyspnea despite well-conducted dual therapy (ICS/LABA or LABA/LAMA).[8] In its 2024 iteration, the Global Initiative on Obstructive Lung Disease (GOLD) strategy document also proposes triple therapy as first line option in patients with exacerbations and >300 blood eosinophils/µL. Despite this maximal inhaled therapy, some patients still experience exacerbations. No studies were conducted in France to assess the economic burden of this specific population. New biologics such as dupilumab today and others tomorrow are developed in GOLD stage E. For accurately addressing cost-effectiveness issues, recent studies dedicated to assess HCRU in GOLD stage E patients are highly required.

The main objective of this study was to describe HCRU and their related costs in uncontrolled COPD patients (ie, those with persistent exacerbations) receiving triple therapy. Secondary objectives were the comparison of HCRU (including sick leaves) and related costs between uncontrolled versus controlled COPD patients receiving triple therapy, and with the general population.

Methods

Study Design and Data Sources

This was an observational longitudinal study conducted using data from the French National Health Insurance (SNDS: "Systeme National des Données de Santé") database from 2015 to 2021. As previously described, SNDS is used for billing and care management purposes and represents an exhaustive national resource to perform economic analyses of reimbursed health care resources in France.[9–11] The SNDS contains socio-demographic data (age, gender, health status and place of residence) and individual-level claims data for all outpatient care (drug dispensation, medical consultations, medical and biological procedures, medical devices and sick leaves), and for private and public inpatient care (reason for hospitalizations, care facility, use of onerous drugs and medical devices). Clinical data are available through several variables. The presence of some long-term diseases is mentioned that grant full reimbursement of related care (Affection de Longue Durée [ALD]) as well as hospital diagnoses which detail the leading cause of hospital admission, patient's management during hospitalization but also major comorbidities and complications. Hospital diagnosis and LTDs are coded according to the International Classification of Diseases, 10th revision (ICD-10).

Study Population

Patients aged over 40 years receiving triple therapy in 2015 (ie, long-acting ß2-agonist (LABA), long-acting antic-holinergic (LAMA) and inhaled corticosteroids (ICS)) for at least 90 continuous days were included (see Supplementary Files 1). The index date was set at the 91st day of triple therapy exposure in 2015. Patients were followed up from the index date until death, loss of follow up or the end of the study period (ie, 31st December 2021), whichever occurred first. Medical history was retrieved using a follow-back period of 5-years before the index date.

Included patients were divided in two subgroups of interest according to the following criteria. COPD was qualified as uncontrolled if patients had at least one severe exacerbation or 2 moderate exacerbations within 12 months before the index date. At least one exacerbation (regardless of severity) must have occurred while the patient was on triple therapy with a minimum delay of 1 month between the initiation of triple therapy and the occurrence of exacerbation. Controlled COPD patients were defined as those not included in the population of uncontrolled COPD patients. Transitions over time between groups were not analysed. Severe exacerbation (ie leading to hospitalization) were identified according to

an algorithm previously described in the literature.[12] Moderate exacerbations were defined as reimbursement of a systemic glucocorticoid with an antibiotic within 7 days (before or after) (see Supplementary Files 1).

In order to compare costs of COPD patients with the general population a random sample of 1 million individuals from the French population in 2015, consisting of non-COPD patients over 40 years old, was also extracted from SNDS. Individuals from the general population were randomly selected and included in 2015 so they could be compared with uncontrolled COPD patients from the same entry point.

HCRU and Economic Endpoints

HCRU was described by calendar year and by category of healthcare resources (ie, medical consultations, paramedical consultations, treatments and medical devices, biological tests, medical imaging procedures, hospitalizations and hospitalization diagnosis, sick leaves).

The cost of care of each cohort was computed from 2016 to 2021 and has been valued from the National Health Insurance perspective and indexed in euro 2022, overall and by category of healthcare resources as described above.

Statistical Analysis

Descriptive statistics were computed using mean and standard deviation or median and interquartile range when relevant for continuous variable and frequency and percentages for categorical variable. The following variables at index date were described: age, sex, Charlson Comorbidity Index, comorbidities and medical history (asthma, pneumopathy, exacerbations (moderate and severe), cardiovascular diseases, diabetes, obesity, undernourishment, anxiety or depression, sleep disorders or sleep apnea syndrome) and tobacco dependence (identified through the prescription of nicotine substitutes). The number of deaths and duration of follow up were also computed.

In order to compare HCRU and related costs of uncontrolled vs controlled COPD patients and with the general population, 2 matching procedures were implemented using propensity score (PS)-matching to control for confounders. Propensity scores were estimated by logistic regression analyses that incorporate potential predictors.

The first PS matching procedure matched uncontrolled COPD patients and individuals from the general population with a 1:2 ratio. Predictors included in the model were age, gender, density of pulmonologist and diseases included in the Charlson Comorbidity Index. Among these matched population, the association between costs and COPD has been calculated using a negative binomial GEE model for each calendar year of the study period. Then, the cost attributable to COPD has been estimated by the difference between the total observed cost of patients with uncontrolled COPD under triple therapy and the estimated cost of these patients if they were not affected by COPD (total observed cost divided by the estimated relative risk). The confidence interval (CI) of the attributable cost was calculated by bootstrapping. HCRU were described in each matched cohort.

The second PS matching procedure matched uncontrolled COPD patients and controlled COPD patients with a 1:1 ratio. PS included the same predictors identified for the first matching procedure plus other comorbidities/clinical events of interest (ie, asthma, pneumopathy, anxiety/depression, osteoporosis, sleep disorders/sleep apnea syndrome, overweight, poor nutritional status) and the Daily Polypharmacy Possession Ratio (DPPR). Supplementary File 2 details the standardized differences between populations for each matching process.

The average annual cost per patient and the average annual numbers of healthcare per patient has been calculated by year for each matched cohort.

Results

Characteristics of the Population

In 2015, 302,984 patients received at least once a triple therapy in France. Of these, 186,963 patients were included as they were aged over 40 years and had prolonged use of triple therapy (≥90 days). Among included patients, 21.3% (N=39,847) were uncontrolled. Figure 1 details the study selection process. Baseline characteristics of controlled and uncontrolled patients were quite close except for tobacco dependance identified more frequently in uncontrolled patients (29.7% versus 21.2%). Mean age at inclusion was around 69 years with a majority of men (approximately 2/3 of patients

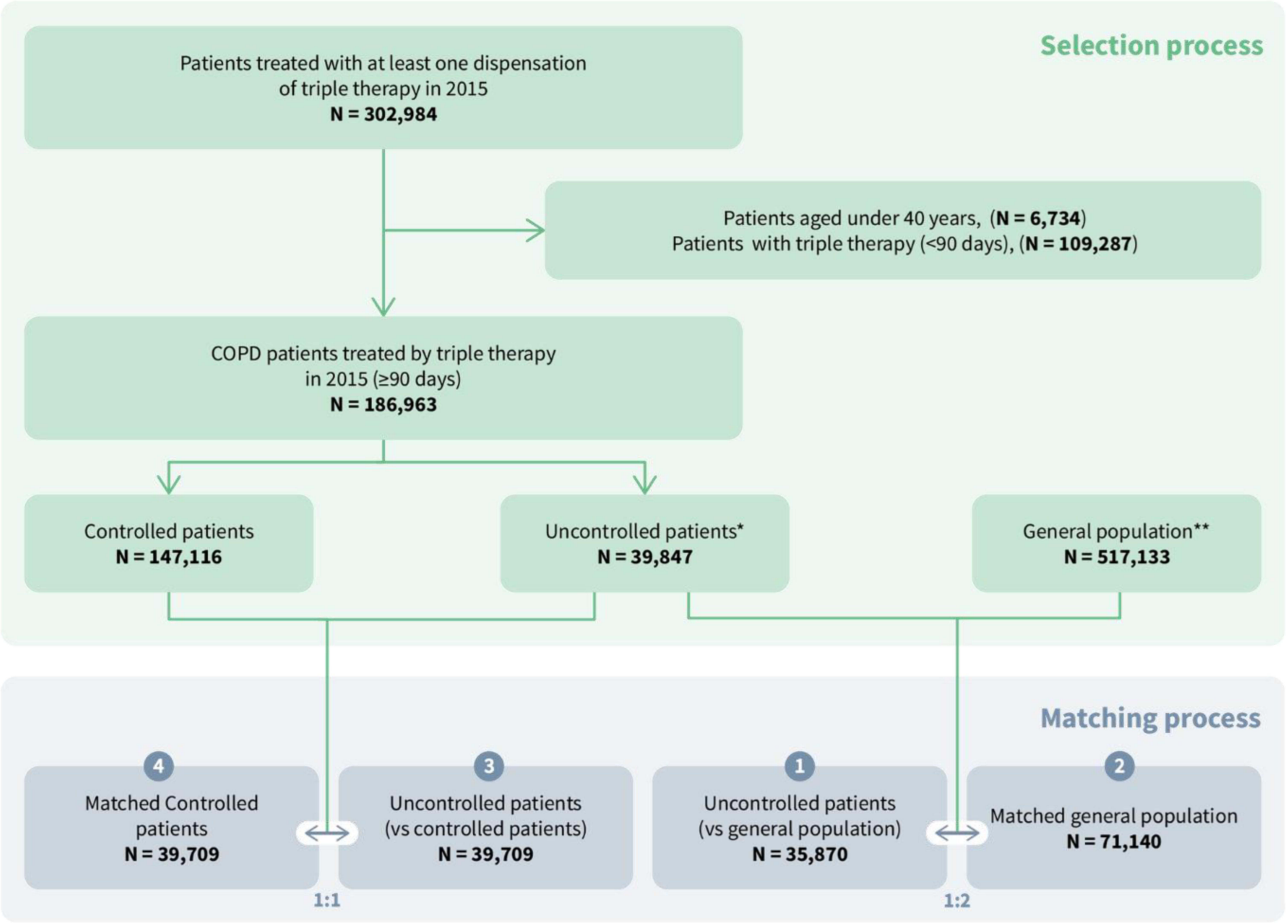

Figure 1 Flow chart of the selection process and matching process. COPD: Chronic obstructive pulmonary disease. *At least one severe or two moderate exacerbations in the past year and one exacerbation during the treatment by triple therapy **Individuals without COPD. 1:1 Propensity score matching with a 1:1 ratio. 1:2 Propensity score matching with a 1:2 ratio.

in both groups). As expected, patients were comorbid with a median Charlson score of 4.0 (IQR 3.0–5.0). Mortality during follow-up was higher in the uncontrolled group (44.7% versus 36.2%). Table 1 presents the patients' characteristics.

Description of HCRU and Costs Attributable to COPD (Uncontrolled Patients versus the General Population)

Over the study period, 79.6% (N=31,726) of matched uncontrolled COPD patients were hospitalized at least once versus 10.4% (N=53,799) in the general population. Analyses by calendar year showed that 51.8% (N=17,030) of uncontrolled patients were hospitalized at least once with a median number of 2.0 hospitalization per patient IQR[1.0–3.0] in 2016. These two indicators were stable over the study period (approximately 50% of patients were hospitalized every year with a median number of 2 hospitalizations per patient per year). A decrease was observed in 2020 and in 2021 (approximately 45% of patients were hospitalized each year over this period). Patients were mainly hospitalized for chronic obstructive pulmonary disease with lower respiratory infection (N=11,733), chronic obstructive pulmonary disease with acute exacerbation (N=8,903) and acute respiratory failure, unspecified whether with hypoxia or hypercapnia (N=4,904). Hospitalizations rate was lower in the matched cohort from the general population (between 26.9% and 29.4%) with a median number of 1.0 IQR[1.0–2.0] hospitalization per patient per year. In this cohort, patients were mainly hospitalized for cataract (N=4,323), chemotherapy session (N=3,790) and transfusion (N=1,346).

Table 1 Characteristics of Controlled and Uncontrolled COPD Patients with Prolonged Triple Therapy Use (≥90 Days) in France

	Uncontrolled COPD Patients* (N = 39,847)	**Controlled COPD patlents** (N = 147,116)**
Age in years, mean (SD)[a]	68.9 (± 11.4)	69.4 (± 11.6)
Male, N (%)[a]	24,2 (60.8)	93,886 (63.8)
Comorbidities and medical history		
Charlson Comorbidity Index score, median (IQR)[a]	4.0 (3.0–5.0)	4.0 (3.0–5.0)
Asthma [b], N (%)	8,549 (21.45%)	20,781 (14.13%)
Cardioneurovascular diseases [b], N (%)	13,500 (33.88%)	42,670 (29.00%)
Diabetes [b], N (%)	6,192 (15.54%)	27,713 (18.84%)
Obesity with hospital stay or bariatric surgery [b], N (%)	6,002 (15.06%)	18,973 (12.90%)
Poor nutritional status [b], N (%)	10,379 (26.05%)	23,633 (16.06%)
Anxiety or depression [b], N (%)	21,365 (53.62%)	67,039 (45.57%)
Sleep disorders or sleep apnea syndrome [b], N (%)	9,741 (24.45%)	31,765 (21.59%)
Tobacco dependence[b], N (%)[b]	11,831 (29.7)	31,165 (21.2)
Exacerbations [d]		
Patients with at least one severe exacerbation, N (%)	13,848 (34.8)	5,682 (3.9)
Patients with at least moderate exacerbation, N (%)	34,911 (87.6)	42,090 (28.6)
Number of severe exacerbation per patients, median (IQR)	1.0 [1.0–2.0]	1.0 [1.0–1.0]
Number of moderate exacerbation per patients, median (IQR)	3.0 [2.0–4.0]	1.0 [1.0–1.0]
Follow-up duration in years, mean (SD),	5.1 (± 2.2)	5.5 (± 2.0)
Deaths, N (%)[c]	17,803 (44.7)	53,333 (36.2)

Notes: *Uncontrolled: Patients with at least one severe exacerbation or with 2 moderate exacerbations within 12 months before the index date. At least one exacerbation (regardless of severity) must have occurred while the patient was on triple therapy with a minimum delay of 1 month between the initiation of triple therapy and the occurrence of exacerbation. **Controlled: patients not included in the uncontrolled population; [a]At index date, [b] during the 5-year follow back period, [c] during follow-up,[d] during the 12 months before the index date (before or during triple therapy).

Abbreviations: COPD, Chronic obstructive pulmonary disease, SD, Standard deviation.

Regarding drugs, uncontrolled COPD patients mainly used acetaminophen (N=34,456) and drugs related to COPD (ie, bronchodilators, corticosteroids) whereas individuals from the general population used mainly acetaminophen, cholecalciferol and proton pump inhibitors.

In uncontrolled patients, the most frequently dispensed medical devices were related to respiratory failure (eg, oxygen), poor nutritional status and loss of autonomy (medical bed, wheelchair and home infusion service). Approximately 95% of patients had at least one GP consultation each year and 65% at least one specialist consultation each year. Median number of GPs consultations per patient ranged from 9.0 IQR[6.0–14.0] in 2016 to 7.0 IQR[5.0–12.0] in 2021. Median number of specialist's consultations per patient was stable over time (2.0 IQR[1.0–5.0]). Similar trends were observed in the matched cohort from the general population.

Figure 2 details the costs attributable to COPD by year after matching process (uncontrolled versus the general population). Costs attributable to COPD in uncontrolled patients were estimated at approximately 7,600€ per patient each year. Between 2016 and 2021, the cost attributable to uncontrolled COPD represented between 60 and 64% of the average cost per patient.

Cost Drivers in Uncontrolled COPD Patients

HCRU related costs in uncontrolled patients were on average 2.7 higher than in the general population (see Figure 3a). Between 2016 and 2021, HCRU related costs varied between 12,828€ and 13,399€ in uncontrolled patients against 4,975 € and 5,336€ in the general population. These differences were due to higher costs related to drugs and medical devices (+3,942€ in average) and hospitalizations (+2,690€ in average).

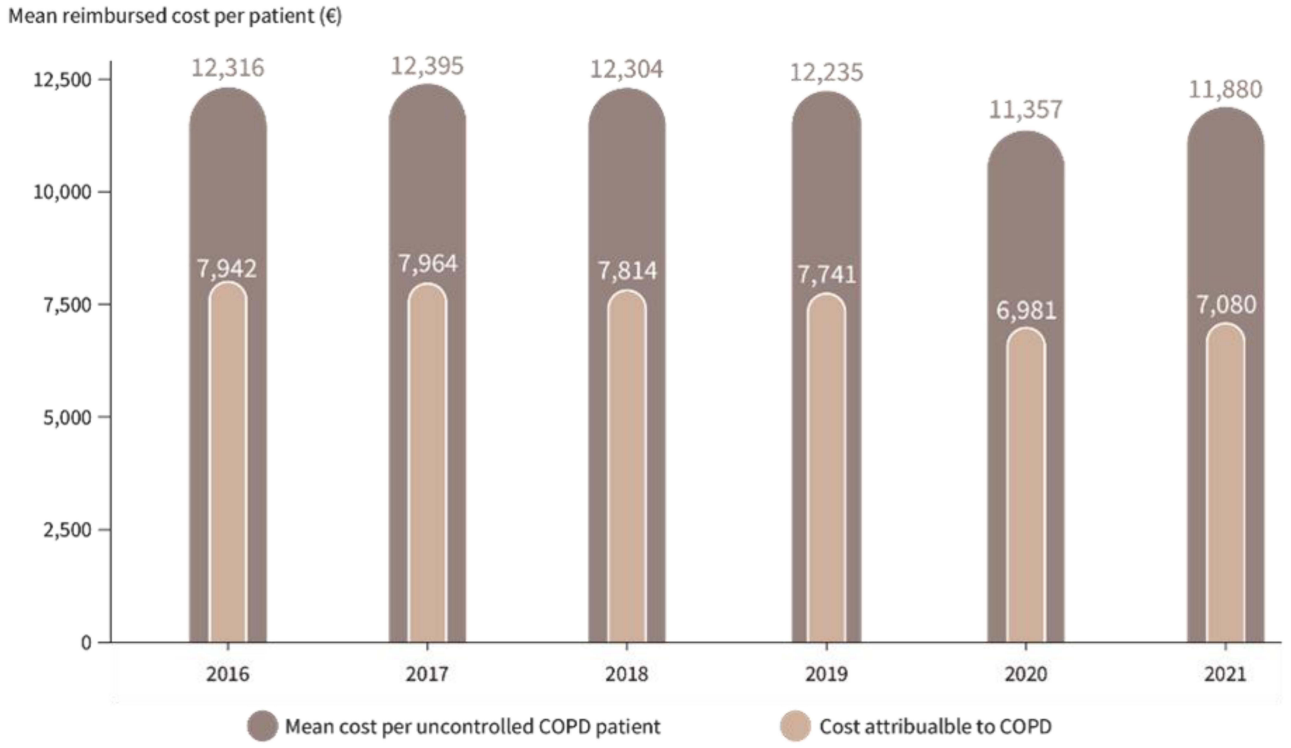

Figure 2 Cost attributable to COPD in uncontrolled patients, estimated by the difference between the total observed cost of patients with COPD and the estimated cost of similar patients with no COPD (total observed cost divided by the estimated relative risk).

HCRU related costs in uncontrolled patients were in average 1.25 higher than in controlled patients (see Figure 3b). Between 2016 and 2021, HCRU related costs varied between 14,630€ and 13,136€ in uncontrolled patients against 10,522€ and 11,288€ in controlled patients. Constantly higher expenses related to drugs and medical devices were observed (+1,508€ in average) and hospitalizations (+1,020€ in average). Patients in each matching cohort were mainly hospitalized for lung infections, exacerbations and respiratory failure. The number of patients hospitalized for these diseases was higher among uncontrolled patients.

The percentages of patients with at least one sick leave were low in uncontrolled COPD patients (<0.05% each year). These percentages were similar for the general population and controlled patients. Sick leaves accounted for a small part of NHI expenses related to COPD. In uncontrolled patients, mean cost of sick leave per patient ranged from €234€ (±2,669) in 2016 to €79 (±964) in 2021. In controlled patients, mean cost of sick leave per patient ranged from €184 (±2,186) in 2016 to €86 (±1,048) in 2021.

Discussion

This is the first study assessing HCRU related costs in uncontrolled COPD patients receiving triple therapy in France using exhaustive data from SNDS. Despite triple therapy, 21.2% (N= 39,647) of patients were identified as uncontrolled. Among these, the average cost related to HCRU per patient was around 12,000€ per year and the main cost drivers were hospitalizations and drugs/medical devices (≈2/3 of expenses). These costs were on average 1.25 higher than in controlled COPD patients and 2.7 higher than the general population. These results were based on baseline status regarding the control of COPD. Thus, we cannot exclude that some patients in the control group became uncontrolled over time, and vice versa.

These results are in line with previous findings which pointed out the substantial economic burden attributable to COPD and depicted higher burden in uncontrolled patients. Indeed, European estimations quantified the total direct costs of respiratory diseases at 6% of the total healthcare expenses, with COPD accounting for 56% of these costs (equaling 38.7 billion Euro).[13] In the United States, the direct and indirect costs were, respectively, estimated at $32 billion and

Figure 3 Mean reimbursed costs per patients (in euro) in total and by category of health care resource by calendar year. Comparisons of matched cohorts: uncontrolled patients versus the general population (**a**) and uncontrolled versus controlled patients (**b**).

$20.4 billion.[5] Estimations are also similar in Asia.[14] Moreover, an increase in the frequency of exacerbation (more than one exacerbation per year) leads to a threefold increase in medication cost of COPD patients.[14] In the USA, annual per patient hospitalization cost were estimated at $6,852. In France, total hospitalizations costs were estimated at 678 million euros in 2012 and costs related to ECOPDs per patient at €9,623.[12,15]

In this study, higher expenses in uncontrolled versus controlled patients were related to drugs and medical devices (+1,508€ on average) and hospitalizations (+1,020€ on average). Costs attributable to uncontrolled COPD were estimated at approximately €7,600 per patient per year. This higher economic burden of uncontrolled patients is in part related to the frailty of these patients (medical devices such as medical bed or to treat respiratory failure), and to a higher number of hospitalizations in this cohort. These results are in concordance with our previous analyses focusing on clinical outcomes in these specific populations highlighting that these patients are highly comorbid in comparison with the general population.[16] There are also in line with previous studies highlighting that frequent exacerbations are correlated with poorer outcomes[17,18] and a higher prevalence of comorbidities in uncontrolled patients.[19,20] Our results are in concordance with a recent nationwide population based study conducted in Denmark indicating that the estimated costs related to COPD increased with increasing disease severity.[5] Thus, in GOLD groups A-D, the total direct costs were, respectively, A: €8,766, B: €13,060, C: €11,113, and D: €17,749. However, we cannot compare exactly our results with these previous findings as we focused on a specific population (patients under triple therapy with frequent and/or severe

exacerbations) whereas they focused on COPD patients. Moreover, disease severity in the Danish study was measured on specific drugs used, exacerbations and symptom scores. The latter were lacking in our database. In France, the medical direct cost per patient was estimated at €9,382 in 2011.[21] In Europe, according to studies and to the data sources used, annual medical direct cost per patient was estimated at: $11,787 in Norway, $10,552 in Denmark, $8,644 in Germany, $8,203 in Italy, $7,760 in Sweden, $3,190 in Greece and$1,889 in Spain.[14] The annual direct medical cost per patient reported in the literature was $10,367 in the USA.

The main cost driver was hospitalization. Indeed, approximately 50% of patients were hospitalized every year with a median number of 2.0 hospitalization per patient per year IQR[1.0–3.0]. Patients in each cohort were mainly hospitalized for lung infections, exacerbations and respiratory failure. The description of HCRU revealed that patients had regular consultations with GPs or specialists indicating close medical monitoring of these patients. Drugs most frequently used by patients were drugs indicated in COPD (ie, bronchodilators, corticosteroids). Medical devices mainly dispensed were related to respiratory failure, malnutrition and loss of autonomy (medical bed, wheelchair and home infusion service). The percentages of patients with at least one sick leave were low in uncontrolled COPD patients (<0.05% each year). Thus, sick leaves accounted for a small part of NHI expenses related to COPD.

The main strength of this study was to investigate the economic outcomes of patients receiving triple therapy for COPD in France using comprehensive data from the SNDS database but also the use of a control population without COPD to estimate attributable costs of COPD. Thus, we were able to provide extensive real-life data generalizable to the whole French population and to follow patients for several years without loss to follow up. As all reimbursed health care consumptions are prospectively and independently collected, this database serves as a relevant resource for assessing healthcare costs and resource utilization patterns. However, we were only able to capture costs corresponding to expenses covered by the healthcare system. Costs for patients corresponding to medications, devices or services that are not reimbursed could not be included in our analysis. Furthermore, the diagnosis of severe COPD could only be estimated based on the identification of exacerbations, as defined by algorithms (ie, at least one severe or two moderate exacerbations within 12-years before the inclusion date). Moreover, the patient inclusion design corresponds to a specific population of interest included in 2015 (patients treated by triple therapy). Thus, a classification bias can not be excluded. Specifically, even if triple therapy is primarily indicated for COPD, it was possible that a small proportion of patients with severe asthma (without COPD) were included in our population, as there is no way to definitively exclude them from the dataset. Indeed, some comorbidities are subject to information bias because of the lack of clinical data in the SNDS. As an example, asthma is identified only in patients with long-term illness recognition or with a hospital diagnosis. Furthermore, patients with COPD and comorbid asthma may also be present. Moreover, although the algorithms used to identify exacerbations in our study are derived from the literature and have been developed by expert consensus, some miscoding of exacerbations is also possible, including coding a COPD instead of asthma exacerbation in an elderly smoker or ex-smoker. Then, our definition of uncontrolled cases was based on the presence of hospitalizations for exacerbations, while some authors propose definitions that take symptoms ± lung function into account. However, our database does not allow us to obtain such information.[22–25] Finally, the identification of moderate exacerbations could have been underestimated. Indeed, some moderate exacerbations could have been treated only with a systemic glucocorticoid or antibiotics, but not both. The indications of treatments are not recorded in the SNDS and there is a wide range of indications for systemic glucocorticoids and antibiotics used in isolation. Thus, taken these treatments used alone into account would have led to a loss of specificity and a too large overestimation of the true frequency of exacerbations, which we considered unacceptable Residual confounding may persist despite the rigorous matching process, since patients from the cohorts of interest can differ regarding other characteristics that are not captured in the SNDS. The main drawback of this database is the lack of precise diagnosis and clinical data, which can only be approximated through hospital diagnoses or obtained for long-term illness patients with diagnosis codes available. Specially, some comorbidities are subject to significant information bias (eg, obesity, tobacco dependency or malnutrition). Indeed, there is no long-term illness for these patients who are not systemically hospitalized for these conditions. For the same reasons, as biological results

including blood EOS count are not recorded in the SNDS we were unable to include these clinical information in our analyses.

Conclusion

Our study offers a robust representation of health care resource consumption and related costs of COPD patients receiving triple therapy in France over several years with a focus on uncontrolled patients. It presents a complete overview of the economic burden for these patients, indicating an average cost related to HCRU per patient around 12,000€ by year. These costs were higher compared to controlled patients and the main cost driver was hospitalizations.

Data Sharing Statement

The data supporting the study findings are part of the National health data system (SNDS, Système national des Données de Santé) and are available from the Health Data Hub (HDH https://www.health-data-hub.fr/). Restrictions apply to the availability of these data and the code used for their analysis, which were used with a special permission for this study. Special permission to access these data for this study was granted by the Ethics and scientific committee for health research, studies, and evaluations (CESREES, Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé) (former CEREES, file No. 8986168) and the French data protection authority (Comité National de l'Informatique et des Libertés, CNIL, file No. 922190, decision DR-2022-194).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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