

Economic Burden of Chronic Obstructive Pulmonary Disease (COPD): A Systematic Literature Review

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Background and Objectives: Chronic obstructive pulmonary disease (COPD) affects over 250 million people globally, carrying a notable economic burden. This systematic literature review aimed to highlight the economic burden associated with moderate-to-very severe COPD and to investigate key drivers of healthcare resource utilization (HRU), direct costs and indirect costs for this patient population.

Materials and Methods: Relevant publications published between January 1, 2006 and November 14, 2016 were captured from the Embase, MEDLINE and MEDLINE In-Process databases. Supplemental searches from relevant 2015–2016 conferences were also performed. Titles and abstracts were reviewed by two independent researchers against pre-defined inclusion and exclusion criteria. Studies were grouped by the type of economic outcome presented (HRU or costs). Where possible, data were also grouped according to COPD severity and/or patient exacerbation history.

Results: In total, 73 primary publications were included in this review: 66 reported HRU, 22 reported direct costs and one reported indirect costs. Most of the studies (94%) reported on data from either Europe or North America. Trends were noted across multiple studies for higher direct costs (including mean costs per patient per year and mean costs per exacerbation) being associated with increasingly severe COPD and/or a history of more frequent or severe exacerbations. Similar trends were noted according to COPD severity and/or exacerbation history for rate of hospitalization and primary care visits. Multivariate analyses were reported by 29 studies and demonstrated the statistical significance of these associations. Several other drivers of increased costs and HRU were highlighted for patients with moderate-to-very severe COPD, including comorbidities, and treatment history.

Conclusion: Moderate-to-very severe COPD represents a considerable economic burden for healthcare providers despite the availability of efficacious treatments and comprehensive guidelines on their use. Further research is warranted to ensure cost-efficient COPD management, to improve treatments and ease budgetary pressures.

Keywords: chronic obstructive pulmonary disease, cost of illness, healthcare utilization, review, systematic literature review, economic burden

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by incurable, progressive airflow restriction and has various clinical forms, including emphysema and chronic bronchitis.¹ Periods of time in which patients experience an acute deterioration in their respiratory symptoms, known as exacerbations, are a common manifestation of the disease.¹ A debilitating yet preventable multifactorial disease, COPD is estimated to affect over 380 million people worldwide.²

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The goals of COPD pharmacologic therapy are to provide symptomatic relief, improve health status and exercise tolerance, and prevent and treat exacerbations.¹ While therapeutic regimens are adapted according to the needs of each individual patient, most pharmacologic maintenance treatments can be categorized as either inhaled corticosteroids (ICS), long-acting muscarinic antagonists (LAMA) or long-acting β_2 -agonists (LABA),¹ and are often administered as combinations. As an example, triple therapy with an ICS, LAMA and LABA has been shown to improve lung function and patient-reported outcomes, including exacerbation risk, compared with ICS/LABA or LAMA monotherapy.¹ Despite recent advances within the field and the availability of guideline-recommended treatments, current management is inadequate for many patients with COPD; this unmet need, coupled with the high prevalence of the condition, suggests a high clinical and economic burden, and this has been demonstrated in a number of studies.

Previous publications have indicated that COPD is associated with a substantial economic burden, both in terms of direct costs to healthcare systems and indirect costs to society.^{1,3–5} In the United States (US), for example, direct costs of COPD were estimated to be \$32 billion in 2010, with indirect costs (incurred by lost working days, for instance) accounting for an additional \$20.4 billion.³

While evidence on the economic burden of COPD exists, it generally comprises individual studies that are limited by factors such as population characteristics, geographical location and clinical setting. To better understand the current COPD-related burden in settings where patients are likely to be managed as per globally recognised treatment algorithms, such as from the Global Initiative for Chronic Obstructive Lung Disease (GOLD),¹ we performed a comprehensive systematic literature review (SLR) of real-world observational studies in patients with moderate-to-very severe disease and/or those with a history of exacerbations, conducted across a number of industrialized countries during the last decade. This evidence was obtained to address two research questions. Firstly, what is the global economic burden associated with moderate-to-very severe COPD? This was examined with a specific focus on regions with high utilization of healthcare resources, such as Australia, Europe, Japan and North America? Secondly, what are the key drivers of economic burden in moderate-to-very severe COPD?

Materials and Methods

Literature Search

This SLR was conducted using processes similar to those outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁶ to identify articles assessing both the economic and/or humanistic burden of COPD. This review summarizes the evidence of COPD's economic burden only; humanistic outcomes will be reported in another publication. Searches were conducted to capture publications of interest from January 1, 2006 to November 14, 2016 using the electronic literature databases Excerpta Medica Database (Embase), via embase.com, MEDLINE (via embase.com) ([Supplementary Table 1](#)) and MEDLINE In-Process (via ncbi.nlm.nih.gov/pubmed) ([Supplementary Table 2](#)).

Supplemental grey literature searches of proceedings from the following relevant conferences that took place in 2015 and 2016 were also conducted: European Respiratory Society (ERS), American Academy of Allergy, Asthma, and Immunology (AAAAI), American Thoracic Society (ATS) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Bibliographies of identified SLRs on the economic burden of COPD were examined for any additional relevant publications and to validate the electronic searches.

Study Selection

During the first level of review, titles and abstracts were screened by two investigators independently using pre-defined inclusion and exclusion criteria ([Supplementary Table 3](#)). To be included, articles needed to be English-language observational studies published between January 1, 2006 and November 14, 2016 examining adult patients with moderate-to-very severe COPD (defined as post-bronchodilator forced expiratory volume in 1 s/forced vital capacity [FEV₁/FVC] of <0.70, plus 50% \leq FEV₁<80% predicted [moderate], 30% \leq FEV₁<50% predicted [severe], or FEV₁<30% [very severe], or in accordance with GOLD recommendations or other measures employed by investigators), or with a history of frequent exacerbations (≥ 2 exacerbations in the previous year that required treatment with oral/systemic corticosteroids and/or antibiotics) or exacerbation-related hospitalizations, in the context of healthcare resource utilization (HRU) and costs. Full-text articles for abstracts deemed to be relevant during the first level of review were retrieved and reviewed. Data were restricted to nine countries of interest: Australia, Canada, France, Germany, Italy, Japan,

Spain, the United Kingdom (UK), and the United States (US). None of the exclusion criteria and all protocol-specified inclusion criteria needed to be met for inclusion. All rejected records were re-reviewed as a quality-assurance step. At both review stages, any discrepancies were resolved through discussion between the two reviewers and/or by a third, more senior, investigator.

Data Extraction and Synthesis

A standardized data extraction template was used to collect key data elements from the Consolidated Standards of Reporting Trials (CONSORT) checklist (www.consort-statement.org), including study type, study characteristics, population/subpopulations of interest, patient characteristics and categories of outcomes reported. Each entry was validated by a second researcher and a third, more senior, investigator was involved as a quality-assurance step to confirm extractions or resolve disagreements.

Given the nature of the data, it was not appropriate to conduct a quantitative analysis; however, studies were grouped according to the type of economic outcome (direct costs, costs per exacerbation/hospitalization, indirect costs and HRU). Throughout this manuscript, costs are presented as mean (standard deviation [SD]) unless otherwise indicated.

Where possible, data were also grouped according to population characteristics: those with moderate-to-very severe COPD as defined by FEV₁% predicted, and/or those with a history of exacerbations and moderate-to-very severe COPD not defined by FEV₁% predicted.

Although no formal quality assessment was conducted on these economic studies, aspects related to the quality of the outcomes of these studies were considered in our interpretation of the evidence, including, for example, sample size and study design.

Results

Literature Search

After duplicates were removed, the electronic database searches yielded 2343 unique publications (Figure 1). Of these, 979 passed the initial title/abstract screening step, and 409 passed the second level of title and abstract screening. A total of 100 publications were excluded at this stage for not reporting on moderate-to-very severe COPD. Overall, 139 publications met the eligibility criteria for inclusion. An additional six publications were identified through manual review of bibliographies, giving

a total of 145 publications reporting data on the humanistic and/or economic burden associated with moderate-to-very severe COPD. The 73 primary publications that reported on COPD's economic burden are included in this manuscript (Table 1), while studies reporting on humanistic burden will be summarized in a separate publication.

Study Characteristics

Most of the studies (94%) reported on data from either Europe or North America, with 3% (n=2) reporting on data from Japan and 4% (n=3) from Australia (Figure 2). Of the 73 studies, most reported on HRU (n=66), followed by direct costs (n=22) and indirect costs (n=1) (Figure 3). In total, 29 publications reported multivariate data on drivers/predictors of costs and/or HRU (Figure 3).

Economic Burden of Moderate-to-Very Severe COPD HRU

In total, 66 studies reported on HRU, including data regarding hospital admission and length of stay, general practice/primary care visits and intensive care unit (ICU) admission. While more details of HRU in the included studies are included in [Supplementary Table 4](#), in the interests of brevity we have chosen to focus this section on the economic burden of care in the primary, secondary and ICU settings. It must be noted, however, that the studies captured in this review were heterogeneous in nature and are thus challenging to summarize.

In the studies that reported annual hospitalization rates according to COPD severity, COPD-related hospitalizations occurred at a mean annual rate of between 0 and 0.57 in patients with moderate COPD (50%≤FEV₁<80% predicted).⁷⁻¹¹ Patients with severe COPD (30%≤FEV₁<50% predicted) experienced between 0 and 0.44 mean COPD-related hospitalizations per year, while patients with very severe COPD (FEV₁<30% predicted) were hospitalized more frequently, from 0 to 0.88 times per year.⁷⁻¹¹ In studies where patients' disease severity was not specified, the highest mean rate of COPD-related annual hospitalizations reported was 1.78 in a population of Spain-based patients who experienced acute exacerbations leading to hospital admission.¹² Conversely, the lowest mean rate of COPD-related annual hospitalizations reported was 0.1, in a Spain-based cohort of patients who had experienced <2 exacerbations in the previous year.¹³

The mean number of annual general practitioner (GP) or primary care visits also varied widely, both within and

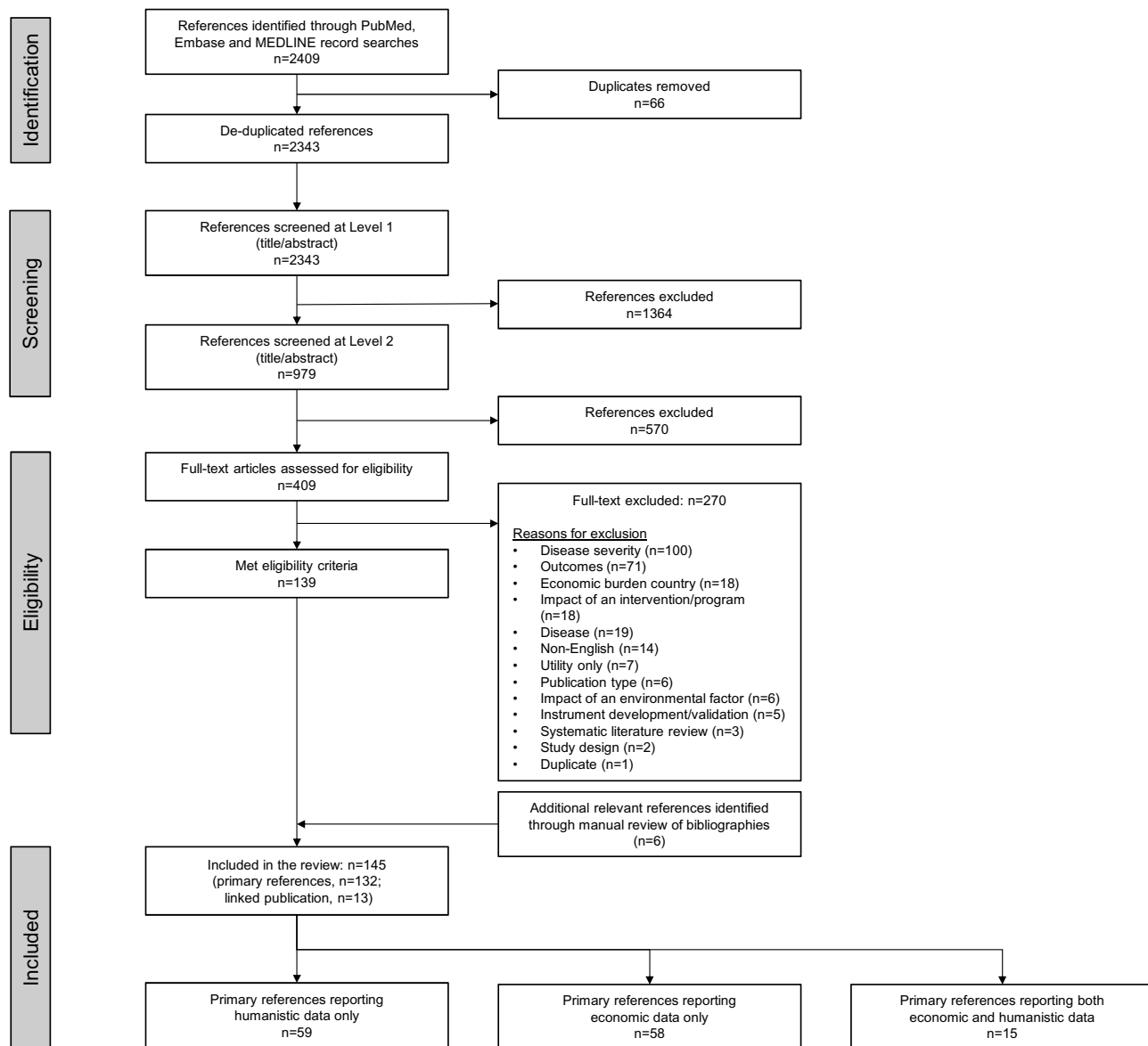


Figure 1 Identification of studies for inclusion in the systematic literature review (following systematic processes outlined in PRISMA guidelines).

Note: Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.⁶

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

between COPD severity subgroups. The mean number of visits per patient per year (PPPY) ranged from 2.33 to 12.99 for mild COPD ($FEV_1 \geq 80\%$ predicted), and from 2.33 to 13.0 for moderate COPD (2.33 visits PPPY was described for patients with “mild-to-moderate COPD” [$FEV_1 \geq 50\%$ predicted]).^{8,11,14–17} Patients with severe COPD seemed to visit their GP more frequently, from 2.8 to 15.06 times per year.^{8,11,14–17} Fewer studies reported the mean number of primary care visits for patients with very severe COPD, but in those that did, the frequency ranged from 3.67 to 12.22 per year.^{8,11,15} The highest number of GP

visits reported was 15.94 per year in a UK-based cohort of patients who experienced ≥ 2 COPD exacerbations that were moderate-to-severe in severity.¹⁸

Only two studies reported length of hospital stay according to COPD severity. One UK-based study reported little variability according to disease severity, with a median stay of 5 days irrespective of whether the patient’s COPD was defined as mild, moderate or severe.¹¹ Length of stay increased to a median of 6 days for patients with very severe disease ($FEV_1 < 30\%$ predicted) in this study.¹¹ A study conducted in Spain observed a difference according to COPD

Table 1 Summary of Included Studies (n=73 Studies)

Author, Year	Study Design [Length of Follow-Up], Sample Size	Country and Setting	Groups of Patients with Economic Data Available
AbuDagga, 2013 ²⁹	Retrospective cohort [1 year] N=17,382	Country: US Setting: Inpatient and outpatient	Patients with ≥ 1 ED visit, ≥ 1 hospitalization or ≥ 2 physician office visits for chronic bronchitis during follow-up period
Abusaid, 2009 ¹⁹	Retrospective cohort [2 years] N=139	Country: US Setting: Inpatient	COPD patients ($FEV_1 < 80\%$ predicted) with history of exacerbations (who were hospitalized for an exacerbation at the time of enrollment) Subgroup data by the presence of DD
Benzo, 2016 ⁴⁸	Cross-sectional [HRU data were obtained for the 12 months preceding study entry] N=310	Country: US Setting: Outpatient	Moderate-to-very severe COPD ($FEV_1 < 80\%$ predicted)
Blasi, 2014 ²⁴	Retrospective cohort [29 months] N=15,857	Country: Italy Setting: Inpatient and outpatient	Patients with history of exacerbations prior to a severe exacerbation at enrollment Subgroup data by frequency and severity of COPD exacerbations that occurred over 3-year period prior to the index event
Bu, 2011 ⁵⁹	Prospective cohort [2 years] N=56	Country: Australia Setting: Community	Moderate-to-very severe COPD patients ($FEV_1 < 80\%$ predicted; GOLD criteria [2006]) Subgroup data by BODE score
Bustamante-Fermosel, 2007 ¹²	Retrospective cohort [1 year] N=763	Country: Spain Setting: Inpatient	Mild-to-very severe COPD patients (GOLD criteria [2005]) with history of exacerbations
Carrasco Garrido, 2006 ⁶⁰ Publications linked by named source: de Miguel-Diez, 2010 ²⁸	Cross-sectional [HRU data provided for 12-month period] N=10,711	Country: Spain Setting: Primary care	Moderate-to-very severe COPD ($FEV_1 < 80\%$ predicted)
Chen, 2009 ⁴¹	Retrospective cohort [1 year] N=108,726	Country: Canada Setting: Inpatient (acute care hospitals)	Patients with history of exacerbations (who were hospitalized for an exacerbation of COPD at enrollment)
Collins, 2012 ⁶¹	Prospective cohort [median 4.8 years] N=90	Country: US Setting: Outpatient	Moderate-to-severe COPD (self-reported severity)
Dalal, 2010a ⁶² Publications linked by named data source: Lindenauer, 2006; ⁶³ Silver, 2010; ³² Xu, 2012 ²¹	Retrospective cohort [30–60 days] N=NR [data were reported in terms of healthcare encounters in 2008, N=28,001 inpatient admissions and N=10,322 ED visits]	Country: US Setting: Inpatient and ED	Patients with moderate (ED) and severe (inpatient hospitalizations) exacerbations at enrollment Subgroup data by study year (2005–2008)

(Continued)

Table 1 (Continued).

Author, Year	Study Design [Length of Follow-Up], Sample Size	Country and Setting	Groups of Patients with Economic Data Available
Dalal, 2010 ⁶⁴	Retrospective cohort [data were obtained for 60 days of index admission and the preceding year] N=NR [data were reported in terms of N=85,789 healthcare episodes (inpatient and ED) related to exacerbations]	Country: US Setting: Inpatient and ED	Patients with moderate (ED) and severe (inpatient hospitalizations) exacerbations at enrollment
Dalal, 2015 ²² Publications linked by sample: Patel, 2013 ⁶⁵	Retrospective cohort [3 years] N=61,750	Country: US Setting: Inpatient	Patients hospitalized at enrollment Subgroup data by year of study and frequency of exacerbations during hospital admission index year
de Miguel-Diez, 2010 ²⁸ Publications linked by named source: Carrasco Garrido, 2006 ⁶⁰	Retrospective cohort [1 year] N=9390	Country: Spain Setting: Outpatient	Moderate-to-severe COPD (FEV ₁ <80% predicted) Subgroup data for patients with or without heart disease
Dhamane, 2016 ³⁵ Publications linked by sample: Dhamane, 2015 ⁶⁶	Cross-sectional [data were collected for the 6 months prior to index] N=2497	Country: US Setting: Community (population-based)	Mild-to-severe COPD (self-reported disease severity) Subgroup data by COPD severity
Dushianthan, 2010 ⁶⁷	Retrospective cohort [NR; data collected during ICU stay for exacerbation of COPD, mean 6.8 days] N=64	Country: UK Setting: ICU	Patients with severe COPD (not further defined) admitted to ICU for an exacerbation of COPD
DuVall, 2015 ⁴⁷	Retrospective cohort [30 and 60 days] N=89,502	Country: US Setting: Inpatient	Patients hospitalized at enrollment
Escarrabill, 2015 ³⁹	Retrospective cohort [90 days] N=910	Country: Spain Setting: Inpatient	Moderate-to-very severe COPD (FEV ₁ <80% predicted) in patients admitted for an acute exacerbation of COPD at enrollment
Esteban, 2016 ⁶⁸	Prospective cohort [2 years] N=543	Country: Spain Setting: Outpatient	Moderate-to-very severe COPD (FEV ₁ <80% predicted) Subgroup data by disease severity clusters (based on pulmonary function, age, smoking history, comorbidities and other factors)
Foo, 2016 ³⁰	Cross-sectional [NA] N=4343	Country: Data reported for UK, US, Mexico, Brazil, France, Germany, Italy, Spain, the Netherlands, Russia, Japan and South Korea separately Setting: Community	COPD patients (costs per exacerbation/hospitalization reported)

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Table 1 (Continued).

Author, Year	Study Design [Length of Follow-Up], Sample Size	Country and Setting	Groups of Patients with Economic Data Available
Gadre, 2014 ⁶⁹	Retrospective cohort [NR] N=677	Country: US Setting: Inpatient	Patients with severe COPD (based on clinical history and chronic hypercapnia/hypoxia) who were hospitalized for acute respiratory failure requiring mechanical ventilation
Gallego, 2016 ³⁴	Prospective cohort [1 year] N=118	Country: Spain Setting: Outpatient	Severe-to-very severe COPD (FEV ₁ <50% predicted; GOLD criteria [2013]) and ≥3 exacerbations in the previous year
Garcia-Aymerich, 2004 ⁷⁰	Cross-sectional [NA] N=346	Country: Spain Setting: Inpatient	Severe COPD (not further defined) who were hospitalized (or remaining in ED for at least 18 hrs) for a COPD exacerbation Subgroup data by energy expenditure in physical activity
Garcia-Aymerich, 2011 ³³	Retrospective cohort [10 years] N=20,571	Country: US Setting: Community (population-based)	COPD patients Subgroup data by COPD disease severity (based on FEV ₁ % predicted)
García-Polo, 2012 ⁵⁰	Cross-sectional [NA] N=115	Country: Spain Setting: NR [likely to be outpatient because although at least some patients in the high HRU group had been hospitalized in the previous year, the study states that data were from patients monitored by the respiratory services of Spanish public hospitals, suggesting that they were not currently hospitalized]	COPD patients (some were hospitalized at enrollment) Subgroup data by HRU (high vs low)
Gatheral, 2014 ⁴⁵	Retrospective cohort [3.5 years] N=406	Country: UK Setting: Inpatient	Patients hospitalized at enrollment
Gavazzi, 2015 ⁷¹	Prospective cohort [mean follow-up of 6 (SD: 4) months] N=267	Country: Italy Setting: Outpatient	Patients with advanced heart failure or COPD (likely to be very severe COPD as all patients had to have FEV ₁ <30% predicted, or hypoxemia [PaO ₂ <55 mmHg], or hypercapnia [PaCO ₂ >45 mmHg, ie above the upper threshold of normal], or to be on LTOT for >8 hrs/day)
Huang, 2014 ⁷²	Retrospective cohort [mean 2 years] N=756	Country: US Setting: Inpatient	Patients hospitalized at enrollment who were on LTOT

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Table 1 (Continued).

Author, Year	Study Design [Length of Follow-Up], Sample Size	Country and Setting	Groups of Patients with Economic Data Available
Keilty, 2013 ⁷³	Prospective cohort [1 year] N=119	Country: UK Setting: Inpatient	Patients hospitalized at enrollment for an acute exacerbation of COPD requiring NIV
Koleva, 2007 ⁷	Prospective cohort [1 year] N=268	Country: Italy Setting: Outpatient	Moderate-to-very severe COPD (FEV ₁ <80% predicted; GOLD criteria [2006]) Subgroup data by disease severity
Lindenauer, 2006 ⁶³ Publications linked by named data source: Dalal, 2010; ⁶² Silver, 2010; ³² Xu, 2012 ²¹	Retrospective cohort [30 days] N=69,820	Country: US Setting: Inpatient	Patients hospitalized at enrollment due to an acute exacerbation of COPD
Lusuardi, 2008 ⁷⁴	Prospective cohort [6 months] N=570	Country: Italy Setting: Inpatient and outpatient	Moderate-to-very severe COPD (stage 2–4; GOLD criteria [2004]) Subgroup data by disease severity and a history of exacerbations
Mahmud, 2015 ³⁷	Retrospective cohort [30 days] N=2,723,541	Country: US Setting: Inpatient	Patients hospitalized at enrollment due to an acute exacerbation of COPD Subgroup data (for patients with/without reflux esophagitis)
Mapel, 2011 ¹⁷	Retrospective cohort [1 year] N=51,072	Country: US Setting: Inpatient	Low-to-high complex COPD (based on comorbid respiratory conditions and medical procedures) Subgroup data by type of healthcare coverage and complexity of disease
Martín, 2008 ¹⁴	Cross-sectional [HRU data provided for a 12-month period] N=9405	Country: Spain Setting: Primary care centers and hospital outpatient clinics	Moderate-to-very severe COPD (FEV ₁ <80% predicted) Subgroup data by disease severity
Matkovic, 2012 ⁷⁵	Prospective cohort [1 month] N=155	Country: Spain Setting: Inpatient	Patients hospitalized at enrollment due to an exacerbation of COPD
McGhan, 2007 ⁴⁰	Retrospective cohort [up to 6 years] N=51,353	Country: US Setting: Inpatient	Patients hospitalized at enrollment due to an exacerbation of COPD
Merinopoulou, 2016 ⁸ Publications linked by named data source: Mullerova, 2014; ⁹ Punekar, 2013a; ⁷⁶ Punekar, 2013b; ⁷⁷ Punekar, 2013c; ⁷⁸ Punekar, 2015; ¹⁵ Punekar, 2014 ¹⁸ Publications linked by sample: Merinopoulou, 2015 ⁷⁹	Retrospective database [accrual years: January 1, 2011–December 31, 2013] N=44,201	Country: UK Setting: Primary and secondary care	Patients with low-to-high risk COPD (A–D; GOLD criteria [2013]) Subgroup data by disease severity and by data accrual year (2011–2013)

(Continued)

Table 1 (Continued).

Author, Year	Study Design [Length of Follow-Up], Sample Size	Country and Setting	Groups of Patients with Economic Data Available
Miravitlles, 2006 ²⁵	Cross-sectional [HRU data provided for 12-month period] N=1057	Country: Spain Setting: Outpatient	Moderate-to-severe COPD (FEV ₁ <70% predicted) Subgroup data by frequency of exacerbations in the previous year
Mittmann, 2008 ²⁰ Publications linked by sample: FitzGerald, 2007 ⁸⁰	Prospective cohort [1 year] N=609	Country: Canada Setting: Primary care	Moderate-to-very severe COPD (FEV ₁ ≤65% predicted) Subgroup data by exacerbation severity
Molinari, 2015 ⁸¹	Retrospective cohort [accrual years: 2007–2012] N=12,751	Country: France Setting: General practice	Patients hospitalized at enrollment due to an exacerbation of COPD Subgroup data by hospitalization severity and hospital admission year
Mullerova, 2014 ⁹ Publications linked by named source: Merinopoulou, 2016, ⁸ Punekar, 2013a, ⁷⁶ Punekar, 2013b, ⁷⁷ Punekar, 2013c, ⁷⁸ Punekar, 2015, ¹⁵ Punekar, 2014 ¹⁸	Retrospective cohort (mean 2.5 [SD: 1.6] years) N=52,237	Country: UK Setting: Primary care	Patients with low-to-high risk COPD (A–D; GOLD criteria [2011/2013]) Subgroup data by disease severity
Nantsupawat, 2012 ⁴⁶	Retrospective cohort [30 days' follow-up, mean 16 days] N=81	Country: US Setting: Inpatient	Mild-to-very severe COPD Subgroup data by disease severity
Nguyen, 2014 ⁴⁴	Retrospective cohort [30 days] N=4871	Country: US Setting: Inpatient	Patients hospitalized at enrollment due to an exacerbation of COPD
Nishi, 2015 ⁴⁹	Retrospective cohort [1 year] N=329,482	Country: US Setting: Inpatient and outpatient	Patients hospitalized at enrollment due to an exacerbation of COPD or who had ≥2 outpatient visits >30 days apart within 1 year of the encounter diagnosis of COPD
Pasquale, 2012 ²³	Retrospective cohort [2 years] N=8554	Country: US Setting: Inpatient and outpatient	COPD patients Subgroup data by exacerbation frequency
Philip, 2010 ⁸²	Retrospective cohort [2 years] N=30,179	Country: Australia Setting: Inpatient	Patients hospitalized at enrollment due to an exacerbation of COPD
Pitassi, 2015 ⁸³	Retrospective cohort [accrual years: 2010–2014] N=212	Country: Italy Setting: Inpatient	Moderate-to-severe COPD (GOLD criteria [2011]) in patients hospitalized for an exacerbation of COPD Subgroup data by bronchiectasis
Preto, 2012 ⁸⁴	Retrospective cohort [3 months] N=203	Country: Australia Setting: Acute care public hospitals	Patients hospitalized at enrollment due to an acute exacerbation of COPD Subgroup data by type of hospital

(Continued)

Table 1 (Continued).

Author, Year	Study Design [Length of Follow-Up], Sample Size	Country and Setting	Groups of Patients with Economic Data Available
Punekar, 2014 ¹⁸ Publications linked by named data source: Punekar, 2013a; ⁷⁶ Punekar, 2013b; ⁷⁷ Punekar, 2013c; ⁷⁸ Punekar, 2015a; ¹⁰ Punekar, 2015b ¹⁵ Publications linked by sample: Punekar, 2013a; ⁷⁶ Punekar, 2013c ⁷⁸	Retrospective cohort [12 months] N=58,589	Country: UK Setting: General practice	Mild-to-very severe COPD (GOLD criteria [2006]) Subgroup data by disease stage (1–4) and frequency of exacerbations
Punekar, 2015a ¹⁰ Publications linked by named data source: Punekar, 2013a; ⁷⁶ Punekar, 2013b; ⁷⁷ Punekar, 2013c; ⁷⁸ Punekar, 2014 ¹⁸ Punekar, 2015b ¹⁵	Retrospective cohort [24 months] N=7881	Country: UK Setting: Primary care	Mild-to-very severe COPD (GOLD criteria [2006]) Subgroup data by disease severity
Punekar, 2015b ¹⁵ Publications linked by named data source: Punekar, 2013a; ⁷⁶ Punekar, 2013b; ⁷⁷ Punekar, 2013c; ⁷⁸ Punekar, 2014 ¹⁸ Punekar, 2015a ¹⁰ Publications linked by sample: Punekar, 2013b ⁷⁷	Retrospective cohort [12 months] N=39,639	Country: UK Setting: General practice	Patients on triple therapy (assumed to have moderate-to-very severe COPD) Subgroup data by type of treatment
Quintana, 2014 ⁴³	Prospective cohort [2 months] N=2332	Country: Spain Setting: Inpatient including ED	Patients visiting ED at enrollment, of whom a portion were hospitalized
Roberts, 2011a ³¹ Publications linked by sample: Short, 2013 ⁸⁵	Retrospective cohort [NR] N=6576	Country: US Setting: Inpatient	Patients hospitalized at enrollment due to an exacerbation of COPD
Roberts, 2011b ⁸⁶	Retrospective cohort [90 days] N=9716	Country: UK Setting: Inpatient	Patients hospitalized at enrollment due to an exacerbation of COPD
Sharafkhaneh, 2014 ⁸⁷	Retrospective cohort [1 year] N=66,004	Country: US Setting: NR (claims database)	Subgroup data on COPD patients with ≥1.5 doses of SABA per day compared with <1.5 doses
Short, 2013 ⁸⁵	Prospective cohort [30 days] N=1343	Country: UK Setting: Inpatient	Patients hospitalized at enrollment due to an exacerbation of COPD
Silver, 2010 ³² Publications linked by named data source: Dalal, 2010; ⁶² Lindenauer, 2006; ⁶³ Xu, 2012 ²¹	Cross-sectional [NA] N=69,841	Country: US Setting: Inpatient	Patients hospitalized at enrollment due to an exacerbation of COPD
Small, 2016 ²⁷	Cross-sectional [NA] N=420	Country: Japan Setting: General practice	Subgroup data by dyspnea severity

(Continued)

Table 1 (Continued).

Author, Year	Study Design [Length of Follow-Up], Sample Size	Country and Setting	Groups of Patients with Economic Data Available
Stanford, 2006 ³⁶	Retrospective cohort [30 days] N=NR [number of hospital encounters, N=59,735]	Country: US Setting: ED and inpatient	Patients hospitalized at enrollment due to an exacerbation of COPD Subgroup data by type of hospital admission
Steer, 2015 ⁸⁸	Prospective cohort [1 year] N=183	Country: UK Setting: Outpatient	Patients hospitalized at enrollment due to an exacerbation of COPD (with data available following discharge from hospital) Subgroup data by ventilation use
Stefan, 2014 ⁸⁹	Prospective cohort [NR] N=3520	Country: US Setting: Inpatient	Patients admitted to ICU at enrollment due to a severe acute exacerbation of COPD
Stefan, 2015 ⁹⁰	Retrospective cohort [1 year] N=NR [number of COPD admissions, N=723,560]	Country: US Setting: Inpatient	Patients hospitalized at enrollment due to an acute exacerbation of COPD
Suissa, 2012 ⁴²	Retrospective cohort [17 years] N=73,106	Country: Canada Setting: NR (health insurance program database study)	Patients with first-ever hospitalization at enrollment due to a severe exacerbation of COPD
Thomas, 2014 ¹¹ Publications linked by sample: Thomas, 2011 ⁹¹	Retrospective cohort [3 years] N=511	Country: UK Setting: General practice	Mild-to-very severe COPD (mild-to-moderate: FEV ₁ ≥50% predicted; severe: FEV ₁ 30–49% predicted; and very severe: FEV ₁ <30% predicted; NICE guideline [2010]). Subgroup data by disease severity and exacerbation frequency
Tran, 2016 ⁵¹	Retrospective cohort [6 months] N=210	Country: US Setting: Inpatient	Patients hospitalized at enrollment due to an acute exacerbation of COPD
Valido, 2014 ¹³	Retrospective cohort [4 months] N=100	Country: Spain Setting: NR	COPD patients Subgroup data by frequency of exacerbations
Vallabhajosyula, 2015 ³⁸	Retrospective cohort [5 years from discharge] N=1145	Country: US Setting: Inpatient	Patients treated for an acute exacerbation at enrollment
Vitacca, 2007 ⁹²	Retrospective cohort [1 year] N=289	Country: Italy Setting: Inpatient and outpatient	Patients on home mechanical ventilation (assumed to have severe disease)
Vitacca, 2011 ²⁶	Prospective cohort [1 year] N=83	Country: Italy Setting: Outpatient	Very severe COPD (FEV ₁ <30% predicted) Subgroup data by type of home treatment

(Continued)

Table 1 (Continued).

Author, Year	Study Design [Length of Follow-Up], Sample Size	Country and Setting	Groups of Patients with Economic Data Available
Wang, 2005 ⁹³	Retrospective cohort [phase I/ baseline data: 12 months; Phase II/follow-up from hospital discharge: 2.5 years] Phase I: N=282 Phase II/follow-up from hospital discharge: N=54	Country: Canada Setting: Inpatient	Moderate-to-very severe COPD (FEV ₁ <80% predicted) in patients hospitalized for an acute exacerbation of COPD at enrollment to the study
Xu, 2012 ²¹ Publications linked by named data source: Dalal, 2010; ⁶² Lindenauer, 2006; ⁶³ Silver, 2010 ³²	Retrospective cohort [NR] N=21,017	Country: US Setting: Inpatient	Patients hospitalized at enrollment into the study due to an acute exacerbation of COPD
Yeo, 2006 ¹⁶	Cross-sectional [NA] N=27	Country: UK Setting: General practice	Moderate-to-very severe COPD (FEV ₁ <80% predicted; BTS guidelines [1997]) Subgroup data by disease severity
Yu, 2011 ⁹⁴	Retrospective cohort [mean 2.9 (SD: 1.3) years] N=228,978	Country: US Setting: Hospital (healthcare service claims)	Patients with ≥1 COPD exacerbation recorded in the Thomson Reuters MarketScan administrative claims database Subgroup data by severity of exacerbations per patient-quarters

Abbreviations: BODE, Body mass index, airflow Obstruction, Dyspnea and Exercise capacity; BTS, British Thoracic Society; COPD, chronic obstructive pulmonary disease; DD, diastolic dysfunction; ED, emergency department; FEV₁, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRU, healthcare resource utilization; ICU, intensive care unit; LTOT, long-term oxygen therapy; NA, not applicable; NICE, National Institute for Health and Care Excellence; NIV, non-invasive ventilation; NR, not reported; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; SABA, short-acting β_2 -agonist; SD, standard deviation; UK, United Kingdom; US, United States.

severity, with mean length of stay being 8.8 days for patients with mild disease and 16.7 days for patients with severe disease.¹⁴ In studies that did not report length of stay

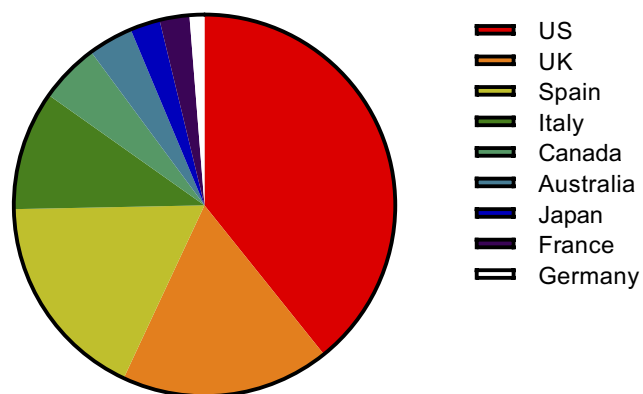


Figure 2 Location of included studies.

Notes: Australia (n=3), Canada (n=4), France (n=2), Germany (n=1), Italy (n=8), Japan (n=2), Spain (n=14), UK (n=14), US (n=31). Some publications reported data from multiple countries.

Abbreviations: UK, United Kingdom; US, United States.

according to disease severity, the shortest mean duration reported was 3.24 days (for patients with no diastolic dysfunction) in a US-based study¹⁹ and the longest was 13.2 days in a Canada-based study.²⁰ ICU admission rates were not reported according to disease severity, but ranged from 5% of all hospitalized exacerbations in a study conducted in Spain¹² to 19% of all hospitalized exacerbations in a US-based study.²¹

It is also important to note that the review identified several studies showing increased COPD-associated HRU with exacerbation frequency and the severity of COPD symptoms, particularly breathlessness/dyspnea. Exacerbations are a key driver of HRU by patients with COPD and studies captured in this SLR indicated that patients who experienced more exacerbations had more frequent primary care interactions,^{11,18,22,23} visits to the emergency department (ED),^{22,23} hospitalizations^{13,18,22–25} and admissions to the ICU^{13,22} than patients with fewer exacerbations did.

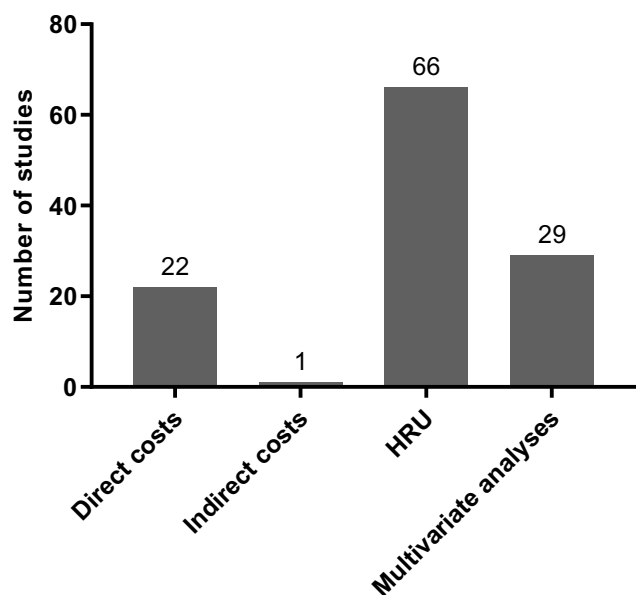


Figure 3 Number of studies reporting on each outcome.
Abbreviation: HRU, healthcare resource utilization.

Similarly, a retrospective study conducted in the UK primary care setting noted that the rate of hospitalization for a severe exacerbation within a 24-month observation period was 0.12 for patients with moderate breathlessness, increasing to 0.14 and 0.19 for patients with severe and very severe breathlessness, respectively.¹⁰ A similar trend was noted for GP home visits, though rates for GP surgery visits were slightly higher for patients with moderate breathlessness (13.00) than those with very severe breathlessness (12.22).¹⁰

Direct Costs

Direct costs were reported by a total of 22 studies and a full summary of these results is presented in [Supplementary Table 5](#). In the interests of brevity, we focus here on mean costs PPPY and mean costs per exacerbation, though differences in currencies and cost years mean that comparisons should be interpreted with caution.

In total, nine studies presented mean costs PPPY and demonstrated that costs can vary widely across and within countries, and according to patient or disease characteristics.^{7,15,18,23,24,26–29} The lowest mean costs PPPY were reported for a population of patients with mild COPD in Italy: €1047 PPPY (cost year, 2004).⁷ The highest costs reported were also found in Italy, not unexpectedly for patients with very severe COPD, whose mean costs PPPY amounted to €38,820 (cost year, not reported [NR]).²⁶

Three studies specifically reported costs according to disease severity, demonstrating clear trends. In two studies based in the UK, costs PPPY increased from £2012–£2087 in patients with moderate disease, to £2092–£2290 in patients with severe disease and to £2258–£2639 in patients with very severe disease (cost year, 2011).^{10,18} A similar trend was observed in Italy: costs PPPY increased from €2319 in patients with moderate disease to €3752 in patients with severe disease and to €5033 in patients with very severe disease (cost year, 2004).⁷

Three studies presented mean costs PPPY according to patient or disease characteristics. A study based in Japan observed a large discrepancy in costs according to presence and severity of dyspnea: patients with moderate-to-severe dyspnea (Medical Research Council [MRC] score ≥ 2) had mean costs PPPY of €6348, compared with only €2797 for patients with mild or no dyspnea (MRC score < 2 ; cost year, 2015).²⁷ A retrospective study based in the UK healthcare setting also noted higher costs PPPY for patients with more severe breathlessness, but the differences according to severity were smaller: £2258 for very severe breathlessness, £2151 for severe breathlessness and £2012 for moderate breathlessness.¹⁰ A trend according to increased costs with comorbidities was also noted; as an example, patients with heart disease had higher costs PPPY compared with patients without heart disease in a study conducted in Spain: €2898.66 vs €1672.64, respectively (cost year, NR).²⁸

This SLR also found that annual costs per patient generally increased according to exacerbation frequency. A study conducted in the UK (cost year, 2011), for example, noted that annual per patient costs related to COPD increased from £1523 in patients with no exacerbations, to £2405 in patients with one exacerbation, and to £3396 in patients with ≥ 2 exacerbations, in the 12 months following study entry.¹⁸ The impact of exacerbation history as a driver of direct costs will be explored in greater detail in a later section of this review.

Exacerbations account for a substantial proportion of the direct costs associated with COPD, and this SLR captured seven studies that reported mean costs per exacerbation,^{20,21,24,29–32} but few studies reported this outcome according to exacerbation severity. Two studies reported mean costs per moderate exacerbation (characterized by the need for management with COPD-specific antibiotics or oral corticosteroids, or a medical diagnosis), which ranged from \$269 in the US (US dollars [USD]; cost year, 2011)²⁹ to \$641 in Canada (Canadian dollars [CAD]; cost year, 2006).²⁰ Where mean costs were

reported for severe exacerbations (defined by the need for hospitalization),^{20,21,24,29–32} costs were higher than those reported for moderate exacerbations. The lowest reported mean cost for a hospitalized exacerbation was \$3164 in Italy (USD; cost year, 2013),³⁰ while the highest was substantially greater: \$18,120 in the US (USD; cost year, 2011).²⁹ The wide range of costs across countries is notable, even when being mindful of differences in currencies and cost years.

Although cross-trial comparisons are challenging due to differences in currencies and cost years, this SLR indicates that, consistent with the higher rates of HRU noted with increasingly severe disease and COPD symptoms, and more frequent exacerbations, direct costs generally increase alongside COPD and symptom severity, and exacerbation frequency. Specific independent drivers of direct costs will be explored by examining multivariate analyses in a later section of this review.

Indirect Costs

Only one study on indirect costs, conducted in Spain, was identified.²⁸ This study reported on outpatients with moderate-to-very severe COPD ($FEV_1 < 80\%$ predicted) and found a statistically significant difference in the cost of sick leave days PPPY in those without heart disease (€76.61) compared with those with heart disease (€38.33 [cost year, NR]; $p < 0.05$). This SLR did not identify any studies that explored potential predictors of indirect costs in patients with moderate-to-very severe COPD.

Key Drivers of Economic Burden

This SLR identified 29 studies in which multivariate analyses were performed to explore potential drivers of economic burden in patients with moderate-to-very severe COPD. Of these studies, 24 reported multivariate analyses of HRU outcomes (Table 2; [Supplementary Table 6](#)) and seven reported direct costs (Table 3; [Supplementary Table 7](#)).

HRU

Independent drivers of more frequent hospitalization for a COPD- or respiratory-related cause included increasing disease severity,³³ restricted lung function³³ and higher baseline C-reactive protein concentrations.³⁴ Increasingly severe disease was also an independent driver of more frequent non-COPD-related hospitalizations,³⁵ as were the number of previous exacerbations, use of short-acting

β_2 -agonists (SABA) and use of long-term oxygen therapy (LTOT) among other variables.²⁵

Factors independently associated with longer hospital stays for a COPD exacerbation were numerous and were reported in six studies.^{31,32,36–39} Drivers included the presence of comorbidities such as stroke³¹ and some cardiac abnormalities,^{31,32} advancing age and being female.³⁶ Furthermore, specific care-related factors such as a hospital's size, location or type were also found to be independent drivers of length of stay. Increased hospital size, for example, was associated with longer stays but admission to a teaching hospital was associated with shorter stays compared with a non-teaching hospital.³⁶

Some cardiac abnormalities, such as congestive heart failure and dysrhythmia,³² alongside pneumonia, anemia and anxiety or depression among other comorbidities, were identified as independent drivers of ICU admission.³² Severe COPD (indicated by the use of home oxygen, oral/intravenous steroids, vasopressors or ventilation) and higher B-type natriuretic peptide levels were both found to be drivers of longer ICU stays.³⁸

Eight studies analyzed potential drivers of COPD-related readmission to hospital for patients admitted with an exacerbation of COPD.^{39–46} Among those that explored readmission for another exacerbation in the shorter term (within 30 days or within 2 months), history of coronary heart disease,⁴⁶ hospitalizations in the previous year⁴⁴ and baseline $FEV_1 < 30\%$ predicted (vs $\geq 50\%$ predicted)⁴³ were identified as independent drivers of increased readmission risk, but this is not an exhaustive summary. Interestingly, though perhaps not surprisingly, taking 150 mins of moderate-to-strenuous exercise each week was independently associated with a lower risk of readmission for an exacerbation within 30 days.⁴⁴ Regular physical activity was also independently associated with lower readmission risk in another study.³⁹ Studies that assessed risks of readmission for another exacerbation in the longer term (with follow-ups ranging from 1 to 6 years) identified congestive heart disease and pulmonary heart disease as independent drivers of increased risk.⁴¹ Notably, ischemic heart disease and cardiac arrhythmia were also identified as drivers of increased readmission risk, but only in female patients.⁴¹ Being male^{40,42} and having a history of previous hospital stays⁴⁰ were similarly associated with an increased risk of readmission. Factors identified as drivers of lower readmission risk for a COPD-related cause in the long term included Hispanic ethnicity and diabetes.⁴⁰

Table 2 Multivariate Analyses of HRU (n=24 Studies)

Type of HRU	Independent Drivers (Positive)	Independent Drivers (Negative)
Hospitalization For a COPD exacerbation or respiratory cause	Restricted lung function; ³³ GOLD stages 0–4 (vs normal lung function); ³³ baseline hypercapnia; ³⁴ C-reactive protein concentration (47.8–100 mg/L; >100 mg/L) ³⁴	NR
For any cause	Use of LTOT; ²⁵ increasing number of previous exacerbations; ²⁵ use of SABA; ²⁵ SGRQ total score; ²⁵ incomplete primary education; ²⁵ disease severity ³⁵	NR
Length of hospital stay for a COPD exacerbation	Level of hospital (number of discharges for acute COPD exacerbations); ³⁹ diagnosis of reflux esophagitis; ³⁷ cor pulmonale; ³¹ stroke; ³¹ left ventricular failure; ³¹ cardiac arrhythmia/dysrhythmia; ^{31,32} other malignant disease; ³¹ thromboembolic disease; ³¹ locomotor problems; ³¹ number of comorbid conditions (vs none); ³¹ congestive heart failure; ³² pulmonary vascular disease; ³² pneumonia; ³² intrathoracic malignancies; ³² anemia; ³² renal failure; ³² weight loss; ³² anxiety/depression; ³² age; ³⁶ female (vs male); ³⁶ CCI; ³⁶ East/South US-based (vs North-based); ³⁶ hospital size; ³⁶ referral, transfer or routine admission (vs ED admission); ³⁶ ICU treatment; ³⁶ intubation; ³⁶ severe COPD; ³⁸ BNP level ³⁸	No diagnosis of reflux disease; ³⁷ chronic airway obstruction (vs chronic bronchitis); ³⁶ West US-based (vs North-based); ³⁶ Medicaid plan (vs Medicare); ³⁶ Blue Cross/Blue Shield (vs Medicare); ³⁶ health maintenance organization (vs Medicare); ³⁶ commercial (vs Medicare); ³⁶ other plan (vs Medicare); ³⁶ teaching hospital (vs non-teaching); ³⁶ other route of admission (vs ED admission) ³⁶
ICU Admission	Congestive heart failure; ³² cardiac dysrhythmia; ³² pulmonary vascular disease; ³² pneumonia; ³² anemia; ³² renal failure; ³² weight loss; ³² anxiety/depression ³²	NR
Length of stay	Severe COPD; ³⁸ BNP level ³⁸	NR
GP/traditional healthcare provider visits	Female gender; ¹⁰ obesity; ¹⁰ depression; ¹⁰ anxiety; ¹⁰ presence of ≥ 1 comorbidity ¹⁰	NR
Ventilation	Year (annual change); ⁹⁰ age-by-year interaction, ≥ 85 years (vs <65 years); ⁹⁰ Gagne Comorbidity score (vs ≤ 1); ⁹⁰ presence of concomitant pneumonia (vs no pneumonia); ⁹⁰ previous admissions for COPD; ⁹⁰ BNP level ³⁸	Female (vs male); ⁹⁰ age-by-year interaction, 65–74 years, 75–84 years (vs <65 years); ⁹⁰ race-by-year interaction, Hispanic, black or other race (vs white race) ⁹⁰
Readmission For a COPD exacerbation or respiratory cause	History of coronary artery disease; ⁴⁶ unilateral pulmonary infiltrates on admission; ⁴⁶ hospitalizations in previous year; ^{43,44} anemia; ⁴⁴ ≥ 3 chronic conditions; ⁴⁴ new oxygen prescription at discharge; ⁴⁴ baseline FEV ₁ % predicted <30% (vs $\geq 50\%$); ⁴³ baseline dyspnea (MRC score 5 vs 1); ⁴³ dyspnea 1 week post-index ED visit; ⁴³ ischemic heart disease (women only); ⁴¹ congestive heart disease; ⁴¹ arrhythmia (women only); ⁴¹ pulmonary heart disease; ⁴¹ CCI; ⁴¹ male gender; ^{40,42} modified chronic disease score (vs first quartile); ⁴² pulmonary hypertension; ⁴⁰ prior hospitalization; ⁴⁰ asthma; ⁴⁰ age; ⁴⁰ no inclusion in a hospital-at-home program; ³⁹ severity of bronchiectasis ⁴⁵	Age (per 10 years); ⁴² cohort entry after year 2000; ⁴² previous COPD diagnosis; ³⁹ LTOT use; ³⁹ better FEV ₁ % predicted; ³⁹ regular physical activity; ^{39,44} diabetes (complicated or uncomplicated); ⁴⁰ hypertension (complicated or uncomplicated); ⁴⁰ Hispanic race ⁴⁰

(Continued)

Table 2 (Continued).

Type of HRU	Independent Drivers (Positive)	Independent Drivers (Negative)
For any cause ^a	Previous hospitalization; ⁴⁷ moderate/severe liver disease; ⁴⁷ paraplegia; ⁴⁷ pulmonary hypertension; ⁴⁷ substance abuse; ⁴⁷ heart failure; ⁴⁷ cor pulmonale; ³¹ lung cancer; ³¹ neurologic condition; ³¹ left ventricular failure; ³¹ alcohol-related condition; ³¹ ischemic heart disease; ³¹ diabetes; ³¹ number of conditions ³¹	Other cardiovascular disease ³¹
ED visits ^b	COPD severity; ³⁵ emotional intelligence ⁴⁸	NR
LTOT	Low socioeconomic status; ⁴⁹ Elixhauser Comorbidity score (vs 0); ⁴⁹ study recruitment years 2002–2008 (vs 2001); ⁴⁹ US region (vs New England) ⁴⁹	Age ≥85 years (vs 66–74 years); ⁴⁹ male gender; ⁴⁹ black or other race (vs white race); ⁴⁹ study recruitment year 2009–2010 (vs 2001) ⁴⁹
High HRU ^c	London Chest Activity of Daily Living Scale score; ⁵⁰ leukocyte count; ⁵⁰ fibrinogen level ⁵⁰	Hemoglobin oxygen saturation ⁵⁰

Notes: ^aLiving alone, COPD exacerbation frequency and not having a family doctor were also described as drivers through multivariate analysis, but inconsistencies in data reporting rendered these results difficult to interpret in terms of the nature of their association.⁹³ ^bAge, comorbidity, FEV₁, % predicted, SGRQ total score, COPD exacerbation frequency, LTOT and not having a family doctor were also described as drivers through multivariate analysis, but inconsistencies in data reporting rendered these results difficult to interpret in terms of the nature of their association.⁹³ ^cDefined as admission for a COPD exacerbation, ≥2 ED visits for COPD exacerbations or ≥2 unscheduled outpatient visits related to COPD.

Abbreviations: BNP, B-type natriuretic peptide; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; ED, emergency department; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV₁, forced expiratory volume in 1 s; GP, general practitioner; HRU, healthcare resource utilization; ICU, intensive care unit; LTOT, long-term oxygen therapy; MRC, Medical Research Council; NR, not reported; SABA, short-acting β_2 -agonist; SGRQ, St. George's Respiratory Questionnaire; US, United States.

Table 3 Multivariate Analyses of Direct Costs (n=7 Studies)

Measure of Direct Costs	Independent Drivers (Positive)	Independent Drivers (Negative)
Costs per patient	MRC dyspnea scale score; ²⁷ receipt of appropriate pharmacotherapy with an inhaled bronchodilator (vs no receipt); ⁵¹ older age (vs younger age); ⁵¹ higher pre-index costs; ⁵¹ longer length of stay at baseline admission; ⁵¹ black or other race (vs white race); ²³ income (high vs not high ^a); ²³ cardiovascular disease (vs no cardiovascular disease); ²³ diabetes (vs no diabetes); ²³ ICS + LABA maintenance medication; ²³ LAMA maintenance medication; ²³ LABA maintenance medication; ²³ LTOT use; ²³ exacerbation severity; ²³ health plan type (vs preferred provider organization); ²⁹ Deyo-Charlson Comorbidity Index; ²⁹ prescription fills for SAMA rescue medications; ²⁹ exacerbation frequency ²⁹	Age; ²³ Northeast US geographical region (vs South); ²⁹ prescription fills for fixed-dose ICS + LABA rescue medication ²⁹
Costs per hospitalized exacerbation ^b	Hispanic race (vs white race); ³¹ age; ³⁶ CCI; ³⁶ female gender (vs male); ³⁶ emphysema (vs chronic bronchitis); ³⁶ ICU treatment (vs no ICU treatment); ³⁶ intubation; ³⁶ East or West US geographical location (vs North); ³⁶ hospital size (medium or large vs small); ³⁶ congestive heart failure; ³² ischemic heart disease; ³² cardiac dysrhythmia; ³² pulmonary vascular disease; ³² pneumonia; ³² intrathoracic malignancies; ³² anemia; ³² renal failure; ³² weight loss/cachexia; ³² anxiety and depression ³²	South US geographical location (vs North); ³⁶ transfer; routine or other admission (vs ED admission); ³⁶ Medicaid or Blue Cross/Blue Shield (vs Medicare); ³⁶ health maintenance organization or commercial cover (vs Medicare) ³⁶

Notes: ^aHigh income was defined as income ≥\$52,480 (USD). ^bCOPD severity, length of hospital stay, number of days in the ICU and treatment in an urban hospital or teaching hospital were also identified as significant drivers of direct costs, but the direction of the association was not clearly reported.³¹

Abbreviations: CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; ED, emergency department; ICS, inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTOT, long-term oxygen therapy; MRC, Medical Research Council; SAMA, short-acting muscarinic antagonist; US, United States; USD, United States dollars.

The majority of factors found to be independently associated with an increased risk of readmission for any cause were comorbidities, ranging from liver disease, paraplegia and substance abuse,⁴⁷ to neurologic conditions and heart disease.³¹ Having an increased number of comorbid conditions was also associated with an increased risk of readmission.³¹

For drivers of primary care utilization, associations between more frequent GP visits and being female, suffering with obesity, depression, anxiety or other comorbidities were noted in one retrospective cohort study.¹⁰ Emergency department visits of any cause were found to be independently associated with COPD severity,³⁵ age, comorbidity, exacerbation frequency¹⁰ and emotional intelligence,⁴⁸ among other factors. One study reported on potential drivers of LTOT and found that female gender, white race (vs black or other races), low socioeconomic status and a higher Elixhauser Comorbidity score (among other variables) were independently associated with an increased likelihood of receiving such therapy.⁴⁹

A cross-sectional study among patients with COPD in Spain identified drivers of high HRU, defined as having had one hospital admission for a COPD exacerbation, ≥ 2 ED visits for COPD exacerbations or ≥ 2 unscheduled outpatient visits related to COPD in the previous year. Independent drivers included London Chest Activity of Daily Living (LCADL) scale score, leukocyte count and fibrinogen level.⁵⁰

Direct Costs

Increasingly severe dyspnea was identified as an independent driver of higher annual COPD management costs per patient,²⁷ while older age, receipt of appropriate bronchodilator therapy and higher pre-index COPD-related costs⁵¹ were found to be independent predictors of higher COPD-related costs per patient at 6 months after discharge. In two retrospective cohort studies that assessed potential drivers of annual exacerbation costs for patients with chronic bronchitis, numerous independent drivers were identified. Regarding increased annual exacerbation costs per patient, these included being of black race, high income, comorbid cardiovascular disease and comorbid diabetes, among other factors.²³ Independent drivers of higher costs per individual exacerbation (of any severity) in patients with chronic bronchitis included Deyo-Charlson's Comorbidity Index score, the number of exacerbations during the previous year and the number of prescription fills for short-acting muscarinic antagonist (SAMA) therapy, among other factors.²⁹

Potential drivers of costs per hospitalized exacerbation were assessed in three studies conducted in the US.^{31,32,36} Independent predictors of higher costs included cardiac comorbidities, such as congestive heart failure and ischemic heart disease,³² the nature of the patient's COPD (emphysema vs chronic bronchitis), as well as advancing age,³⁶ Hispanic race (vs white race), and ICU treatment,^{31,36} among other factors. Severity score was also described as a predictor of costs, but the nature of this association was unclear in the source publication.³¹

Discussion

It is important to understand the economic burden associated with moderate-to-very severe COPD and its treatment, particularly given that COPD presents major challenges for patients, healthcare providers and society. Optimal management of patients, their symptoms and exacerbations is one such challenge. This SLR investigated the current impact of COPD on HRU needs and both direct and indirect costs, based on a broad definition of patients whose COPD severity was typically confirmed by FEV₁% predicted or assumed (from exacerbation history) to be at least moderate. The analysis was intentionally limited to nine industrialized countries of interest (and to a 10-year time frame) to ensure inclusion of evidence from settings where patients were likely to be receiving guideline-recommended therapeutic management; the US was the most well-represented country.

Fewer studies reported costs compared with those that provided HRU evidence and, considering the inherent variation in geographical location, timing and methodology between the available studies, cross-study comparisons should be interpreted with caution. Overall, however, direct costs were found to generally increase with COPD severity, exacerbation frequency and severity of COPD symptoms. The SLR also found higher rates of HRU, in terms of hospitalization, length of hospital stay and primary care interactions, for patients with more severe COPD, more frequent COPD exacerbations and more severe COPD symptoms.

As shown by the numerous studies that performed multivariate analyses, independent drivers of HRU and costs are diverse. Factors related to disease severity, the frequency and severity of COPD exacerbations, comorbidities and treatment history (among others) were significantly associated with elements of HRU, ranging from hospitalization to LTOT. More severe COPD and a history of frequent exacerbations, for example, were

each positively associated with an increased likelihood of hospitalization.^{25,33,35} Disease severity was also identified as a driver of ED visits,³⁵ and longer hospital or ICU stays.³⁸ These multivariate data support trends reported in other studies, captured both in this SLR and others in the broader literature. As an example, a cross-sectional survey conducted across France, Germany, Italy, Spain and the UK found that moderate-to-severe dyspnea was associated with a significant disease burden in patients with COPD, and was associated with significantly more frequent hospitalizations, specialist and physician consultations, LTOT use and pulmonary rehabilitation (all $p < 0.0001$).⁵²

Examining multivariate analyses of direct costs per patient for COPD also identified dyspnea severity,²⁷ and exacerbation frequency²⁹ and severity²³ as significant drivers. This was perhaps to be expected: a more intensive treatment regimen may be required to manage symptoms and/or exacerbations and thus is likely to carry a burden of increased costs. These results are in keeping with the SLR of economic burden in COPD by Srivastava et al (2015), which found that direct and indirect costs per patient increased with symptoms, dyspnea severity and disease duration.⁵³ The data are also supported by results reported by other studies captured in this SLR that did not employ multivariate analyses: trends for higher costs according to more severe disease were noted in both Italy^{7,26} and the UK.^{10,18}

Other key drivers identified through multivariate analysis as predictors of economic burden in moderate-to-very severe COPD included the number of previous exacerbations, as well as the presence and types of comorbidities. Comorbidities have frequently been associated with significantly higher costs for patients with COPD in the wider literature.^{53–56} An SLR of 12 studies from the US and across Europe/Asia that analyzed the excess costs of comorbidities in COPD found that pneumonia, cardiovascular disease and diabetes were associated with the highest excess costs.⁵⁵ This SLR supports these findings: comorbid diabetes and comorbid cardiovascular disease were found to be potential predictors of annual exacerbation-related costs²³ and pneumonia was found to be an independent predictor of the cost of exacerbation-related hospitalization.³² These findings highlight the importance of careful management of comorbidities alongside optimal COPD-specific therapy, to minimize HRU and associated costs.

A limitation of this study was perhaps the paucity of data available on indirect costs. However, among the studies identified by the SLR was a 2016 population-based survey across 12 countries (including the US, the UK, Germany, Italy and Spain), which described how indirect costs were several times greater than direct costs in many countries.³⁰ This highlights the extreme, and often hidden, economic burden carried by loss of productivity and absenteeism. A US-based survey focusing on all COPD severities (not just moderate-to-very severe) observed that COPD-attributable absenteeism accounted for costs of approximately \$3.9 billion dollars in 2010, with an estimated 16.4 million work days lost due to COPD; these costs are expected to rise in coming years.⁵⁷ With their clear impact on economic burden, the indirect costs of COPD certainly warrant further investigation across regions and healthcare systems.

This study employed a pragmatic approach and allowed a flexible definition of moderate-to-very-severe COPD, though this automatically introduced a degree of between-study heterogeneity in the SLR, which made comparing data between studies more challenging. Nonetheless, many of the key outcomes were consistently demonstrated across studies, and, where possible, we qualitatively compared HRU and costs according to disease severity. The trends observed and inferences made through qualitative analysis were supported by multivariate analysis studies captured by this SLR, which were specifically designed to identify independent predictors of COPD's economic burden.

This study focused on moderate-to-very severe COPD: studies examining only mild COPD were excluded. Although widening the search parameters may have delivered a more comprehensive dataset, COPD is underdiagnosed in its early stages. As many patients do not become known to healthcare systems until their disease has advanced to moderate-to-severe stages,⁵⁸ it is likely that the parameters employed by this SLR captured the majority of patients with a confirmed COPD diagnosis.

This SLR provides detailed evidence of the considerable real-world economic burden carried by moderate-to-very severe COPD, especially for patients with a history of exacerbations and/or more severe COPD, despite the availability of efficacious treatments and well-defined guidance on their use.

With worldwide healthcare budgets facing increasing financial pressures, understanding the economic burden of diseases such as COPD is essential to ensure that the

disease is managed efficiently and that emerging therapies are made available to the patients who need them. Further progress in the management of COPD exacerbations and HRU is required to improve patient care and to reduce the associated strain on healthcare budgets around the world.

Abbreviations

AAAAI, American Academy of Allergy, Asthma, and Immunology; ATS, American Thoracic Society; CAD, Canadian dollar; CONSORT, Consolidated Standards of Reporting Trials; COPD, chronic obstructive pulmonary disease; ED, emergency department; ERS, European Respiratory Society; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GP, general practitioner; HRU, healthcare resource utilization; ICS, inhaled corticosteroid; ICU, intensive care unit; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LCADL, London Chest Activity of Daily Living; LTOT, long-term oxygen therapy; MRC, Medical Research Council; NR, not reported; PPPY, per patient per year; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SABA, short-acting β_2 -agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; SLR, systematic literature review; UK, United Kingdom; US, United States.

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Author Contributions

All authors contributed to the study conceptualization, data sourcing, data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare the following conflicts of interest during the last 3 years in relation to this article: SZ and ASI are

employees of, and hold shares in, GlaxoSmithKline plc.; ASI is also a part-time unpaid professor at McMaster University, Canada. Evidera (II) was contracted by GlaxoSmithKline plc. to conduct the systematic literature review but was not paid for the development of this manuscript. MR is an employee of Xcenda UK and was previously employed by Evidera and contracted by GlaxoSmithKline plc. to conduct the systematic literature review but was not paid for the development of this publication. DK is a former GlaxoSmithKline plc. employee and is currently employed by Forest Systematic Reviews Ltd, contracted by GlaxoSmithKline plc. The authors report no other conflicts of interest in this work.

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