

Economic Burden of Chronic Obstructive Pulmonary Disease: A Systematic Review

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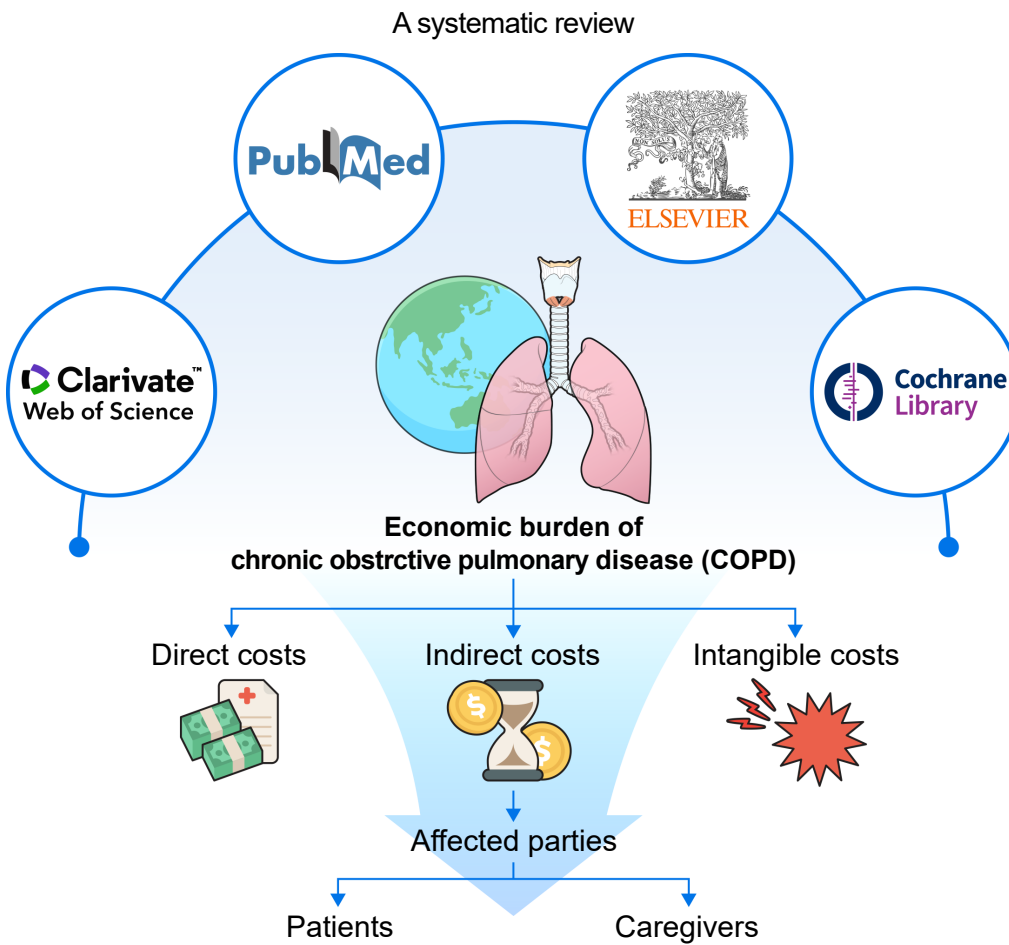
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Abstract

Globally, providing evidence on the economic burden of chronic obstructive pulmonary disease (COPD) is becoming essential as it assists the health authorities to efficiently allocate resources. This study aimed to summarize the literature on economic burden evidence for COPD from 1990 to 2019. This study examined the economic burden of COPD through a systematic review of studies from 1990 to 2019. A search was done in online databases, including Web of Science, PubMed/Medline, Scopus, and the Cochrane Library. After screening 12,734 studies, 43 articles that met the inclusion criteria were identified. General study information and data on direct, indirect, and intangible costs were extracted and converted to 2018 international dollars (Int\$). Findings revealed that the total direct costs ranged from Int\$ 52.08 (India) to Int\$ 13,776.33 (Canada) across 16 studies, with drug costs ranging from Int\$ 70.07 (Vietnam) to Int\$ 8,706.9 (China) in 11 studies. Eight studies explored indirect costs, while one highlighted caregivers' direct costs at approximately Int\$ 1,207.8 (Greece). This study underscores the limited research on COPD caregivers' economic burdens, particularly in developing countries, emphasizing the importance of increased research support, particularly in high-resource settings. This study provides information about the demographics and economic burden of COPD from 1990 to 2019. More strategies to reduce the frequency of hospital admissions and acute care services should be implemented to improve the quality of COPD patients' lives and reduce the disease's rising economic burden.

Keywords: Chronic Obstructive Pulmonary Disease; Health Economics; Financial Stress; Systematic Review

Introduction

Chronic obstructive pulmonary disease (COPD) was ranked as the third highest contributor to global mortality in 2019, accounting for 3.23 million fatalities. Additionally, COPD held the seventh position among the leading causes of disability-adjusted life years lost worldwide¹. In 2017, it was estimated that more than 300 million people were living with COPD worldwide, of which the major contributors were low- and middle-income countries². Annually, COPD causes more than three million deaths globally³. In developed countries, the cost of COPD is estimated to range from 1,030 billion in 2010 to 2,200 billion US dollars (USD) in 2030, while in developing countries the cost is projected to be USD 2,600 billion in 2030. The cost of illness per person living with COPD will reach USD 4,800 in 2030⁴. Additionally, approximately 10% of global productivity losses have been attributable to COPD, and this loss could equate to USD 6,700 per COPD patient⁵.

The costs of COPD treatment and care are burdensome. Previous literature recorded a high rate of catastrophic health expenditure (CHE) among people with COPD^{6,7}. A study in Australia observed that 46%

of participants shared CHE⁸. This exceptionally high incidence of CHEs is likely due to the significant out-of-pocket payment for COPD treatment. Some studies indicated that COPD treatment cost (USD 236.2)⁹ was superior to other severe non-communicable conditions such as mental health (USD 215)¹⁰ and ischemic heart disease (USD 78)¹¹. The average treatment cost of COPD increased from USD 6,300 in 2004 to USD 9,545 in 2010³. Hospitalization is the major cost component. The mean cost of hospitalization exceeds USD 3,500, with medical expenses making up the majority (over 45.3% [USD 1,500])³. Diagnosis and general medical expenses follow, totaling to more than USD 900 and USD 400, respectively³. In addition, a study in Greece showed that one-third of patients relied on support from family, relatives, or a supportive environment for daily activities, accounting for about 3.6 hours per day, across 4.1 days per week, of unpaid caregivers' time¹².

Previous systematic reviews and meta-analyses of intervention and treatment provided appropriate evidence for clinical practice and policy development¹³. These studies collected available empirical research evidence to answer research questions regarding the treatments and interventions for COPD¹⁴⁻¹⁶. Although

there is existing evidence concerning the economic implications of COPD, it predominantly consists of individual studies that are constrained by variables such as focusing only on a single nation^{17,18}, providing a concise overview of the economic impact of COPD¹⁹, and conducting 10 years and drawing data from three databases¹⁹. Further rigorous investigation is warranted to achieve a more comprehensive understanding of the current COPD burden in settings adhering to globally recognized treatment guidelines, such as those outlined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). This review used studies from four databases to validate the COPD economic burden worldwide, providing direct, indirect, and intangible costs of COPD.

In conclusion, this study aimed to provide evidence on the burden of COPD, which is becoming globally urgent. Our results might help health authorities improve resource allocation and encourage people to have an adequate lifestyle²⁰.

Materials and Methods

This systematic review included studies on the economic burden of COPD in the period 1990 to 2019.

1. Eligible criteria

1) Inclusion criteria

We applied the Population–Indicator–Outcomes–Study types (PIO-S) question structure to develop an inclusion criteria and search strategy for articles as follows:

(1) Population (P): People with a diagnosis and treatment for COPD or who are the caregivers of COPD patients.

(2) Indicator (I): Studies mentioned patient characteristics, COPD symptoms, and treatment type.

(3) Outcomes (O): The economic burden among studies' subjects:

- Direct cost is the cost of resources used direction

for patient care: drugs or staff.

- Indirect cost is the expenses that cannot be directly attributed to a single, specific final cost objective. Rather, these costs are related to multiple final cost objectives or serve an intermediate cost objective (production loss, transportation).
- Intangible costs are indicators that cannot be measured or quantified. Therefore, in this study, intangible cost refers to pain, suffering, social stigma, and patient quality of life change.

(4) Study types (S): Every type of preliminary study, cross-sectional, case-control, and appropriate waves of longitudinal studies, and randomized clinical trials, were eligible for inclusion.

(5) The papers of our choice were research articles and research reviews in English.

(6) Period of included research articles was 1990 to 2019.

2) Exclusion criteria

- (1) Research study is not written in English.
- (2) Systematic review and meta-analysis studies.

2. Selection of studies and data extraction

The data selection was as follows:

Step 1: The following keywords were chosen based on the experts' recommendations in the field and previous studies. The "search terms" were combined with Boolean operators "AND" to connect keywords related to COPD, population, and economic cost (Table 1).

Step 2: Web of Science, PubMed/Medline, Scopus, and the Cochrane Library were used to download the papers. Two researchers downloaded the data independently to ensure accuracy.

Step 3: The results were exported to Endnote 7 and duplicate records were removed. After that, the papers' titles and abstracts were examined to see if they satisfied the eligibility criteria based on the structured PIO-S questions. Studies that were unrelated to the

Table 1. Keywords for search strategy

| Topic | Search terms |
|------------|--|
| COPD | Chronic bronchitis OR pulmonary emphysema OR COPD OR chronic obstructive pulmonary disease OR chronic obstructive airway disease OR COAD OR chronic obstructive lung disease OR chronic airflow obstruction* |
| Population | Patients OR caregivers OR relates |
| Outcome | Cost OR economics OR economic burden OR cost analysis OR cost measures OR affordability OR productivity loss OR responsibility OR cost of illness OR quality of life |

COPD: chronic obstructive pulmonary disease; COAD: chronic obstructive airway disease.

study's goal were omitted. The full texts of studies that satisfied the selection criteria were downloaded.

Step 4: Two reviewers piloted a data extraction form, which was then used for all investigations. Each review author separately extracted: (1) author-date; (2) study design; (3) participant description; (4) sample size; (5) follow-up period; (6) outcomes; (7) study findings; and

(8) quality evaluation. The data extraction results of the two reviewers were reviewed to ensure reliability and discrepancies were solved through discussion.

3. Data analysis

Two reviewers extracted direct and indirect costs data from the dataset. After that, purchasing power parities

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the searching and screening process.

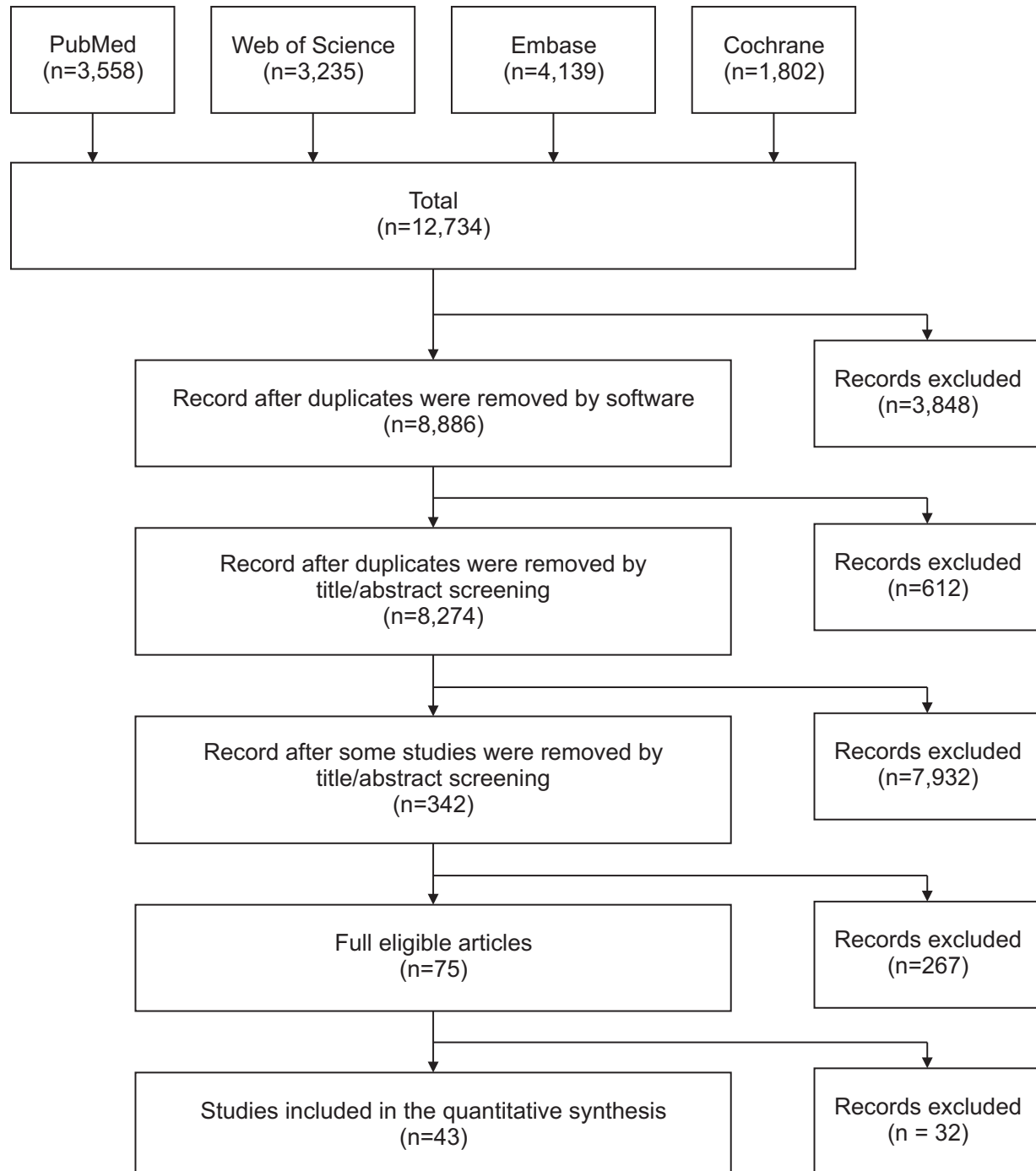


Table 2. List of included studies

| No. | Main objective | Year | Country | Sample size | Study design | Perspective | Reference |
|-----|--|------|-------------------------------|-------------|----------------------------------|----------------------|---------------|
| 1 | Assess the cost-effectiveness of a home-based disease management intervention compared to usual management (U.M.) in individuals participating in the COPD Patient Management European Trial (COMET). | 2019 | France, Italy, Germany, Spain | 319 | Health economic evaluation study | Patients | ²⁵ |
| 2 | Examine the overall healthcare costs linked to nebulized budesonide (nBUD) versus systemic corticosteroids (SCS) in patients experiencing acute exacerbations of COPD (AECOPD). | 2019 | China | 2,550 | Post hoc study | Patients | ²⁶ |
| 3 | Systematically gather prospective outcome data from household members and demonstrate how these data can be integrated into a cost-utility analysis of a behavior change intervention for individuals with COPD. | 2019 | UK | 153 | Randomized controlled-trial | Patients/ Caregivers | ²⁷ |
| 4 | Comprehensively investigate the socioeconomic impact and resource utilization associated with COPD. | 2019 | Italy | NA | Retrospective study | Patients | ²⁸ |
| 5 | Compare the utilization of healthcare resources at the end of life among three distinct groups of patients based on their "do not resuscitate" (DNR) directive status: those without a DNR directive, those with an early DNR (EDNR) directive established before entering the terminal hospitalization phase, and those with a late DNR (LDNR) directive established during the terminal hospitalization phase. | 2019 | China | 361 | Cross-sectional study | Patients | ²⁹ |
| 6 | Evaluate both the direct and indirect costs associated with severe AECOPD within a tertiary care healthcare environment located in a high-prevalence region of North India. | 2019 | India | 129 | Cross-sectional study | Patients | ³⁰ |
| 7 | Evaluate the economic burden of COPD in Greece. Additionally, the study aimed to identify and analyze potential determinants of the COPD economic burden. | 2019 | Greece | 351 | Cross-sectional study | Patients | ³¹ |
| 8 | The main objective of this study was to assess the long-term economic burden and benefits of implementing a regular program of systematic active case-finding for COPD in comparison to routine practice. | 2019 | UK | - | Cost-utility analysis | Patients | ³² |
| 9 | Investigate the association between clinically important deterioration(CID) in COPD and its impact on future economic and quality of life (QoL) outcomes. In addition, utilize a novel composite endpoint, CID, which evaluates the stability of the disease in COPD patients. | 2019 | USA | 3,769 | Post hoc study | Patients | ³³ |
| 10 | Investigate and quantify the health-seeking costs associated with chronic cough, a distressing symptom often indicative of underlying health conditions like tuberculosis and chronic airways diseases, in the context of developing countries, with a particular focus on Malawi. Explore the coping mechanisms employed by individuals facing the financial burden of seeking care for chronic cough, such as borrowing money or selling household assets. | 2019 | Malawi | 608 | Economic study | Patients | ³⁴ |

Table 2. Continued

| No. | Main objective | Year | Country | Sample size | Study design | Perspective | Reference |
|-----|--|------|---------|-------------|----------------------------------|------------------------|---------------|
| 11 | Describe the clinical and economic outcomes for patients with COPD based on their blood eosinophil (EOS) count. | 2019 | USA | 48,090 | Retrospective cohort study | Patients | ³⁵ |
| 12 | Investigate healthcare resource utilization (HCRU) and related costs in patients with COPD in a specialty care hospital setting in Finland | 2019 | Finland | 9,042 | Retrospective study | Patients | ³⁶ |
| 13 | To explore and quantify the direct medical costs associated with COPD. To identify and understand the main factors or variables that drive the costs of managing COPD. | 2018 | Vietnam | 33,617 | Retrospective study | Patients | ³⁷ |
| 14 | To evaluate the consequences of applying the GOLD 2017 grading system to existing patients in the UK primary care. To estimate the potential cost savings that could be achieved by implementing the treatment recommendations outlined in the GOLD 2017 guidelines for patients in the UK primary care. | 2018 | UK | 100 | Cohort study | Patients | ³⁸ |
| 15 | The objective of this research was to investigate the economic impact, encompassing both direct and indirect costs, experienced by COPD patients who were receiving treatment at selected tertiary care hospitals in South India. | 2018 | India | 24 | Cross-sectional study | Patients | ³⁹ |
| 16 | To investigate how these costs vary across different dimensions, including time, age, and disease stage. | 2018 | Sweden | 17,479 | Retrospective study | Patients | ⁴⁰ |
| 17 | Assess how COPD, a condition associated with numerous comorbidities and substantial healthcare resource utilization, influences the social and economic aspects in Spain. | 2018 | Spain | 386 | Retrospective study | Patients/ Caregiver | ⁴¹ |
| 18 | Measure the comprehensive burden of COPD by calculating both incremental direct and indirect costs associated with COPD. Assessing various aspects of cost, such as direct medical resource use, productivity metrics, and COPD-specific resource use and the associated expenses. | 2018 | USA | 5,701 | Retrospective study | Patients | ⁵ |
| 19 | Conduct a cost-effectiveness analysis comparing the use of free O2 technology to manual oxygen-titration technology in the treatment of COPD patients who are hospitalized for acute exacerbations. | 2018 | Canada | 47 | Health economic evaluation study | Patients | ⁴² |
| 20 | Estimate the annual cost incurred by patients with COPD during the maintenance phase in Greece. | 2018 | Greece | 245 | Retrospective study | Patients | ⁴³ |
| 21 | Determine the prevalence of COPD and cost of medical conditions treated on general internal medicine (GIM) inpatient services in seven hospital sites located in Toronto, Canada. | 2018 | Canada | 148,442 | Retrospective study | Patients | ⁴⁴ |
| 22 | Investigate the hypothesis that incorporating total healthcare cost into the body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index would improve the prediction of mortality in patients with COPD. | 2017 | Italy | 275 | Cross-sectional study | Patients | ⁴⁵ |

Table 2. Continued

| No. | Main objective | Year | Country | Sample size | Study design | Perspective | Reference |
|-----|--|------|---------------------------|-------------|-----------------------|-------------|---------------|
| 23 | Assess and understand the clinical characteristics, treatment patterns, and the socioeconomic burden of COPD in Eastern Europe, with a specific focus on Bulgaria. | 2017 | Bulgaria | 426 | Cross-sectional study | Patients | ⁴⁶ |
| 24 | Provide understanding of the cost-effectiveness of antibiotic prescriptions for COPD exacerbations and demonstrate the applicability of electronic health records (EHRs) in conducting such economic evaluations, particularly in the context of pragmatic RCTs. | 2017 | UK | 45,375 | Cohort study | Patients | ⁴⁷ |
| 25 | Explore the economic burden of COPD in Greece. | 2017 | Greece | NA | Retrospective study | Patients | ¹² |
| 26 | Evaluate the cost of treatment for patients with COPD in the context of Greece and assess the impact of the financial crisis on COPD patients. | 2017 | Greece | 189 | Cross-sectional study | Patients | ⁴⁸ |
| 27 | Analyze the association between frequent comorbidities and common symptoms and the annual direct and indirect costs incurred by patients with COPD in Germany. | 2017 | Germany | 2,139 | Cohort study | Patients | ⁴⁹ |
| 28 | Understand the disease burden associated with respiratory disorders, including allergic rhinitis (AR), asthma, COPD, and rhinosinusitis. | 2016 | South Korea | 999 | Cross-sectional study | Patients | ⁵⁰ |
| 29 | Quantify and assess the total costs associated with COPD management in urban areas of China. Explore and identify the factors that contribute to the high economic burden of COPD in these urban areas. | 2016 | China | 678 | Cross-sectional study | Patients | ⁵¹ |
| 30 | Quantify and analyze the annual cost of treating bronchiectasis (BE) in Spain, stratified by the severity of the disease as assessed by the FACED score. Identify and examine the specific parameters or factors that are associated with increased costs in the treatment of BE. | 2016 | Spain | 456 | Cohort study | Patients | ⁵² |
| 31 | Evaluate and compare the cost-effectiveness of tiotropium (TIO) and glycopyrronium (GLY) in the management of COPD. Consider the latest clinical evidence from the SPARK trial, which suggests that TIO is superior to GLY in reducing severe exacerbations. | 2016 | Canada, Sweden, Spain, UK | NA | Cohort study | Patients | ⁵³ |
| 32 | Assess and report the prevalence and severity of respiratory symptoms in adults with a primary diagnosis of AR, asthma, COPD, and rhinosinusitis. Evaluate the impact of these respiratory diseases on work productivity, including work-related impairment and activity limitations experienced by affected individuals. Analyze the economic burden associated with AR, asthma, COPD, and rhinosinusitis in terms of direct and indirect costs, including healthcare expenses and productivity losses. | 2016 | Thailand | 1,000 | Cross-sectional study | Patients | ⁵⁴ |

Table 2. Continued

| No. | Main objective | Year | Country | Sample size | Study design | Perspective | Reference |
|-----|--|------|---|-------------|----------------------------|-------------|---------------|
| 33 | Quantify and analyze the total economic burden of COPD in Italy. | 2015 | Italy | 275 | Retrospective study | Patients | ⁵⁵ |
| 34 | Evaluate the economic implications of COPD in the period an official diagnosis. Analyze the economic consequences of COPD after diagnosis. | 2014 | Denmark | 131,881 | Retrospective study | Patients | ⁵⁶ |
| 35 | Provide an overview of the economic and management aspects of COPD in the United States. | 2013 | USA | | Retrospective study | Patients | ⁵⁷ |
| 36 | Quantify and analyze the total costs associated with maintaining COPD therapy and managing acute exacerbations over a one-year timeframe. | 2012 | Canada | 285 | Retrospective study | Patients | ⁵⁸ |
| 37 | Determine how the presence of anxiety and depression, as comorbidities, affect the utilization of healthcare resources and the associated costs among individuals with COPD. | 2011 | USA | 3,761 | Cohort study | Patients | ⁵⁹ |
| 38 | Calculate and compare the annual COPD-related healthcare costs for each cohort, including both patient- and payer-paid costs. Determine the adjusted episode-level costs for various types of COPD-related visits, including outpatient, urgent outpatient, emergency department, standard admission, and intensive care unit stays. | 2010 | USA | 37,089 | Retrospective study | Patients | ⁶⁰ |
| 39 | Estimate healthcare resources utilization and costs of patients with COPD at the Italian pneumology departments. Understand how the utilization of healthcare resources and costs vary among COPD patients at different stages of the disease. | 2007 | Italy | 268 | Prospective study | Patients | ⁶¹ |
| 40 | Employing two different methods for cost estimation. The first method involved estimating the resources used and expenditures incurred by individuals with COPD that were directly attributable to the disease. Determining the average direct costs of COPD per patient, including a breakdown of costs associated with hospitalization and other healthcare utilization. | 2005 | USA | 8,300 | Retrospective study | Patient | ⁶² |
| 41 | Investigate and assess the economic burden of COPD in seven countries: Canada, France, Italy, the Netherlands, Spain, the UK, and the United States. | 2003 | Canada, France, UK, USA, Spain, Netherlands, France | 3,265 | Economic analysis | Patient | ⁶³ |
| 42 | Assess the direct medical costs associated with the provision of respiratory care for COPD patients on long-term oxygen therapy, taking into consideration both not-for-profit (NP) and profit-making (PM) health organizations responsible for home oxygen delivery. | 1996 | France | 234 | Retrospective study | Patient | ⁶⁴ |
| 43 | Assess the cost-effectiveness of bronchodilators, theophylline (T) and ipratropium bromide (IB) therapies, taking into consideration their impact on the outcome of COPD, healthcare costs, and their known toxicity profiles. | 1993 | USA | 311 | Retrospective cohort study | Patient | ⁶⁵ |

COPD: chronic obstructive pulmonary disease; NA: not available; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FACED: assessment of severity tool, validated for people with non-cystic fibrosis bronchiectasis; SPARK: Effect of QVA149 versus NVA237 and Tiotropium on COPD Exacerbations.

Table 3. Direct costs of COPD

| Study | Country | Population/ subpopulation | Total cost | Total medical cost | Pharmaceutical therapy | Outpatient cost | Total nonmedical cost |
|---------------------------------------|----------|--------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------|--------------------------|
| Dal Negro (2019) ²⁸ | Italy | Patients with COPD | 3,988.09 (95% CI, 3,594.9–4,517.3) | 2,594.26 (95% CI, 1,316.6–4,043.3) | 678.15 (95% CI, 343.4–1,012.4) | 630.00 (95% CI, 282.2–977.8) | |
| Kourilaba et al. (2019) ³¹ | Greece | Patients with COPD | 3,223.05 (95% CI, 2,816.8–3,662.3) | 2,986.19 (95% CI, 260.8–3,368.5) | 1,163.30 (95% CI, 1,077.8–1,248.7) | | |
| Corsico et al. (2019) ⁶⁶ | Italy | Patients with COPD | | 3,600.19±6,391.0 | 1,549.16±1,668.7 | | |
| Fu et al. (2019) ²⁹ | China | Patients with COPD | | 7,685.23 | 7,685.23 | | |
| Koul et al. (2019) ³⁰ | India | Patients with COPD | | 1,404.38 | 258.71 | | 108.49 |
| Lambe et al. (2019) ³² | UK | Patients with COPD | 1,098.29 | | | | |
| Vo et al. (2018) ³⁷ | Vietnam | Patients in Dong Nai Hospital | | 70.07 | | | |
| | | Patients in Pham Ngoc Thanh Hospital | | 1,291.55 | | | |
| Lakiang et al. (2018) ³⁹ | India | Patients with COPD | 1,131.99±534.8 | 514.42±324.1 | | 52.08±6.3 | 331.82±99.5 |
| Lisspers et al. (2018) ⁴⁰ | Sweden | Patients with COPD | 12,921.30 | | | | |
| Merino et al. (2018) ⁴¹ | Spain | Patients with COPD | | 2,216.79±3,002.2 | 981.07±839.0 | 509.30±1,858.9 | 1,929.97±5,452.2 |
| Poder et al. (2018) ⁴² | Canada | Patients with COPD | 13,766.33 | | | | |
| Verma et al. (2018) ⁴⁴ | Canada | Patients with COPD | 10,180.53±15,842.7 | | | | |
| Dzingina et al. (2017) ⁶⁷ | Bulgaria | Patients with COPD | 3,096.70 | | | | |
| Chen et al. (2016) ⁶¹ | China | Patients with COPD | 9,537.7±35,816.4 | 8,706.9±35,081.1 | | 1,999.54±14,833.8 | |

Table 3. Continued

| Study | Country | Population/ subpopulation | Total cost | Total medical cost | Pharmaceutical therapy | Outpatient cost | Total nonmedical cost |
|---------------------------------------|---------|------------------------------|------------|------------------------------------|--------------------------------|------------------------------|--------------------------|
| Dal Negro et al. (2015) ⁵⁵ | Italy | Patients with COPD | | 2,679.95 (95% CI, 1,316.6–4,043.3) | 678.15 (95% CI, 343.4–1,012.9) | 630.00 (95% CI, 282.2–977.8) | |
| | | Male COPD patients | | 2,724.69 (95% CI, 2,053.2–3,396.2) | 667.27 (95% CI, 525.1–809.4) | 637.34 (95% CI, 462.7–810.6) | |
| | | Female COPD patients | | 2,473.76 (95% CI, 1,462.4–2,507.0) | 688.48 (95% CI, 353.5–638.8) | 599.67 (95% CI, 403.7–795.7) | |
| Miller et al. (2005) ⁶² | USA | COPD patients | 2,507.00 | | 375.00 | | |

Values are presented as cost (95% CI) or mean \pm standard deviation. All costs are denominated in International dollars. COPD: chronic obstructive pulmonary disease; CI: confidence interval.

(PPPs) data was downloaded from the World Bank website (<https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD>). PPPs represent currency conversion rates aimed at equalizing the purchasing power of diverse currencies by adjusting for variations in price levels among countries²¹. For comparative analysis, we gathered PPP data for the year 2018 to convert all costs into international data.

In this study, we also evaluated the burden and changes in the quality of life among COPD patients reported in the previous studies, which used the scales for the COPD Assessment Test (CAT), St. George's Respiratory Questionnaire for COPD (SGRQ-C), and Caregiver Burden Questionnaire. CAT is a numerical scale questionnaire consisting of eight statements. It assesses various aspects by prompting respondents to assign a score from 0 to 5 for each of the eight areas. A score of 0 signifies no impairment in the respective area, while a score of 5 indicates severe impairment. The overall score, ranging from 0 to 40, reflects the extent to which COPD affects one's overall health and well-being, with higher scores indicating a more significant impact²². The SGRQ-C is a condensed iteration of the SGRQ, crafted through the thorough analysis of extensive data from sizable studies in COPD. Since it is specifically designed using COPD data, the SGRQ-C is considered valid for assessing COPD. While its applicability to other conditions has not been formally established, it is expected to exhibit performance similar to the comprehensive SGRQ-C²³. The Caregiver Burden Scale, developed by Elmstahl et al.²⁴ in 1996, is a 22-item questionnaire designed to assess the subjective burden experienced by caregivers across five domains: general strain, isolation, disappointment, emotional involvement, and environment. Respondents express the frequency with which each item applies to them using a 4-point scale, ranging from "not at all" to "often"²⁴.

The study applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to illustrate the search and screening flow.

Figure 1 indicates the screening process and the decisions taken during study selection. Initially, 12,734 documents were determined as relevant. After deduplication (n=3,848) and exclusion through screening the title and abstract (n=612), 342 records remained. Finally, out of the 342 studies, only 43 articles met the inclusion criteria.

Results

1. Study characteristics

A total of 43 studies met the inclusion criteria. Table 2

shows the descriptive characteristics of all the selected articles^{5,12,25-65}. The main target populations were people living with COPD and caregivers. The majority of studies were conducted in developed countries: the USA (nine studies), followed by the United Kingdom (six studies), Italy (five studies), and Spain (five studies). The most common study design was retrospective study design (18 studies), followed by a cross-sectional study design (12 studies), and a cohort study design (six studies).

2. Direct cost

Total cost (10 studies), drug costs (10 studies), and nonmedical costs (three studies) were among the 16

reported direct costs. All the costs in Table 3 have been converted to international dollars (Int\$; year 2018)^{28-32,39-42,44,51,55,62,66,67}. The total direct cost, total medical direct cost, pharmaceutical therapy cost, outpatient cost, and total nonmedical cost were calculated. The total direct costs ranged from Int\$ 1,098 (UK) to Int\$ 43,994 (India). In terms of components of the nonmedical direct cost, we discovered differences between studies. There were also cost-effectiveness studies; therefore, there were differences in treatment techniques^{26,47}. Results showed that, direct costs are much higher in developed countries than in developing countries. Hospital stays, medicine prices, and treatment expenses contribute to most of the direct costs.

Table 4. The indirect cost of COPD

| Study | Country | Population/subpopulation | Year | Indirect cost/ Productivity loss | 95% CI |
|---------------------------------------|---------|---|------|--|-----------------|
| Dal Negro (2019) ²⁸ | Italy | Patients with COPD | 2019 | 487.6 | 161.85–813.34 |
| Koul et al. (2019) ³⁰ | India | Patients with COPD | 2019 | 94.8 | |
| Kourlaba et al. (2019) ³¹ | Greece | Patients with COPD | 2019 | 236.9 | 149.91–350.79 |
| | | Patients with COPD and CAT score ≤10 | | 45.0 | 7.5–98.94 |
| | | Patients with COPD and CAT score >10 | | 274.3 | 163.40–411.25 |
| | | Patients with mild level on Medical Research Council breathless scale | | 199.4 | 80.95–370.28 |
| | | Patients with mild level on Medical Research Council breathless scale | | 290.8 | 148.41–473.71 |
| | | Patients with mild level on Medical Research Council breathless scale | | 269.8 | 92.94–454.22 |
| | | Patients with COPD at GOLD A | | 33.0 | 0–76.45 |
| | | Patients with COPD at GOLD B | | 97.4 | 47.97–157.40 |
| | | Patients with COPD at GOLD D | | 398.8 | 223.36–613.13 |
| Merino et al. (2018) ⁴¹ | Spain | Patients with COPD | 2018 | 900.7 | 399.40–1,403.25 |
| Patel et al. (2018) ⁵ | USA | Patients with COPD | 2018 | 1,150.0 | |
| Souliotis et al. (2017) ¹² | Greece | Patients with COPD | 2017 | 1,451.7 | |
| | | Nonpaid caregivers' time | | 1,207.8 | |
| Chen et al. (2016) ⁵¹ | China | Patients with COPD | 2016 | 3,265.3 | |
| Dal Negro et al. (2015) ⁵⁵ | Italy | Patients with COPD | 2015 | 487.6 | 161.85–813.34 |
| | | Male COPD patient | | 496.2 | 353.49–638.84 |
| | | Female COPD patient | | 475.1 | 139.00–811.17 |

All costs are denominated in International dollars.
 COPD: chronic obstructive pulmonary disease; CI: confidence interval; CAT: COPD Assessment Test; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Nonmedical costs are typically low but can be higher in impoverished countries. The cost of immediate treatment varies substantially depending on the type and model of treatment. Notably, while the procedures might be the same, their efficiency may vary depending on the features of the health system and the resources available in each country. Indeed, the economic burden of COPD significantly differs depending on a country's specific circumstances, including factors such as average income, access to health insurance, and gross domestic product (GDP) *per capita*.

3. Indirect cost

Table 4 described the indirect cost of COPD in ITN\$. Nine studies reported indirect costs^{5,12,28,30,31,41,51,55,67}. The survey of Kourlaba et al.³¹ reported the most details when the study used the CAT score, modified Medical Research Council (mMRC) breathless scale, and GOLD for categories. The indirect cost ranged from Int\$ 33.0

to ITN\$ 3,265.3. Significant differences existed between levels in each scale and among the three scales. Dal Negro et al.⁵⁵ found out that there was no significant difference in total indirect cost between male and female patients. According to Souliotis et al.¹², over 33% of patients received daily assistance from family, friends, and a friendly environment, consuming 3.6 hours per day, 4.1 days per week, and accounting for Int\$ 1,207.8 of nonpaid caregivers' time and money.

4. Intangible cost

Intangible costs are the unquantifiable impacts of an identifiable cause, such as pain, joy, or physical limitations, which can impact total productive performance. Intangible costs in this study were assessed using the patients' and relatives' variation of biopsychosocial quality of life after the diagnosis; quality of life in this context includes physical health, social contacts, and emotional health (Table 5). The research synthesizes six studies

Table 5. The burden and change in the quality of life

| Scale | Study | Population/subpopulation | Difference | SD | 95% CI |
|--|---|--|------------|-------|----------------|
| EQ-5D-5L score | Bhadhuri et al. (2019) ²⁷ | Family members of patients on telephone coaching self-management | -0.029 | 0.14 | |
| | | Family members of patients on usual management | -0.019 | 0.10 | |
| | O'Reilly et al. (2007) ⁶¹ | Patients on admissions | -0.24 | 0.373 | -0.38 to -0.10 |
| Happiness (scale 0 – 10) | Bhadhuri et al. (2019) ²⁷ | Family members of patients on telephone coaching self-management | 0.22 | 1.41 | |
| | | Family member of patients with usual management | -0.11 | 1.24 | |
| The COPD Assessment Test | Ladziak et al. (2019) ⁶⁹ | Patients with triple-therapy inhaler combinations | -0.84 | | -3.57 to 1.89 |
| St George's Respiratory Questionnaire for COPD | Bikmoradi et al. (2019) ⁷² | Patients with continuity of care model | 11.93 | | |
| | | Patients with routine care model | -1.15 | | |
| | Folch-Ayora et al. (2019) ⁸² | Male patients | -3.51 | | |
| | | Female patients | -2.24 | | |
| | | Patients who had telephone education session | -6.83 | | |
| Patient with usual management | -0.26 | | | | |
| Caregiver burden questionnaire | Chu et al. (2019) ⁶⁸ | Caregivers with <2 caregiving hours per day | 34.5 | 15.1 | |
| | | Caregivers with <3 caregiving hours per day | 45.8 | 10.5 | |
| | | Caregivers with <5 caregiving hours per day | 59.8 | 5.1 | |
| | | Caregivers with ≥6 caregiving hours per day | 67.4 | 6.3 | |
| | | Caregivers of COPD patient | 57.3 | 14.6 | |

SD: standard deviation; CI: confidence interval; EQ-5D-5L: EuroQol 5-dimension 5-level; COPD: chronic obstructive pulmonary disease.

on the intangible cost in patients and caregivers. On all scales, the quality of life was reduced compared to before and after diagnosis. The caregiver's burden increases as the time to care for the patient increases⁶⁸.

In Table 5, various health-related measures and their impact on individuals' well-being are presented across different studies. The EuroQol 5-dimension 5-level (EQ-5D-5L) scores show a slight decrease for family members of patients undergoing telephone coaching self-management compared to usual management^{27,61}. Happiness scores, on a scale of 0 to 10, indicated a positive change for those in telephone coaching self-management but a decrease for those in usual management²⁷. The CAT indicated an improvement in scores for patients using the modified inhaler combinations. However, it is noteworthy that this improvement was not statistically significant (95% confidence interval [CI], -3.57 to 1.89; $p=0.525$)⁶⁹.

The SGRQ-C highlights diverse impacts on quality of life, with different scores for continuity of care and routine care models and variations based on gender, education sections, and management types^{70,71}. Lastly, the Caregiver Burden Questionnaire reveals increasing burden scores for caregivers with higher daily caregiving hours and those caring for COPD patients⁶⁸. These findings provide insights into the multidimensional aspects of health and well-being in the context of COPD and its management.

Discussion

This study provided evidence of the economic burden and factors associated with the cost of COPD from 1990 to 2019. The outpatient visits and pharmaceutical therapy costs were the highest direct costs; meanwhile, the indirect costs were less researched. The findings of this study confirmed little research on economic burdens on caregivers of COPD patients and those conducted in developing countries.

In our dataset, four studies were conducted in lower-middle- and low-income countries^{30,34,36,40}, and seven for the upper-income countries^{26,29,51,72,73}. Similar to results of several previous studies, these findings emphasize the lack of research on the economic costs of COPD in developing countries²⁶. Probably due to human resources, finance, and infrastructure limitations in these countries⁷⁰. This phenomenon calls for action from global researchers and the need to cooperate with researchers in high-resource settings.

The findings show that the most significant direct costs related to COPD were outpatient visits and pharmaceutical therapy costs^{31,35,71}. As the disease worsens, patients need to spend more on palliative

care, life maintenance, and hospital stay, which leads to an increase in the cost of hospitalization^{58,74}. Other healthcare resources might contribute to COPD's direct costs, such as home oxygen therapy and physician or specialist home visits^{32,33}. In our dataset, no studies mentioned catastrophic costs due to COPD. However, the annual increase in COPD's cost and long-term treatment characteristics could lead to a long-term economic burden on COPD patients.

Regarding indirect cost, our study included several dimensions of workforce participation, for instance, work and wage loss of COPD patients and caregivers, limitation, and disability in activities⁷⁵. In our dataset, one study mentioned caregiver's indirect cost¹². Some studies also show that indirect costs can sometimes account for approximately 10% of the total economic burden^{12,56}. However, the indirect cost of COPD is more challenging to control than the direct cost due to the various analytical components in indirect cost measurement⁷⁶. The method of calculating the indirect cost burden is inconsistent among countries due to the different determinations of the workday value.

The study results indicate that the studies on the economic burden on caregivers of COPD patients are limited. Five studies in our dataset mentioned theme focusing on quality of life, the amount of time that caregivers spend for caring, family caregivers psychology, and burden^{27,41,68,77,78}. Besides, there has been a lack of studies on mental or physical health of family caregivers' of COPD patients.

This research found a link between the more significant reported burden of COPD (breathlessness, symptoms, and comorbidities) and higher overall societal expenses per patient^{26,59,77,78}. Thus, the severity of the disease and symptoms might be one of the factors that influence the economic burden of COPD.

Health risk behaviors such as alcohol consumption have been proven to increase cross-reinforcement among COPD patients who struggle to achieve smoking cessation⁷⁹. Regarding insurance and economic factors, developing countries have a wide range of community-based health insurance schemes and every insurance scheme aims to protect the vulnerable people in the system by sharing risk⁸⁰.

Finally, the management of the severity and symptoms of COPD is critical. Under well-controlled circumstances, the patient's symptoms and health effects are slow and not frantic. However, when patients progress to exacerbation of COPD, their lives may be affected immediately. Preventing exacerbation in people with COPD can help them live healthier lives and reduce the risk of death⁸¹. Models of monitoring and telemedicine

care, home-based models, and utilizing local primary care facilities are effective treatment and palliative care methods for COPD patients^{27,69,78,82}. Our study found out that there have been valuable categorization methods in providing appropriate services to patients, such as GOLD, mMRC breathless scale, and CAT limiting the economic burden of COPD treatment^{31,32,35,36,66}. However, future well-designed studies must compare these options with large populations to reach accurate conclusions.

The findings of this study have several implications. First, due to the insufficient economic burden of research related to caregivers, future research should focus on the characteristics and problems of caregivers. Therefore, suitable public health programs should be implemented to reduce the economic burden and negative impacts on caregivers. Second, there are differences in treatment costs of COPD among smokers, former smokers, and nonsmokers, which suggest the negative effects of smoking on progression COPD. Thus, smoking prevention and cessation programs should be implemented early at schools and universities to prevent high-risk behaviors. In addition, when managing symptoms and severity of COPD, it is essential to raise awareness about COPD and self-management COPD intervention among people. Due to limited financial resources, self-management COPD intervention should be implemented in developing countries such as Vietnam. Further cost-effectiveness research about options, drugs, and treatment models for COPD is required to identify the most optimal guideline for patients and relatives to reduce the economic burden of COPD.

In this study, some limitations need to be considered. First, only English publications were selected, which restricted our sample. Second, our study focused on the economic burden of COPD with the results having many exact numbers regarding economic cost. Finally, the database was limited to the peer-review papers only. Grey literatures and proceedings were not included, which may affect the results.

In conclusion, our findings highlight the considerable variation in COPD-related costs worldwide. This study confirmed a wide variation in the total direct cost of COPD, a diverse drug cost, and a limited exploration of the indirect cost associated with COPD in different countries. In addition, our findings emphasize the limited research on the economic burdens COPD caregivers face. It advocates for increased research support, especially by high-resource settings. These results highlight the need for more studies to better understand and address the economic aspects of COPD,

with a focus on caregivers and diverse global contexts.

Authors' Contributions

Conceptualization: Pham HQ, Pham KHT, Ha GH, Nguyen THT. Methodology: Pham HQ, Ha GH, Nguyen THT. Formal analysis: Pham HQ, Ha GH, Nguyen THT. Data curation: Pham TT, Nguyen HT. Writing - original draft preparation: Pham HQ, Ha GH, Nguyen THT. Writing - review and editing: Pham KHT, Oh JK. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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