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Direct Hospitalization Cost of Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review

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COPD is the third leading cause of death worldwide, causing 3.23 million deaths in 2019. COPD is also the 4th leading cause of death in the USA. Smoking accounts for more than 70% of COPD cases in high-income countries. COPD is a health problem with severe economic and social consequences and causes a burden of direct and indirect costs for outpatients. Direct costs include medication costs, diagnostic utility costs, disease management and follow-up costs as well as hospitalization and emergency costs. Searches were performed in PubMed, SCOPUS, and the Google Scholar databases for cost-related research on COPD published in English from 2015 to 2023. The criteria for inclusion involved identifying documented disease costs, economic impact, medical care expenditures for COPD, along with the methodology, data sources, and variables examined. COPD leads to significant expenses within the healthcare system, primarily linked to the disease's moderate to severe stages, exacerbations, and associated complications. Strengthening healthcare systems through monitoring, assessment, and health education models is crucial. These approaches aim to help patients maintain stability, preventing deterioration and subsequent hospital admissions.
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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterised by chronic airflow obstruction and pathological changes in the lung. Airway airflow obstruction is progressive and not fully reversible and is associated with an abnormal inflammatory response of the lungs to harmful gases or particles. Associated with an abnormal inflammatory response of the lungs to noxious gases or particles (PDPI, 2003). According to World Health Organization (WHO) COPD is the third leading cause of death worldwide, causing 3.23 million deaths in 2019 (WHO, 2021).

COPD is also the 4th leading cause of death in the USA. Smoking accounts for more than 70% of COPD cases in high-income countries. In developing countries, smoking accounts for 30-40% of COPD cases and household air pollution is a major risk factor. From an epidemiological standpoint, COPD ranks as the third most common cause of death globally and stands out as a significant contributor to heightened morbidity, leading to a growing economic and societal burden. The levels of morbidity and mortality associated with COPD vary between countries and different demographic groups, resulting in widely varying prevalence data.

The natural course of COPD involves periods of exacerbation, which become more frequent as the disease progresses to moderate and severe stages. These exacerbations significantly raise the burden of illness, healthcare resource usage (resulting in increased costs), and contribute to reduced productivity and a decline in the patients' health-related quality of life (HRQoL). Exacerbations are defined as sudden instances of clinical instability marked by a worsening of respiratory symptoms. On average, COPD patients undergo anywhere from one to four exacerbations annually, but the severity and duration vary among individuals,

making it challenging to precisely gauge their specific impacts. They are primarily associated with respiratory infections or environmental stressors, though at times, they can also be influenced by coexisting health conditions. These additional pathologies can intensify symptoms, making recovery more challenging for the patient.

Globally, COPD has caused huge burden on health systems. As disease progresses, patients are more likely to be hospitalized for the necessary treatment. The treatment costs of COPD patients have a strong correlation with the disease severity, in which hospitalization costs account for most of the direct treatment costs. A study in the US reported that the hospitalization costs significantly drove the total health care costs in COPD patients who were commercially insured. In Taiwan, the hospitalization costs for COPD patients accounted for 74%–95% of their total health care costs. COPD is a health problem with severe economic and social consequences and causes a burden of direct and indirect costs for outpatients. Direct costs include medication costs, diagnostic utility costs, disease management and follow-up costs as well as hospitalization and emergency costs. The most important component of direct costs is hospitalization costs. In the USA, direct costs can cost $18 billion. 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. 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.

2. Methods

Search Strategy

This systematic review followed procedures to the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to identify articles that evaluate the cost burden associated with COPD. The studies were discovered and chosen through a literature exploration across three electronic databases: PubMed, SCOPUS, and Google Scholar. The search approach targeted publications in English or Bahasa Indonesia. To enhance the results, an extra review was carried out on Google Scholar using free-text language and specific keywords related to this topic, filtering the search. The database were searched for publications from 2015 until 2023.

No	Database	Keywords	Result
1	Pubmed	*COPD* AND *Cost* AND *Analysis*	120
2	Scopus	*COPD* AND *Cost* AND *Analysis* AND *Inpatient*	198
3	Google Scholar	*COPD* AND *Medical Cost* AND *Analysis* AND *Inpatient*	274

Eligibility Criteria

Studies were eligible for inculsion if met this criteria: (i) Published between 2015 until 2023; (ii) Publications in English or Bahasa Indonesia; (iii) Involved identifying documented disease costs, economic impact, medical care expenditures for COPD and discuss about cost analysis of COPD, cost of illness COPD or economic burden of COPD; (iv) Contain relevant and information of the cost of COPD. The study were excluded (i) article was published before 2015 (ii) systematic review or meta-analysis (iii) not available in full text (iv) The article is irrelevant and incomplete according to required database

Quality Asessment

This study used the JBI (Joanna Briggs Institute) critical appraisal tools for economic evaluations as a quality assasment tool to analysis the quality of all included studies. There are 11 poin question as a tool and each poin was marked “yes” If the article met the criteria of included studies; “no” if the article didn’t meet the

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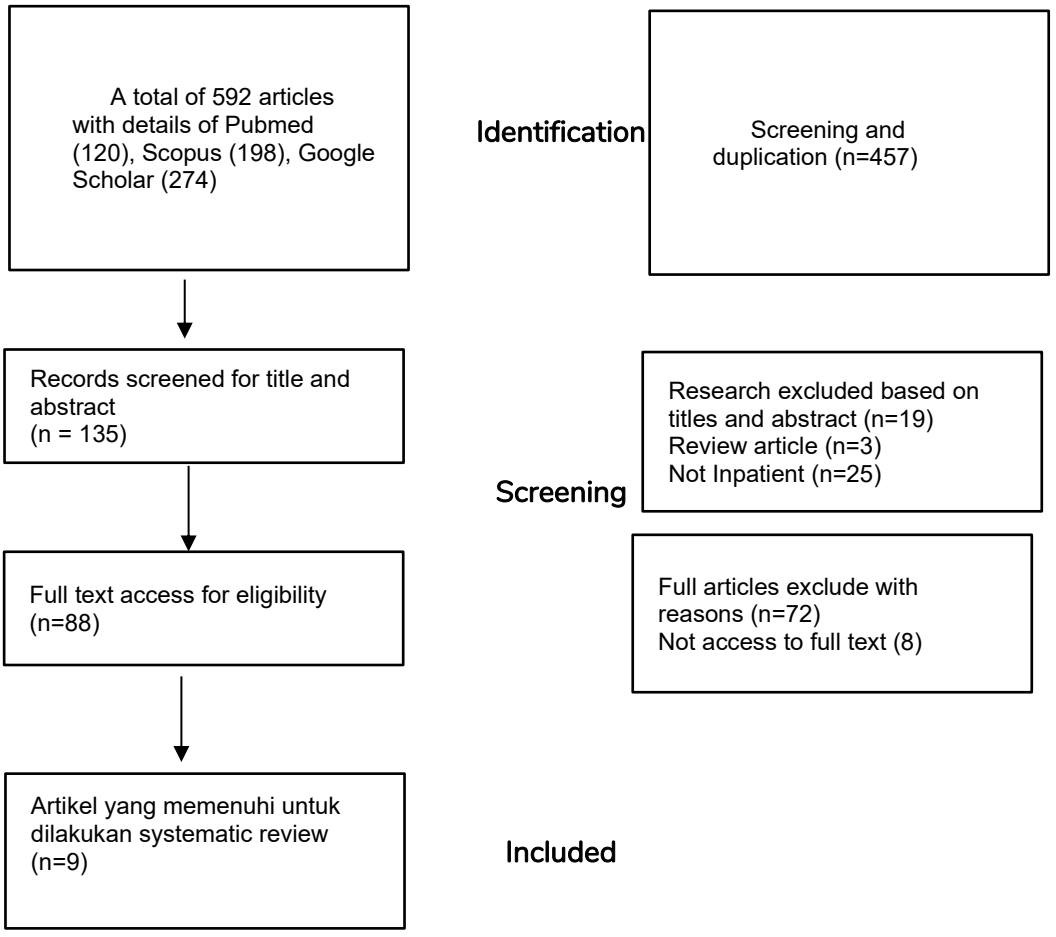
criteria; “unclear” if sufficient information to make decision and “Not Applicable” if the poin didn’t find on the article

3. Result and Discussion

Study Selection

The search for articles yielded a total of 592 articles (120 from Pubmed, 198 from Scopus and 274 from Google Scholar). The selection process overview is illustrated in Figure 1 the PRISMA diagram. The research article search process obtained 592 articles, then filtering and duplication in the title aspect obtained 135 articles. Then 52 articles were excluded because based on titles and abstract, review article and not inpatient. The next process of research articles that have complete methods is 9 articles. The literature search process is depicted in a PRISMA diagram as follows:



Study Characteristics

Table 2 displays the features of the studies included. There are nine articles were published either English or Indonesian within the period from 2015 until 2023. This research was conducted across various hospital and characteristics in the world. Background of this study from several countries such as Indonesia (n=1), North India (n=1), Greece (n=1), Iran (n=1), Vietnam (n=1), Philippine (n=1), Malaysia (n=1), Buenos Aires (n=1) and Spain (n=1). Overal for this study used non-experimental quantitative methods with retrospective observation.

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Table 2. Selected articles and their relevant characteristics: a year of publication, study design, country, year of data, prespective and principal study aim

Articles	Year of publication	Country	Year of Data	Perspective	Principal aim
Wulandari et al.,	2020	Indonesia	2018	Hospital	Providing direct medical research results of COPD Hospitalization at Fatmawati General Hospital seen from the prospective of the Hospital
Koul et al	2019	North India	2012-2013	Society	The purpose of this study is to calculate direct and indirect costs incurred due to absence from work by absence from work by the patient himself or his caregiver due to an COPD exacerbation.
Souliotis et al	2017	Greece	2015	Society	The aim of this study was to explore the direct and indirect costs associated with COPD and identify the main cost triggers of disease management in Greece.
Torabipour et al,	2016	Iran	2011-2013	Hospital	Analyzing the cost of hospitalization of COPD patients
Ngo et al,	2018	Vietnam	2018	Hospital	This study aims to assess the direct costs of COPD hospitalization and determine potentially associated factors, so as to identify areas for improvement in cost reduction, resource utilization, and general disease management
Blake et al,	2023	Philippine	2019	Society	This study aimed to prospectively evaluate the overall cost of admissions for COPD exacerbation in a tertiary government hospital over a 6-month period.
Rehman et al,	2021	Malaysia	2018-2019	Society	The aim of this study was to assess the economic burden of COPD in Malaysia, including direct costs for the management of COPD and indirect costs due to productivity losses for COPD patients.
Pascansky et al,	2022	Buenos Aires	2018	Hospital	To determine the structure of direct costs in hospitalized patients due to COPD exacerbations in a public hospital of Buenos Aires in 2018.
Merino et al,	2018	Spain	2015	Society	This study aimed to estimate the social economic impact of COPD in the autonomous community of Extremadura (Spain) in 2015.

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Table 3. Methodological aspects of the articles: variable collected to estimate direct medical cost and limitation

Articles	Variable Collected	Limitations
Wulandari et al.,	Sociodemographic characteristics of the patients: sex and age Direct Healthcare costs: Medication cost, room cost, laboratory cost, medical service cost and other action cost	The retrospective design of the study means that it may be subject to bias and confounding.
Koul et al	Sociodemographic characteristics of the patients: sex, age, duration of hospital stay Direct Healthcare costs: Pre-hospitalization, medications, diagnostic-related, hospital charges, discharge medication, hospital costs per patients	India bears a disproportionate burden of COPD morbidity and mortality not only because of the size of the population, but also because of under-treatment. In addition, given limitations in insurance coverage, most COPD care cost is borne by the patients or their caregivers. Thus, appropriate management of COPD may require national programs to provide quality care to those patients that could not otherwise afford healthcare.
Souliotis et al,	Sociodemographic characteristics of the patients: sex, age, duration of hospital stay Direct Healthcare costs: Pharmaceutical treatment, medical treatment, hospitalization, ICU admission, Laboratory tests, Functional/imaging test	First, study results are based on expert opinion rather than patient-level data. However, given the lack of a registry for COPD in Greece, the Delphi panel survey could be considered to be the second-best method to collect data that could map the current clinical practice and resource use associated with the disease management. Second, resource use data were elicited from pulmonologists only, while the study revealed that the disease is currently being managed by both pulmonologists (60%) and GPs/internists (40% of total patients).
Torabipour et al,	Sociodemographic characteristics of the patients: sex, age, urban/rural, type of medical insurance, family/disease history Direct Healthcare costs: nursing services, laboratory cost, radiology cost, medicines, hospitalization, consultation and other services	The current study had some limitations; in this cost analysis, there were no data available regarding indirect costs, or costs related to ICU admissions. The studied hospitals did not provide any ICU data. Estimation of indirect costs is a difficult part of cost of illness studies and only a few studies have previously attempted to do so.
Ngo et al,	Sociodemographic characteristics of the patients: Gender, Living location, comorbidities. Direct Healthcare costs: hospitalization cost (bed-day, blood tests, imaging diagnosis, functional tests, procedures, medication, equipment and supplies);	This study has several limitations. First, this study had a small sample size and used a convenient sampling technique, resulting in the constrained generalizability of the study results. Second, they employed a retrospective study design, which largely depended on the quality of existing data. This study addressed this issue by standardizing

Articles	Variable Collected	Limitations
	Duration of hospitalization and cost per day	the instrument, as well as calling the patients to verify the information in the medical records. Third, this study was performed in only one tertiary hospital, which might limit generalizability to other hospital settings. Thus, further studies with a larger sample size in more hospitals would be warranted.
Blake et al,	Sociodemographic characteristics of the patients: Age, Sex, Type of Residence, Gold Classification, Comorbidities, Smoking History Direct Healthcare costs: Professional fee, Medication cost, Diagnostic tests cost and Procedural cost, hospitazlitaion cost	Therefore, limiting unnecessary clinical consultations, adequate management of comorbidities, and shortening hospitalization stay may potentially equate to lower hospitalization costs for COPD. This study did not measure the following, and therefore represent potential limitations, including indirect costs and productivity losses, discharge medication costs and procedures (rehabilitation, long-term oxygen therapy).
Rehman et al,	Sociodemographic characteristics of the patients: BMI, Sex, Age, Working status, Smoking status, Years with COPD, Percentage of patents according to severity of COPD Direct Healthcare costs: Chest ward, Pharmacy, Procedures X-Ray, Spiromery, Laboratory,	The data used in this study only reflect the public healthcare system and may not reflect the management costs in private health care systems. The actual costs in private healthcare systems may vary, resulting in underestimation of the economic burden of COPD. However, the study population is likely to be representative of the general population as the public healthcare system provides health services to approximately 65% of the Malaysian population. Moreover, used tariff-based cost estimates applicable across Malaysia, which improves the generalizability of our findings. The cost of non-prescribed medications and indirect costs due to productivity losses of caregivers were excluded from the study, suggesting that COPD may have a higher economic burden than that reported.
Pascansky et al,	Sociodemographic characteristics of the patients: Age, Gender, Time since COPD diagnosis, smoking history, comorbidities, spirometry, adherence, hospitalization length of stay Direct Healthcare costs: Medical visit, Medication, Hospitalizations, Diagnostic tests and material for control and medical transportation	Regarding the limitations of this study, that data collection from the medical records was retrospective. Another limitation is the fact that the extrapolation of conclusions for other health systems in our country or other regions (external validity) is not recommended, due to the different cost structures.
Merino et al,	Sociodemographic characteristics of the patients: Age, Gender, Smoking	This study is not without limitations. First, the severity level of the patient's COPD corresponds to

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Articles	Variable Collected	Limitations
	history, Daily Cigarettes, Education Level, Employment status Direct Healthcare costs: medical tests, pulmonology visits, emergency visit, use of ambulance, use of home oxygen therapy, hospital admissions, medication.	a variable constructed from information provided by the clinical history. However, this information was missing for the majority (58.3%) of the participants, for primary care records only collect information on the number of spirometries the patient had in the past 12 months, but do not necessarily provide the results of the spirometries, nor the GOLD classification of the patient.

In short, the studies' diversity complicates result comparisons. As a result, costs fluctuate significantly depending on the countries studied, their healthcare system types (public or private), and their status as developed or developing nations. To summarize, there's substantial variation in reported costs across studies, indicating marked differences in total expenses per COPD patient among geographically distant regions (Villegas, 2021).

Table 4. Economic Aspects of the articles: currency/year and estimate cost

Articles	Year of publication	Currency/Year	Calculated Cost
Wulandari et al.,	2020	Rupiah/2018	The direct medical costs incurred by a hospitalized patient were Rp.12,155,822 with an average length of stay of > 6 days. The treatment class (Rp.4,013,571) is the highest cost of the total cost of patient care. Average costs related to drug use amounted to Rp.2,238,747, room costs Rp.4,013,571, laboratory costs Rp.1,944,493, media services costs Rp.1,723,782 and other action costs Rp.2,235,229.
Koul et al	2019	INR/2012	The median cost of hospitalization was INR 44,390 per admission with interquartile range (IQR): INR 33,354-63,642. The median cost of discharge medications was INR 700 (IQR: INR 500–900)
Souliotis et al	2017	Euros/2015	Direct medical cost total per-patient is €2,809.7
Torabipour et al,	2016	USD	The mean cost per each extra day of hospital stay was estimated to be US $115.80. The mean costs per patient with and without hypertension were US $1,422.5 and US $627.4.
Ngo et al,	2018	VND	The mean total and daily hospitalization cost were 18.3 million VND (SD = 12.9) and 2.5 million VND (SD = 3.2), respectively. Medication cost accounted for 53.9% of hospitalization cost (from 44.0% in the Global Initiative for Chronic Obstructive Lung Disease Classification A (GOLD A) to 55.3% in GOLD C). Patients having GOLD D COPD (Coef. = 5.78; 95% CI = 0.73–10.83), higher age (Coef. = 0.37; 95% CI = 0.13–0.61), and higher

Articles	Year of publication	Currency/Year	Calculated Cost
			duration of hospitalization (Coef. = 1.91; 95% CI = 1.28–2.53) had higher hospitalization costs ($p < 0.05$).
Blake et al,	2023	Philippine pesos (Php)	Our study indicated that the mean hospitalization cost for COPD exacerbation is 28,200 with significantly lower cost for charity admissions at 22,870 Philippine pesos (mean) versus private admissions at 51,320 pesos (mean) in the Philippines
Rehman et al,	2021	USD	The mean annual per-patient direct cost for the management of COPD was calculated as US$506.92. The mean annual costs per patient in the management phase, emergency department visits, and hospital admissions were reported as US$395.65, US$86.4, and US$297.79, respectively; 31.66% of COPD patients visited the emergency department and 42.47% of COPD patients were admitted to the hospital due to exacerbation.
Pascansky et al,	2022	USD	The final direct cost per hospitalized patient in the regular ward was USD 1,462.62 (IQR 25%-75%, 763.85-2,915.95), which considering the 26 hospitalized patients, gives a total direct cost of USD 117,480, that is, USD 162.44 per patient,per day.
Merino et al,	2018	Euros	Direct health care costs represented 43.8% (1,645 euros)

COPD represents a major chronic condition prevalent in developed countries. Current epidemiological data indicate a notable increase, expected to amplify further in the future, chiefly attributed to aging populations and widespread smoking habits in Western societies, displaying alarming statistics. The identified morbidity and mortality of this condition significantly disrupt the financial stability of healthcare institutions, a crucial foundation for any nation, subsequently driving up costs for society as a whole (Villegas, 2021).
Starting with direct healthcare expenses, the analysis presents data specific to the various geographical regions under study. In Europe (the primary focus of most studies in this review), costs vary significantly, ranging from high-cost regions like Norway at €10,701 (€/2019) per patient per year to Belgium at €1963 (€/2019) per patient per year. The average total direct costs per patient per year among eight European countries (Greece, Buenos Aires and Spain) stand at €6182 (€/2019). Moving to Asia, in terms of direct healthcare costs, notable differences weren't evident among developed Asian nations (Indonesia, Malaysia, Vietnam, Philiphines, India and Iran). The estimated average hovers around $9172 (USD/2017).

In reviewing the characteristics outlined in the selected articles (Table 2) and their methodological aspects (Table 3), It was crucial to highlight that the wide range of costs reported is primarily a result of methodological disparities and diverse research objectives. These variations impact the categorization of costs, how available resources are identified, measured, valued, and utilized by COPD patients across different study settings. This variability may also stem from genuine disparities between countries, including epidemiological distinctions, variances in the sociodemographic profiles of analyzed patients, fundamental characteristics of healthcare systems in each region, disparities in COPD prevention and treatment strategies, as well as differences in professional practices and cultural norms.

Regarding the economic features outlined in the selected articles (Table 4), a notable limitation is the diverse reporting of health cost study outcomes in various currencies, except for certain intangible cost studies. As this systematic review encompasses global studies conducted in different geographical settings, each study presents its findings in distinct currencies (euros, Indian rupee, Canadian dollar, or US dollar). Additionally, these values are computed across different years, ranging from 2015 for the oldest study to 2023 for the most recent. This variance complicates the task of standardizing and comparing results uniformly, leading to disparities and heterogeneity when presenting and analyzing the findings.

Furthermore, the studies identified in this review demonstrate a lack of simultaneous estimation of direct healthcare costs. Less than half of the identified studies included this component in some manner, often as a supplement to healthcare costs. However, none incorporated family costs related to caring for individuals affected by the disease. Additionally, it's essential to note that certain studies focus on calculating COPD costs from the perspective of the disease, while others encompass the total attributable costs in COPD patients, including costs stemming from comorbidities and specific patient characteristics within the study sample, particularly among older patients.

Considering the objectives of this manuscript, it's crucial to note that the 9 cost studies identified in this systematic review underscore the significant impact of COPD on overall economic costs. This leads to notably higher excess costs for individuals with COPD compared to those without the disease. Delving into the factors elevating costs among COPD patients, an analysis of the 9 reviewed articles reveals that the primary contributor to cost escalation in this condition is AECOPD (acute exacerbation of COPD), the predominant complication more prevalent and severe in advanced COPD stages and poorly managed cases.

Consequently, patients causing the highest costs within this condition are those in moderate to severe disease stages and additionally exhibit poor disease control. Suboptimal management of respiratory illness in general, particularly in COPD patients, stems from inadequate adherence to treatment regimens and insufficient proficiency or technique in executing prescribed pharmacological treatments. This, coupled with other risk factors like smoking, obesity, and external factors beyond the patient's control such as environmental conditions and aging, leads to a rise in exacerbations. In many instances, this escalation results in emergency department visits or even hospitalizations, incurring substantial costs, further compounded by the patient's comorbidities that can prolong hospital stays.

4. Conclusion

COPD leads to significant expenses within the healthcare system, primarily linked to the disease's moderate to severe stages, exacerbations, and associated complications. Strengthening healthcare systems through monitoring, assessment, and health education models is crucial. These approaches aim to help patients maintain stability, preventing deterioration and subsequent hospital admissions.

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