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Chronic Obstructive Pulmonary Disease in Brazil: Cost of Illness Analysis

Doença Pulmonar Obstrutiva Crônica no Brasil: Análise de custo da doença

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ABSTRACT

Objective: To measure the cost of Chronic Obstructive Pulmonary Disease (COPD) in Brazil to present an updated overview of the economic impact. **Methods:** A descriptive and retrospective analysis was carried out using macro and micro-costing techniques. It was based on information available in the Brazilian Ministry of Health's databases, national and international guidelines for the clinical management of COPD, and the opinion of specialists. The time horizon adopted included the period from January to December 2019 and considered the direct medical costs linked to the provision of health care. **Results:** The analysis revealed that the costs of hospital management of COPD totaled BRL107,867,664.40. In addition, it was evidenced that there is a substantial increase in the cost related to the management of the stable phase of the disease according to the severity of the condition, ranging from BRL 418.50 [2019] (USD 253.69 [price year 2024]) for Stage I to BRL 4,257.53 [2019] (USD 2,580.88 [price year 2024]) for Stage IV. **Conclusion:** This cost analysis and the estimated prevalence of COPD identified in Brazil demonstrate the importance of implementing effective strategies and public policies aiming to reduce risk factors associated with the disease.

Keywords: Chronic Obstructive Pulmonary Disease (COPD); Cost of Illness; Unified Health System; Brazil

RESUMO

Objetivos: Mensurar o custo da Doença Pulmonar Obstrutiva Crônica (DPOC) no Brasil para apresentar um panorama atualizado do impacto econômico. **Métodos:** Foi realizada uma análise descritiva e retrospetiva, utilizando técnicas de macro e micro-custeio. Sendo baseadas em informações disponíveis nas bases de dados do Ministério da Saúde do Brasil, em diretrizes nacionais e internacionais para o manejo clínico da DPOC e na opinião de especialistas. O horizonte temporal adotado compreendeu o período de janeiro a dezembro de 2019 e considerou os custos médicos diretos vinculados à prestação de assistência à saúde. **Resultados:** A análise revelou que os custos da gestão hospitalar da DPOC totalizaram R$107.867.664,40. Além disso, evidenciou-se que há um aumento substancial no custo relacionado ao manejo da fase estável da doença de acordo com a gravidade do quadro, variando de R$ 418,50 [2019] (USD 253,69 [preço ano 2024]) para o Estágio I a R$ 4.257,53 [2019] (USD 2.580,88 [preço ano 2024]) para o Estágio IV. **Conclusões:** Esta análise de custos e a prevalência estimada de DPOC identificada no Brasil demonstram a importância da implementação de estratégias e políticas públicas efetivas visando à redução dos fatores de risco associados à doença.

Palavras-chave: Doença Pulmonar Obstrutiva Crônica (DPOC); Custo da Doença: Sistema Único de Saúde; Brasil

Introduction

Chronic Obstructive Pulmonary Disease (COPD), a condition characterized by persistent respiratory symptoms and airflow limitation, is a pathology with high mortality, morbidity, and economic impact on the world.[1-3] The main etiology associated with the disease is smoking, identified as the primary cause of the development of COPD, including passive exposure.[4] Other triggering factors involve occupational exposure, contact with polluting chemical agents, infections, and genetic predisposition.[5] The diagnosis is traditionally made in the presence of chronic respiratory signs and symptoms, associated with risk factors for the disease and an irreversible obstructive ventilatory disorder on pulmonary function tests.[6] The Global Initiative for Chronic Obstructive Lung Disease (GOLD), an international reference document for COPD management, classifies the disease into four stages, according to the severity of airflow limitation, ranging from mild cases (Stage I), in which Forced Expiratory Volume (FEV1) values after administration of a bronchodilator are equal to or greater than 80% of predicted, to very severe cases (Stage IV), in which these values are less than 30% of predicted.[1]

Global estimates indicate that the prevalence of the disease is related to the population's different geographic regions and lifestyles. A systematic review that synthesized global data on the prevalence and severity of COPD by geographic region, age groups, and smoking habits, found global prevalence values of 12.16% (95% CI, 10.91 -13.40%), being the most common clinical presentation in the early stages of the disease.[7]

As an illness of wide prevalence in different regions of the world, COPD can substantially impact health systems due to the costs of its treatment and hospitalizations caused by its clinical exacerbations. A systematic review that evaluated the economic burden associated with severe and very severe COPD, highlighted that the disease severity, frequency of exacerbations, and symptoms were significantly associated with increased use of health resources. In addition, the same research stressed the number of previous exacerbations and the presence of comorbidities as predictors of COPD-related economic burden.[8] A study coordinated by *the Instituto de Efectividad Clínica y Sanitaria* and *Fundação Oswaldo Cruz*, which sought to study the burden of diseases attributable to tobacco use in Brazil, estimated a total cost in Brazilian real (BRL) of 22.47 billion for COPD in 2015, being 71% of this attributed to smoking.[9]

Given the expressive values found in previous evaluations, the need to understand the components of the costs associated with this disease is evident. In this context, Cost of Illness studies can help in the evaluation of priority demands, as they encompass several aspects of the impact of diseases and health outcomes in a given country, region, or community, contributing to the formulation and prioritization of public policies, in addition to allowing greater efficiency in the allocation of health resources.[10]

The present study aimed to measure the cost of COPD in Brazil, from the perspective of Brazilian Unified Health System, through the computation of direct medical costs associated with the provision of health care. Thus, this research intends to present an updated scenario regarding the cost of illness studies of this illness in the country.

Methods

A descriptive and retrospective study was conducted following the recommendations proposed by international guidelines for the reporting of economic evaluations (Consolidated Health Economic Evaluation Reporting Standards/CHEERS), International Society for Pharmacoeconomics and Outcomes Research/ISPOR)[11] and the scientific literature regarding the cost of illness studies.[12-14]

Perspective and time horizon

The analysis was conducted from the perspective of the Brazilian Unified Health System, a public health system that is the only way to access health care for more than 70% of the Brazilian population.[15] The time horizon adopted included the period from January to December 2019, considering the availability of consolidated information in the accessed databases. In addition, the year 2019 was chosen to avoid possible influences of the Covid-19 pandemic on the analyses.

Approach and types of costs analyzed

The study design was based on the prevalence of COPD in Brazil and used a combination of macro and micro-costing techniques with a top-down approach, according to the type and availability of each data analyzed. The prevalence of COPD within the country was a critical factor that guided the cost analysis. The prevalence data allowed for the extrapolation of our findings to the national population, thereby providing a more accurate depiction of the economic burden across the healthcare system. Distinct approaches were adopted for various cost components to ensure a nuanced understanding of the economic burden of COPD.

For hospitalization costs, we used a top-down approach – this method allowed us to capture the total expenditures for COPD – related hospital admissions during 2019, offering a macroscopic view of the hospitalization costs within the healthcare system.

In contrast, the costs associated with the stable phase of COPD – encompassing clinical follow-up, pulmonary rehabilitation, oxygen therapy, vaccination, and pharmacological treatment – were assessed using a mixed approach. This approach combined top-down and bottom-up methods, where the top-down aspect involved the extraction of broad expenditure categories from health system databases.

Concurrently, the bottom-up method was employed to meticulously itemize and calculate the costs associated with individual components of outpatient COPD care. This detailed, mixed methodology facilitated the estimation of average per-patient annual costs, segmented by disease stage. Through this approach, we aimed to provide a detailed breakdown of the direct medical costs associated with COPD management, reflecting the intricacies of cost allocation across different care components and stages of the disease. Further details regarding each phase are described below.

Costs related to hospitalizations: Data were obtained in a grouped way, using the macro-costing technique, based on information available in the *Sistema de Informações Hospitalares* (SIH; Hospital Information System). The platform allows the assessment of total hospital costs, considering all *Autorizações de Internação Hospitalar* (AIH, Hospital Admission Authorizations) paid in the period. To visualize these values, the TABNET tool was used (link: https://datasus.saude.gov.br/informacoes-de-saude-tabnet/) following this path: it was chosen on the menu bar "*Epidemiológicas e Morbidade > Morbidade Hospitalar do SUS (SIH) > Geral*", by place of residence - from 2008. Chapter ICD-10 X – Respiratory Tract Diseases was selected, including the CID-10 Morbidity Tabulation List code 175, covering ICD-10 classifications from J40 to J44. The total costs related to the management of related clinical conditions were estimated from January to December 2019.

Costs related to the stable phase of the disease: The direct medical costs were obtained by micro-costing, estimating the average cost of follow-up of one patient per year, according to the stage of the disease. The composition of these costs included the following elements:

Clinical follow-up: The procedures performed during the care of patients with COPD were listed according to the conduct recommended by the *Protoloco Clínico e Diretriz Terapêutica* (PCDT; Clinical Protocol and Therapeutic Guidelines) of COPD issued by the Brazilian Ministry of Health[16] and the International Guideline of GOLD.[1] The individual values were extracted from the *Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos,* Órteses, *Próteses e Materiais Especiais* (SIGTAP; Management System of the Table of Procedures, Medications, Orthotics, Prostheses, and Special Materials) of the Brazilian Unified Health System. Given the need to establish the respective frequencies of each performed clinical procedure, we chose to use a panel of pulmonology specialists based on a modified Delphi technique.[17,18] For this, a simplified questionnaire was developed (supplementary material), based on previous literature,[17,18] aiming to reflect the clinical practice in the management of the disease. Three pulmonologists were consulted, after sending the respective questionnaire via e-mail. As there were no significant disagreements between the answers, the panel was set up in just one round, estimating the average frequency of performance of each procedure per year. These val-

ues were multiplied by the individual costs of each procedure, obtaining the annual cost of clinical follow-up according to the stage of the disease. The consulted experts were physicians who reside and work in the state of Paraná, southern Brazil. They have experience in the private and public healthcare sectors.

Pulmonary rehabilitation and home oxygen therapy: The costs related to physical therapy support and home oxygen therapy for the treatment of the disease were estimated based on literature recommendations,[1,16] extracting their respective individual values from the SIGTAP Table.

Vaccination: The costs associated with reducing exposure to risk factors for exacerbations, through vaccination, were evaluated against influenza and pneumococcal pneumonia, using the information provided by informational materials from the Brazilian Ministry of Health.[19,20]

Pharmacological treatment: The individual values of each drug and presentation were obtained from the weighted averages present in the reports of the *Banco de Preços em Saúde* (BPS; Health Price Database) and prices stipulated by the *Tabela da Câmara de Regulação do Mercado de Medicamentos* (Table of the Medicines Market Regulation Chamber) of 2019, considering the following columns: tax rate (ICMS) of 0% and *Preço* Máximo de Venda *ao Governo* (Maximum Price of Sale to the Government). The data were related to the dosage recommended by the PCDT (ORDINANCE SAS/MS No. 609, OF JUNE 6, 2013), estimating the cost per dose, the annual cost of the minimum dose, and the annual cost of the maximum dose.

Calculation of the final costs of disease: After obtaining the individual values of each component of the costs related to the management of the stable phase of COPD, these were added according to the stage of the disease, presenting the estimated annual values for the treatment and follow-up of one patient per year, according to the degree of airflow limitation.

To ensure the integrity of our cost analysis when using varying unitary prices, we have closely examined the pricing structures provided by SIGTAP, hospital reimbursement rates, and the Medicines Price Tables. It is important to clarify that SIGTAP, which operates under Brazil's Unified Health System, standardizes prices nationally and does not adjust for geographical or institutional factors, such as the type of hospital. This contrasts with systems like that of the United States, where reimbursement can vary based on hospital teaching status or location.

Costs are presented in Brazilian Reais (BRL) for the year 2019. Total costs are presented in Brazilian Reais (BRL) and in US Dollars (USD) for the price years 2019 and 2024. We used CCEMG–EPPI Centre Cost Converter (available at https://eppi.ioe.ac.uk/costconversion/) for currency conversion and adjusting estimates for the price year 2024.

Ethical Aspects

Due to the use of secondary data, obtained from publicly accessible databases, this analysis did not require consideration and approval by the Research Ethics Committee.

Results

Costs related to the clinical management of the disease during hospitalizations

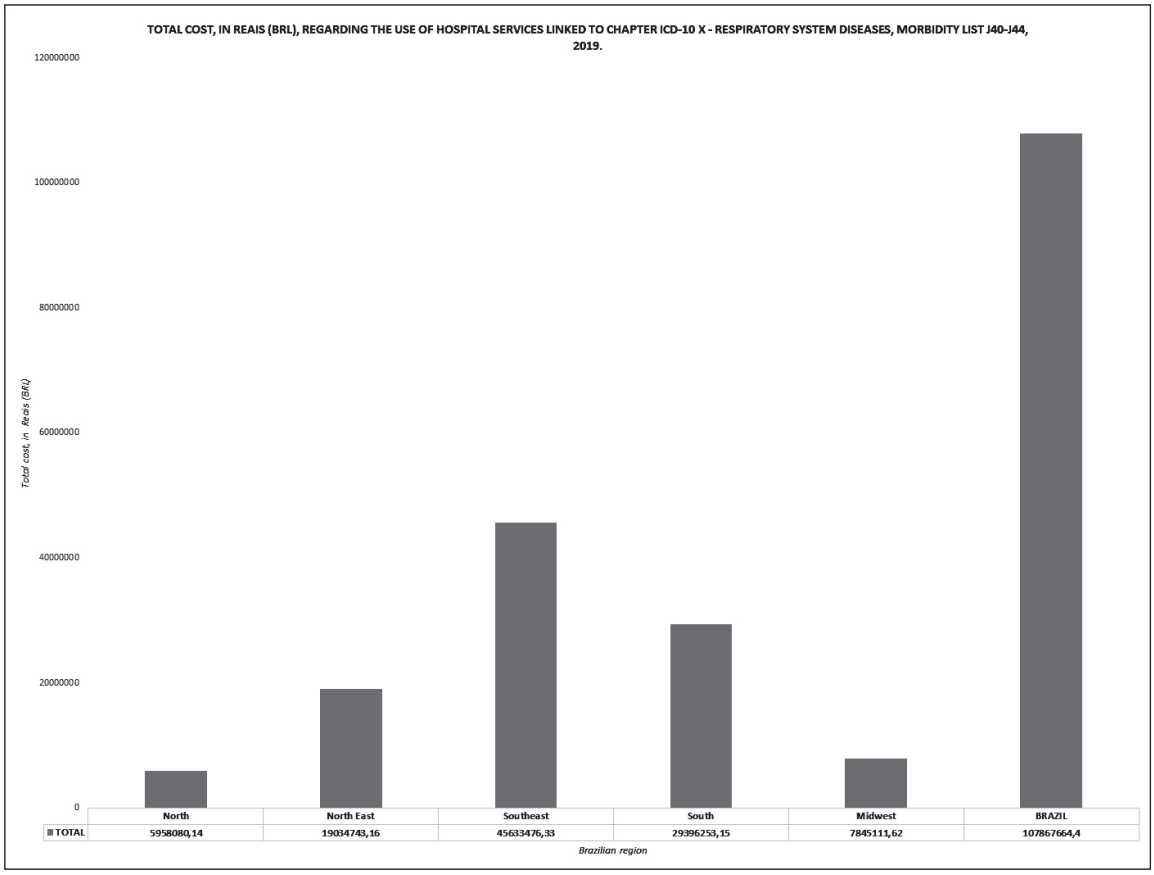
Considering all the AIH linked to the hospital treatment of the conditions contemplated by the ICD-10 J40-J44 classifications in 2019, the results pointed to a total value of BRL 107,867,664.40 (FIGURE 1). The national average cost per hospitalization, which corresponds to the estimate of the average individual cost per hospitalization, was BRL 980.66.

Costs related to the clinical management of the disease during the stable phase

Clinical procedures

The individual values of each clinical procedure were associated with the average frequencies established by the Panel of Experts, allowing the determination of the average annual cost of clinical follow-up of patients with COPD, according to the degree of airflow obstruction (TABLE 1).

Figure 1. Total value of AIH approvals from January to December 2019.



Pulmonary rehabilitation

Given the heterogeneity of studies concerning the duration of pulmonary rehabilitation programs, the values of this procedure within the scope of the Brazilian Unified Health System were estimated considering a rehabilitation program of 36 sessions, according to relevant literature.[21,22] Based on the procedure code 03.02.04.002-1 (PHYSIOTHERAPY CARE IN PATIENTS WITH RESPIRATORY DISORDER WITHOUT SYSTEMIC COMPLICATIONS) of the SIGTAP table, with a unit value of BRL 4.67, an average value of BRL 168.12 was obtained.

Vaccination

COPD is one of the priority conditions included in vaccination both against Influenza and in the prevention of pneumococcal pneumonia. According to the technical report of the 21st National Influenza Vaccination Campaign, published by the Ministry of Health in April 2019, 64 million doses were purchased at a unit price of BRL 15.14 for the annual campaign.[19] Since vaccination occurs in a single dose, this data was considered as the respective annual dose to be accounted for in the final calculation of the analysis, in a more realistic estimate of the value practiced. Regarding the pneumococcal vaccine, considering its availability by the Brazilian Unified Health System from the second half of 2019, and indication in a single dose[20], the unit values of this immunobiological were not included, according to the perspective and time horizon adopted in the study.

Oxygen therapy

The indication of home oxygen therapy is directed to chronic hypoxemic patients, who are usually in more severe stages of the disease. The values of the procedure code 03.01.05.006-6 (INSTALLATION/MAINTENANCE OF NON-INVASIVE

MECHANICAL VENTILATION AT HOME) are BRL 27.50 and for procedure code 03.01.05.00-15 (FOLLOW-UP AND HOME ASSESSMENT OF PATIENTS SUBMITTED TO NON-INVASIVE MECHANICAL VENTILATION - PATIENT/MONTH) are BRL 55.00. The total amount of BRL 687.50 was included for the follow-up of patients in stage IV of the disease.

Pharmacological treatment

The drugs used in the treatment of the stable phase of COPD are standardized by the Brazilian PCDT. The weighted averages for each pharmaceutical presentation were obtained in BRL from the BPS reports, relating the cost per dose, the annual cost of the minimum dose, and the annual cost of the maximum dose, according to the respective dosages (TABLE 2).

Considering the complexity of the possible drug associations for the pharmacological therapy of COPD, scenarios were established for each stage of the disease, according to the minimum and maximum standardized doses and indications of an association between therapies recommended by clinical guidelines (TABLE 3).

Based on the definition of the average costs related to clinical follow-up and maintenance of pharmacological therapy in the stable phase of COPD, it was possible to estimate the total annual costs, per patient, linked to the outpatient management of each stage of the disease. In the total values, the impact of the pharmacological treatment of COPD was verified, being the most representative component in the increase of costs according to the severity of the condition. The total costs in BRL and USD for the price years 2019 and 2024 are presented in Table 4.

Table 1. Average annual cost, in BRL*, of clinical follow-up performed on an outpatient basis for patients with COPD[+] in the stable phase, related through the mean frequencies of each procedure and the corresponding values in the SIGTAP[++] Table

PROCEDURE	UNIT VALUE (BRL)	AVERAGE FREQUENCY OF PERFORMANCE			
		STAGE I	STAGE II	STAGE III	STAGE IV
Follow-up consultation	10	1	2	3	4
Spirometry	6.36	1	1	1	2
Complete blood count	4.11	1	1	1	2
Erythrocyte sedimentation rate (ESR)	2.73	1	1	1	1
C-reactive protein (CRP)	2.83	1	1	1	1
Arterial blood gas	2.78	0	0	1	1
Biochemical profile[a]	16.95	1	1	1	2
Sputum culture	5.15	0	0	1	1
Chest X-ray	9.50	1	1	1	1
Electrocardiogram	5.15	1	1	1	1
Lung tomography	136.41	1	1	1	1
TOTAL VALUE (BRL*)		194.04	204.04	221.97	259.39

*BRL (Braziliam Real); [+]COPD (Chronic Obstructive Pulmonary Disease); [++]SIGTAP (Management System of the Table of Procedures, Medications, Orthotics, Prostheses, and Special Materials); [a]Biochemical profile: urea, creatinine, sodium, potassium, serum calcium, oxalacetic transaminase/aspartate aminotransferase, pyruvic transaminase/alanine aminotransferase, lactate dehydrogenase.

Table 2. Weighted averages of the values of drugs available for the treatment of COPD*, obtained from the BPS+ platform, and estimates of annual costs in the recommended minimum and maximum doses

Drug	Presentation	Unit value (BRL) [average Weighted (BPS)]	Unit amount	Dosage	Annual cost (minimum dose) (BRL++)	Annual cost (maximum dose) (BRL++)
Ipratropium bromide	Nebulizer solution 0.25 Mg/ml	0.35	20 m	0.25-0.5mg/1 to 2ml of nebulizer solution) every 4-6 hours	25.55	76.65
	Inhalation aerosol of 0.02 Mg/dose	21.54	200 doses	40-80 mcg; dosimetric aerosol 3 to 4 times a day	235.79	628.17
	Inhalation aerosol of 0.02 Mg/dose	18.21	10 mL	40-80 mcg; dosimetric aerosol 3 to 4 times a day	199.29	531.44
Albuterol	Inhalation aerosol 100 mcg	6.91	200 doses	200-400 mcg every 4-6 hours	100.74	297.84
	Nebulizer solution 5 mg/ml	10.61	10 mL	200-400 mcg every 4-6 hours	193.63	387.27
Fenoterol	Inhalation aerosol 100 mcg	19.28	200 doses	200-400 mcg every 4-6 hours	281.49	843.15
Formoterol	Inhalation capsule 12 mcg	0.52	1 capsule	12-24 mcg, 2 times/day	379.60	1,518.40
	Inhalation powder 12 mcg	64.83	60 doses	12-24 mcg, 2 times/day	780.37	1,560.74
Formoterol + budesonide	Inhalation capsule 12+400 mcg	1.60	1 capsule	12-24 mcg, 2 times/day	1,168.00	2,336.00
	Inhalation powder 12+400 mcg	60.46	60 doses	12-24 mcg, 2 times/day	735.48	1,470.22
	Inhalation powder[a] 6+200 mcg	67.26	60 doses	12-24 mcg, 2 times/day	1,636.66	3,273.32
Budesonide	Inhalation capsule 200 mcg	0.38	1 capsule	800-1,500 mcg/day	554.80	1,109.60
	Inhalation capsule 400 mcg	0.53	1 capsule	800-1,500 mcg/day	386.90	773.80
	Inhalation aerosol 200 mcg	84.00	100 doses	800-1,500 mcg/day	1,226.40	2,452.80
Beclomethasone	Inhalation capsule 200 mcg	0.36	1 capsule	800-1,500 mcg/day	525.60	1,051.20
	Inhalation powder 200 mcg	85.81	100 doses	800-1,500 mcg/day	1,252.68	2,505.36
	Inhalation powder 200 mcg	44.23	200 doses	800-1,500 mcg/day	322.66	645.32
	Inhalation capsule[a] 400 mcg	0.40	1 capsule	800-1,500 mcg/day	297.11	594.22
	Inhalation powder 400 mcg	55.31	100 doses	800-1,500 mcg/day	403.76	807.53+++
	Inhalation aerosol 250mcg.	49.55	200 doses	800-1,500 mcg/day	271.23	542.46
	Inhalation aerosol 200 mcg	46.19	200 doses	800-1,500 mcg/day	335.80	671.60

* COPD (Chronic Obstructive Pulmonary Disease); +BPS (Health Price Database); ++BRL (Braziliam Real); a In view of the incongruity of data present in the database, due to possible registration errors, the values in the Medicines Market Regulation Chamber table were used for the presentations formoterol 6 mcg + budesonide 200 mcg (inhalation powder) and beclomethasone 400 mcg (inhalation capsule), considering the values of tax rates at 0% and the Maximum Price of Sale to the Government.

Table 3. Costs of pharmacological treatment for each stage of COPD*, considering the indications of association of therapies recommended by the PCDT[+] of the Ministry of Health.

Copd stage	Pharmacological Therapy			Total Cost Annual (BRL[++])		Average Annual Cost per Stage (BRL[++])	
	SABA[¶]	LABA[§]	ICS[||]	Dose Min[#]	Dose Max[±]	Dose Min[#]	Dose Max[±]
I	Ipratropium Bromide			199.29	531.44		
	Albuterol			147.19	342.55	209.32	572.38
	Fenoterol			281.49	843.15		
II	Ipratropium Bromide	Formoterol		779.28	2,071.01		
	Albuterol	Formoterol		727.17	1,882.12	789.31	2,111.95
	Fenoterol	Formoterol		861.48	2,382.72		
III and IV	Ipratropium Bromide	Formoterol	beclomethasone	1,115.08	2,742.61		
	Albuterol	Formoterol	beclomethasone	1,062.97	2,553.72		
	Fenoterol	Formoterol	beclomethasone	1,197.28	3,054.32	1,360.29	3,127.38
	Ipratropium Bromide	Formoterol + Budesonide		1,601.62	3,336.10		
	Albuterol	Formoterol + Budesonide		1,549.52	3,147.21		
	Fenoterol	Formoterol + Budesonide		1,683.82	3,647.81		

*COPD (Chronic Obstructive Pulmonary Disease); *PCDT (Clinical Protocol and Therapeutic Guidelines); [++]BRL (Braziliam Real); [¶]SABA (*short-acting* [¶]*2 agonists*); [§]LABA (*long-acting* [β]*2 agonists*); [||]ICS (*inhaled corticosteroids*); [#]MIN (minimum), [±]MAX (maximum).

Table 4. Total costs, by stage, of treatment and clinical follow-up of patients with COPD in the stable phase, considering the average annual values per patient. Costs are presented in Brazilian Reais (BRL) for the price year 2019 and in US Dollars (USD) for the price years 2019 and 2024.

	AVERAGE ANNUAL COST PER PATIENT							
	STAGE I		STAGE II		STAGE III		STAGE IV	
Clinical procedures	194.04 (BRL/2019) 93.78 (USD/2019) 117.63 (USD/2024)		204.04 (BRL/2019) 98.62 (USD/2019) 123.69 (USD/2024)		221.97 (BRL/2019) 107.28(USD/2019) 134.56 (USD/2024)		259.39 (BRL/2019) 125.37 (USD/2019) 157.24 (USD/2024)	
Pulmonary rehabilitation			168.12 (BRL/2019) 81.26 (USD/2019) 101.91 (USD/2024)		168.12 (BRL/2019) 81.26 (USD/2019) 101.91 (USD/2024)		168.12 (BRL/2019) 81.26 (USD/2019) 101.91 (USD/2024)	
Vaccination	15.14 (BRL/2019) 7.32 (USD/2019) 9.18 (USD/2024)		15.14 (BRL/2019) 7.32 (USD/2019) 9.18 (USD/2024)		15.14 (BRL/2019) 7.32 (USD/2019) 9.18 (USD/2024)		15.14 (BRL/2019) 7.32 (USD/2019) 9.18 (USD/2024)	
Oxygen therapy							687.50 (BRL/2019) 332.29 (USD/2019) 416.76 (USD/2024)	
Pharmacological treatment (Minimum dose/ Maximum dose)	MIN. DOSE	MAX. DOSE	MIN. DOSE	MAX. DOSE	MIN. DOSE	MAX. DOSE	MIN. DOSE	MAX. DOSE
	209.32 (BRL/2019) 101.17 (USD/2019) 126.89 (USD/2024)	572.38 (BRL/2019) 276.65 (USD/2019) 346.97 (USD/2024)	789.31 (BRL/2019) 381.49 (USD/2019) 478.47 (USD/2024)	2,111.95 (BRL/2019) 1,020.76 (USD/2019) 1,280.25 (USD/2024)	1,360.29 (BRL/2019) 657.46 (USD/2019) 824.60 (USD/2024)	3,127.38 (BRL/2019) 1,511.54 (USD/2019) 1,895.79 (USD/2024)	1,360.29 (BRL/2019) 657.46 (USD/2019) 824.60 (USD/2024)	3,127.38 (BRL/2019) 1,511.54 (USD/2019) 1,895.79 (USD/2024)
TOTAL	418.50 (BRL/2019) 202.27 (USD/2019) 253.69 (USD/2024)	781.56 (BRL/2019) 377.75 (USD/2019) 473.77 (USD/2024)	1,176.61 (BRL/2019) 568.69 (USD/2019) 713.25 (USD/2024)	2,499.25 (BRL/2019) 1,207.95 (USD/2019) 1,515.02 (USD/2024)	1,765.52 (BRL/2019) 853.32 (USD/2019) 1,070.24 (USD/2024)	3,532.61 (BRL/2019) 1,707.40 (USD/2019) 2,141.44 (USD/2024)	2,490.44 (BRL/2019) 1,203.69 (USD/2019) 1,509.68 (USD/2024)	4,257.53 (BRL/2019) 2,057.77 (USD/2019) 2,580.88 (USD/2024)

Discussion

Given the context presented, it is possible to perceive the economic impact of COPD at the hospital and outpatient levels on the use of health resources in Brazil. Even with defined clinical guidelines and availability of access to standardized drugs for treatment, some factors can negatively impact the management of the disease, leading the patient to frequent exacerbations. One of them is low adherence to treatment and the other is failures in the indication and difficulties in accessing pulmonary rehabilitation programs.[23,24] It is important to notice that, despite the free access policy to COPD treatment in Brazil, a high frequency of undertreatment is observed. A cohort study conducted with patients with moderate to severe COPD followed in a public disease management program in Brazil showed that non-adherent patients were almost twice as likely to die compared to those who were adherent, highlighting the need of adherence monitoring and optimization strategies.[25] In this sense, the lack of treatment and poor adherence to the prescribed drugs are related to more severe COPD, which leads to a higher hospitalization rate, increasing the costs associated to hospital services, and a higher mortality rate, which also impacts on the costs of the disease for the health system.[26]

Regarding pharmacological treatment, it is necessary to highlight the absence of bronchodilators of the class of antimuscarinics (long-acting muscarinic antagonists – LAMAs) standardized within the PCDT for COPD management in Brazil during the study period. The last update by GOLD for advanced stages of the disease and patients with greater symptoms recommends the use of LAMA as a bronchodilator agent, reserving the use of the association of LABA+ICS (long-acting β2 agonists + inhaled corticosteroids) for symptomatic patients with an eosinophil count greater than 300 cells/μl. Previous studies have demonstrated the superiority of LAMA bronchodilators in terms of controlling exacerbations and improving quality of life indicators. A study compared the benefits and harms of the LABA+LAMA versus LABA+ICS associations in a systematic review that included 11 studies and 9,839 participants, revealing the superiority of the LABA+LAMA association in outcomes related to exacerbation rates (OR 0.82, 95% CI: 0.70 - 0.96, P = 0.01, I^2 = 17%) and improvement in FEV1 (MD 0.08 L, 95% CI: 0.06 - 0.09 L P < 0.0001, I^2 = 50%). In addition, the same study pointed to a reduction in the risk of pneumonia and improvement in the St. George's Respiratory Questionnaire.[27]

Furthermore, in the face of a possible inappropriate therapy, the lack of accessibility to drugs classified as LAMA can also trigger other burdens on health systems, such as judicialization processes. An exploratory study that aimed to survey the types of lawsuits filed for the drug tiotropium bromide identified that between 2010 and 2016 tiotropium bromide presented an increase of more than 61% in the number of units dispensed, being the drug with the highest number of lawsuits in the Brazilian state of Paraná. This study states that the possible costs of acquiring tiotropium bromide by making it available to the patients would be lower than values spent on legal proceedings initiated by patients who demand the drug judicially, representing a potential saving of public resources.[28]

Regarding the stable phase of the disease, the severity of the condition is highlighted as a major factor in the increase in costs, with pharmacological treatment representing the component with the greatest burden on the total values. A systematic review on the cost analysis of COPD published in 2021 included 18 publications reporting data from developed and European countries (no study from Brazil was retrieved). The results of the systematic review showed that the higher costs associated with COPD corresponded to more severe disease conditions, mainly exacerbations. In addition, the highest costs were related to hospitalizations and the pharmacological treatment associated.[29] The results found in our study are in line with international data that demonstrate the increase in costs linked to the severity of the disease. A cross-sectional study with 189 patients treated at the pulmonology department of the University Hospital of Larissa, in Greece, evaluated the cost of COPD maintenance treatment and the impact of the country's financial crisis on these patients. The study estimated an annual cost ranging from €615.44 for patients in Stage I of the disease, to €1,302.03 for patients in Stage

IV. The costs of pharmacological treatment were also estimated considering the ABCD classification, ranging from €715.01 for patients classified in group A, to €1,101.05 for patients in group D. The authors highlighted that the costs of the drug treatment of COPD were significantly higher for patients in the most severe stages of the disease (Stages III and IV) and at high risk of exacerbation (groups C-D).[30] The annual cost-of-illness of COPD was also evaluated by Dal Negro (2021) in Italy, revealing that in the last two decades, the major cost component included direct costs, mainly hospitalization costs due to exacerbations, which corresponded to almost 70% of total direct costs. As in our study, the author also exposed that the mean cost per patient depends on COPD severity, ranging from € 1830.60 (mild COPD) to € 5451.70 (severe COPD). Despite our analysis including only direct costs focusing on the pharmacological treatment, Dal Negro (2021) highlights that in his review on the cost-of-illness of COPD in Italy, direct costs accounted for almost 90% of total costs related to COPD management.[31] Hence, it is fair to state that our analysis provides valuable information for decision-makers in planning economic and political strategies for COPD management from the perspective of the public health system.

It is also necessary to highlight the current cost of disease management, considering its prevalence in the Brazilian population. A systematic review that summarized the prevalence of COPD in Brazil included 12 studies in the meta-analysis, obtaining a prevalence of 17% (95% CI: 13-22%) among adults over 40 years of age.[32] Although the epidemiological data do not relate the prevalence according to the severity of the disease, it is possible to estimate, based on the measures of central tendency of the costs by stage obtained in this analysis, a value of BRL 29,036,988,226.85 destined to the management of the disease. Although this value reflects only an estimate and may be overestimated due to the lack of concise data on the proportion of individuals affected in each degree of disease severity, the repercussion of COPD on the demand for the use of health resources in the country is visible.

Being a preventable situation, the need to encourage the development of strategies that can avoid the occurrence of the disease is even more evident. The World Health Organization recommends the following interventions to reduce the global impact of COPD: smoking cessation, encouragement of physical activity, vaccination, adequate use of inhalation devices, and access to pulmonary rehabilitation programs. In addition, COPD is one of the pathologies included in the Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2030, a global strategy that aims to reduce the avoidable burden of morbidity, mortality, and disability related to non-communicable diseases. Such actions are key elements in reducing the incidence and worsening of the illness, consequently leading to a reduction in the economic burden associated with its clinical management.

Study limitations

In the hospitalization cost analysis, our study primarily accounted for the *per diem* (daily rates) charged by hospitals. These rates typically include room charges and routine care but do not encompass additional expenses such as medical materials, specific drug costs, the utilization of medical equipment, or other infrastructural costs. The reliance on per diem rates was dictated by the data available from the Sistema de Informações Hospitalares (SIH), which predominantly captures these daily charges. Consequently, the exclusion of these supplementary costs may limit the comprehensiveness of our hospitalization cost estimates, potentially underrepresenting the full economic burden of COPD-related hospital stays.

The lack of information on the prevalence of COPD by disease stage also made it impossible to correlate hospitalizations with the severity of the condition, as it could be included in the total cost per patient per year. As for pharmacological treatment, charges linked to access to medicines through supplementary health care (health insurance) were not included. Moreover, while adopting the Brazilian Unified Health System perspective, our study did not include costs associated with judicialization – legal actions taken by patients to access treatments outside the standard Brazilian Unified Health System coverage – due to the challenges in estimating

these costs with the available data, despite their potential impact on the overall economic burden of COPD.

In conclusion, it is estimated that the cost of treatment and follow-up of a patient with COPD in the stable phase in Brazil can range from BRL 418.50 [price year 2019] (USD 202.27 [price year 2019] / USD 253.69 [price year 2024]) to BRL 4,257.53 [price year 2019] (USD 2,057.77 [price year 2019] / USD 2,580.88 [price year 2024]), and the exacerbations of this condition also present a considerable impact on costs related to hospital management of respiratory diseases in the country. Given this scenario, it is necessary to highlight the importance of promoting and implementing effective strategies and public policies to reduce exposure to risk factors for the disease, early diagnostic methods, and control the progression of the condition.

Furthermore, the study's methodology, which employs an eclectic mix of cost approaches and relies on input from a small expert panel, carries inherent limitations. The cost of illness methodology may not fully capture indirect costs or the intangible aspects of disease burden, and the limited panel size may not reflect a broader range of clinical practice, potentially introducing bias. Additionally, the combination of macro and micro-costing techniques, while comprehensive, may lead to inconsistencies due to varying data resolution. These methodological considerations are crucial in interpreting the findings and should inform future research that might benefit from a more uniform costing approach and an expanded multidisciplinary expert panel.

Authors' contributions
Conceptualization: H.H.L. and A.C.M.; Data curation: S.M.; Formal analysis: S.M., H.H.L. and A.C.M.; Funding acquisition: A.C.M.; Investigation: S.M., H.H.L. and A.C.M.; Methodology: H.H.L. and A.C.M.; Project administration: A.C.M.; Resources: H.H.L. and A.C.M.; Supervision: H.H.L. and A.C.M.; Validation: W.E.B., H.H.L. and A.C.M.; Visualization: W.E.B.; Writing – original draft: S.M. and W.E.B.; Writing - review & editing: W.E.B. and H.H.L.

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