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Economic Burden and Key Cost Drivers of Managing Hospitalized Chronic Obstructive Pulmonary Disease Patients Admitted with an Exacerbation in Türkiye: A Cost of Illness Study from Payer Perspective

Türkiye'de Alevlenme ile Yatırılan Kronik Obstrüktif Akciğer Hastalarının Yönetiminde Anahtar Maliyet Kalemleri ve Ekonomik Yük: Geri Ödeyici Perspektifinden Hastalık Maliyeti Çalışması

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ABSTRACT Objective: To estimate the economic burden and key cost drivers of managing exacerbated and hospitalized chronic obstructive pulmonary disease (COPD) patients in Türkiye. **Material and Methods:** This cost of illness study was based on an estimation of per patient annual direct medical costs for the management of exacerbated and hospitalized COPD patients in Türkiye from a payer perspective. The average per patient direct medical cost was calculated based on cost items related to outpatient visits, diagnostic laboratory and radiological tests, hospitalizations and interventions, training and rehabilitation, drug treatment and equipment, drug-related adverse events, and co-morbidities/complications. **Results:** Based on average annual per patient costs calculated for outpatient admission ($88.5), laboratory and radiological tests ($68.6), hospitalizations and interventions/training/rehabilitation ($1,181.3), drug treatment/equipment ($1,088.0), co-morbidities/complications ($1,291.7) and drug related adverse events ($11.8) cost items, per patient annual direct medical cost related to the management of exacerbated and hospitalized COPD patients was calculated to be $3,729.9 from the payer perspective. Co-morbidities/complications (34.6%), hospitalizations/interventions (31.7%) and drug treatment/equipment (29.2%) were the key cost driver. **Results:** In conclusion, our findings indicate that managing exacerbated and hospitalized COPD patients pose a considerable burden to health economics in Türkiye, with co-morbidities and hospitalizations estimated as the main cost drivers. Our findings emphasize the need for cost-effective prevention strategies and the likelihood of potential cost-savings by timely recognition and proper management of co-morbidities and by better disease control with reduced frequency of exacerbations and hospitalizations.

Keywords: Chronic obstructive pulmonary disease; exacerbations; practice patterns; cost analysis; Türkiye

ÖZET Amaç: Türkiye'de alevlenme geçiren ve hastanede yatırılarak tedavi edilen kronik obstrüktif akciğer hastalığı (KOAH) hastalarının ekonomik yükünü tespit etmek ve anahtar maliyet kalemlerini saptamak çalışmanın amacıdır. **Gereç ve Yöntemler:** Bu hastalık maliyeti çalışması geri ödeyici perspektifinden, yatırılarak tedavi edilen KOAH hastalığının yönetiminde hasta başı direkt maliyetleri hesaplamaya odaklanmıştır. Ortalama direkt tıbbi maliyetler poliklinik ziyaretleri, tanıda laboratuvar ve görüntüleme maliyetleri, yatış ve müdahaleler, eğitim ve rehabilitasyon, ilaç tedavisi ve komorbid ve komplikasyonlara ait maliyetleri kapsamaktadır. **Bulgular:** Ortalama hasta başı poliklinik ziyaretleri (88,5$), laboratuvar ve radyolojik test maliyeti (68,6 $), yatış ve müdahale/eğitim/rehabilitasyon (1.181,3$) ilaç tedavisi/tıbbi cihaz maliyeti (1.088,0$), komorbid/komplikasyon (1.291,7$) ve ilaç ilişkili yan etki maliyeti (11,8$) ve toplam hasta başı ortalama alevlenme ile yatış maliyeti 3.729,9 $ olarak geri ödeyici perspektifinden belirlenmiştir. Komorbiditeler ve komplikasyonlar (%34,6), yatış/müdahale (%31,7) ve ilaç tedavi/cihaz maliyeti (%29,2) ile en yüksek maliyet kalemleri olarak tespit edilmiştir. **Sonuç:** Bulgularımız, alevlenme ile hastaneye yatan KOAH hastalarının Türkiye sağlık ekonomisine önemli bir yük getirdiğini göstermektedir. Komorbid hastalıklar ve yatış en önemli maliyet belirleyicileridir. Maliyet etkili ve zamanında maliyet tasarruflu potansiyel önleme stratejileri ile daha iyi hastalık kontrolü, komorbidlerin yönetimi ile alevlenmeler ve yatış sıklıkları azaltılabilir.

Anahtar Kelimeler: Kronik obstrüktif akciğer hastalığı; alevlenme; uygulama modeli; maliyet analizi; Türkiye

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Chronic obstructive pulmonary disease (COPD) is a highly prevalent global health problem, with 384 million COPD patients and a global prevalence of 11.7%. The Global Burden of Disease Study ranked in 2010 as the third leading cause of mortality and the ninth leading cause of disability-adjusted life years lost.[1,2]

COPD is characterized by persistent respiratory symptoms and airflow limitation, the severity of which depends on the frequency of exacerbations and the presence of comorbidities.[1] Exacerbations of COPD is considered the most important adverse prognostic factor that accelerates disease progression, deteriorates quality of life, and increases mortality risk.[3] In addition, the frequency and severity of exacerbations increase with the progression of underlying COPD.[4] Accordingly, COPD exacerbations are considered the main cost driver in COPD due to their association with an increased number of emergency admissions and hospitalizations in studies from Türkiye consistent with worldwide data.[5-9]

Therefore, prevention and optimal management of COPD exacerbations according to best practice guidelines are considered a key component of COPD management strategies and an essential cost-saving strategy in terms of both indirect and direct costs by slowing down the progression of the disease.[1,5,10,11]

According to data from the Türkiye arm of European COPD Audit that recruited 612 patients from 22 centers, COPD patients with an exacerbation resulting in hospital admission in Türkiye had Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage III-IV in 70.4% of cases with an emergency admission rate of 68.2% and a hospitalization rate of 26.0% overall, and 55.3% in GOLD Stage III-IV COPD patients with severe exacerbation along with an overall readmission rate of 36.1%.[12]

In view of a considerable difference in COPD related cost estimates between countries due to varied treatment patterns, labor market and caregiving practices emphasizing a need for country-specific data, this cost of illness study was designed to estimate economic burden and key cost drivers of managing exacerbated and hospitalized COPD patients in Türkiye, based on per patient annual direct medical costs from payer perspective.[13-15]

MATERIAL AND METHODS

DESIGN

This cost of illness study (descriptive research) was based on estimation of per patient annual direct medical costs for managing COPD in Türkiye concerning practice patterns in clinical practice and guideline recommendations. The direct medical cost was calculated based on cost items related to outpatient visits, laboratory and radiological tests, hospitalizations and interventions/training and rehabilitation, drug treatment/equipment, drug-related adverse events and co-morbidities/complications. Helsinki Declaration was applied in this study.

DATA ON REAL LIFE CLINICAL PRACTICE

Data on real-life practice patterns in the management of COPD in Türkiye, including outpatient clinic admission rates, laboratory and imaging investigations, selected medications, treatment-related adverse event rates, hospitalizations and interventions, and pulmonary rehabilitation and patient training, were obtained from the findings provided in the Türkiye arm of The European COPD Audit that recruited 612 exacerbated and hospitalized COPD patients at 22 centers across Türkiye and National Disease Burden Study in Türkiye or estimated concerning Global Strategy for Diagnosis, Management, and Prevention of COPD updated 2014 recommendations and Turkish Thoracic Society 2010 Consensus Report on Diagnosis and Treatment of COPD.[1,12,16]

COST ANALYSIS

According to the cost of illness method developed by the World Health Organization, average per-patient direct medical costs were calculated based on cost items such as outpatient visits, laboratory and radiological tests, hospitalizations and interventions, training and rehabilitation, drug treatment/equipment, drug-related adverse events and co-morbidities/complications for the payer perspective (only direct medical costs using prices of the public payer “Social Security Institution (SSI)” in Türkiye). For drugs, retail prices from the updated price list and updated institution discount list of SSI for July 2016 were taken into account in calculation of the unit costs. Costs re-

lated to diagnostic tests were calculated considering the Health Implementation Notification by SSI. Physician visit costs were calculated using unit prices also based on the same SSI notification. Hospitalization costs were calculated using unit prices based on Healthcare Organization Price List in Health Practice Declaration and Treatment Assist Practice Declaration. Monetary results were converted by using 2.97 USD/TL July 2016 exchange rate. Direct non-medical costs (e.g. transfers of patient and caregivers or home care, etc.) and indirect costs were excluded from the cost analysis.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize results on practice patterns for COPD management. Expenses related to managing COPD exacerbations were the main cost-analysis related parameter of the study. The cost model for COPD was developed in Excel. All inputs came from published research. Cost model was based on the following equation: "Cost = ∑ (Frequency; %) X (Unit price; TL) X (patient ratio; %)". The model focused on the average cost per patient. To find average cost per patient, all data frequency was evaluated.

RESULTS

OUTPATIENT ADMISSION COST ITEM

Outpatient admission was estimated to occur in 100.0% of patients and four times per patient per year at Chest Diseases outpatient clinics, in 18.0% of patients and four times per patient per year at chest surgery outpatient clinics, in 55.0% of patients and for once in a year per patient at internal medicine outpatient clinics, in 5.0% of patients and four times per patient per year at immunology and allergic diseases outpatient clinics, in 37%, and 22% of patients and for twice in a year per patient at physical therapy and rehabilitation outpatient clinics (Table 1).

TABLE 1: Outpatient admission- Laboratory and radiological tests cost item: Clinical practice, unit costs and total cost.

Outpatient admissions	Annual admission rate (%)	Annual visit # per patient	Unit cost ($)	Total cost ($) (n=1,000)
Chest diseases	100.0	4	14.04	56,166.3
Chest surgery	18.0	4	14.03	10,103.4
Internal medicine	55.0	1	15.09	8,302.6
Immunology and allergic diseases	5.0	4	15.09	3,019.1
Emergency admission	68.2	1	.00	.00
Physical therapy and rehabilitation	37.0	2	2.02	2,424.2
	22.0	2	10.59	8,469.9
Total				88,485.6
Per patient outpatient admission cost ($)				**88.5**
Pulmonary function test	100.0	1	8.42	8,417.8
Arterial blood gas analysis	100.0	1	1.72	1,717.1
Sputum smear	100.0	1	1.18	1,178.0
Sputum culture	100.0	1	.84	842.6
Abdominal USG	37.0	1	8.01	2,964.6
CT-PA (GOLD Stage II-IV)	85.7	1	23.77	20,377.3
Thorax CT	44.0	1	18.52	8,148.3
CT-PA	32.2	1	18.52	5,968.6
Pulmonary function test (repeat)	100	2	8.42	16,835.6
Arterial blood gas analysis (repeat)	93.5	1	1.72	1,605.5
Alpha-1 antitrypsin	10.0	1	2.79	279.5
Theophylline levels	15.0	1	1.72	257.6
Total				68,592.5
Per patient laboratory and radiological tests cost ($)				**68.6**

USG: Ultrasonography; CT-PA: Computed tomographic-pulmonary angiography; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Based on unit costs, total per-patient annual cost related to outpatient admissions was $88.5 (Table 1).

LABORATORY AND RADIOLOGICAL TESTS COST ITEM

Pulmonary function tests, arterial blood gas analysis, sputum smear, and sputum culture were estimated to be applied in all COPD-related admissions in Türkiye, while pulmonary function tests and arterial blood gas analysis were repeated in the majority of patients. Annual rates for alpha-1 antitrypsin and theophylline measurements were 10.0% and 15.0%, while computed tomographic pulmonary angiography (CT-PA) was applied in 85.7% of patients with GOLD Stage II-IV COPD, and CT-PA was required in 32.2% of patients (Table 1).[12]

Based on unit costs, total per-patient annual cost related to laboratory and radiological tests was $68.6 (Table 1).

HOSPITALIZATIONS AND INTERVENTIONS/ TRAINING/REHABILITATION COST ITEM

Overall, exacerbated hospitalized COPD patients were hospitalized for median 9 days per year.[12] When analyzed based on GOLD Stage and severity of exacerbation, 70.44% of patients were at GOLD Stage III-IV, 15.28% were at GOLD Stage II and 14.29% were at GOLD Stage I with 2.6 exacerbations/year (5.7% were severe), 1.8 exacerbations/year (12.0% were severe) and 0.8 exacerbations/year (2.5% were severe), respectively.[1,2] Severe exacerbation was associated with hospitalization in service or in intensive care unit (ICU) in 55.3% (Length of stay (LOS): 9 days) and 5.7% (LOS: 1 day) of patients with GOLD stage III-IV COPD, in 3.3% (LOS: 9 days) and 2.2% (LOS: 1 day) of patients with GOLD stage II COPD, and in 0.3% (LOS: 2 days) and 0.2% (LOS: 1 day) of patients with GOLD stage I COPD, respectively. Non-severe exacerbation was associated with hospitalization in service or in ICU in 11.0% (LOS: 9 days and 1 day, respectively) of patients with GOLD stage III-IV COPD, in 2.2% (LOS: 9 days and 1 day, respectively) of patients with GOLD stage II COPD, while associated with hospitalization in service in 1.0% (LOS: 1 day) of patients with GOLD stage I COPD. Readmission within 90 days was estimated to occur in 36.1% of patients and associated with ICU hospitalization for 1 day (Table 2).[1,12,16]

Training on inhaler device and education on COPD were given to all patients, while training on concentrator devices and non-invasive devices was given to 3.96% and 14.5% of GOLD Stage III and IV patients, respectively. Pulmonary rehabilitation was applied in 40.0% and 60.0% of patients with GOLD Stage I-II COPD and GOLD Stage III-IV COPD, respectively (Table 2).[12]

Cost estimations regarding surgical interventions were not provided due to low likelihood of possible complications.

Based on unit costs, total per-patient annual cost related to hospitalizations and interventions/training/rehabilitation was $1,181.3 (Table 2).

DRUG TREATMENT AND EQUIPMENT COST ITEM

Based on prescription rates in Türkiye, maintenance doses and annual dose and unit cost per box for each drug regimen and unit costs of equipment, total per-patient annual cost related to drug treatment and equipment was $1,088.0 (Table 3).[12]

CO-MORBIDITIES/COMPLICATIONS COST ITEM

Cost related to co-morbidities and complications was calculated to be $1,291.7 per patient for COPD treatment based on the prevalence of comorbid disorders in Türkiye (Table 4).[12]

DRUG RELATED ADVERSE EVENTS COST-ITEM

Advers events cost calculation based on the cost of illness methodology. Frequency of adverse events data was obtained from summary of product characteristics of drugs. Then clinical guidelines were followed to calculate adverse events cost. Based on highly prevalent (1.53%: headache, palpitation, tremor, oropharyngeal candidiasis) and less prevalent (1%: agitation, bronchitis, nausea, dyspnea/asthma exacerbation, bacterial pharyngitis, fatigue, hypokalemia, irritability, myalgia/muscle spasms, convulsion, nasopharyngitis, cough, pneumonia, hoarseness, sleep disturbance and difficulty in swallowing; 0.98%: xerostomia, gastrointestinal dysmotility) and unit costs, total per patient annual cost related to drug related adverse events was $11.8 (Table 5).[12]

TABLE 2: Hospitalizations and interventions/training/rehabilitation cost item: clinical practice, unit costs and total cost.

Hospitalizations and interventions/training/rehabilitation			Rate (%)	LOS (day) per admission (median)	Unit daily cost ($)	Total cost ($) (n=1,000)
Hospitalizations			26.0	9	10.10	23,636.4
GOLD Stage III-IV exacerbation	severe	Chest diseases	55.3	9	10.10	50,281.1
		ICU	5.7	1	269.55	15,364.0
	not severe	Chest diseases	11.0	9	10.10	10,000.0
		ICU	11.0	1	269.55	29,650.2
GOLD stage II exacerbation	severe	Chest diseases	3.3	9	10.10	3,000.3
		ICU	2.2	1	269.55	5,871.7
	not severe	Chest diseases	2.2	9	10.10	1,980.1
		ICU	2.2	1	269.55	5,871.7
GOLD Stage I exacerbation	severe	Chest diseases	0.3	2	10.10	57.6
		ICU	0.2	1	269.55	508.4
	not severe	Chest diseases	1.0	1	269.55	2704.0
		ICU	0.0	0	10.10	0.0
Interventions			**Rate (%)**	**# of interventions**	**Unit cost ($)**	**Total cost ($)**
Volume reduction surgery (GOLD Stage IV)				0.1	1	287.54 308.8
Lung transplantation (GOLD Stage IV)			0.1	1	15,782.83	16,955.9
Bullectomy (GOLD Stage IV)			0.1	1	191.58	205.7
Related hospitalizations			**Rate (%)**	**LOS (day) per admission (median)**	**Unit daily cost ($)**	**Total cost ($)**
Chest diseases (for volume reduction and bullectomy)			0.2	5	10.10	108.4
ICU (for volume reduction and lung transplantation)			0.2	2	269.55	1,158.3
Readmission for COPD within 90 days			36.1	1	125.29	40,797.0
Patient training/education on			**Rate (%)**	**Package # per patient**	**Unit cost ($)**	**Total cost ($)**
Inhaler device (GOLD Stage III-IV)			100.0	1	2.02	2,020.6
Concentrator device (GOLD Stage III)			3.96	1	2.02	80.0
Non-invasive device (GOLD Stage IV)			14.5	1	2.02	293.0
COPD (GOLD Stage I-IV)			100.0	1	0.61	607.0
Pulmonary rehabilitation			**Rate (%)**	**Package # per patient**	**Unit cost ($)**	**Total cost ($)**
GOLD Stage I-II			40.0	1	606.06	242,423.2
GOLD Stage III-IV			60.0	1	1,212.11	727,269.6
Total						1,181,329.0
Per patient hospitalizations and interventions/training/rehabilitation cost ($)						**1,181.3**

LOS: Length of stay; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICU: Intensive care unit; COPD: Chronic obstructive pulmonary disease.

TABLE 3: Drug treatment and equipment cost item: clinical practice, unit costs and total cost.

Drug and equipment	Prescription rate (%)	Unit cost (box/year; $)	Total cost ($) (n=1,000)
Drug treatment			
Long-acting beta2 agonists + inhaled steroids	63.70	209.98	133,755.6
Short-acting beta2 agonists	40.0	95.52	38,205.7
	95.8	95.52	91,502.7
Short-acting anticholinergics	30.10	108.52	32,663.1
	92.5	108.52	100,376.5
Long-acting anticholinergics	67.60	145.74	98,518.5
Long-acting beta2 agonists	15.50	254.40	39,431.9
Inhaled steroids	61.90	84.32	52,194.2
Theophylline	93.30	24.24	22,616.1
Systemic steroids	66.10	106.86	70,632.6
Post-discharge antibiotics	22.10	19.55	4,321.0
Antibiotics for exacerbation	87.60	51.92	45,478.3
	62.90	19.55	11,515.3
Oral steroid for exacerbation	58.90	106.86	62,934.3
Short-acting beta2 agonist for mild exacerbation	13.68	95.52	12,587.2
Pneumococcal vaccine	100.0	4.87	4,868.7
Influenza vaccine	100.0	2.43	2,427.6
Pneumonia treatment	24.30	134.38	32,654.1
Lung transplantation	0.18	380.13	665.2
Total drug treatment cost			857,348.5
Equipment	**Rate (%)**	**Unit cost (TL)**	**Total cost (TL)**
Oxygen tube and cap	3.96	42.76	1693.3
Oxygen concentrator	3.96	280.47	11,106.7
Mask set	3.96	58.33	2,309.7
Nebulizator	14.50	33.67	4,882.2
Oxygen gas	3.96	1.35	64,533.3
Nebulizer set	14.50	0.45	24,056.8
Non-invasive mechanic ventilator	14.50	841.75	122,053.9
Total equipment cost			230,635.9
Total			1,087,984.4
Per patient drug treatment and equipment cost ($)			**1,088.0**

PER PATIENT TOTAL ANNUAL DIRECT MEDICAL COST

Based on average annual per-patient costs calculated for outpatient admission ($88.5), laboratory and radiological tests ($68.6), hospitalizations and interventions/training/rehabilitation ($1,181.3), drug treatment ($1,088.0), co-morbidities/complications ($1,291.7) and drug-related adverse events ($11.8) cost items, per-patient annual direct medical cost related to management of exacerbated and hospitalized COPD patients was calculated to be $3,729.9 from payer perspective (Table 6).

Co-morbidities/complications (34.6%) and hospitalizations and interventions (31.7%), and drug treatment/equipment (29.2%) were the key cost drivers in the management of COPD patient admitted with an exacerbation (Table 6).

DISCUSSION

Our findings revealed that per-patient annual direct medical cost related to the management of exacerbated and hospitalized COPD patients in Türkiye was $3,729.9 from payer perspective. Co-morbidities/complications ($1,291.7; 34.6%), hospitalizations/interventions ($1,181.3; 31.7%) and drug treatment ($1,088.0; 23.0%) were the major cost drivers.

TABLE 4: Co-morbidities/complications cost item: clinical practice, unit costs and total cost.

Co-morbidities/complications	Rate (%)	Unit cost ($)	Total cost ($) (n=1,000)
Congestive heart failure	22.5	1,596.7	359,256.3
Diabetes	17.8	485.3	86,380.9
Other chronic pulmonary diseases	8.0	3,252.9	260,229.0
Myocardial infarction	7.5	1,312.2	98,414.1
Peripheral vascular disease	6.2	657.0	40,735.4
Moderate-to-severe kidney disease	2.9	8,904.8	258,238.2
Tumor	2.5	2,916.5	72,911.5
Ulcer	2.1	259.7	5,453.8
Cerebrovascular disease	2.0	1,632.3	32,646.7
Dementia	1.0	383.5	3,834.9
Connective tissue diseases	0.7	2,645.0	18,514.7
Hemiplegia	0.5	1,669.9	8,349.7
Diabetes with end-organ damage	0.3	1,174.3	3,522.8
Leukemia	0.2	21,626.9	43,253.8
Total			1,291,741.7
Per patient co-morbidities/complications cost ($)			**1,291.7**

TABLE 5: Drug related adverse events cost-item: clinical practice, unit costs and total cost.

Drug related adverse events	Rate (%)	Unit cost ($)	Total cost ($) (n=1,000)
Headache	1.53	15.4	235.6
Palpitation	1.53	152.5	2,337.0
Tremor	1.53	41.0	627.6
Oropharyngeal candidiasis	1.53	26.0	398.3
Agitation	1.00	131.7	1,317.4
Bronchitis	1.00	19.6	195.5
Nausea	1.00	15.8	158.0
Dyspnea/asthma exacerbation	1.00	123.6	1,236.0
Bacterial Pharyngitis	1.00	3.6	36.1
Fatigue	1.00	14.0	140.4
Hypokalemia	1.00	14.0	140.4
Irritability	1.00	13.7	136.7
Myalgia/muscle spasms	1.00	15.8	158.1
Convulsion	1.00	167.2	1,672.2
Nasopharyngitis	1.00	3.6	36.1
Cough	1.00	2.7	27.2
Pneumonia	1.00	134.4	1,343.8
Hoarseness	1.00	3.6	36.1
Sleep disturbance	1.00	131.7	1,317.4
Difficulty in swallowing	1.00	3.2	31.7
Dizziness	0.98	18.5	180.9
Xerostomia	0.98	3.2	31.0
Gastrointestinal dysmotiliy	0.98	0.0	0.0
Total			11,793.2
Per patient drug related adverse events cost ($)			**11.8**

TABLE 6: Per patient annual direct medical cost related to management of exacerbated and hospitalized COPD patients.

Cost items	Per patient annual cost ($)	Contribution to total cost (%)
Outpatient admission	88.5	2.4
Laboratory and radiological tests	68.6	1.8
Hospitalizations and interventions/ training/rehabilitation	1,181.3	31.7
Drug treatment and equipment	1,088.0	29.2
Co-morbidities/complications	1,291.7	34.6
Drug related adverse events	11.8	0.3
Total Per patient annual cost ($)	**3,729.9**	

COPD: Chronic obstructive pulmonary disease.

Annual direct costs per patient in COPD were reported to range from $2,088 to $5,900 in the USA, to €3,027 in Germany, to range from $3,694 to $9,893 in Japan, from $1,876 to $3,570 in Spain, from €1,047 to €2,319 in Italy, from $522 (France) to $4,119 (USA) in Confronting COPD Survey conducted in seven countries in Europe and North America, and from $504 South Korea to $9,981 USA in the Continuing to Confront COPD International Patient Survey conducted in 12 countries.[14,15,17-22]

Alongside variability in treatment patterns, labor market and caregiving practices, and unit costs of healthcare resources and services that result in significant cost differences between countries, it should also be noted that severity of COPD and frequency of exacerbations have a substantial impact on healthcare resource consumption and related healthcare costs.[6-8,14,15,23-25]

Analysis of COPD-related healthcare resource consumption in Better Respiratory Education and Treatment Help Empower (BREATHE) study conducted in eleven countries in the Middle East and North Africa (MENA region) revealed deterioration of COPD symptoms and increased frequency of exacerbations as the two factors that drive increased healthcare resource consumption.[23]

In a past study on direct medical costs of COPD in Southern Germany, an increase in disease severity was reported to be associated with an almost 54% cost increment in adjusted annual costs, from € 1,830 in GOLD Stage I to €2,812 in GOLD Stage II-IV.[13] In a study among Iranian COPD patients hospitalized with exacerbation, the mean cost was reported to increase from $481.3 in patients with LOS <9 days to $2,465.4 in patients with LOS ≥9 days along with an increase in hospitalization cost over the three-years from US$ 423.3 in 2011 to US$ 2,436.2 in 2013.[25]

Exacerbation was also reported to be associated with a seven-fold increase in mean COPD-related total costs in a retrospective cohort study in the USA, from $1,605 in patients without exacerbations to $12,257 in patients with ≥3 exacerbations.[8]

Similarly, in past analysis of 61,750 COPD patients, average annual per-patient COPD-related costs for frequent exacerbators ($3,528) and infrequent exacerbators ($2,265) were shown to be more than three times and two times higher compared with non-exacerbators ($1,027).[6] Besides, the exacerbation severity was also reported to be associated with cost increment in COPD patients, with increase in the estimated cost of exacerbation from £1,347 for severe exacerbation to £3,564 for non-severe exacerbation in UK.[26]

According to data from the Türkiye arm of European COPD Audit, COPD patients with an exacerbation resulting in hospital admission in Türkiye had GOLD Stage III-IV in 70.4% of patients, while severe exacerbation in GOLD Stage III-IV COPD patients was associated with a hospitalization rate of 55.3%.[12] Hence, per-patient direct cost ($3,729.9) of managing COPD patients admitted with exacerbation in the present study seems to follow GOLD Stage III-IV's predominance in Türkiye and confirm that exacerbations in COPD cause a substantial burden to public health.

Co-morbidities/complications (34.6%), hospitalizations/interventions (31.7%) and drug treatment/equipment (29.2%) were found to be the major cost drivers in our study. This seems consistent with estimation of hospitalization as the key driver of direct costs in several studies, that accounted for 35% to 70% of all direct costs depending on the severity of COPD as followed by medication costs that ranged from 31% to 57.1%.[13-15,18,20,24,25,27,28]

Notably, based on the estimation of co-morbidities/complications and hospitalizations as similarly important key cost drivers in direct costs related to management of exacerbated and hospitalized COPD patients, our findings emphasize that not only increased number of hospitalizations but also presence of comorbid conditions in COPD exacerbations are of importance in consideration of COPD exacerbations as the main contributor to the cost of COPD.[5-8,29,30]

Accordingly, a significant contribution of co-morbidities (34.6%) to overall direct costs in our study seems consistent with the increasingly recognized role of co-morbidities in COPD as an essential driver of the costs, being associated with 4.3 to 4.7 times cost increment compared with COPD patients without co-morbidity and directly correlated with the number of comorbid diseases.[5,7,29,31-33]

Notably, co-morbidities were associated with an increased risk of experiencing COPD exacerbations, increased healthcare resource utilization with a higher number hospitalizations, and higher health care costs, particularly in patients hospitalized due to exacerbations.[7,8,15,23]

The comorbidities are highly prevalent among COPD patients, including cardiovascular diseases mainly with an estimated five-fold-higher risk of cardiovascular diseases, threefold-higher risk of stroke, and a twofold-higher risk of diabetes reported in COPD patients. Similarly, data from COPD Life Study from Türkiye revealed evidence of co-morbidities in 60% of the stable COPD patients with cardiovascular diseases in one-third of the population.[34] Also, data from Türkiye arm of the BREATHE study revealed co-morbidities in 28.2% of COPD patients, while data from Türkiye arm of Europe-Audit revealed that morbidities were evident as congestive heart failure in 22.5% and diabetes in 17.8% of COPD patients admitted with exacerbation.[12,23] This seems notable given that the presence of cardiovascular disease (1.69 to 3.4 times higher) and diabetes mellitus (1.46 to 2.4 times higher) were associated with increased yearly costs for COPD patients.[5,11]

In a past study with 3,095 patients with 5,237 exacerbations from Türkiye, 880 of the patients (28.9%), or 3,852 of the exacerbations (73.1%), at least one comorbid disease was identified. The mean cost of each exacerbation was reported to be $808.5, with hospital stays ($325.1, 40.7%) and medications ($223.1, 27.6%) estimated as the key cost drivers. Authors also reported an increment in exacerbation-related costs with the presence of comorbidity in patients with COPD, from $523 ($233.6 per exacerbation) in patients without any comorbidity to $2,273 ($1,014.9 per exacerbation) in patients with at least one comorbidity.[5]

Given that co-morbidities and hospitalizations were the major cost drivers in the present analysis of exacerbated and hospitalized COPD patients and the role of co-morbidities in increasing the likelihood of exacerbations and exacerbation-related hospitalizations, our findings emphasize the need for strategies for the prevention, timely recognition and effective management of comorbidities in patients presenting with exacerbations as well as targeting a reduction of exacerbation risk and appropriate management of exacerbations to decrease the overall financial burden associated with acute exacerbations of COPD.[1,5,7,8,23]

It should also be noted that a significant association was reported between patient education and decreased risk of exacerbations. Implementation of a continuum of self-management patient education programs specific to COPD vs. usual care over 12 months was shown to be associated with significant reduction in hospital admissions for exacerbation of COPD by 39.8% and for other health problems by 57.1%, alongside a decrease in emergency department visits by 41.0% and unscheduled physician visits by 58.9%.[35] Nonetheless, while COPD exacerbation was defined as “the worsening of respiratory symptoms beyond the normal day-to-day variation and led to change in medication in previous guidelines, COPD exacerbation in GOLD 2017 guidelines is defined as acute worsening of respiratory symptoms. While treatment-based definition is adopted in clinical trials, it has been suggested to be associated with standardization problems according to the attending doctor or hospital policy in real life.[1]

A significant strength of this study seems to be the provision of estimations based on the COPD Audit data and additional literature and the inclusion of hospital resources (i.e., technical equipment, ICU) and real-life data on hospitalized patients. There are certain limitations in this study. First, Because of a lack of data on indirect costs (loss of productivity due to the illness) or intangible costs of illness (costs of suffering for the patient and their family), we focused only on direct medical costs. It seems to be the major limitation of the present study. It will likely result in a downward bias in our estimates of the economic cost of exacerbated and hospitalized COPD patients. Second, the use of epidemiological studies published to date rather than national databases to obtain data on practice patterns that were used to estimate direct medical costs might raise a concern about the validity and reliability of the data. Third, the use of probability models in calculations and estimation of direct costs per se without indirect costs, as well as analysis of data from university hospitals rather than training and research hospitals and state hospitals with the likelihood of variability in hospitalization and follow up criteria among study centers seem to be the other limitations. Nevertheless, providing cost estimates for management of exacerbated and hospitalized COPD patients in terms of outpatient visits, laboratory and radiological tests, hospitalizations and interventions, training and rehabilitation, drug treatment and equipment, drug-related adverse events and co-morbidities/complications in clinical practice for the first time in Türkiye, our findings represent a valuable contribution to the literature.

CONCLUSION

In conclusion, our findings indicate that managing exacerbated and hospitalized COPD patients pose a considerable burden to health economics in Türkiye, with co-morbidities and hospitalizations estimated as the main cost drivers. In this regard, our findings emphasize the need for cost-effective prevention strategies to reduce the financial burden of acute exacerbations of COPD and the likelihood of potential cost-savings by timely recognition and proper management of co-morbidities and better disease control with reduced frequency of exacerbations and hospitalizations.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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