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The cost of COPD exacerbations: A university hospital – based study in Greece

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Summary
Background: Hospitalization attributed to severe exacerbations is the major cost driver of Chronic Obstructive Pulmonary Disease (COPD). Given that in Greece no previous studies have addressed the economic burden of COPD, the aim of the study was to examine the hospitalization cost of COPD patients with severe exacerbations in the region of Thrace.
Methods: Sample consisted of 142 COPD patients with severe exacerbations who were admitted to the pneumonology department of the University Teaching Hospital of Alexandroupolis (UTHA) in 2006 and 2007. Data collection was performed retrospectively and resource utilization was derived from patients' files. General Linear Model univariate analysis was applied in order to test the influence of disease severity on costs.
Results: Mean actual cost per severe exacerbation was €1711; the amount of €621 is reimbursed by social security funds. Price discrepancies are observed between the actual and the nominal cost per patient in all disease stage categories. Mean hospitalization cost per COPD patient increases slightly with the severity of the disease. However, in the very severe stage it greatly increases mainly due to Intensive Care Unit (ICU) admission. In multivariate analysis the length of stay and the stage of the disease were both related to significantly

Abbreviation: ABC, activity based costing; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GOLD, global initiative for chronic obstructive pulmonary disease; HRQoL, health related quality of life; LoS, length of stay; ICU, intensive care unit; NHS, national health system; SD, standard deviation; CI, confidence intervals; Q1, quarter 1; Q3, quarter 3; UTHA, University Teaching Hospital of Alexandroupolis.

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increased costs, while the existence of co-morbidities exhibited marginal significant relation to increased cost.
Conclusions: The cost estimation of severe exacerbations is important as it could trigger further research and also provide the opportunity of creating national epidemiological and economic data. Such data could contribute to the estimation of the total economic and societal burden of COPD in the country.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality with a substantial and increasing societal burden on the developed world.[1–6] The World Health Organisation (WHO) predicts that COPD will become the third leading cause of death by 2030 on a world scale.[7] Although the prevalence of COPD varies from country to country, population-based studies have shown an overall prevalence ranging from 4 to 10% in the general adult population.[8–11] The effects of COPD on morbidity and mortality both in terms of life-years lost and disability-adjusted life-years (DALYs) are important when considering the overall disease burden.

The direct and indirect costs of COPD vary considerably among countries, however, they appear to be greater in the USA than those in Europe and in Canada.[12] Direct cost accounted for 73% of the total cost of COPD in the USA.[13] Furthermore, the loss of productivity in patients of working age is reported to range from 41% in Spain to 82% in the USA, bringing with it a significant societal strain.[12]

Patients suffering from COPD frequently develop exacerbations which lead to major clinical implications and healthcare utilisation. Severe exacerbations that require hospitalization are the major cost drivers in COPD and are frequently associated with increased mortality and impaired health related quality of life (HRQoL).[14–16] Recent studies indicate that hospitalization costs represent approximately 35—54% of the total COPD treatment expenditures.[17–23] For this reason, prevention and treatment of exacerbations is an important objective of COPD maintenance therapy.

The economic and societal burden of COPD has never been studied in Greece. However, the prevalence of COPD in Greece is estimated to be 8.4% of the overall population, 6% in Athens, 15.1% in men living in rural areas, up to 17.1% in the older population.[6,24] COPD is found in 10.4% of people with smoking history, twice the rate of non-smokers which is 4.8%[6] while two thirds of those who suffer from COPD remain undiagnosed.[24]

The aim of this study was to estimate hospitalization cost of COPD patients with severe exacerbations who had been admitted to the University Teaching Hospital of Alexandroupolis (UTHA) and to subsequently investigate any discrepancies between actual hospitalization cost and reimbursement from social insurance funds. The National Health System (NHS) perspective has been considered in the analysis. By identifying the cost of COPD exacerbation both healthcare professionals and policy-makers will be better informed which may, in turn, contribute to public health policy interventions Additionally, these studies will help to develop a framework for creating economic and epidemiological databases in countries where there is limited data available.

Materials and methods

The study sample consisted of 142 COPD patients with severe exacerbations admitted to the UTHA's Department of Pneumonology in 2006 and 2007. Data was collected retrospectively and patients eligible for inclusion were those who had been diagnosed with COPD at least 6 months prior to their visits to the UTHA Emergency Department and whose spirometric data (pre and post broncodilation) was available. Selected patients were categorized into four stages disease severity, based on their condition prior to exacerbation. Diagnosis, exacerbation and patient categorization were based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[25] COPD exacerbation is defined as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum, which is beyond normal day-to-day variations, is acute in onset and may warrant a change in medication in a patient with underlying COPD". Patients with severe exacerbations were considered those requiring hospitalization, according to GOLD indications for hospital admissions for exacerbations of COPD.[25]

A total number of 208 patients were admitted to the UTHA with COPD severe exacerbations in 2006 and 2007, 88 and 120 patients respectively. 142 patients met the inclusion criteria and also submitted consent forms while 66 patients were excluded from the analysis. Of those excluded, 41 had no pre- or post-bronchodilation spirometry, 6 had experienced more than one severe exacerbation (only the first exacerbation was included in the analysis) and 19 patients declined to participate. The study was approved by the hospital's Ethics Committee.

UTHA, the leading hospital in the Thrace region, is affiliated with Democritus University of Thrace and located in Alexandroupolis, the region's largest city. Thrace's economy is primarily dependent on agriculture. The decision to conduct the analysis in this particular region was made to ensure that the results can be representative to the rural areas with the highest prevalence rates of COPD, and cannot be generalised to the entire population of the country. Healthcare delivery and funding mechanisms are uniform across Greece; specifically, health insurance is compulsory and universal while free access to healthcare is provided by all NHS hospitals. Primary healthcare is provided by the Social Security Funds polyclinics, outpatient units at NHS hospitals and health centres. Hospital

care is mostly provided by the NHS hospitals and is financed by Social Insurance Funds.

Cost analysis was based on the estimation of patients' actual and nominal costs. Actual cost refers to the resources patients consumed during their hospital stay. Nominal cost refers to a fixed amount for each day of hospitalization reimbursed by the social security funds (per diem payment) in all NHS hospitals, irrespective of patients' diagnosis, disease severity and resource consumption. The analysis was based on the estimation of the COPD patients' hospitalization cost adopting the perspective of the National Health System (NHS). Cost estimates of hospitalization was conducted using the Activity Based Costing (ABC) bottom-up approach, which identifies all resources directly employed for the provision of healthcare.[26] This microeconomic analysis was selected to ensure consistency and transparency of results, as no national cost data was available.

Clinical and epidemiological data was collected using patient records; while economic data was obtained from the hospital's administrative and finance departments. Utilization data consisted of a) resource consumption including supplies, medication, laboratory and imaging testing b) operational and other overhead costs and c) personnel costs. Capital asset depreciation was also included in the analysis obtained from the hospital balance sheet and allocated by the total number of admitted patients to the UTHA.

The estimated actual cost per patient was compared to the amount reimbursed from social security funds based on the per diem payment for inpatient care. The cost per patient in the intensive care unit (ICU) was based on published data and it inflated to the 2006 Euro rate.[27]

Pharmaceutical cost was based on national pharmaceutical formulary prices and the cost of diagnostic tests was estimated using official NHS prices. The per diem payment was obtained from the Official Government Gazette and estimated at the rate of €94 per inpatient day and €188 for ICU day (Government Gazette 99B/10-2-98).

All data associated with personnel cost was obtained using budgetary control statements provided by the hospital's Finance Department. Personnel cost includes salaries for full-time medical and nursing staff employed by the Department of Pneumonology, averaged by the number of patients treated annually in the department. Other personnel costs associated with paramedical, administrative and technical staff that provide services for the overall operation of the hospital, were allocated by the number of patients admitted to the hospital on an annual basis. The cost of consumables was reported on a per patient basis and was obtained by the hospital's Supplies Department. Operational and general overhead costs including electricity, water, heating, telephone and other utilities were obtained from budget control statements representing the total overhead hospital expenses. The allocation of overhead expenses was based on the space occupied and used by the Pneumonology Department (in square meters) over the total area of the hospital. The Pneumonology Department's overhead costs were then averaged over all patients admitted to the department on an annual basis. The cost of diagnostic testing, medication, oxygen therapy and any other specialized medical examinations was reported on a per-case basis.

Statistical analysis

Univariate analyses were performed in order to determine the relation between age, gender, smoking patterns, time of year, Length of Stay (LoS), disease severity and co-morbidity and the outcome (cost of hospitalization). Co-morbidity was defined as the presence of at least one of the following conditions: respiratory infection and/or fever (25/39), cardiovascular disease under medication (12/39) (i.e. heart failure, hypertension, stroke) and kidney failure (2/39). Using the univariate approach, hospitalization costs were analysed by i) all patients except eight admitted to the ICU ii) all patients excluding ICU costs and iii) all patients including ICU costs, in order to identify each relevant variable. The only variable that exhibited a significant relation was that of LoS. Season and disease stage showed weak but not significant relations ($p \sim 0.2$). In the final multivariate modeling, General Linear Model (GLM) analysis was applied; the first two models (i and ii) fitted greatly to GLM assumptions while the third did not fit so well as the costs of ICU admission caused a right skewing in the data. ICU costs (originated from 8 patients, all categorized in the very severe stage of COPD) were very strongly dependant on LoS and showed no significant relation to time of year, co-morbidity and smoking pattern ($p = 0.10-0.20$). Based on the aforementioned approach and findings, and the modest sample size, the parametric approach was maintained as it is proven to fit well and illustrates the underlying causes of variance and skewing in our data. Data analyses were conducted using SPSS for Windows 16.1.0 statistical package.

A bootstrap simulation of 1.000 iterations was run in Microsoft Excel to illustrate variations in cost estimates for all COPD disease stage categories. In addition, a sensitivity analysis was performed using the median in order to examine the degree of arithmetic mean unreliability and standard deviation as well as to serve as a guide for the degree of skew. Furthermore, a sensitivity analysis was performed in order to test the effect of varying assumptions by reducing the major cost drivers, personnel and consumables costs by 20%.

Results

The characteristics of the sample, classified according to disease severity, are presented in Table 1. The majority of COPD patients were men (93%), farmers (62%) and smokers (60.6%) with an average of 79 pack-years. Only 8.4% of the sample had never smoked in the past. It is also observed that the length of stay (LoS) does not deviate much according to the COPD stage. Nine patients in stage IV were admitted to the ICU, resulting in the prolongation of their length of stay.

The cost analysis according to stage of disease severity and the various cost drivers is presented in Table 2. Personnel cost is the leading cost driver representing 54.5% of the total hospitalization cost, followed by the cost of intensive care at 17.3% based on the care of only 9 patients. The cost of consumables is relatively high representing 15.4% of the total hospitalization cost. Laboratory and pharmaceutical costs account for 7% and 4% of total cost respectively. Pharmaceutical cost distribution was

Table 1 Patients' characteristics ($n = 142$).

Patients' characteristics	Mild COPD (Stage I) $n = 3$	Moderate COPD (Stage II) $n = 38$	Severe COPD (Stage III) $n = 66$	Very severe COPD (Stage IV) $n = 35$	All patients $n = 142$
Men (*n*, (%))	3 (100)	33 (87)	62 (94)	34 (97)	132 (93)
Age (in years, mean, (sd))	72.7 (0.6)	70.7 (11.3)	70.7 (7.9)	72.8 (5.7)	71.2 (8.4)
Farmers (*n*, (%))	2 (66.6)	13 (34.2)	48 (72.7)	25 (71.4)	88 (61.9)
Current smoker (n, (%))	3 (100)	19 (50)	38 (57.6)	26 (74.3)	86 (60.6)
Pack-Years (mean, (sd))	65 (50.7)	67.3 (22.8)	70.9 (29.4)	100.8 (29)	78.6 (31.9)
Ex-smoker (*n*, (%))	—	14 (36.8)	22 (33.3)	8 (22.9)	44 (31)
Pack-years (mean, (sd))	—	103.6 (101.2)	71.4 (17.1)	60.9 (32.5)	79.7 (60.8)
Never smoker (n, (%))	—	5 (13.2)	6 (9.1)	1 (2.9)	12 (8.4)
FEV1% (mean, (sd))	83 (5.2)	62.7 (11.3)	52.3 (16.5)	38.8 (11.7)	52.4 (16.9)
LoS (in days, mean, (sd))	6 (3)	5.4 (5.2)	6.5 (3.9)	5.5 (3)	6 (4.1)
ICU LoS (in days, mean, (sd))	—	—	—	6.9 (1.9)	6.9 (1.9)

Abbreviations: LoS: Length of Stay, COPD: Chronic Obstructive Pulmonary Disease, ICU: Intensive Care Unit, SD: Standard Deviation.

based on 67% for antibiotics, 16% oral corticosteroids and 13% Short Acting Bronchodilator Agent (SABAs) and only 3% for other pharmaceuticals, mainly for gastro protection.

In Table 3 the estimated mean actual and nominal cost per patient according to the stage of disease severity is presented. Hospitalization cost per COPD patient increases slightly with the severity of the disease and varies considerably in the very severe stage given the patient's admission to the ICU. Additionally, a discrepancy is observed between the actual and the nominal cost per patient in all disease stage categories. This variation ranges from €793 to €1.800 depending on the disease stage; the greatest difference is seen in patients at the very severe stage where the actual cost was three times higher than the amount reimbursed by Greek social security funds.

Statistical analysis

According to the general linear model presented in Table 4, total costs have a skewed distribution which is indicated by the relatively low median values in the severity groups compared to the average. The very severe COPD category is the most costly category due to the high costs of ICU care. Despite cost increases related to women, older age, present smoking habits and time of year (seasons), none of these particular variables reached statistical significance. The length of stay and the existence of co-morbid conditions were, however, related to increased cost. A log transformation of the total costs did not improve the model fit, as judging from the residuals.

Sensitivity analysis

The median value was used to examine cost variations per COPD stage. According to Table 5, variations were small in the three COPD stages, excluding stage IV, to safely conclude that the results were reliable. Bootstrap simulation was performed with 1000 iterations to illustrate variations in estimates from the arithmetic mean. The results of the simulation did not deviate enough from the original analysis. The bootstrap simulation led to the observation of a slight difference in the narrowing of the confidence intervals due to a larger sample size. Additionally, results of the sensitivity analysis, revealed a 3% reduction in the mean cost per patient in the case of consumables and almost an 11% reduction in personnel costs.

Discussion

This bottom-up micro-costing study highlighted the discrepancies between actual and nominal cost per patient with severe exacerbation in all disease stage categories. Mean hospitalization cost per COPD patient increases slightly with the severity of the disease and it varies considerably in the very severe stage due to the patient's admission to the ICU. Personnel costs are shown to be the major cost driver, representing almost 55% of the total cost of hospitalization.

The mean actual cost per patient with severe exacerbation was €1.711; almost three times the amount reimbursed by social security funds (€621). This finding appears to be very important as the per diem payment, which reflects the nominal cost, does not, in fact, cover the patient's actual cost of hospitalization. The continuation of this situation over years has resulted in deficits across all NHS hospital budgets as the amount reimbursed by social funds remains common to all NHS hospitals. Therefore, hospital deficits must be covered by state funding thereby creating an ongoing burden to the national economy. Additionally, there are further implications whenever any economic evaluation is undertaken in Greece, whether for COPD or any other diseases. Given the lack of actual hospitalization cost, economic evaluation studies take nominal cost data into account which, in turn, bring about the question in terms of accuracy of results and comparability with international data.

The majority of our results are consistent with those found in international literature. The multivariate analysis showed that LoS and disease stage were significantly related to increased costs while the existence of co-morbidities exhibited a marginally significant relation to increased cost. This finding is in keeping with studies performed in France, the Netherlands and Belgium[28–30] indicating that direct costs increase with disease severity. In a study conducted in 2000 in

Table 2 Total costs breakdown by COPD patients' classification in Euros.

COPD Stage	Number of patients (%)	Pharmaceutical cost	Laboratory cost	Consumables cost	Total ancillary cost[a]	Cost of personnel	Overhead cost	Intensive care Cost	Total Cost	Mean cost per patient
Stage I	3 (2)	65	340	792	1.197	2.799	75	0	4.071	**1.357**
Stage II	38 (27)	2.759	4.172	10.032	16.963	35.454	950	0	53.367	**1.404**
Stage III	66 (46)	5.020	8.345	17.424	30.789	61.578	1.650	0	94.017	**1.425**
Stage IV	35 (25)	2.454	4.197	9.240	15.891	32.655	875	42.068	91.489	**2.614**
Total	142 (100)	10.298	17.054	37.488	64.840	132.486	3.550	42.068	242.944	**1.711**

The bold values represent the mean cost per COPD stage patient.
[a] Total Ancillary cost includes expenses for pharmaceutical, laboratory and consumables.

the UK, the cost per COPD patient was estimated at €1270 per patient.[22] In 2002 study carried out in Sweden,[31] focusing on the direct cost of exacerbation, substantial cost differentiations among the disease severity stages were observed, which are not found in the present study. Additionally, the very severe exacerbation cost found in the Swedish study appears to be approximately the same as that found in the present study; €2325 in Sweden and €2614 in Greece. By converting the aforementioned costs into US dollars using Gross Domestic Product (GDP) Purchasing Power Parities (PPPs) (2006 values),[32] and in order to be able to provide an equivalent cost of severe exacerbations between the two countries, great variations are observed. Specifically, the costs are $3738 and $2463 in Greece and in Sweden respectively. Several studies also report that the cost of pharmaceuticals is a relatively minor driver of hospitalization cost.[18,19,29]

A key result of the present study which should be noted is the high rate of tobacco consumption (80 pack-years). This finding is in accordance with the OECD data reporting Greece with the highest percentage of adult tobacco use among OECD countries.[33,34] It is worth noting that an epidemiological study on smoking, carried out in the general population of Northern Greece,[35] found that men aged between 61 and 80 years had a smoking history of 55.5 (±30.5) pack-years and considering that this study focused on a disease specific population, our findings of 80 pack-years is not surprising.

It is worth stating that there are differences in COPD cost estimates among various international studies.[20,28–30,36] Given the methodological issues raised in cost-of-illness studies and the question of incomparability among international cost estimates, the aforementioned differences appear to depend on the use of different research hypothesis and methodologies, sample selection and size, data sources and organizational structure of the healthcare systems mainly with regard to healthcare delivery and financing. Great cost variations are observed in an international survey investigating the COPD cost of treatment, although data collection was based on a standardised micro-costing methodology.[22,37] Specifically, in 2000 the annual direct cost of treatment was $522 in France, $1258 in Canada, $3196 in Spain and $4119 in the USA.[12] Typically, cross-country cost-of-illness comparisons are made at the macro-level and based on standardised data available from a variety of international databases. However, the macro-costing perspective may not always analyse the differences in resource consumption and related costs.[38] Using cost data at the micro-level for an individual patient is more useful in cases where data is usually not available in a standardised form, even though it might result to cost underestimation.[27] The fact that micro-costing data analysis was performed in this study, may contribute to the standardisation of hospital data, the enhancement of cost comparability among hospitals and consequently, increased efficiency of NHS hospitals.[30,37,39] It is important to note that the above mentioned studies report inpatient hospitalization as the most important key-driver.

The present study has some limitations that may merit consideration such as the fact that the results generally apply to COPD patients living in rural areas. However, the decision to study the specific university hospital was based

Table 3 Actual versus nominal cost per COPD patient, in €.

COPD Stage	Number of patients	Mean actual cost per patient (95% CI)	Nominal cost per patient[a]
Stage I	3	1.357 (1.231−1.482)	564
Stage II	38	1.404 (1.369−1.440)	505
Stage III	66	1.425 (1.398−1.454)	602
Stage IV	35	2.614 (1.816−3.412)	814
All	142	1.711 (1.503−1.920)	621

[a] Nominal cost is based on fixed prices.

on the lack of available national or local COPD registries and the goal of establishing a pilot project that will gather preliminary epidemiological, clinical and economic data from the specific region. The cost of personnel divided proportionally by the number of patients, regardless of their length of stay or disease severity, also constitutes another limitation. The lack of analytical NHS hospital registries regarding patient classification per disease severity as well as personnel time dedicated to each patient, did not allow for such estimation. The classification of patients related to resource consumption carried out in the current analysis, may, however provide important and useful information to policy-makers in order to establish per-case payment rates as well as for the use of hospital benchmarking. Finally, estimation of the ICU cost was not recorded on a per patient basis but was based on published data.[27] In addition, indirect cost was not included in the analysis.

The need for scientific evidence in treating the specific chronic condition should be strongly supported particularly in Greece as it has one of the highest prevalence rates of heavy smokers, undiagnosed and undertreated patients.[6,24,34,35,40] Consequently, carrying out cost analysis studies is key to identifying major cost drivers of COPD treatment and allocating rationally health resources. Moreover, results of economic evaluation studies would more accurately reflect reality and would be comparable to international literature.

In an era of economic recession, healthcare professionals must take the results of economic evaluation studies under careful consideration in their decision making processes so as to improve health outcomes and minimize cost. Further epidemiological and economic research on COPD will undoubtedly contribute to the creation of national registries. As a result, this will contribute to establishing a more accurate picture of the disease's total implications for the country.

Table 4 General linear model of total cost due to hospitalization of COPD exacerbations.

	Coefficient	95% Confidence Interval		*P* value
		Lower Bound	Upper Bound	
Intercept	1534.98	−565.25	3635.21	0.151
Season (admission)				
Spring	224.26	−255.33	703.85	0.357
Summer	220	−343.11	783.1	0.441
Autumn	−206.06	−743.95	331.83	0.45
Winter	0			
Smoking				
Never	−228.22	−912.57	456.13	0.511
Ex	−199.1	−611.77	213.57	0.342
Current	0			
Disease stage				
Mild (Stage I)	−1330	−2665.69	5.68	0.051
Moderate (Stage II)	−958.6	−1493.68	−423.52	0.001
Severe (Stage III)	−1020.35	−1490.85	−549.85	<10−3
Very severe (Stage IV)	0			
Gender				
Male	−70.2	−822.46	682.06	0.854
Female	0			
Age	9.43	−13.64	32.5	0.42
Length of stay (day)	98.84	54.99	142.7	<10−3
Co-morbidity				
No	−392.54	−821.52	36.44	0.073
Yes	0			

Table 5 Sensitivity Analysis Results.

COPD Stage	Median cost per patient (€)	Q1 (€)	Q3 (€)	Bootstrapp simulation mean cost (€) (95% CIs)	Mean cost per patient (€)[a]	Mean cost per patient (€)[b]
Stage I	1369	1335	1384.5	1355 (1301—1400)	1170.2	1304
Stage II	1406.5	1318	1456.25	1405 (1372—1440)	1217.8	1351.6
Stage III	1417	1330.5	1509.75	1425 (1398—1454)	1237.9	1371.7
Stage IV	2622	1873	3459	2603 (1925—3394)	2427.4	2561.2

Abbreviations: Q1: Quarter 1, Q3: Quarter 3, CIs: Confidence Intervals.
[a] Mean cost per patient with 20% personnel cost reduction.
[b] Mean cost per patient with 20% consumables cost reduction.

Authorship

Prof. M. Geitona was responsible for the original conception and the writing of the manuscript. Dr. M. Hatzikou and MD. P. Steiropoulos contributed to the collection of data, its analysis and interpretation. Prof. E. Alexopoulos carried out the statistical analysis and contributed to the writing of the statistical components. Prof. D. Bouros was responsible for the assessment and critical revision of the final manuscript.

Conflict of interest

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Supplementary data

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