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Healthcare costs of the SATisfaction and adherence to COPD treatment (SAT) study follow-up

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is characterised by recurring exacerbations. We estimated the costs of healthcare resources for COPD management funded by the Italian National Healthcare Service (INHS) for one year.

Methods: We examined the demographic, clinical, and economic variables at enrolment and follow-up visits (at 6 and 12 months) of COPD patients participating in the SAT study and referred to 20 Italian pulmonary centres with different institutional characteristics. Costs were expressed in Euro (€) 2018. A random effects log-linear panel regression model was performed to predict the average cost per patient.

Results: Most of the centres were public institutions (90%; public university hospital: 30%). The total average cost of COPD was €2647.38/patient and ICS/LABA/LAMA therapy contributed the most (€1541.45). The average cost was €6206.19/patient for severe COPD (+139.67% vs the cost/patient with mild or moderate COPD). The regression model showed that, others things being equal, increases in the predicted average logged cost per patient were due to liquid oxygen therapy (+468.31%), three COPD exacerbations during the follow-up (+254.54%), and ICS/LABA or ICS/LABA/LAMA associated therapy (+59.26%). Moreover, a 1.19% increment was observed for each additional score of the CAT questionnaire. Conversely, a 36.52% reduction in the predicted average logged cost was reported for hospitals managed by local healthcare authorities.

Conclusions: The health econometric approach is innovative in the management of COPD patients in Italy. The results of the random effects log-linear panel data regression model may help clinicians estimate INHS costs when managing COPD patients.

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1. Introduction

In chronic obstructive pulmonary disease (COPD), reducing risk factors, preventing comorbidities, evaluating disease severity, and treating acute exacerbations are key elements of proper management of the disease. The primary treatment goals are the reduction of symptoms and exacerbations, and bronchodilation is a pivotal tool. The main classes of medications used to treat patients with COPD are: 1) LABA (long-acting or ultra-long-acting β-2 agonists), 2) LAMA (long-acting muscarinic antagonists), and 3) inhaled corticosteroids (ICS). These agents can be administered alone and/or as double (that is, LABA-LAMA) or triple (LABA-LAMA-ICS) combinations [1].

The appropriate use of the different therapeutic approaches currently available is crucial to optimise COPD management, both in terms

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of efficacy for patients and sustainability for healthcare systems. The evaluation of the resource consumption required for COPD management is indispensable to drive decision makers in future health policies at both the national and regional levels.

In Italy, the mean annual cost per patient has increased in recent years and in 2015 was approximately €3.290, which was 20.8% and 82.7% higher than the costs estimated in 2008 and 2002, respectively [2]. Moreover, the inappropriate use of drugs has contributed to increasing pharmaceutical expenditure for COPD patients funded by the Italian National Health Service (INHS) in the last few decades. As highlighted by OsMed data, the reduction of ICS use in patients without exacerbations could lead to resource savings, re-investable for increasing adherence to treatment and into a better election of the patient to the appropriate treatment [3].

The health econometric approach adopted in this research (called panel data regression) aims to fill a gap in the Italian literature on the economics of COPD, that is the lack of cost prediction supported by longitudinal studies performed on COPD patients with different characteristics and/or referred to different hospital categories.

1.1. Patients and methods

Study design and procedures. SAT was designed as a multi-centre, non-interventional study and was conducted in 401 patients with COPD enrolled by 20 Italian pulmonary centres with different institutional characteristics.

The patients were followed up for 1 year, with an intermediate evaluation after 6 (± 1) months from enrolment according to the current clinical practice in Italy for the management of patients with COPD [4]. All of the patients were over 40 years old and had received a diagnosis of COPD based on symptoms, spirometry, and the standard definition according to the Global Initiative for Chronic Obstructive Lung Disease [1]. According to the inclusion criteria, the patients were free from exacerbations for at least 3 months and had stably received an inhaled treatment for at least 3 months. The main exclusion criteria included patients naïve/without chronic inhaled treatment and/or a concomitant diagnosis of asthma. The details of this study design have been published elsewhere (Contoli et al., submitted). The study was conducted in accordance with the Declaration of Helsinki and was approved by the local institutional ethics committees. Informed written consent was obtained from each subject. This study is registered with *ClinicalTrials.gov, number NCT02689492*.

During the study period, the patients were treated according to standard clinical practice. Demographic variables, smoking habits, medical history, and history of COPD exacerbations in the previous year were collected at enrolment. Moreover, lung function data, including forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC ratio, and residual volume (RV), were measured at enrolment and at follow-up. Any switch of treatment or exacerbation events that occurred from the previous visit were collected (that occurred after the previous visit). At each visit during the study period, the patients answered several validated questionnaires. Among them, the COPD Assessment Test (CAT) evaluating disease-related health status [5,6] and the Modified Medical Research Council (MMRC) scale assessing the severity of dyspnoea [6,7] were included in the present analysis.

Resources consumption and costs evaluation. The SAT study adopts a cost description model that follows the INHS perspective [8]. The cost description aims to evaluate healthcare resources dedicated solely to the management of COPD as reported by patients during follow-up.

Hospital admissions were stratified according to the hospitalization setting (day hospital or inpatient) and valued via Diagnosis-Related Group tariffs [9,10]. Emergency visits and outpatient visits conducted by specialists and general practitioners (GPs) were also quantified and estimated using professional and institutional tariffs [11–13].

The volume and the duration of oxygen (liquid or by concentrator) therapy expressed in hours and days were calculated. Upon subdivision into 11 therapeutic schemes [LABA, LAMA, short-acting β-2 agonists (SABA), short-acting muscarinic antagonists (SAMA), enteral or parenteral route corticosteroids, ICS, ICS-LABA, ICS-LABA-LAMA, LABA-LAMA, SABA-SAMA, and other], the pharmacologic therapies administered to patients during follow-up were evaluated according both to the single therapeutic schemes and irrespective of the therapeutic scheme.

Oxygen therapy and drug costs were obtained from freely accessible sources [14,15]. Costs were expressed in € at 2018 values on a per-patient basis.

Statistical analysis. Continuous variables were expressed as mean plus standard deviation (± SD), median and range. Binary variables were reported as absolute and relative frequencies. Missing observations, for which no imputation procedure was performed, were indicated whenever appropriate. Unless otherwise stated, total, 6 month follow-up, and 12 month follow-up data were considered for the cost description, by specifying the patients permanently lost to follow-up at 6 or 12 months (right censored), lost at 6 months but again observed at the 12 months follow-up (interval censored) [16]. While data from the right-censored and interval-censored patients are considered incomplete, the death patients' data are considered as complete at the time of death [17]. As this study is characterised by both a cross-sectional dimension (401 patients observed) and a time series dimension (two follow-up visits), a random effects log-linear panel data regression model was performed to evaluate longitudinal changes in the total average cost per patients. As per the log-linear regression model definition [18], the natural logarithm transformation was applied only to the dependent variable (that is, the total annual cost) [19,20].

Regression predictors, which include some non-monetary variables collected in the SAT study (demographics, clinical characteristics and outcomes, therapeutic schemes, and characteristics of the centres), have been identified based on the literature [21].

As both heteroskedasticity and autocorrelation in the distribution of the idiosyncratic error of the panel data regression model were detected, default standard errors (SEs) were replaced by cluster-robust SEs [18–20].

The statistical analysis was supported by Stata/SE software v15.1 (StataCorp LP, College Station, TX, USA).

2. Results

The large majority of the institutions participating in the study were public (18 centres, 90% of total); the public university hospitals predominated (6 centres, 30%) over local health authorities (LHAs) and public self-governing hospitals (25% and 20%, respectively). The remaining healthcare facilities were public (15%) and private (10%) research hospitals. Most of the participating centres were distributed in northern Italy (55%), while 15% and 30% of the institutions were located in central and southern Italy, respectively. The distribution of patients in the different areas mirrored that of the centres. The average number of patients enrolled at each centre participating in the SAT study was 20 ± 8 (median 22, range 4–31). The highest average number of enrolled patients was in northern Italy (22 ± 7; median 22, range 7–31). The higher average number of patients enrolled was in private research hospitals (mean 26 ± 8; median 26, range 20–31) (Table 1).

Most of the 401 patients enrolled in the SAT study were males of Caucasian origin, aged 65–75 years, married or cohabiting, living with the family, retired, and with primary school education. Their age varied between 44 and 89 years (mean 72 ± 8, median 72). The majority of the patients were ex-smokers (282 at 12-month follow-up, corresponding to approximately 70%), followed by smokers (approximately 24%) and patients who never smoked (approximately 5%) (Table 2).

Clinical characteristics of patients and disease. The diagnosis of COPD occurred between 66 and 75 years of age in most of the patients (n = 160, 40%), and 318 patients in the sample (79%) were affected by

Table 1
Institutional and geographical features of the centres participating in the SAT study.

	Centres		Patients		
	n	%	n	%	Mean ± SD
Total	20	100	401	100	20.50 ± 8.12
Institution					
Public university hospital	6	30	130	32.42	21.67 ± 7.71
Public self-governing hospital	4	20	75	18.70	18.75 ± 5.06
Public LHA hospital	5	25	72	17.96	14.40 ± 10.88
Public research hospital	3	15	73	18.20	24.33 ± 4.93
Private research hospital	2	10	51	2.72	25.50 ± 7.78
Geographical region					
Northern Italy	11	55	238	59.35	21.64 ± 7.45
Central Italy	3	15	48	11.97	16.00 ± 9.54
Southern Italy	6	30	115	28.68	19.17 ± 9.33

LHA: local health authority.

Table 2
Demographics of the patients enrolled in the SAT study.

Demographic characteristic	Patients	
	n	%
Total	401	100
Gender		
Male	299	74.56
Female	102	25.44
Ethnicity		
Caucasian	400	99.75
African	1	0.25
Age (years)		
44-65	16	3.99
56-65	56	13.97
66-75	194	48.38
76-85	128	31.92
> 85	7	1.75
Marital status		
Single	15	3.74
Married/cohabiting	254	63.34
Widowed	41	10.22
Divorced/separated	18	4.49
Missing	73	18.23
Living arrangement		
Alone	56	13.97
With family	278	69.33
Missing	67	16.71
Education		
None	6	1.50
Primary school	138	34.41
Junior high school	105	26.18
High school	51	12.72
Academic degree	23	5.74
Missing	78	19.45
Occupational status		
Employed	39	9.73
Domestic worker	19	4.74
Retired	290	73.32
Unemployed	5	1.25
Missing	48	11.97

COPD for no more than 10 years. The average age of the patients at diagnosis was 65 ± 9 years (median 66, range 14–84) and the average disease duration from diagnosis was 7 ± 7 years (median 5, range 0–67). For most of the patients, no exacerbations occurred since the previous visit (n = 258, 64%). Patients experiencing one exacerbation amounted to 72 (18%), while 23 (6%) had two exacerbations and 4 (1%) had three exacerbations. Missing, censored, and dead patients amounted to 44 (11%). The mean number of COPD exacerbations was 0.35 ± 0.65 (median 0, range 0–3).

Status, severity, and progression of COPD were evaluated at enrolment and at the follow-up visits based on spirometry data on post-bronchodilator FEV1 and FEV1/FVC and on the number of exacerbations [1]. Moreover, the patient scores attributed to the CAT and modified MMRC questionnaires were recorded at each visit (Table 3).

At 6 months, a minority of the patients had severe COPD (11 patients, 3%), and at the 12-month follow-up visit, this number further decreased (5 patients, 1%). The difference between the two follow-up visits was confirmed by the decreasing trends of the CAT and MMRC scores (Table 3).

Healthcare resource consumption. The majority of the patients used the following healthcare resources: hospitalisations, day hospital care, emergency room access, outpatient specialist visits, GP visits, and laboratory, instrumental, and imaging examinations (Table 4).

Some of the patients (78 patients, 19%) were on oxygen therapy, mainly via liquid oxygen systems (76 patients, 97% of those on oxygen), with an average duration of 309 ± 98 days.

Most of the patients (315 patients, 79%) received at least one of the 11 COPD therapeutic schemes administered during the SAT study with an average therapy duration per patient of 317 ± 78 days. The longest duration was for SABA (mean 331 ± 98). A fraction of the patients underwent a therapeutic switch (78 patients, 19%), accounting for the therapeutic scheme based on LAMA the higher number of drug replacements (30 patients, 19% of patients with LAMA). Causes of the therapeutic switches were patient decision (2 patients, 7%), lack of adherence to therapy (4 patients, 13%), lack of efficacy (16 patients, 53%), and other causes (8 patients, 27%).

Healthcare cost evaluation. After one-year follow-up, the total average cost of COPD was €2647.38 per patient. The cost drivers were oxygen therapy (€1404.92) and pharmacological therapies (€1139.11) (Fig. 1). The associated therapy ICS/LABA/LAMA showed the highest cost (€1541.45) among the 11 therapeutic schemes (Fig. 2).

When the total healthcare costs were stratified by the severity of COPD, the total average cost was €6206.19 for the patients with severe COPD, an increase of 139.67% over the corresponding cost per patient with mild or moderate COPD (€2589.51). For the patients who had one or more therapeutic switches, the average cost was €3426.11 per patient, compared to €2516.38 for the patients who did not switch therapy (+36.15%) (Fig. 3).

2.1. Log-linear panel data regression model with random effects

The log-linear panel data regression model included 344 observations concerning 225 out of 401 patients, who totalled on average 1.5 follow-up visits (range: 1–2).

When adjusted for the other regressors, the predicted background average annual logged cost per patient (that is, the constant of the log-linear panel data regression model) increased by 468.31% in the patients receiving oxygen therapy (reference category: no oxygen therapy), 254.54% if the patient experienced three COPD exacerbations during the follow-up period (reference category: absence of COPD exacerbations), and 59.26% in the patients administered ICS/LABA or ICS/LABA/LAMA. Moreover, a 1.19% increment was observed for each additional score of the CAT questionnaire (Table 5). Conversely, other things being equal, the predicted background average annual logged cost per patient decreased by 36.52% if the centre participating in the SAT study was a hospital managed by an LHA. Patient gender and age, COPD duration and severity, changes in smoking habit, MMRC questionnaire scores, and geographical location of centres had no statistically significant effect in determining the variation of the predicted background average annual logged cost per patient with COPD (Table 5).

3. Discussion

This paper aims to evaluate the INHS-funded healthcare costs for COPD management for one year. Demographic, clinical, quantitative,

Table 3
Status, severity, and progression of COPD in the patients enrolled in the SAT study.

	6-month follow-up		12-month follow-up	
	mean ± SD	Median (min-max)	mean ± SD	Median (min-max)
Respiratory function				
FEV1 (litres)	1.52 ± 0.62	1.43 (0.50–3.76)	1.54 ± 0.61	1.44 (0.51–3.54)
FEV1 (% pred.)	60.46 ± 20.17	59 (23–117)	60.80 ± 19.53	59.30 (19.20–117)
FVC (litres)	2.68 ± 0.86	2.56 (0.83–5.68)	2.72 ± 0.83	2.61 (1.06–6.12)
FEV1/FVC (%)	60.23 ± 16.11	58.94 (24–100)	58.71 ± 14.54	59 (27–96)
CAT score	15.95 ± 7.59	16 (0–36)	15.04 ± 7.43	14.50 (1–35)
MMRC score	1.77 ± 1.13	2 (0–4)	1.64 ± 1.08	2 (0–4)

FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; CAT: COPD assessment test; MMRC: modified Medical Research Council; pred: predicted; SD: standard deviation.

Table 4
Utilisation of healthcare resources exclusively for COPD.

	n	%
Missing, censored, or deceased	36	8.98
Inpatient hospitalization		
Yes	16	3.99
No	349	87.03
Day hospital		
Yes	2	0.50
No	363	90.52
Emergency room access		
Yes	20	4.98
No	345	86.03
Outpatient specialist visit		
Yes	48	11.97
No	317	79.05
GP visit		
Yes	81	20.20
No	284	70.82
Laboratory, instrumental, and imaging examination		
Yes	44	10.99
No	321	80.05

Categories Yes/No: resource used only for COPD, or all-cause utilization, respectively; GP: general practitioner.

and economic variables collected during the enrolment and follow-up visits of the patients with COPD participating in the SAT study were examined and some were used as predictors in a panel log-linear regression model with random effects. This statistical analysis is innovative for Italy because it introduces a health econometric contribution to the management of patients with COPD.

The main results of this study are as follows:

1) The total average cost of COPD during the study was €2647.38/patient, which increased to €6206.19/patient in those with severe COPD (139.67% increase over the cost/patient with mild or moderate COPD) and there was a 1.19% increment for each additional score of the CAT questionnaire
2) The average cost per patient increased by 254.54% in case of 3 COPD exacerbations during the follow-up, by 468.31% in patients receiving oxygen therapy, and by 59.26% in patients treated with ICS/LABA or ICS/LABA/LAMA
3) The average cost per patient decreased by 36.52% in hospitals run by local healthcare authorities

Once methodological differences are considered, our general findings are comparable to other national and international studies. According to the most recent Italian research, after a 12-month follow-

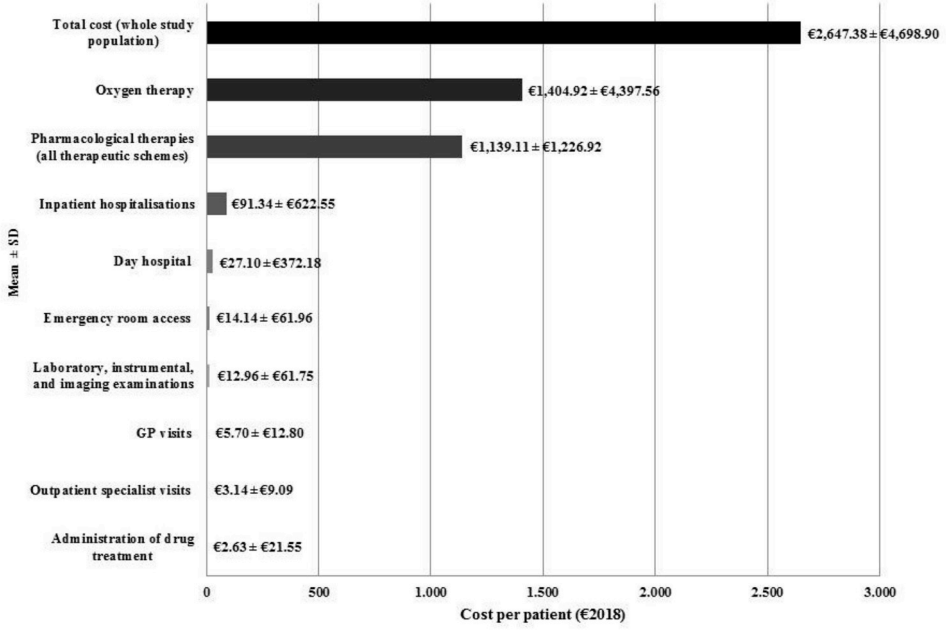

Fig. 1. INHS costs of healthcare resources for COPD. GP: General practitioner; INHS: Italian National Health Service; SD: standard deviation.

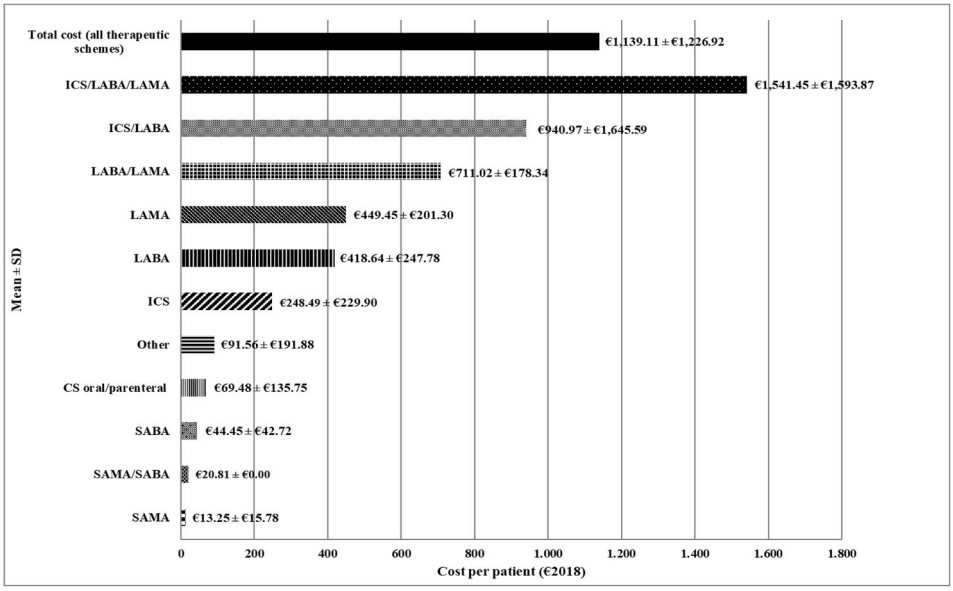

Fig. 2. INHS costs of healthcare resources for COPD; details on drug expenditures. INHS: Italian National Health Service; SD: standard deviation.

up, the average cost per COPD patient funded by the INHS varied between €2932.7 (2013 values) and €6725 (2003 values) [2,21,22]. These studies identified inpatient hospitalisation due to COPD exacerbation as the main cost driver. In agreement with our study, a telephone survey conducted in Sweden in 2010 on a cohort of COPD patients showed that the costs of COPD were strongly related to disease severity and reported higher estimated mean annual costs per subject with respect to 1999 in patients with mild and moderate COPD. Hospitalisations due to exacerbations and oxygen therapy were the main cost drivers for very severe subjects and drugs for severe, mild, and moderate COPD [23]. A study conducted in the US from 2002 to 2010 using the National Inpatient Sample databases (constituting a 20% stratified sample of all US hospitals) showed that despite the stable trends in the overall COPD hospitalisation rates from acute exacerbation, healthcare costs and financial burden on healthcare system increased [24]. In France, the SCOPE study in 2004 estimated a €2863 cost per patient per year [25]; a subsequent large study of the French population in 2011 showed a consistent increase in the annual cost attributable to COPD [26]. Dal Negro recently showed that in Italy, the mean annual cost per patient in 2015 was approximately 82.7% higher than the costs estimated in 2002 [2].

The common finding of these studies is represented by the increasingly high overall burden of COPD, with the increase in costs proportional to its clinical severity. The major cost components mainly depend on the COPD exacerbations, the need for long-term oxygen therapy, and drugs.

The relatively low number of exacerbations experienced by the patients of the SAT study may be responsible for the lack of a predictive role for hospitalisation, as shown by a previous analysis of the economic impact of COPD exacerbations [20]. However, the log-linear panel data regression model shows that the occurrence of 3 or more exacerbations leads to a statistically significant increase in the annual healthcare costs when adjusted for the other predictors. This is of relevant potential assistance to clinicians, who may better stratify patients by COPD status

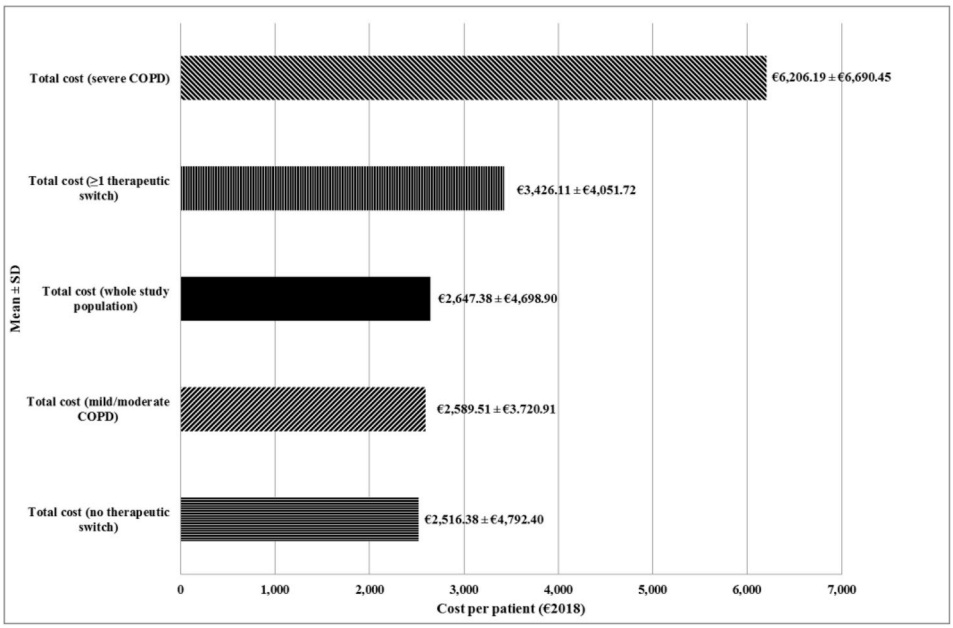

Fig. 3. INHS costs of healthcare resources for COPD; details on COPD severity and therapeutic switch. INHS: Italian National Health Service; SD: standard deviation.

Table 5
Dependent variable (y): ln (INHS annual average healthcare costs).

	Coefficient	Cluster robust SE	p-value	% variation in y per 1 unit variation in x
Independent variables (x)				
Demographics				
Female gender (vs male)	−0.114	0.125	0.362	
Age (years)	0.007	0.006	0.187	
Clinical characteristics				
COPD duration (years)	−0.013	0.014	0.332	
Number of exacerbations (vs 0)				
1 exacerbation	−0.031	0.079	0.070	
2 exacerbations	0.414	0.225	0.065	
3 exacerbations	1.266	0.092	< 0.0001	+254.54%
COPD severity (vs not severe)	0.075	0.137	0.582	
Smoking habit (vs yes, smoker)				
Stopped smoking	−0.222	0.169	0.189	
No variation	−0.012	0.165	0.940	
CAT questionnaire score	0.012	0.005	0.024	+1.19%
MMRC score (vs MMRC < 2)				
MMRC ≥ 2	0.100	0.075	0.181	
Therapeutics characteristics				
Oxygen therapy (vs no oxygen therapy)				
Liquid oxygen	1.738	0.124	< 0.0001	+468.31%
Oxygen concentrator	1.395	0.794	0.079	
Drug therapy (vs LABA or LAMA)				
LABA/LAMA	0.148	0.098	0.129	
ICS/LABA or ICS/LABA/LAMA	0.465	0.091	< 0.0001	+59.26%
Characteristics of the centres				
Institution (vs public university hospital)				
Public research hospital	−0.792	0.173	0.646	
Private research hospital	−0.255	0.168	0.129	
Public self-governing hospital	−0.147	0.124	0.236	
Public LHA hospital	−0.454	0.111	< 0.0001	−36.52%
Geographical location (vs northern Italy)				
Central Italy	−0.002	0.131	0.985	
Southern Italy	−0.034	0.097	0.727	
Constant	5.560	0.407	< 0.0001	

Panel log-linear regression model with random effects on INHS healthcare costs.
INHS: Italian National Health Service; LHA: local health authority; ln: natural logarithm; SE: standard error; % variation of y per 1 unit of x, calculated as [exp (coefficient)-1]*100% and indicated only for statistically significant coefficients ($p < 0.05$), constant excluded.

and expected costs.

The most recent advances in the study of COPD clearly show that this condition cannot be managed with a sole therapeutic approach, while focusing on the most appropriate treatment in any selected patient is increasingly deemed as a critical strategy [27,28].

Patients with COPD may have dyspnoea, decreased physical activity, and decreased health-related quality of life (HRQoL) due to illness and exacerbations [29]. No pharmacological treatment has thus far proved to be significantly effective in modifying the progressive course of the disease. In general, pharmacological interventions aim to improve patient HRQoL by controlling or reducing the symptoms and reducing the frequency of exacerbations [1].

ICS are indicated in combination with LABA for patients with a history of exacerbations [1]. However, in clinical practise, ICS are often prescribed to patients with no history of exacerbations, while other therapeutic options may be more favourable for these patients. Long-term treatment with long-acting bronchodilators has been shown to improve respiratory function, reduce dyspnoea, and increase exercise tolerance [30,31].

The range of therapeutic interventions offered for the treatment of COPD has been enriched recently by new LABA/LAMA fixed combinations recommended as a first choice, or as an alternative choice, for patients in GOLD groups B, C, and D. Based on the reimbursement indications in Italy and the classification criteria of COPD reported by the GOLD guidelines, this new class of fixed combinations are recommended for patients with symptomatic COPD (that is, dyspnoeic patients) first, followed by GOLD D patients, a portion of B patients, and GOLD C patients with frequent flare-ups. To date, the results of the SPARK [32] and FLAME [33] studies showed preliminary evidence that a significant improvement in exacerbations was obtained by the glycopyrronium/indacaterol association, leading to the use of dual bronchodilation in patients considered at high risk. Studies are under way on the same endpoint with other associations, such as umeclidinium/vilanterol, tiotropium/olodaterol, and aclidinium/formoterol. Moreover, this evidence supports therapy with LABA/LAMA even in very symptomatic GOLD group B naïve patients because the goal of any treatment is to optimise, rather than maximise, bronchodilator activity. Indeed, the dual bronchodilation approach improves symptoms, HRQoL, inhalation needs, and tolerability. For patients already being treated with other medications for COPD, there are more indications on the step-up rather than on the step-down or on the switch of therapy. In the simplest case of symptoms not controlled by a single long-acting bronchodilator, the combination of bronchodilators with a different mechanism of action (LABA/LAMA) is superior to the dose increase of a single bronchodilator. Therefore, double bronchodilation is an important potential maintenance therapeutic option in all patients with COPD, except for poorly symptomatic patients with conserved respiratory function.

The most commonly prescribed strategies considered in our analysis according to the most recent evidence are: 1) LABA monotherapy (salmeterol, indacaterol, other LABA approved and used in Italy) and LAMA monotherapy (tiotropium, glycopyrronium, and aclidinium); 2) ICS/LABA fixed combinations (fluticasone furoate/vilanterol, fluticasone propionate/salmeterol, budesonide/formoterol, beclomethasone/formoterol, and fluticasone propionate/formoterol); 3) triple extemporaneous association therapy (ICS/LABA/LAMA); and 4) LABA/LAMA as extemporaneous associations or as closed combinations.

In the analysis of drug use and treatment adherence in the OsMed 2015 Report, a 1% reduction in the inappropriate administration rate of ICS (estimated as approximately 53% of the total number of patients treated with ICS) resulted in saving €353,515 in INHS-funded drug expenditures [3]. The replacement of the extemporaneous associations of LABA/LAMA with the closed combination of the same agents may provide a further potential advantage in terms of adherence to treatment and simplification of the therapy, resulting in increased effectiveness. Notably, as per the log-linear panel data regression results, the use of double bronchodilation compared to single (the least expensive treatment) shows no evidence of variation in the average logged cost. According to the present analysis, the administration of single or double combination of bronchodilators in patients with COPD reduces costs for the INHS. The savings resulting from the substitution of the current use of extemporaneous associations of LABA/LAMA and associations with inhaled corticosteroids (ICS/LABA and ICS/LABA/LAMA), which are considered inappropriate treatments, would be approximately €130,000.

A reduction in the average logged cost per patient was observed in LHA-managed hospitals. This finding is supported by the lowest average cost for both oxygen therapy and ICS/LABA or ICS/LABA/LAMA therapies totalled by patients referred to LHA hospitals (−20.18% and −55.94%, respectively, vs the average cost per patient for the same healthcare resources calculated on the whole study population), possibly due to a more extensive multidisciplinary approach to the management of COPD adopted in the other hospitals. Finally, the

composition of the study population was predominantly retired Caucasian males. These features are superimposable to those of similar studies on COPD conducted in Italy and reflect the characteristics of Italian patients with COPD [25,34]. However, the previous studies did not consider the race of the subjects. In our study, there is a greater overrepresentation of Caucasians than expected. In agreement with a recent survey of the Italian National Institute of Statistics (Istat) on the health status of the immigrant population in Italy [35], a possible explanation could be that foreigners have a lower probability than Italians of undergoing medical examinations.

The distribution of the patients within age groups and occupational status indicate a modest impact of COPD on society's economic potential, which was not estimated because our research followed the INHS standpoint [8]. Consistently with this perspective, only healthcare resources funded by the INHS were valued. It would have been interesting to collect and value non-healthcare resource usage, such as out-of-pocket expenses, loss of leisure time, and informal care provided by caregivers, as in health economic research following the societal viewpoint [8]. However, switching from the INHS to the societal perspective would have imposed on investigators a formidable effort in data collection and, in our opinion, a possible increase in missing data due to patients' recall bias [36]. For the aforementioned reasons, we limited our research to the INHS perspective.

The strength of our study is the health econometric approach adopted (called panel data regression) that provides a cost prediction on a one-year longitudinal study of a given sample of COPD patients with different characteristics and/or referred to different hospital categories.

To date, only one longitudinal study on COPD in Italy presented a linear regression aimed at investigating the most relevant predictors of the cost of COPD, but it was centred only on hospitalisations for exacerbation [37].

A limitation of our approach may be represented by censored and missing data for some of the variables measured. This issue inevitably impacts the calculation of resource consumption and costs. Another limitation is that the population of this study was not the result of an epidemiological design, but only represented patients who were referred to the clinics of the units participating in the study. The centres were chosen as a sample of convenience [38] because they involved pulmonologists who wanted to participate and who volunteered for the study purely for scientific interest. Nevertheless, the population is very similar to the kind of COPD patients reported in most clinical studies. Eventually, marked differences in the number of centres participating in the study among the three geographical regions of the country and the number of patients enrolled was not equally distributed among the different types of centres, being more represented by university hospitals, possibly due to their higher propensity for research than LHA hospitals. Notwithstanding these limitations, our study provides relevant information that may represent a valuable source of insight for better interpretation and prediction of the costs of COPD management in Italy that are funded by the INHS.

4. Conclusions

The message for the INHS and national healthcare systems at large is that the cost of COPD is dramatically increasing. There are effective strategies for controlling COPD that may blunt the current drift in healthcare costs in the most ageing country in Europe for the benefit of the whole community.

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Declaration of interest

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