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Impacto da Depressão nos Resultados de Hospitalização por Doença Pulmonar Obstrutiva Crónica: Dados de um Estudo Nacional Português

Impact of Depression on Chronic Obstructive Pulmonary Disease Hospitalization Outcomes: Findings from a Portuguese Nationwide Study

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e
Mestre Manuel António Gonçalves de Pinho

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Impact of Depression on Chronic Obstructive Pulmonary Disease Hospitalization Outcomes: Findings from a Portuguese Nationwide Study

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Aos que sabem

Impact of Depression on Chronic Obstructive Pulmonary Disease Hospitalization Outcomes: Findings from a Portuguese Nationwide Study

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Abstract

Objective: Depression is a frequent comorbidity of chronic obstructive pulmonary disease (COPD). This study aims to assess the impact of comorbid depression on COPD-related hospitalization outcomes in the context of the Portuguese National Health Service (NHS), and to explore their regional distribution.

Methods: An observational retrospective study was conducted using administrative data regarding all hospitalizations with a primary diagnosis of COPD held in mainland Portuguese public hospitals (2000-2015). To select episodes with a secondary diagnosis of depression, a dichotomous variable was created grouping ICD-9-CM codes related to depressive disorders (296.2x, 296.3x, 300.4, and 311). To avoid potential bias, propensity score matching was used to select a comparable sample without depression. In-hospital mortality, length of stay (LoS), and estimated hospital charges were treated as outcomes. Univariate and multivariate analyses were performed and adjusted odds ratios (aOR) were calculated between patients' variables and chosen outcomes.

Results: Of a total of 135378 hospitalizations with a primary diagnosis of COPD, 4389 cases had a concurrent depression code. According to 1:1 proportion for propensity score matching, 4245 episodes without depression were selected. Comorbid depression increased LoS (aOR = 1.11; CI 95% = 1.07-1.15) and estimated hospital charges (aOR = 9.86; CI 95% = 8.48-11.46). While multivariate analysis showed no significant association of depression with mortality (aOR = 1.21; CI 95% = 0.88-1.37), univariate analysis revealed greater mortality in male patients (6.2% vs 4.5%; *p*=0.032).

Conclusion: These results describe the impact depressive disorders have on COPD hospitalizations. Greater efforts should be made to diagnose and address these conditions to provide the best care and prevent patients' negative health outcomes.

Keywords: Chronic obstructive pulmonary disease, depression, comorbidity, hospital charges, mortality, length of stay

Resumo

Objetivo: A depressão é uma comorbilidade frequente em doentes com doença pulmonar obstrutiva crónica (DPOC). Este estudo pretende determinar o efeito que depressão enquanto comorbilidade da DPOC tem em resultados de hospitalização no contexto específico do Serviço Nacional de Saúde (SNS) português, bem como explorar a sua distribuição regional.

Métodos: Foi realizado um estudo observacional retrospetivo com recurso a dados administrativos relativos a todas as hospitalizações de doentes com um diagnóstico primário de DPOC em hospitais públicos de Portugal continental (2000-2015). De modo a selecionar episódios com um diagnóstico secundário de depressão, foi criada uma variável dicotómica baseado no agrupamento dos códigos ICD-9-CM associados a perturbações depressivas (296.2x, 296.3x, 300.4 and 311). Para evitar potenciais vieses, foi utilizado *propensity score matching* para escolher uma amostra comparável sem registo de depressão. Mortalidade intra-hospitalar, tempo de internamento e preço estimado da hospitalização foram selecionados como resultados da hospitalização. Análises univariada e multivariada foram realizadas e foram calculados *odds ratios* ajustados entre as variáveis incluídas e os resultados de hospitalização.

Resultados: Do total de 135378 hospitalizações associadas a DPOC, 4389 casos tinham um registo concomitante de síndromes depressivos. De acordo com proporção 1:1 usada para o *propensity score matching*, 4245 episódios sem depressão foram selecionados. Enquanto comorbilidade, a depressão aumenta tempo de internamento (aOR = 1.11; CI 95% = 1.07-1.15) e o preço estimado da hospitalização (aOR = 9.86; CI 95% = 8.48-11.46). Embora a análise multivariada não tenha apontado uma relação significativa entre depressão e mortalidade intra-hospitalar (aOR = 1.21; CI 95% = 0.88-1.37), a análise univariada demonstrou que doentes com depressão e do sexo masculino (6.2% vs 4.5%; p=0.032) tinham maior probabilidade de morte.

Conclusão: Os presentes resultados descrevem o impacto negativo que perturbações depressivas têm ao nível do doente hospitalizado por DPOC. Deverão direcionar-se esforços para o diagnóstico e tratamento destas doenças psiquiátricas de modo a providenciar o melhor cuidado e a prevenir resultados negativos neste subgrupo de doentes.

Palavras-Chave: Doença pulmonar obstrutiva crónica, depressão, comorbilidade, preço de hospitalização, mortalidade, duração de internamento

Introduction

Background rationale

According to World Health Organization, chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide [1]. Patients with COPD usually present several comorbidities, that range from physical conditions, such as heart failure, coronary artery disease, lung cancer, or osteoporosis, to mental health conditions, such as anxiety and depressive disorders [2]. The clinical relationship between depressive disorders and COPD is well-established. In these patients, depression is known to be a proponent of increased mortality, prolonged hospital stays, risk of acute exacerbations, and rehospitalization [4-6;11;26;36]. Comorbid depression has also been associated with more intense dyspnea, worse survival, and inferior physical health and functional status [14;20;24;36;37], further adding to the COPD toll. Consequently, depressive disorders negatively impact recovery and day-to-day life of these patients, while simultaneously decreasing adherence to different aspects of COPD treatment and management [5;7-10;14-20;24;25;36]. Moreover, symptoms of depression can frequently overlap and correlate with pulmonary-specific symptoms, so depression itself is also a predictor of fatigue, shortness of breath, and disability in patients with COPD, regardless of disease severity [11;27].

Not only are depressive disorders in COPD impactful; they are also quite prevalent [3]. A systematic review of 64 studies has found that 30% to 71% of patients with severe COPD had comorbid depression. These rates were higher than in other advanced chronic illnesses such as heart and kidney disease, cancer, and acquired immunodeficiency syndrome (AIDS) [12]. Incidence-wise, a longitudinal study by *Schneider et al.* with a follow-up period of 10 years has shown an incidence of 16.2 cases of depression *per* 1000 person-years in the COPD group, exceeding the 9.4 cases *per* 1000 person-years in the non-COPD control group [4]. Estimates also vary greatly depending on the patients' clinical context, as a comprehensive analysis by Janet Maurer *et al*. found that, in stable COPD, the prevalence of depressive symptoms ranges between 10% and 42%, while in patients who had recently recovered from acute exacerbations of COPD it ranged between 19,4% and 50% [11].

However, the severity of depressive symptoms in COPD patients also differs: some studies have found that approximately two-thirds of these patients have moderate-to-severe depression, and the prevalence of subclinical depression may be even higher [13-15]. Parallel to general population estimates, female patients with COPD exhibit higher prevalence rates of depressive disorders when compared to their male counterparts [36]. Other patient-related factors such as younger age, current smoking, alcohol consumption, and lower education level and socioeconomic status have also been linked to a higher likelihood of concurrent depression [36;37].

Despite this outlook, it is worth noting that depression is often underdiagnosed and undertreated in COPD patients [3;11]. Although current treatment guidelines advise that depression should be targeted for treatment independent of the therapy offered for other manifestations of COPD, i.e. as separate illnesses, some studies have found that standard-of-care treatments for depression have uncertain efficacy on patients with comorbid COPD

[14;16;17]. Pulmonary rehabilitation and other approaches, however, have been found to yield positive results, both alone and in conjunction with psychotherapy [3;5;11;21-23]. Benzodiazepines, commonly used to aid COPD patients with depressive symptoms, are of uncertain benefit and may even be harmful [30-34].

According to the Portuguese Society of Pulmonology, around 14% of Portuguese citizens have been diagnosed with COPD, and in 2016 this disease was responsible for 20,7% of all respiratory-related deaths [35]. Depressive disorders also affect a sizeable subset of the Portuguese population, with an estimated annual prevalence of 7,9% [28], and an estimated 10% of the Portuguese population suffering from depressive symptoms [29]. Notwithstanding mental health conditions can influence the pathophysiology of COPD with a proven impact on the prognosis, in Portugal depression's impact on COPD-related hospitalization outcomes has not been fully investigated. As a result, the extent to which depression contributes to healthcare utilization, morbidity and mortality is still poorly recognized.

Objectives

To address this gap the present study aims to assess, quantify and describe possible differences in hospitalization outcomes of COPD patients with and without depression in the context of the Portuguese healthcare system, and to explore their regional distribution.

Methods

Study Design

The present study consists of a retrospective observational analysis of COPD-related hospitalizations between 2000 and 2015. This analysis was conducted using administrative data registered in the Portuguese National Health Service's (NHS) central database managed by the *Central Administration of the Health System of the Portuguese Ministry of Health* (ACSS). The Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement was used to guide data analysis and reporting [70].

Setting

This study analyses administrative data from NHS mainland Portuguese hospitals. Portuguese NHS is primarily tax-funded and composed of all public entities and services that provide and manage healthcare. This publicly covered sector coexists with the private one which comprises private hospitals that are fully paid out-of-pocket or by voluntary health insurance. As private hospitals are not included in the NHS, clinical and administrative data from these institutions are not compiled alongside data from public hospitals and were not included in this analysis.

The temporal window was selected considering the latest available data coded with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) in the Portuguese NHS. While ensuring that findings are still of relevance to contemporary health practices and care delivery, the use of data from 2016 and 2017 was avoided as these were transition years to International Classification of Diseases, 10th Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS) clinical coding. Caution has been advised when reusing such data to avoid bias attributable to this transition process [71;72].

Participants

All episodes of patients hospitalized in public mainland hospitals and discharged between 2000 and 2015 with a primary diagnosis of COPD – as defined by The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 491.x (chronic bronchitis), 492.x (emphysema), 496 (chronic airway obstruction, not elsewhere classified) and 491.21 (obstructive chronic bronchitis with (acute) exacerbation) – were initially selected. From these, all of those with specific secondary depressive disorder diagnoses – defined by ICD-9-CM codes 296.2x and 296.3x (major depressive disorder, single episode, and recurrent episode, respectively), 300.4 (dysthymic disorder), and 311 (depressive disorder not elsewhere specified) – were identified. These codes were selected following prior studies that have shown them to be moderately accurate in identifying these patients [66-69].

Because the number of patients without a secondarily diagnosed depressive disorder far exceeded that of the patients with one of the abovementioned psychiatric diagnoses, two

cohorts of matched samples were derived to reduce confounding biases. Propensity score matching (PSM) (ratio of 1:1) was used [61], adjusting for age, sex, year of discharge, and Charlson Comorbidity Index (CCI). Consequently, an analogous group of COPD patients without a secondary depressive disorder diagnosis (which would function as the control group) was included.

Variables and outcomes

For each episode sociodemographic variables examined included age (continuous variable), sex (dichotomous variable – male/female), and patient residence (categorical variable). The latter was coded *per* NUTS 2 (*Nomenclature of Territorial Units for Statistics, Level 2*), that divides Portugal into seven regions: North, Center, Lisbon metropolitan area, Alentejo, Algarve, Madeira, and Azores Islands. In this study, the last two were grouped into a single category because of their small number of cases.

As for clinical variables, secondary depressive disorder diagnosis was analyzed by grouping the relevant ICD-9-CM codes into a dichotomous variable (yes/no). Charlson Comorbidity Index (discrete variable), specifically the version proposed by Quan *et al.* [38], was used as a representation of patients' health status and prognosis. Type of admission (codified as a categorical variable into planned/urgent) was also extracted from the database.

The outcomes were defined as in-hospital mortality (dichotomous variable – yes/no), length of stay (LoS) referring the number of days in the hospital (continuous variable), and estimated hospital charges (continuous variable). Hospital charges were estimated by a budget allocation model based on diagnosis-related groups (DRG), which uses expenditure tables established by governmental decree in 2009 for the purposes of hospital reimbursement [65]. In the original database, hospital charges were inputted as preset values. However, for analysis purposes this variable this variable was dichotomized using the mean as a cutoff point (<=2130.74€/>2130.74€). Similarly, LoS was also dichotomized by cutting at the median sample LoS (<=8 days/>8 days), allowing to approach this outcome variable both as continuous and categorical.

Data source

Anonymized data regarding COPD-related hospitalizations used in this study was sourced from the national database of the *Central Administration of the Health System of the Portuguese Ministry of Health* (ACSS). This administrative database compiles both administrative and clinical data related to hospitalizations held in the Portuguese National Health Service, which according to official statistics account for 72% of all inpatient stays in the country by the last year under analysis [73].

Statistical analysis

Clinical data and outcomes were compared between episodes with and without a secondary depressive disorder diagnosis code. Categorical variables are expressed as number (percentage), while continuous variables are expressed as mean (standard deviation, SD) or median (percentile 25 – percentile 75, P25-P75), depending on their distribution.

Univariate analyses were carried out using Pearson's Chi-Square test for categorical variables and Mann-Whitney U test for continuous variables, as no continuous variable was normally distributed. Subgroup analysis was also performed using these methods.

To further assess associations between comorbid depressive disorders and relevant outcomes, regression models were used to parse out and control for every variables' effect. Multivariate analysis by means of binary logistic regression was used to calculate adjusted odds ratios (aOR), with respective 95% confidence intervals (CI 95%), which was possible in all outcomes due to prior dichotomization of hospital charges and LoS variables. As it was originally a continuous variable, LoS was also studied using multiple linear regression, yielding semi partial correlations for all predictor variables.

Data analysis was performed using the IBM SPSS Statistics ® Software (version 27). Statistical significance was defined as p-value < 0.05.

Data access and cleaning

Access to relevant data was granted following an established protocol between *Faculdade de Medicina da Universidade do Porto* (FMUP) and ACSS.

Formatting errors and duplicates were absent from the database. The residence variable had data appearing as strings; these were converted into numerical data by attributing values to each category. Missing values were only present in the residence variable. Such cases were excluded from analyses in which this variable was relevant, as they constituted a minute part of the dataset (n=30), and were unlikely to bias the results due to the large sample size of the current study.

Results

Study population

According to the ACSS database, a total of 135378 hospitalizations with a primary diagnosis of COPD occurred between 2000 and 2015. Secondary diagnoses of depressive disorders were registered in 4389 of these episodes (3.2%). To allow a proper comparative analysis, PSM for age, sex, year of discharge, and CCI was performed, and 4245 hospitalizations with a primary diagnosis of COPD without a depression register were selected. As such, a total of 8634 cases were subject to analysis in this study.

Descriptive data

Detailed demographics and clinical characteristics of the study population - segregated by presence or absence of a depression register - are present in **Table 1**. Age at admission did not significantly differ between COPD patients with and without a depression register (70.82 vs 70.45; *p*=0.216). The two groups were also similar in terms of sex distribution (*p*=0.428), with a higher proportion of women in both groups (53.3% of patients without depression registers; 54.1% of patients with depression registers). This lack of statistically significant differences was expected, due to the aforementioned matching process. Regarding patient residence, the most represented regions were the North (59.5% of patients without depression registers; 35.2% of patients with depression registers), followed by Centre (26.2% of patients without depression registers; 23.6% of patients with depression registers), and Lisbon (9.6% of patients without depression registers; 34.2% of patients with depression registers) regions. The North region and Lisbon are far more represented within the group of COPD patients without depression register, with a more even distribution between the three main regions in the opposite group.

Regarding clinical variables, no statistically significant differences were found on CCI (1.08 vs 1.17; *p*=0.053), as anticipated due to PSM. Type of admission did not differ significantly between the two groups (*p*=0.913), with most hospitalizations resulting from urgent admission (94.7% of patients without depression registers; 94.6% of patients with depression registers).

Table 1 Patient characteristics (N=8634) and univariate analysis of outcomes

	Patients without depression register (n=4245)	Patients with depression register (n=4389)	*p-value*
Sociodemographic variables			
Sex [N(%)]			0.428
Male	1984 (46.7%)	2014 (45.9%)	
Female	2261 (53.3%)	2375 (54.1%)	
Age at admission (mean ± SD)	70.82 (±10.89)	70.45 (±11.20)	0.216
Residence (NUTS 2) [N(%)]			
North	2524 (59.5%)	1545 (35.2%)	
Center	1111 (26.2%)	1037 (23.6%)	
Lisbon	409 (9.6%)	1499 (34.2%)	
Alentejo	132 (3.1%)	232 (5.4%)	
Algarve	57 (1.3%)	52 (1.2%)	
Islands	0	0	
Missing	12 (0.3%)	18 (0.4%)	
Clinical variables			
Charlson Index (mean ± SD)	1.08 (±1.20)	1.17 (1.34)	0.053
Type of Admission [N(%)]			0.913
Planned	226 (5.3%)	236 (5.4%)	
Urgent	4019 (94.7%)	4153 (94.6%)	
Outcomes			
Length of Stay [median (P25-P75)]	7.0 (5.0-11.0)	8.0 (6.0-13.0)	<0.001*
In-hospital Mortality [N(%)]	171 (4.0%)	201 (4.6%)	0.207
Hospital Charge (mean ± SD)	1689.48 (±1026.73) €	2557.52 (±3115.21) €	<0.001*

Abbreviation: N, number of hospitalizations; P25-P75, 25th Percentile – 75th Percentile; NUTS 2, Nomenclature of Territorial Units for Statistics, Level 2
*: Statistically significant

Outcomes

Univariate outcome analyses for both patient groups are detailed in **Table 1**. LoS was significantly longer in patients with comorbid depression (7.0 vs 8.0; *p*<0.001). However, in-hospital mortality did not significantly differ (4.0% vs 4.6%; p=0.206). Regarding the associated mean estimated charges of hospitalization, episodes with a secondary depressive disorder diagnosis exhibited greater estimates (1689.48 € vs 2557.52 €; *p*<0.001).

Additional univariate analyses in **Tables 2** and **3** highlight possible sex and region-related differences in the abovementioned outcomes, respectively. In-hospital mortality was significantly higher in male episodes with comorbid depression when compared to those without (4.5% vs 6.1%; *p*=0.032), while women's episodes does not depict the same distinction (3.6% vs 3.3%; *p*=0.633). Concerning regional differences, unlike the other Portuguese regions patients with depression registers from Lisbon show a significant increase in mortality over those without (5.2% vs 2.7%; *p*=0.033).

Table 2 Univariate outcome analysis with focus on patient sex

	Patients without depression register	**Patients with depression register**	***p-value***
Length of Stay [median (P25-P75)]			
Sex			
Male	7.00 (5.00-11.00)	9.00 (6.00-14.00)	<0.001*
Female	7.00 (5.00-11.00)	8.00 (5.00-12.00)	<0.001*
In-Hospital Mortality [N(%)]			
Sex			
Male	90 (4.5%)	122 (6.1%)	0.032*
Female	81 (3.6%)	79 (3.3%)	0.633
Hospital Charges (above mean) [N(%)]			
Sex			
Male	142 (7.2%)	868 (43.1%)	<0.001*
Female	139 (6.1%)	891 (37.5%)	<0.001*

Abbreviation: N, number of hospitalizations; P25-P75, 25th Percentile – 75th Percentile
*: Statistically significant

Table 3 Univariate outcome analysis with focus on patient residence

	Patients without depression register	Patients with depression register	*p-value*
Length of Stay [median (P25-P75)]			
Residence (NUTS II)			
North	7.0 (5.0-11.0)	8.0 (6.0-12.0)	<0.001*
Center	7.0 (4.0-10.0)	8.0 (5.0-12.0)	<0.001*
Lisbon	7.0 (5.0-10.0)	9.0 (6.0-14.0)	<0.001*
Alentejo	7.0 (4.0-11.8)	8.5 (6.0-14.0)	0.009*
Algarve	8.0 (5.0-12.0)	10.5 (7.0-14.8)	0.015*
In-Hospital Mortality [N(%)]			
Residence (NUTS II)			
North	107 (4.2%)	73 (4.7%)	0.456
Center	43 (3.9%)	33 (3.2%)	0.388
Lisbon	11 (2.7%)	78 (5.2%)	0.033*
Alentejo	7 (5.3%)	12 (5.0%)	0.913
Algarve	3 (5.3%)	4 (7.7%)	0.707
Hospital Charges (above mean) [N(%)]			
Residence (NUTS II)			
North	88 (3.5%)	568 (36.8%)	<0.001*
Center	90 (8.1%)	338 (32.6%)	<0.001*
Lisbon	83 (20.3%)	755 (50.4%)	<0.001*
Alentejo	12 (9.1%)	68 (28.6%)	<0.001*
Algarve	5 (8.8%)	23 (44.2%)	<0.001*

Abbreviation: N, number of hospitalizations; P25-P75, 25th Percentile – 75th Percentile; NUTS 2, Nomenclature of Territorial Units for Statistics, Level 2

*: Statistically significant

Concerning LoS, male and female episodes with comorbid depression registered longer hospital stays. For all regions, LoS was also significantly prolonged in COPD-episodes with a concomitant depression register. As for estimated hospital charges, episodes with depression registers more frequently belonged to the more expensive category compared to episodes without depression registers; this was true for both males (7.2% vs 43.1%; p<0.001) and females (6.1% vs 37.5%; p<0.001), as well as for all patients' residence region.

Tables 4, **5,** and **6** detail results from multivariate logistic analyses. After adjusting for all variables (sex, age, residence, CCI, type of admission), secondary depression registers did not significantly influence patient mortality (*p*=0.411) (**Table 4**). However, comorbid depressive disorders were associated with greater odds of increased hospitalization charges (aOR = 9.86; CI 95% = 8.48-11.46) (**Table 5**). Depression registers also increased the odds for lengthier hospital stays (aOR = 1.11; CI 95% = 1.07-1.15) (**Table 6**).

Table 4 Variables associated with in-hospital mortality among COPD-related hospitalizations

		Adjusted Odds Ratio	**CI 95%**	***p-value***
Depression register				
	No	Ref	Ref	Ref
	Yes	1.21	0.88-1.37	0.411
Sex				
	Male	Ref	Ref	Ref
	Female	0.62	0.50-0.77	<0.001*
Age		1.04	1.03-1.05	<0.001*
Residence (NUTS II)				
	North	Ref	Ref	Ref
	Center	0.82	0.63-1.09	0.171
	Lisbon	1.12	0.85-1.49	0.413
	Alentejo	1.17	0.71-1.92	0.536
	Algarve	1.72	0.78-3.80	0.178
Type of admission				
	Planned	Ref	Ref	Ref
	Urgent	2.18	1.06-4.46	0.034*
Charlson Index		1.21	1.13-1.29	<0.001*

Abbreviation: CI 95%, 95% confidence interval; COPD, Chronic Obstructive Pulmonary Disease

*: Statistically significant

Table 5 Variables associated with length of stay (dichotomized as <=8 days/>8 days) among COPD-related hospitalizations

		Adjusted Odds Ratio	CI 95%	*p-value*
Depression register				
	No	Ref	Ref	Ref
	Yes	1.11	1.07-1.15	<0.001*
Sex				
	Male	Ref	Ref	Ref
	Female	0.86	0.76-0.93	<0.001*
Age		1.01	1.00-1.01	<0.001*
Residence (NUTS II)				
	North	Ref	Ref	Ref
	Center	0.97	0.87-1.10	0.533
	Lisbon	1.21	1.01-1.36	<0.001*
	Alentejo	1.10	0.88-1.35	0.450
	Algarve	1.51	1.03-2.22	0.036*
Type of admission				
	Planned	Ref	Ref	Ref
	Urgent	1.39	1.14-1.70	<0.001*
Charlson Index		1.11	1.07-1.15	<0.001*

Abbreviation: CI 95%, 95% confidence interval; COPD, Chronic Obstructive Pulmonary Disease

*: Statistically significant

Table 6 Variables associated with hospital charges (dichotomized as <=2130.74€/>2130.74€) among COPD-related hospitalizations

		Adjusted Odds Ratio	CI 95%	*p-value*
Depression register				
	No	Ref	Ref	Ref
	Yes	9.86	8.48-11.46	<0.001*
Sex				
	Male	Ref	Ref	Ref
	Female	0.87	0.78-0.98	0.020*
Age		0.98	0.98-0.99	<0.001*
Residence (NUTS II)				
	North	Ref	Ref	Ref
	Center	0.99	0.85-1.15	0.892
	Lisbon	1.85	1.61-2.12	<0.001*
	Alentejo	0.82	0.61-1.08	0.161
	Algarve	1.34	0.82-2.20	0.250
Type of admission				
	Planned	Ref	Ref	Ref
	Urgent	0.13	0.10-0.17	<0.001*
Charlson Index		1.15	1.10-1.20	<0.001*

Abbreviation: CI 95%, 95% confidence interval; COPD, Chronic Obstructive Pulmonary Disease

*: Statistically significant

While multiple linear regression was performed, the assumptions of homoscedasticity and multivariate normality were not met. The resulting model had an R^2 of 0.027 (p<0.001), meaning that only 2.7% of the variance in LoS was explained by the chosen set of predictor variables. Due to not all assumptions being met, and the weak relationship with the response variable (LoS), these results were disregarded.

Sociodemographic variables

Regarding in-hospital mortality, a fatal outcome was close to half as likely for women's episodes (aOR = 0.62; CI 95% = 0.50-0.77) as it was for men. Increased age also increased mortality (aOR = 1.04; CI 95% = 1.03-1.05). However, no significant relationship was found between the patient's region of residence (using the North region as reference) and in-hospital mortality.

Women's episodes were also associated with lower mean hospitalization charges (aOR = 0.87; CI 95% = 0.78-0.98), with older patients mirroring that same relationship (aOR = 0.98; CI 95% = 0.98-99). When compared to the North region, COPD-related hospitalizations in Lisbon had an 85% increase in odds of falling into the higher category (aOR = 1.85; CI 95% = 1.61-2.12); other regions showed no significant differences.

Adjusting for all other variables, a one-year increase in age increased the odds of longer LoS by 1% (aOR = 1.01; CI 95% = 1.00-1.01), while female episodes reduce the likelihood of lengthier stays (aOR = 0.86; CI 95 % = 0.76-0.93). Regional differences were also noticeable, with patients from Lisbon (aOR = 1.21; CI 95% = 1.01-1.36) and Algarve (aOR = 1.51; CI 95% = 1.03-2.22) being more likely to stay admitted for extended periods (using the North region as reference).

Clinical variables

Urgent-type admissions more than doubled the likelihood of death (aOR = 2.18; CI 95% =1.06-4.46) when compared to planned hospitalizations. Also, higher CCI scores also corresponded to increased odds of death (aOR = 1.21; CI 95% = 1.13-1.29).

Type of admission also significantly influenced the odds of higher hospitalization charges, with urgent admissions showing to be associated with below-average costs (aOR = 0.13; CI 95% = 0.10-0.17). In contrast, patients with more severe CCI comorbidity profiles were more likely to incur in costlier hospital stays (aOR = 1.15; CI 95% = 1.10-1.17).

As for the duration of hospital stay, patients with higher CCI were more likely to be admitted for longer periods (aOR = 1.11; CI 95% = 1.07-1.15). Similarly, urgent-type admissions had increased odds of lengthier hospitalizations (aOR = 1.39; CI 95% = 1.14-1.70).

Other analyses

In-group analysis showed significant differences in hospital stays between male and female episodes with a depression register (9.0 vs 8.0; $p<0.001$). No such distinction was present between episodes without depressive disorders (7.0 vs 7.0; $p=0.783$). The same pattern of difference between male and female episodes with regard to depression register was apparent concerning in-hospital mortality (6.1% vs 3.3%; $p<0.001$) and estimated hospital charges (43.1% vs 37.5%; $p<0.001$).

Discussion

Over 8000 COPD-related hospitalization episodes that occurred during a 15-year period were analyzed and compared. Comorbid depression was more prevalent in older, female patients with a greater number of comorbidities, and was shown to increase estimated hospital charges and length of stay in all patients, as well as mortality in males and patients from the Lisbon metropolitan area. In addition, no significant associations were found between comorbid depression registers and the clinical and sociodemographic variables included in the study.

Comorbid depressive disorders

Analyses performed in this study indicate COPD patients with comorbid depression have lengthier hospitalizations and higher associated episodes' charges (regardless of sex or region), with these patients being close to 10 times as likely to have more expensive admissions, and 10% more likely to be hospitalized for extended periods. These results are in line with other studies on COPD patients [6;11;26;36].

However, and in contrast with those same reports, our analysis showed comorbid depression did not influence in-hospital mortality in all patients (p=0.411). We can, nevertheless, report increased mortality in patients with comorbid depression from Lisbon (p=0.033), and of the male sex (p=0.032). Additionally, in-group analysis showed statistically significant differences in mortality, LoS, and estimated hospital charges between male and female episodes with depression registers, but not among those without. On one hand, the association between increased mortality and male sex is of uncertain significance due to conflicting findings in prior studies, though most point to a positive association [40;41;47]. On the other hand, and seemingly contradicting our results, a 2015 study reported greater LoS in women admitted with acute exacerbations of COPD (AECOPD) [48], and prior studies have shown longer hospital stays to be associated with greater expenditure [47;48].

As is described in current literature, comorbid depressive disorders are a negative prognostic factor, as they have been associated with increased morbidity, mortality, and decreased quality of life [4-6;14;20;24]. However, they are also underdiagnosed and undertreated in COPD patients, with the amount of time they remain untreated significantly impacting patient outcomes, including response to antidepressants and disability ratings [3;11;43]. Beyond that, undiagnosed depression is thought to be far more common in men - as reporting rates for depressive symptoms are far lower in the male sex - while women exhibit greater care-seeking behavior and are more proactive in their treatment [42]. Despite this, comorbid depression was found to have a greater impact on the outcomes of male patients with COPD. Still, other variables such as type of patient residence, health status, time between COPD and depressive disorder diagnoses, and therapeutic approach for depression (which in Portugal is still very dependent on benzodiazepines [29]) were not controlled for in this study, and their effects could not be accounted for.

Sociodemographic variables

Over half of COPD patients with a secondary depression register included in this study were women, which is consistent with the higher prevalence of depressive disorders in female COPD patients described by most studies [36]. Due to the matching process, the percentage of women without depression registers was similar, such that univariate analysis showed no significant relationship between sex and probability of comorbid depression.

Adjusting for all other variables, female patients were 48% less likely to die during their hospitalizations, in accordance with most studies on COPD-related mortality [38;39]. Lengthier hospital stays and above-average charges were 14% and 13% less likely for women's episodes, respectively. In a 2019 study by Goel K. *et al.*, women were tendentially diagnosed with COPD at a younger age, and a larger proportion of women were characterized with minor to severe lack of function, while men showed a greater proportion of severe COPD-related lack of function [45]. Regarding exacerbation risk, a greater rehospitalization risk in male patients (with less time between events) has been reported [46], though not consistently, as other studies have described a higher rate of AECOPD and more frequent hospitalizations in women [41]. Even so, patients with increased function would be expected to have shorter and therefore less expensive hospital stays, with less propensity for early rehospitalization and more time to recuperate.

Patients of both study groups were on average around 70 years old, with no significant difference between them, again a result of the matching process. Otherwise, it should be noted that some level of age discrepancy was expected, as studies have shown a greater prevalence of depression and anxiety in younger COPD patients [36;49].

Multiple studies on patients with COPD have highlighted the positive correlations between age, mortality, LoS, and hospitalization costs [49-55]. In the present study, a one-year increase in age raised the odds of in-patient death by 4% and longer hospital stays by 1%. Conversely, the odds of higher estimated hospitalization charges decreased by 2%, which may come from more conservative therapeutic choices accounting for the increased frailty and likelihood of death in older patients (due to aging, multicomorbidity, and more advanced progression of COPD), potentially resulting in cheaper but more protracted hospital stays.

The distribution of patients with comorbid depression seems to reflect how the Portuguese population is spread through the country, and not the regional prevalence of depressive disorders [56;57]. This is likely due to the relatively small regional differences in the latter not having the same influence in the results as the differences in regional distribution of the general Portuguese population. As for why the groups differ, it might be related to the matching process or the distribution of COPD patients around the country. Despite how no information on the latter could be obtained, it is important to notice that substantial inequalities in the supply of health services between Portuguese country regions have been reported [74], and these may also have accounted for the present results.

Using the North region as a reference, while no differences in in-hospital mortality were found, hospital charges and LoS were significantly greater for patients hospitalized in the Lisbon metropolitan area, as was LoS for COPD patients in Algarve. Further research on regional

differences in these outcomes with focus on patients with COPD could be important in balancing healthcare at the national level.

On the abovementioned increase in mortality in patients with comorbid depression from Lisbon, we suspect it may have to do with the distribution of male and female patients between the study groups, as a result of the matching process. Nevertheless, this result should be verified in future studies.

Clinical variables

The majority of admissions for patients both with and without comorbid depression were urgent, owing to the fact that most COPD-related hospitalizations are due to AECOPD [3;52]. Urgent admissions were more than twice as likely to resolve fatally and show a 39% increase in odds of longer hospitalizations. Despite this, urgent admissions were found to be nearly 8 times as likely to have reduced hospital charges, which seems to contradict diverse articles that show an increase in hospitalization costs for patients presenting with AECOPD in need of urgent care [53-55]. It is possible that the difference in magnitude between both groups (462 planned admissions vs 8172 urgent admissions), alongside the method used to estimate hospital charges (using Diagnosis Related Groups), might have contributed to the observed discrepant results. Moreover, one must also account for the differences in healthcare systems, cross-country reimbursement criteria and variations regarding hospital discharge rates [75]. As some of these outcomes are probably influenced by structural factors of the individuals' health care systems, additional research should be conducted on this topic to further assess how the type of admission influences COPD-related hospitalization costs.

COPD patients with more severe comorbidity profiles are more likely to develop comorbid depression, which is associated with worse health status [3]. To properly evaluate the impact comorbid depression has on hospitalization outcomes, it was necessary to match patients with comorbid depression to patients without comorbid depression of similar CCI to eliminate the confounding influence of other comorbidities. This made the average CCI score of the two groups artificially similar. Even so, the difference in the average CCI value between the two groups was nearly significant, which would indicate patients with comorbid depression have worse comorbidity profiles, thus being more prone to less favorable health outcomes [39;58;59]. Additional exploratory analysis using the total sample of COPD hospitalizations without a depression register (instead of the matched sample) indicated a significant difference in CCI burden between the two study groups. This is in line with our current understanding of depression as a promoter of comorbidity, and worse outcomes in COPD patients [3;60]. In fact, a one-unit increase in CCI score led to significantly increased odds of in-hospital mortality (21%), LoS (11%), and hospital charges (15%). Still, two patients can have equal CCI values while having completely distinct comorbidities, so further research is advised to discern which comorbidities are most associated with depression and thus more likely to affect COPD patients.

Study limitations

As a retrospective study, the principal limitation was the use of secondary data, or data not originally meant for our investigation. The dataset used in this study is primarily intended for processing hospital reimbursements. Beyond that, the register and codification of diagnoses are subject to human experience and error, as well as changes in quality over time [62-64]. Also, a patient with no register of depression could have been diagnosed prior to their hospitalization of interest (clinical error) or have had their diagnosis registered after (administrative error). As we were not provided access to detailed clinical information and notes, the data used could be partially inaccurate or incomplete for some variables. It was also impossible to verify how the diagnosis of depression was done, how severe it was, and its temporal relation in regard to COPD diagnosis. These details could have allowed for more in-depth analysis into the impact of comorbid depressive disorders on COPD outcomes and should be addressed in future studies.

Another important limitation stemming from the observational study design is the inability to randomly allocate the variable of interest in the chosen contingent of subjects. As such, differences in outcomes may be due to the variable of interest (depression register) or confounding variables (age, sex). Propensity score matching is likely to have balanced this possible bias by making both study groups more comparable in regard to those characteristics, in a sense mimicking randomization [61]. In this study, patients were matched for age, sex, year of discharge, and CCI. Consequently, we were able to more adequately characterize the effect of comorbid depression on COPD outcomes, as these are well-known confounding variables. However, the effects of the matching variables cannot be effectively derived and need to be carefully interpreted.

Finally, previous studies on the validity of using ICD-9-CM codes in administrative data to identify individuals with COPD or AECOPD have shown different levels of sensitivity and specificity, though they seem to more accurately represent and capture depression [66-69]. While misdiagnosed patients are likely to have been included in our study, both groups are likely to have been similarly affected, thus making this aspect less informative.

Clinical implications

Our study benefits from a large sample and a long study period, as well as from the fact that it was pioneering in characterizing the impact of comorbid depression in COPD-related Portuguese hospitalizations. By using ACSS data, which codifies admissions to NHS hospitals, the external validity of this study was strengthened by our analysis of a broad group of patients largely representative of the target population - Portuguese COPD patients. In addition, as far as the authors are aware, the analysis at the regional level is the first conducted in the country, and made it possible to highlight regional differences in hospital spending and duration of patient stay that, while requiring further research, could prove useful in handling and balancing quality of care and health investment at the national level.

This study further solidifies the significant influence comorbid depression has on COPD-related outcomes, specifically hospitalization outcomes. Because depressive disorders favored lengthier hospitalizations and higher associated charges, they represent an important social and

economic toll at both the patient and the healthcare system levels. Additional measures are required to ensure early screening and diagnosis of these conditions in COPD patients, and awareness among healthcare professionals regarding their symptoms, frequent overlap and impact needs to be improved. Moreover, male patients could benefit the most from these measures, as they have higher rates of undiagnosed and untreated depression, and fared worse in all COPD-related hospitalization outcomes.

Furthermore, a multidisciplinary therapeutic approach including medication, rehabilitation, and patient support groups, all alongside appropriately spaced reevaluations of both physical and mental status could offer these patients the best disease control and quality of life. In Portugal, and particularly in COPD patients, an additional effort should be made to prescribe fewer benzodiazepines, as they could negatively impact these patients. Further research should also be carried out to ascertain country regional differences in the studied outcomes, particularly Lisbon and the Algarve region, since it could help to reduce the known inequities of care across the NHS.

Conclusion

In COPD, comorbid depression was associated with increased duration of hospital stay and estimated hospital charges, while differences in mortality were observed only in male patients and those from the Lisbon region. The present study reinforces the important impact of these disorders on COPD-related hospitalizations and the NHS at large, while similarly highlighting the need for better and timely assessment, diagnosis and care of comorbid depression as it may be an avenue to prevent patients' negative health outcomes.

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Declarations of Interest

None.

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Appendices

Appendix 1 – RECORD reporting guidelines checklist

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	a) Página 2 (Parágrafo 2): "An observational retrospective study was conducted using administrative data regarding all hospitalizations with a primary diagnosis of COPD held in mainland Portuguese public hospitals (2000-2015)" b) Página 2 (Parágrafo 2, 3): "To select patients with a secondary diagnosis of depression, a dichotomous variable was created grouping ICD-9-CM codes related to depressive disorders (296.2x, 296.3x, 300.4, and 311). To avoid potential bias, propensity score matching was used to select a comparable sample without depression. (…) adjusted odds ratios (aOR) were calculated between patients' variables and chosen outcomes. (…) Comorbid depression increased LoS and estimated hospital charges (…) univariate analysis revealed greater mortality in male patients(…)"	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1) / 1.2) Página 2 (parágrafo 2): "(…) study was conducted using administrative data (…)" 1.3) Não aplicável, pois só uma base de dados foi usada

Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Página 4 (Parágrafo 1 - 4); Página 5 (Parágrafo 1): "The clinical relationship between depressive disorders and COPD is well-established. In these patients, depression is known to be a proponent of increased mortality, prolonged hospital stays, risk of acute exacerbations, and rehospitalization (…). Not only are depressive disorders in COPD impactful; they are also quite prevalent. (…) it is worth noting that depression is often underdiagnosed and undertreated in COPD patients(…)."		
Objectives	3	State specific objectives, including any prespecified hypotheses	Página 5 (Parágrafo 2): "To address this gap the present study aims to assess, quantify and describe possible differences in hospitalization outcomes of COPD patients with and without depression in the context of the Portuguese healthcare system, and to explore their regional distribution. "		
Methods					
Study Design	4	Present key elements of study design early in the paper	Página 6 (Parágrafo 1): "The present study consists of a retrospective observational analysis of COPD-related hospitalizations between 2000 and 2015"		

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Página 6 (Parágrafo 2, 3): "This study analyses administrative data from NHS mainland Portuguese hospitals. (…) clinical coding."		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Página 6 (Parágrafo 4, 5): "All episodes of patients hospitalized in public mainland hospitals and discharged between 2000 and 2015 with a primary diagnosis of COPD (…) an analogous group of COPD patients without a secondary depressive disorder diagnosis (which would function as the control group) was included."	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1) Página 6 (Parágrafo 4): "(…) primary diagnosis of COPD – as defined by The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (…) were identified. 6.2) Página 6 (Parágrafo 4): "These codes were selected following prior studies that have shown them to be moderately accurate in identifying these patients (…)." 6.3) Não aplicável, pois não foi realizado linkage
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect	Página 7 (Parágrafos 1, 2, 3): "For each episode sociodemographic variables examined included (…)	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and	7.1) Não aplicável

		modifiers. Give diagnostic criteria, if applicable.	estimated hospital charges (continuous variable).”	effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Página 7 (Parágrafo 4): “Anonymized data regarding COPD-related hospitalizations used in this study was sourced from the national database of the *Central Administration of the Health System of the Portuguese Ministry of Health* (ACSS).”		
Bias	9	Describe any efforts to address potential sources of bias	Página 6 (Parágrafo 5): “Because the number of patients without a secondarily diagnosed depressive disorder far exceeded that of the patients with one of the abovementioned psychiatric diagnoses, two cohorts of matched samples were derived to reduce confounding biases, Propensity score matching (PSM) (ratio of 1:1) was used.”		
Study size	10	Explain how the study size was arrived at	Página 6 (Parágrafo 2, 3): “This study analyses administrative data from NHS mainland Portuguese hospitals (…) transition process.”		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Página 7 (Parágrafo 3): “In the original database, hospital charges were inputted as preset values. (…) both as continuous and categorical.”		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	a) Página 6 (Parágrafo 5); Página 8 (Parágrafo 1, 2, 3, 4): “Because the number of patients without a secondarily diagnosed depressive disorder far exceeded		

		(b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	that of the patients with one of the abovementioned psychiatric diagnoses (…) was included."; "Clinical data and outcomes were compared between episodes with and without a secondary depressive disorder diagnosis code (…) yielding semi partial correlations for all predictor variables." b) Página 8 (Parágrafo 2): "Subgroup analysis was also performed using these methods." c) Página 8 (Parágrafo 6): "Missing values were only present in the residence variable. Such cases were excluded from analyses (…)" d) Não aplicável, pois não foram realizados e) Não aplicável, pois não foram realizadas		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.1) Página 8 (Parágrafo 5,6): Access to relevant data was granted following an established protocol between *Faculdade de Medicina da Universidade do Porto* (FMUP) and ACSS."

					12.2) Página 8 (Parágrafo 6): "Formatting errors and duplicates were absent from the database. (…) large sample size of the current study."
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	12.3) Não aplicável, pois não foi realizado linkage
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	a) Página 9 (Parágrafo 1): "According to the ACSS database (…) were subject to analysis in this study." b) Não aplicável, pois não houve não-participantes c) Não aplicável, pois nenhum foi usado	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	13.1) Página 9 (Parágrafo 1): "Secondary diagnoses of depressive disorders were registered in 4389 of these episodes (…) were subject to analysis in this study"
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest	a) Página 9 (Parágrafo 2, 3): "Detailed demographics and clinical characteristics of the study population - segregated by presence or absence of a depression register - are present in **Table 1**. (…) with most		

		(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	hospitalizations resulting from urgent admission (…)" b) Página 8 (Parágrafo 6): "Missing values were only present in the residence variable. Such cases were excluded from analyses in which this variable was relevant, as they constituted a minute part of the dataset (n=30) (…)"		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Página 11 (Parágrafo 1): "Univariate outcome analyses for both patient groups are detailed in **Table 1**. (…) episodes with a secondary depressive disorder diagnosis exhibited greater estimates (…)"		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	a) Página 11 (Parágrafo 1, 2), Página 12 (Parágrafo 1), Página 13 (Parágrafo 1): "Univariate outcome analyses for both patient groups are detailed in **Table 1**. (…) Depression registers also increased the odds for lengthier hospital (…)" b) Página 7 (Parágrafo 3): "However, for analysis purposes this variable this variable was dichotomized using the mean as a cutoff point (<=2130.74€/>2130.74€). Similarly, LoS was also dichotomized by cutting at the median sample LoS (<=8		

			days/>8 days), allowing to approach this outcome variable both as continuous and categorical." c) Não aplicável, pois não foi realizado		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Página 16 (Parágrafo 7): "In-group analysis showed significant differences (…) concerning in-hospital mortality (…) and estimated hospital charges (…)."		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Página 17 (Parágrafo 1): "Over 8000 COPD-related hospitalization episodes (…) clinical and sociodemographic variables included in the study."		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Página 20 (Parágrafo 1, 2, 3): "As a retrospective study, the principal limitation (…) thus making this aspect less informative".	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	19.1) Página 20 (Parágrafo 1, 2, 3): "As a retrospective study, the principal limitation (…) thus making this aspect less informative".
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	Páginas 17 (Parágrafos 2, 3 ,4), Páginas 18 e 19: "Analyses performed in this study indicate		

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	COPD patients (…) further research is advised to discern which comorbidities are most associated with depression and thus more likely to affect COPD patients"		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Página 20 (Parágrafo 4): "By using ACSS data, which codifies admissions to NHS hospitals, the external validity of this study was strengthened by our analysis of a broad group of patients largely representative of the target population - Portuguese COPD patients"		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Página 21 (Parágrafo 3): "This research did not receive grant funding from any agency in the public, commercial or not-for-profit sectors."		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Não aplicável

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Appendix 2 - Respiratory Medicine Guide for Authors

GUIDE FOR AUTHORS

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[5] Cancer Research UK, Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/, 2003 (accessed 13 March 2003).
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[dataset] [6] M. Oguro, S. Imahiro, S. Saito, T. Nakashizuka, Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1, 2015. https://doi.org/10.17632/xwj98nb39r.1.
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[7] E. Coon, M. Berndt, A. Jan, D. Svyatsky, A. Atchley, E. Kikinzon, D. Harp, G. Manzini, E. Shelef, K. Lipnikov, R. Garimella, C. Xu, D. Moulton, S. Karra, S. Painter, E. Jafarov, S. Molins, Advanced Terrestrial Simulator (ATS) v0.88 (Version 0.88), Zenodo, March 25, 2020. https://doi.org/10.5281/zenodo.3727209.

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