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Bipolar disorder and pulmonary embolism: A Portuguese population-based observational retrospective study (2008–2015)

Inês Maria Souto Silva

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FACULDADE DE **MEDICINA**

Trabalho organizado de acordo com as normas
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NOME

Inês Maria Souto Silva

NÚMERO DE ESTUDANTE	E-MAIL
201905190	inesmariasilva01@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Neurociências clínicas e Saúde Mental

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Bipolar disorder and pulmonary embolism: A Portuguese population-based observational retrospective study (2008–2015)

ORIENTADOR

Dr. Manuel António Gonçalves de Pinho

COORIENTADOR (se aplicável)

Drª. Inês Conde Pacheco Barros Albuquerque

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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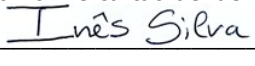

UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Inês Maria Souto Silva, abaixo assinado, nº mecanográfico 201905190, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 06/03/2025

Assinatura conforme cartão de identificação:
Inês Silva

Bipolar disorder and pulmonary embolism: A Portuguese population-based observational retrospective study (2008–2015)

Inês Souto Silva[a]; Alberto Freitas[b] ; Inês Albuquerque[c,d]; Manuel Gonçalves-Pinho[e,f]

[a]Faculty of Medicine, University of Porto, Porto, Portugal; [b]RISE-Health, MEDCIDS, Faculty of Medicine, University of Porto, Porto, Portugal; [c]Department of Internal Medicine, Unidade Local de Saúde São João; [d]Department of Medicine, Faculty of Medicine, University of Porto, Portugal; [e]RISE-Health, Department of Clinical Neurosciences and Mental Health, Faculty of Medicine, University of Porto, Porto, Portugal; [f]Department of Psychiatry and Mental Health, Unidade Local de Saúde Tâmega e Sousa, Penafiel, Portugal

*Corresponding Author: Manuel Gonçalves-Pinho manuelgpinho@med.up.pt
Rua Dr. Plácido da Costa, 4200 - 450 Porto, Portugal; Tel: +351 225 513 622

Orcid:

Inês Souto Silva: 0009-0009-6126-5022

Alberto Freitas: 0000-0003-2113-9653

Inês Albuquerque: 0000-0001-9401-526X

Manuel Gonçalves-Pinho: 0000-0001-6098-429X

Abstract

Bipolar Disorder (BD) is a chronic mood disorder associated with significant morbidity and a higher mortality rate compared to the general population. Previous studies have shown an association between BD and an increased risk of pulmonary embolism (PE).
The aim of this study is to study the correlation between BD and PE in Portuguese patients, and relate it to sociodemographic data, comorbidities and inpatient treatment.
We performed an observational retrospective study using a national hospitalization database that gathers all hospitalizations in Portuguese hospitals from 2008-2015. Episodes of BD, PE, and other data were selected using the International Classification of Diseases version 9, Clinical Modification (ICD-9-CM).
All hospitalizations with a primary diagnosis of PE were selected using the codes 415.1x. BD was identified based on the codes 296.xx (excluding 296.2x; 296.3x and 296.9x).
A total of 22140 hospitalizations with a primary diagnosis of PE were analyzed and among these hospitalizations, 92 had a secondary diagnosis of BD (0.42%).
Both groups of patients who experienced a PE event, regardless of the diagnosis of BD, showed a higher prevalence of female patients. The median age at admission for the BD group was significantly lower when compared to the control group, and BD patients had a significantly higher percentage of obesity and tobacco use, which are both known risk factors for PE.
This is the first study aimed at correlating BD and PE in Portuguese patients, as there are no similar studies currently available in scientific literature.

Keywords: bipolar disorder, pulmonary embolism, administrative data, inpatient, hospitalization, big data

1. Introduction

Bipolar disorder (BD) is a severe and recurrent chronic mood disorder associated with great morbidity. It affects more than 1% of the world's population [1] and, in Portugal, a prevalence of 1.1% for bipolar disorder has been reported in an epidemiological study [2]. BD patients are recurrently hospitalized during their lives and this disorder is responsible for an important number of hospitalizations in the mental health system in Portugal [3]. These patients have a 2 to 3 times higher mortality rate than the general population and have an estimated 15-year decrease in life-expectancy [3-5].

The clinical manifestations of bipolar disorder are diverse and can range from hypomania or mild depression to severe forms of mania or depression [6]. Manic states of BP are the main cause of hospitalization when compared to depressive episodes [3, 7].

Several studies that associate BD with a near double increase in the risk of cardiovascular mortality when compared to general population estimates, which may be explained by the significant burden of cardiovascular risk factors found in this population [8]. There is also an association between BD and an increased risk of thromboembolism and pulmonary embolism (PE), as shown in previous studies [9-14]. For instance, a Danish study conducted in 2005 showed that patients with BD have a significantly increased occurrence of PE (increased incidence rate ratio of 1.61) compared to a non-psychiatric age- and sex-matched group [9].

Besides the higher risk of cardiovascular mortality and PE in BD patients, these patients also have higher morbidity from obesity and type 2 diabetes when compared to the general population, as a study conducted by Morriss, R. and Mohammed, FA. has shown [11]. This additional risk may be explained by reduced exercise and inactivity, poor diet, comorbidity with substance misuse and poor quality medical care common in these patients [11]. The existing literature even suggests that patients with BD receive fewer or delayed medical interventions, when admitted with severe somatic diseases, compared to those not diagnosed with BD [15].

The association between BD and thromboembolism can be explained by various factors, particularly the adverse effects of the medications used to treat BD [10, 16-22].

Antipsychotic agents (AP) users have a significantly increased risk of venous thromboembolism (VTE) and PE [16-22]. This increased risk of VTE and PE was observed in taking haloperidol, risperidone, olanzapine and prochlorperazine [21]. Zonberg and Jick demonstrated that low-potency antipsychotics drugs like chlorpromazine and thioridazine were more strongly associated with VTE than high-potency antipsychotic drugs such as haloperidol [22].

AP agents have immobilization [23], lethargy and apathy as frequent side-effects. This immobilization causes venous stasis in the lower extremities, which might cause VTE in the lower extremities and in the pelvis.

Patients prescribed lithium also have a higher risk of venous thromboembolism, as shown by Ponzer, K., et al. [10].

Patients hospitalized with an acute psychiatric illness are also more prone to acute and chronic stress, which increases catecholamine levels and precipitates a state of hypercoagulability [9, 24].

Another explanation for the higher risk of PE in BD patients is that many psychiatric patients have comorbid substance use disorders, and the use of intravenously administered drugs is associated with a higher risk of deep vein thrombosis (DVT)

[9, 25, 26]. These patients can also develop infectious endocarditis, which can result in embolism in the pulmonary arteries [27].
Although many studies [9-14] show an association between BD and PE, there are no studies on a link between these conditions in Portuguese patients. Thus, the primary aim of this study is to describe a perspective of BD and PE in a nationwide Portuguese hospitalization database.

2. Methods

Study Design and Setting
We conducted a retrospective observational study using a national hospitalization database that gathers clinical and administrative data from all hospitalizations of patients ≥18 years old occurring in Portuguese mainland public hospitals, with discharges from 2008 to 2015. This anonymized database was provided by ACSS – *Administração Central do Sistema de Saúde I.P.* Data analysis, reporting, and manuscript formatting follow the Reporting of Studies Conducted using Observational Routinely-Collected Data (RECORD) statement recommendations [28].

Study Population
In this database, episodes of BD, PE and other diagnoses of interest, comorbidities, and procedures where selected based on International Classification of Diseases version 9, Clinical Modification (ICD-9-CM).
All hospitalizations with a primary diagnosis of PE registered from 2008 to 2015 were selected using the codes 415.1x. BD was considered a secondary diagnosis and patients with the diagnosis of BD were selected using the codes 296.xx (excluding 296.2x; 296.3x and 296.9x).
Thus, subsequently, two groups of patients were created: one group corresponded to hospitalized patients diagnosed with PE and who do not have a diagnosis of BD, and the other group corresponded to hospitalized patients who have both these diagnoses.

Variables
Other clinical variables were analysed in both groups – namely, the diagnosis of obesity (278.0), type 2 diabetes (250.x), hypertension (401.x-405.x), hyperlipidaemia (272.0-272.4), tobacco use (305.1, V15.82) and alcohol abuse (305.0).
The type of treatment prescribed to patients with PE was also considered. We analysed the infusion of a thrombolytic agent (99.10), the use of a vena cava filter (38.7), pulmonary embolectomy (38.05) and extracorporeal membrane oxygenation (39.65).
Age, sex, primary and secondary diagnoses, length of stay (LoS) and in-hospital mortality were also extracted from each single hospitalization episode with the primary diagnosis of PE.

Statistical methods
Descriptive statistical analyses, independent sample t-tests and Chi-squared tests were performed using IBM SPSS Statistics v.29 (Armonk, NY: IBM Corp).
A p-value of <0.05 was used to determine the statistical significance of the test results.

3. Results

A total of 22140 hospitalizations with a primary diagnosis of PE were retrieved from a national hospitalization database, with discharges between 2008 and 2015. Among these hospitalizations, 92 had a secondary diagnosis of BD (0.42%).

Sociodemographic variables

Regarding sociodemographic characteristics, Table 1 shows that both groups have a higher proportion of female patients. The group with a secondary diagnosis of BD has a higher percentage of female patients (64.1%) compared to those without BD (61.0%). However, this difference is not statistically significant ($p = 0.543$).

The mean age at admission was approximately 61 years (SD of 13 years) for the BD group and 70 years (SD of 16 years) for the non-BD group. These results are statistically different ($p < 0.01$); hence BD patients tend to experience a PE event at an earlier age.

The median length of stay was 9 days with interquartile ranges (P25-P75) of 7-16 days in the BD group and 10 days with interquartile ranges of 6-15 days in the non-BD group ($p = 0.810$).

In-hospital mortality was higher in the non-BD group (13.1%) vs. the BD patients (8.7%) ($p = 0.213$).

Comorbidity variables

Regarding comorbidity variables (Table 2), the group with comorbid BD has a higher percentage of obesity (28.3%) and tobacco use (21.7%), when compared to those without a BD diagnosis (12.8% and 9.0%, respectively), ($p < 0.001$). The group with BD also has a higher percentage of alcohol abuse (1.1%), in contrast to those without a secondary diagnosis of BD (0.4%), ($p=0.333$).

Type 2 diabetes (18.0%), hyperlipidemia (20.9%) and hypertension (48.8%) were more common in PE hospitalizations without the secondary diagnosis of BD. Those diagnosed with BD had a percentage of 14.1%, 14.1% and 41.3%, and a p of 0.334, 0.110 and 0.150, respectively.

Treatment variables

Regarding treatment variables (Table 3), none of the results showed a statistically significant difference.

Thrombolytic infusion was more common in BD patients (7.6%) compared to those without this diagnosis (5.1%), ($p=0.241$).

There were no cases of patients with BD and PE treated with a vena cava filter, pulmonary embolectomy or extracorporeal membrane oxygenation. Furthermore, very few patients without a BD diagnosis underwent these treatment modalities.

4. Discussion

This study uses a national hospitalization database that gathers clinical and administrative data from all hospitalizations in Portuguese mainland public hospitals from 2008 to 2015. To our knowledge, it is the first study to analyse BD and PE in a nationwide Portuguese hospitalization database, and one of the few international studies investigating this association.

The register of a secondary diagnosis of BD in patients hospitalized with PE during the study period was 0.42%. The relatively low prevalence of BD may partially

explain this low prevalence. As previously mentioned, BD has an estimated prevalence of 1.1% in the Portuguese population [2]. A study conducted in Portugal reported an estimated incidence rate of PE of 46/100.000 inhabitants/year in 2018 [29]. Thus, similarly to BD, PE is an event with a relatively low incidence.
Furthermore, both groups of patients with a PE event, regardless of the diagnosis of BD, showed a higher prevalence of female patients. This trend is consistent with previous studies on BD, which indicate that this condition is more prevalent in females [3]. Although this study demonstrates a higher prevalence of PE in female patients, the overall age-adjusted incidence of PE is similar between sexes [30].
The median age at admission for the BD group was significantly lower when compared to the non-BD group. This finding may suggest an association between BD and PE, as supported by previous studies [9]. The earlier occurrence of PE in patients with BD could indicate that BD contributes to a more premature development of PE in these individuals. This association can be further explained by the significantly higher register of obesity and tobacco use in BD patients, as presented in our findings. Both obesity and tobacco use are well-established risk factors for PE [31, 32]. The higher prevalence of obesity and tobacco use in the BD group, relative to the non-BD group, aligns with prior research showing that these comorbidities are more common among BD patients compared to the general population [33].
BD patients might have higher rates of obesity than the general population due to medication side effects, as certain antipsychotics and mood stabilizers used to treat this condition are associated with weight gain, and also due to excessive carbohydrate consumption, low rate and intensity of exercise, reduced fat oxidation, substance misuse, and maladaptive efforts at self-modulation of mood by over-eating [34]. Obesity contributes to an increased risk of venous thromboembolism and PE [31, 32] through several mechanisms. Excess body weight can lead to decreased mobility and venous stasis, promoting clot formation [35]. Obesity is also associated with a chronic inflammatory state, which increases activated protein C resistance and contributes to a hypercoagulable state [36].
Heffner, Jaimee L., et al. [37] demonstrated that individuals with BD are two to three times more likely to start smoking and may face greater challenges in initiating or maintaining smoking abstinence compared to those without psychiatric disorders. Although smoking cessation is achievable for this population, factors such as chronic mood dysregulation, a high prevalence of substance use, severe nicotine dependence, and limited social support can make the process more difficult [37]. Tobacco use further increases the risk of PE by raising plasma fibrinogen levels, a critical factor in thrombogenesis [38], and by enhancing coagulation through nicotine-induced upregulation of plasminogen activator inhibitor-1, a key regulator of fibrinolysis [38].
Regarding the other comorbidities analyzed in this study, no significant differences were observed in the diagnoses of type 2 diabetes, hypertension, hyperlipidemia, or alcohol abuse between the BD and non-BD groups. As a result, no conclusions can be drawn about the association of these comorbidities with the occurrence of PE in BD patients. Although a study conducted by Morriss, R. and Mohammed, FA. [11] showed a higher morbidity from obesity and type 2 diabetes in BD patients when compared to the general population, this study shows no statistical difference in the register of type 2 diabetes between the BD and non-BD group.
Another known risk factor for PE is immobilization [33], which was not analyzed in this study.

Patients without BD exhibited a higher in-hospital mortality rate. Although these results were not statistically significant, they could be attributed to the significantly higher age at admission of these patients. Patients without BD are significantly older compared to those with a secondary diagnosis of BD, which may account for the observed difference in in-hospital mortality.

5. Study Limitations

The presented article is a retrospective study. Thus, the main limitation of this study is the use of secondary data, as the information in the administrative database was not collected with the intention of this investigation.

As mentioned in the introduction of this study, the use of antipsychotic drugs is associated with an increased risk of PE [16-22]. However, in the database used for this study, we could not access information regarding the medication prescribed to patients hospitalized with PE. Therefore, this study has the limitation of not analyzing this highly relevant risk factor due to lack of access, considering that BD patients are frequently treated with antipsychotic drugs.
According to the ESC guidelines [39], only a small subset of patients require reperfusion therapy (thrombolysis/thrombectomy/catheter directed therapy): it is the standard of care for high risk patients and might be used as rescue therapy for intermediate-high risk patients who worsen on anticoagulation. Intermediate low and low risk patients are treated with anticoagulation [39].
As previously mentioned, we do not have access to patient medication data in the database used, which means we cannot determine the number of patients treated with anticoagulation, either in the group of patients with BD or in the group without this secondary diagnosis. This represents another limitation of this study, as it prevents a comprehensive analysis of the treatment approaches used for these patients.

In this study, we were only able to gather 92 hospitalized patients with both a diagnosis of PE and BD. As mentioned, BD and PE events are rare. However, the sample size is small, and the ability to obtain reproducible and significant results is also limited.

Administrative databases offer valuable and broadly applicable information suitable for descriptive studies such as this one. However, it is essential to consider that the accuracy of all recorded variables in these databases relies on the clinician's diagnostic precision and proper documentation. In Portugal, diagnostic and procedure coding is exclusively conducted by trained medical doctors, which enhances the quality of our data.

This study is restricted to hospitalizations in mainland public Portuguese hospitals and does not include information from private-sector hospitals, outpatient clinics, and primary care encounters. Consequently, this study may not reflect the reality of all Portuguese patients diagnosed with PE and BD.

6. Conclusion

This is the first study aimed at correlating BD and PE in Portuguese patients, as no similar studies are currently available in the international scientific literature.

This phenomenon must be studied in BD patients to promote prophylactic and preventive measures for PE in these individuals. Additionally, this study could alert healthcare professionals treating BD patients to the risk of PE, leading to an earlier diagnosis and treatment. Although it could not be studied in this sample, it is of great importance to further clarify if and how PE risk can be increased by BD medication, as it would have broad treatment implications, namely either switching BD medication or the need to prolong anticoagulation if the first option is not feasible.

We found that hospitalized patients with both PE and BD are predominantly female and younger than the general population diagnosed with PE. When compared to patients hospitalized for PE without a secondary diagnosis of BD, the BD group shows a significantly higher prevalence of obesity and tobacco use, both factors associated with an increased risk of PE. Therefore, we can infer that the Portuguese patients with BD in this study are diagnosed with PE earlier than the general population with this condition and have a higher prevalence of some risk factors for this event. This suggests a possible correlation between BD and an increased risk of PE.

Further research is needed, particularly with access to a larger study sample, on the association between BD and PE in Portuguese patients. This would help confirm this correlation and relate it to other sociodemographic factors, comorbidities, and treatment approaches for these patients.

Author Contributions: author Inês Souto Silva participated in all phases of the study. Authors Inês Souto Silva and Alberto Freitas undertook the statistical analysis. Author Manuel Gonçalves-Pinho participated in the study design and the review and editing of the whole article. Author Inês Albuquerque participated in the clinical analysis of the paper. All authors contributed to and have approved the final manuscript.

Conflict of interest: The authors declare no conflicts of interest.

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Ethics Approval: The ethics committee of the Faculty of Medicine of the University of Porto approved this project on October 31, 2024. The *Administração Central do Sistema de Saúde I.P.* (ACSS) provided an anonymized administrative database regarding mainland Portuguese hospitalizations to CINTESIS/FMUP and approved its use for research purposes. The database is anonymous. Informed consent is not required, as we used an administrative database created for hospital billing purposes, without access to patient identification.

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Variables		Total PE hospitalizations		P value
		With BD (n=92)	**Without BD** (n=22048)	
Sex [N(%)]	Male	33 (35.9%)	8591 (39.0%)	0.543[A)]
	Female	59 (64.1%)	13457 (61.0%)	
Age at admission (mean ± SD)		61.3 ± 13.3	70 ± 16.4	<0.01*[B)]
Length of Stay [median (P25-P75)]		9 (7-16)	10 (6-15)	0.870[C)]
In-hospital mortality [N(%)]	Yes	8 (8.7%)	2885 (13.1%)	0.213[A)]
	No	84 (91.3%)	19163 (86.9%)	

Table 1: Analysis of sociodemographic data in the study population

A) Pearson Chi square test
B) Independent sample T test
C) Mann-Whitney U test

Variables		Total PE hospitalizations		P value
		With BD (n=92)	Without BD (n=22048)	
Obesity [a)] [N(%)]	Yes	26 (28.3%)	2829 (12.8%)	<0.001*[I)]
	No	66 (71.7%)	19219 (87.2%)	
Type 2 Diabetes[d)] [N(%)]	Yes	13 (14.1%)	3971 (18.0%)	0.334[I)]
	No	79 (85.9%)	18077 (82.0%)	
Hypertension[e)] [N(%)]	Yes	38 (41.3%)	10766 (48.8%)	0.150[I)]
	No	54 (58.7%)	11282 (51.2%)	
Hyperlipidemia[f)] [N(%)]	Yes	13 (14.1%)	4610 (20.9%)	0.110[I)]
	No	79 (85.9%)	17438 (79.1%)	
Tobacco use[g)] [N(%)]	Yes	20 (21.7%)	1981 (9.0%)	<0.001*[I)]
	No	72 (78.3%)	20067 (91.0%)	
Alcohol abuse[h)] [N(%)]	Yes	1 (1.1%)	96 (0.4%)	0.333[II)]
	No	91 (98.9%)	21952 (99.6%)	

Table 2: Analysis of comorbidities in the study population

a) Coded as ICD-9-CM code 278.0
b) Coded as ICD-9-CM code 250.x
c) Coded as ICD-9-CM code 431, 432, 434.x and 435.x

d) Coded as ICD-9-CM code 412 and 410.x
e) Coded as ICD-9-CM code 401.x- 405.x
f) Coded as ICD-9-CM code 272.0-272.4
g) Coded as ICD-9-CM code 305.1, V15.82
h) Coded as ICD-9-CM code 305.0

I) Pearson Chi square test
II) Fisher's exact test

Variables		Total PE hospitalizations		P value
		With BD (n=92)	Without BD (n=22048)	
Infusion of thrombolytic agent [N(%)][1]	Yes	7 (7.6%)	1132 (5.1%)	0.241[I)]
	No	85 (92.4%)	20916 (94.9%)	
Vena cava filter [N(%)][2]	Yes	0 (0.0%)	92 (0.4%)	1[II)]
	No	92 (100.0%)	21956 (99.6%)	
Pulmonary Embolectomy [N(%)][3]	Yes	0 (0.0%)	9 (0.0%)	1[II)]
	No	92 (100.0%)	22039 (0.0%)	
Extracorporeal membrane oxygenation [N(%)][4]	Yes	0 (0.0%)	4 (0.0%)	1[II)]
	No	92 (100.0%)	22044 (100.0%)	

Table 3: Analysis of treatment options in the study population
1 Coded as ICD-9-CM code 99.10
2 Coded as ICD-9-CM code 38.7
3 Coded as ICD-9-CM code 38.05
4 Coded as ICD-9-CM code 39.65

I) Pearson Chi square test
II) Fisher's exact test

APPENDIX

Reporting guidelines RECORD 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	Page 6 and 7 – "We performed an observational retrospective study"	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.	Page 6 and 7 – "We performed an observational retrospective study"
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 8 "Although many studies show an association between BD and PE, there are no studies on a link between these conditions in Portuguese patients."		Page 8 "Although many studies show an association between BD and PE, there are no studies on a link between these conditions in Portuguese patients."
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 9 "The primary aim of this study is to describe a perspective of BD and PE in a nationwide Portuguese hospitalization database."		Page 9 "The primary aim of this study is to describe a perspective of BD and PE in a nationwide Portuguese

					hospitalization database."
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 9 - "We conducted a retrospective observational study using a national hospitalization database that gathers clinical and administrative data from all hospitalizations of patients ≥18 years old occurring in Portuguese mainland public hospitals, with discharges from 2008 to 2015."		Page 9 - "We conducted a retrospective observational study using a national hospitalization database that gathers clinical and administrative data from all hospitalizations of patients ≥18 years old occurring in Portuguese mainland public hospitals, with discharges from 2008 to 2015."
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 9 - "[…] all hospitalizations of patients ≥18 years old occurring in Portuguese mainland public hospitals, with discharges from 2008 to 2015."		Page 9 - "[…] all hospitalizations of patients ≥18 years old occurring in Portuguese mainland public hospitals, with discharges from 2008 to 2015."

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	Page 9 - "All hospitalizations with a primary diagnosis of PE registered from 2008 to 2015 were selected using the codes 415.1x. BD was considered a secondary diagnosis and patients with the diagnosis of BD were selected using the codes 296.xx"	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.	Page 9 - "All hospitalizations with a primary diagnosis of PE registered from 2008 to 2015 were selected using the codes 415.1x. BD was considered a secondary diagnosis and patients with the diagnosis of BD were selected using the codes 296.xx"
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 9 – "Other clinical variables were analysed in both groups – namely, the diagnosis of obesity (278.0), type 2 diabetes (250.x), hypertension (401.x-405.x), hyperlipidaemia (272.0-272.4), tobacco use (305.1, V15.82) and alcohol abuse (305.0)."	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 9 – "Other clinical variables were analysed in both groups – namely, the diagnosis of obesity (278.0), type 2 diabetes (250.x), hypertension (401.x-405.x), hyperlipidaemia (272.0-272.4), tobacco use (305.1, V15.82) and alcohol abuse (305.0)."
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	Page 16 – Table 1 "Analysis of sociodemographic data in the study population"		Page 16 – Table 1 "Analysis of sociodemographic data in the study population"

Bias	9	Describe any efforts to address potential sources of bias	Not applicable		Not applicable
Study size	10	Explain how the study size was arrived at	Not applicable – a study size was not calculated		Not applicable – a study size was not calculated
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Pages 16 and 17 – Tables 1, 2 and 3		Pages 16 and 17 – Tables 1, 2 and 3
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (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	Page 9 – "Descriptive statistical analyses, independent sample t-tests and Chi-squared tests were performed using IBM SPSS Statistics v.29 (Armonk, NY: IBM Corp)."		Page 9 – "Descriptive statistical analyses, independent sample t-tests and Chi-squared tests were performed using IBM SPSS Statistics v.29 (Armonk, NY: IBM Corp)."
Data access and cleaning methods		..	Page 9 "All hospitalizations with a primary diagnosis of PE registered from 2008 to 2015 were selected using the codes 415.1x."	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page 9 "All hospitalizations with a primary diagnosis of PE registered from 2008 to 2015 were selected using the codes 415.1x."

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..	Not applicable – only one database was used	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.	Not applicable – only one database was used
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	Page 10 "A total of 22140 hospitalizations with a primary diagnosis of PE were retrieved from a national hospitalization database, with discharges between 2008 and 2015. Among these hospitalizations, 92 had a secondary diagnosis of BD"	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.	Page 10 "A total of 22140 hospitalizations with a primary diagnosis of PE were retrieved from a national hospitalization database, with discharges between 2008 and 2015. Among these hospitalizations, 92 had a secondary diagnosis of BD"
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 (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Page 16 – Table 1 "Analysis of sociodemographic data in the study population"		Page 16 – Table 1 "Analysis of sociodemographic data in the study population"
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	Page 16 and 17 – Tables 1, 2 and 3		Page 16 and 17 – Tables 1, 2 and 3

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
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	Page 10 "The mean age at admission was approximately 61 years for the BD group and 70 years for the non-BD group." "Regarding comorbidity variables, the group with comorbid BD has a higher percentage of obesity and tobacco use"		Page 10 "The mean age at admission was approximately 61 years for the BD group and 70 years for the non-BD group." "Regarding comorbidity variables, the group with comorbid BD has a higher percentage of obesity and tobacco use"
Other analyses	17	Report other analyses done— e.g., analyses of subgroups and interactions, and sensitivity analyses	Not applicable – other analyses were not performed		Not applicable – other analyses were not performed
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 10 and 11 "The median age at admission for the BD group was significantly lower when compared to the non-BD group."		Page 10 and 11 "The median age at admission for the BD group was significantly lower when compared to the non-BD group."
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	Page 12 "this study has the limitation of not analyzing this highly relevant risk factor due to lack of access, considering that BD patients are frequently treated with antipsychotic drugs."	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.	Page 12 "this study has the limitation of not analyzing this highly relevant risk factor due to lack of access, considering that BD patients are frequently treated with antipsychotic drugs."

Interpretation	20	Give a cautious overall interpretation of results considering objectives,	Page 10 and 11 "The earlier occurrence of PE in patients with BD could indicate that BD contributes to a more premature development of PE in these individuals. This association can be further explained by the significantly higher register of obesity and tobacco use in BD patients, as presented in our findings."		Page 10 and 11 "The earlier occurrence of PE in patients with BD could indicate that BD contributes to a more premature development of PE in these individuals. This association can be further explained by the significantly higher register of obesity and tobacco use in BD patients, as presented in our findings."
		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13 "Further research is needed, particularly with access to a larger study sample, on the association between BD and PE in Portuguese patients."		Page 13 "Further research is needed, particularly with access to a larger study sample, on the association between BD and PE in Portuguese 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	Page 14 "this study did not receive any funding."		Page 14 "this study did not receive any funding."
Accessibility of protocol, raw data, and programming code		..	Page 6 – contact corresponding author	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 6 – contact corresponding author

*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.

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Título do projeto/ Project title: Perturbação Afetiva Bipolar e Tromboembolismo Pulmonar: um Estudo Observacional Retrospetivo de base na população Portuguesa (2008-2015)

Investigador/ Researcher: Inês Silva

Parecer/ Rapport:

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Relatora: Prof.ª Doutora Ivone Duarte

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