Registered Report

Research protocol: the impact of peptic ulcers on patients with chronic obstructive pulmonary disease

Protocolo da pesquisa: impacto da presença de úlcera péptica em portadores de doença pulmonar obstrutiva crônica

Karla Ramos Melo Oliveira[1]
Juliana Santana Montalvão Galliza[2]
Aquiles Assunção Camelier[3]
Fernanda Warken Rosa[4]

[1]Corresponding author. Escola Bahiana de Medicina e Saúde Pública (Salvador). Bahia, Brazil. karlamelo.pos@bahiana.edu.br
[2-3]Escola Bahiana de Medicina e Saúde Pública (Salvador). Bahia, Brazil. juliana_galizza9@hotmail.com, aquilescamelier@bahiana.edu.com.br
[4]Universidade do Estado da Bahia (Salvador). Bahia, Brazil. fcamelier@uneb.br

ABSTRACT | INTRODUCTION: Among important non-communicable diseases in Brazil, Chronic Obstructive Pulmonary Disease (COPD) has been emphasized due to its association with smoking, a highly prevalent habit worldwide. Of several comorbidities strongly associated with COPD, peptic ulcer disease has been linked to smoking. The present descriptive study involving patients with COPD aimed to investigate the prevalence of gastroduodenal peptic ulcers, their impact on the quality of life of affected patients and verify associations between smoking and peptic ulcers. **MATERIALS AND METHODS:** The patients to be studied will be seen on an outpatient basis at the pulmonology service of the Bahia State University (UNEB). All patients will receive specific treatment for their condition after undergoing staging following the GOLD (Global Initiative for Obstructive Lung Disease) consensus and will answer validated questionnaires containing questions on health conditions, coexisting diseases, and current treatment use, as well as provide other information to assess the quality of life and flare-ups. **SAMPLE:** A retrospective analysis of data from 150 patients stored at the Exercise Physiology Laboratory, Department of Life Sciences (UNEB), will be retrospectively analyzed. Statistical analysis will be performed using Student's t-test, chi-squared, and multivariate regression analysis where appropriate, with results presented descriptively for the variables of interest; P values <0.05 will be considered significant. All analyzed data will be exported and analyzed by SPSS software v.26 (IBM).

KEYWORDS: COPD. Peptic ulcer. Gastroduodenal ulcer. Quality of life

RESUMO | INTRODUÇÃO: Dentro das doenças não transmissíveis em destaque no nosso país, a Doença Pulmonar Obstrutiva Crônica (DPOC) ganha ênfase por sua relação com o tabagismo, hábito de elevada prevalência em todo o mundo. Associada a DPOC ocorrem diversas comorbidades bem estabelecidas, sendo uma delas a úlcera péptica, conhecidamente relacionada ao hábito de fumar. Nesse estudo descritivo de pacientes portadores de DPOC, temos como objetivo demonstrar a prevalência de úlcera péptica gastroduodenal, sua relação com o tabagismo, seu impacto na qualidade de vida e exacerbações nesses pacientes. **MATERIAIS E MÉTODOS:** os pacientes estudados serão pacientes em acompanhamento ambulatorial no serviço de pneumologia em tratamento específico para sua condição na Universidade do Estado da Bahia (UNEB), estadiados de acordo com o consenso GOLD (*Global Initiative for Obstructive Lung Disease*) e responderão a questionários validados com perguntas sobre suas condições de saúde, doenças coexistentes (incluindo úlcera péptica), tratamento em uso, além de dados capazes de avaliar a qualidade de vida desses pacientes. **AMOSTRA:** serão obtidos dados presentes em banco de informações do Laboratório de Fisiologia do Exercício do Departamento de Ciências da vida da UNEB de 150 pacientes de forma retrospectiva. Os resultados do estudo serão apresentados sob forma de estatística descritiva das variáveis de interesse, teste T de Student, Qui-quadrado e análise multivariada quando apropriados. Serão considerados significantes o valor de P<0,05. As informações estudadas serão exportadas e analisadas pelo programa IBM SPSS versão 26.

PALAVRAS-CHAVE: DPOC. Úlcera péptica. Úlcera gastroduodenal. Qualidade de vida.

Submitted 22/07/2021, Accepted 08/02/2022, Published 04/27/2022
J. Évid-Based Healthc., Salvador, 2022;4:e3984
http://dx.doi.org/10.17267/2675-021Xevidence.2022.e3984
ISSN: 2675-021X
Assigned editor: Luis Claudio Correia

How to cite this article: Oliveira KRM, Galliza JSM, Camelier AA, Rosa FW. Research protocol: the impact of peptic ulcers on patients with chronic obstructive pulmonary disease. J Évid-Based Healthc. 2022;4:e3984. http://dx.doi.org/10.17267/2675-021Xevidence.2022.e3984

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common disease, characterized by chronic and persistent obstruction of the small and medium-sized airways, generally of a progressive nature (GOLD 2021- Global Initiative for Obstructive Lung Disease).[1] It is the third leading cause of death in the world according to the World Health Organization.[2] In the national literature, the most important COPD prevalence study carried out in Brazil, the PLATINO study (Latin American Project for Obstruction Research), showed a COPD prevalence of 15.8% in the city of São Paulo.[3] It is associated with a pulmonary inflammatory reaction caused mainly by exposure to tobacco smoke, occupational exposure and biomass combustion.[4-5] Because it is heterogeneous in clinical aspects and in its evolution, it may or may not be accompanied by symptoms such as dyspnea, cough and expectoration, exacerbations and comorbidities.[5] In addition to changes in the respiratory system, the disease also causes systemic effects, and because it is a chronic inflammatory disease, the coexistence of more than one morbidity is frequent.[6] Studies show that approximately 80% of individuals with COPD are likely to have at least one comorbid disease[7], resulting in different clinical pictures, with functional decline, reduced quality of life, worsened prognosis, difficulty in managing the disease, and increased hospitalizations and mortality.[8-9] There is also an association between comorbid diseases and frequent exacerbations.[10-11] However, the pathophysiology that explains these relationships has not been fully understood.

Several associations between this illness and specific comorbidities are shown. In our study, we will evaluate the relationship between smoking, the presence of Chronic Obstructive Pulmonary Disease, and peptic ulcer disease, which involves known pathophysiologic mechanisms that contribute to gastric and duodenal ulcer formation by increasing gastric acid secretion or weakening the mucosal protective barrier.[12]

A large American population-based study shows a prevalence of peptic ulcer disease of 8.4% and in patients with COPD a high risk for ulcer occurrence with OR 2.34.[13] Peptic ulcer complicated with gastrointestinal bleeding in individuals with COPD was cited in a population-based study in Taiwan[14], rebleeding in these patients was more frequent.[15]

Thus, it is important to identify the relationship between peptic ulcer disease and COPD, to estimate the respective frequencies, as well as to understand the impact of these diseases on the health of the individual. This theme, despite having already been studied by other researchers, still needs better description in the local environment of Brazil and in the state of Bahia, being of great relevance the study in the population assisted by the service.[16] Therefore, the objective of the present study is to demonstrate the prevalence of gastroduodenal peptic ulcer disease, its impact on the quality of life of these patients, as well as to verify if there is an association between smoking burden, exacerbations and peptic ulcer disease in patients with COPD.

Objectives

Primary:

- To describe the prevalence of peptic ulcer disease in patients with COPD (Chronic Obstructive Pulmonary Disease).

Secondary:

- To verify whether there is an association between exposure and smoking load and the occurrence of peptic ulcer in patients with COPD;
- To verify whether there is an association between a history of COPD exacerbations and the presence of peptic ulcer disease;
- To identify whether the presence of peptic ulcer disease is associated with different levels of perceived quality of life in COPD patients.

Methods

This is a descriptive, observational, retrospective cross-sectional study of data collection obtained from the medical record of patients previously diagnosed with COPD in regular medical follow-up and seen at the Exercise Physiology outpatient clinic in the Department of Life Sciences of the *Universidade Estadual da Bahia* (UNEB) between January and December 2019.

Although the study is based on the retrospective collection of existing data in medical records, it is important to detail that the registration of the variables that were contained in the database had been, at a time prior to the conception of this study, performed after routine medical care, in a previously scheduled appointment, when the patients were informed about the current research and then their participation was offered. Those who participated in the research signed the Free and Informed Consent Form and answered the proposed questionnaires. We will have only one group for the study respecting the inclusion and exclusion criteria. Those who did not agree to participate in the study continued their routine clinical follow-up without any harm to them.

Inclusion Criteria

- Age over 40 years;
- Diagnosis of COPD according to GOLD 2021 (Global Initiative for Obstructive Lung Disease)[1];
- Clinical stability according to the following criteria: no hospitalization for any reason during the study period or 30 days prior to initiation of the study; no worsening of symptoms, as assessed by a COPD Assessment Test (CAT) symptom questionnaire;
- Chart 1 and no change in FEV1 < 10% (in either direction) from baseline; no change in dosage of any medication taken by the patient during the study.

Exclusion Criteria

- Presence of chronic respiratory diseases other than COPD or a diagnosis of asthma;
- Non-lung diseases that were disabling, severe or difficult to control;
- Inability to read and understand texts in Portuguese without the help of others, regardless of the level of formal education.

Research procedures

Classification of COPD

The patients with COPD will be divided according to the spirometric and clinical classification of COPD (described in Table 1) and according to their clinical group (Table 2)

Questionnaires

The following questionnaires, validated for the Portuguese language, will be used: CAT - Chart 1 (eight questions with scores from 0 to 5, with a minimum score of 0 and a maximum of 40 points); mMRC - Chart 2 (quantifies dyspnea in grades from 0 minimum to 4 maximum); AQ20 "Airways questionnaire 20" - Chart 3 twenty questions about the quality of life, ranging from 0 (excellent quality of life) to 100 points (worst quality of life). Questionnaires on the presence of comorbidities Charlson index - Figure 1.

Sample Calculation

Our study will be conducted on medical record data collected from a previously selected sample of patients with Chronic Obstructive Pulmonary Disease from a specialized outpatient clinic. This is a convenience sample contained in the 150 (one hundred and fifty) patients in the database. However, the authors of the present study retrospectively performed the sample calculation in a specific calculator (WinPep Version 11.65 of 2016), to increase the accuracy of the certainty of the conclusions regarding the acceptance or rejection of the null hypothesis. We followed the primary objective of the descriptive study for estimation of the proportion of the presence of peptic ulcers with a 95% confidence interval, an acceptable difference of 5%, and an assumed proportion of 10%, obtaining the result of 139 patients. We emphasize that our data were based on previous studies of the prevalence of peptic ulcer occurrence in the general population around 10% and we estimated that our specific population would have 5% more peptic ulcer occurrence. We did not consider the patient loss in this convenience sample.

Study Variables

Date of assessment, sex, hospital record, date of hospitalization, date of discharge from the service, date of birth, calculated age (from date of onset of care), measured weight, ethnicity, education, municipality of residence, and occupation. Presence of previous comorbidities or diseases (Hypertension, Heart failure, Arrhythmias, Coronary heart disease, Diabetes, Liver disease, Peptic ulcer disease, Chronic neurological or neuromuscular disease, Immunodeficiency, Chronic HIV infection non-dialysis kidney disease, dialysis kidney disease, asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, bronchiectasis, allergic rhinitis, obstructive sleep apnea syndrome, cystic fibrosis, neoplasia (solid or hematological tumor) and primary site. Use of previous medications (IECA or ARB), other antihypertensives, oral hypoglycemic agents, insulin, corticosteroids, bronchodilators, immunosuppressants, statins, and platelet antagonists, anticoagulants. Type of exposure to tobacco and other smoke, time, and burden of exposure. Laboratory tests in documents or databases at the time of admission to the service: sodium, potassium, urea, creatinine, troponin, d-dimer, BNP (natriuretic peptide), blood glucose, CRP (C- Reactive Protein), LDH (Lactate dehydrogenase), triglycerides, ferritin, TGO, TGP, total bilirubin, direct bilirubin, indirect bilirubin, prothrombin time and INR, TTPa, Fibrinogen, arterial and venous blood gas, pH, PCO2, PO2, PO2/FIO2, HCO3, Sat O2, lactate, complete blood count, hemoglobin, hematocrit. Dates and results of imaging and pulmonary function tests, dates of performance, and reports: spirometry, chest X-ray and CT scan, ultrasound, CT and MRI scans of the skull, chest, or abdomen, echocardiography, cardiac magnetic resonance imaging, venous Doppler ultrasound of the lower limbs. Pharmacological therapies associated with respiratory diseases and mentioned in the documents/databases. Hospital and emergency department outcomes and their dates: number of emergency department visits and hospital admissions.

Statistical analysis

This will be performed with IBM SPSS version 26 software. The primary outcome, peptic ulcer frequency, as well as general and demographic data of COPD patients will be described as absolute number and proportion with confidence interval or the mean and standard deviation or median and interquartile range. Smoking-related data will be described as mean and standard deviation or median and interquartile range. Comparison of variables between peptic ulcer and non-peptic ulcer groups will be described as a proportion or mean and standard deviation. For dichotomous variables, we will use the chi-square test. In the analysis of the secondary outcomes, to test for the presence of ulcer and smoking burden, exacerbations, and quality of life, we will use the unpaired t-test (or Mann-Whitney). We will perform a multivariate analysis of peptic ulcer occurrence with the confounding variables: age and smoking, related to an ulcer as independent factors. We will consider a p-value < 0.05 statistically significant. Multiple imputations will be performed For more than 5% missing data values of the variables of interest.

Ethical aspects

Work approved by the Research Ethics Committee of the Universidade Estadual da Bahia (UNEB) on 20/10/2021, CAEE 37222620.0.0000.0057. In this study, the Informed Consent Form was not required.

Acknowledgments

We thank the Universidade Estadual da Bahia for providing the data for the study. We thank the Escola Bahiana de Medicina e Saúde Pública for their support in the execution and publication of the study. The author Camelier AA thanks Fundação Maria Emília (http://mariaemilia.org.br/) for supporting the research.

Authors' Contributions

Oliveira KRM was responsible for the conception, design, and writing of the study. Galliza JSM was responsible for the conception and design of the study. Rosa FW responsible for the study conception (data collection form), data collection, and database creation. Camelier AA was responsible for the conception of the study, data collection and database construction, design, reading, and approval of the final version of the manuscript.

Conflicts Of Interest

No financial, legal, or political conflicts involving third parties such as government, corporations, and private foundations have been declared for any aspect of this work, including funding, study design, manuscript preparation, or statistical analysis.

References

1. The Global Initiative for Chronic Obstructive Lung Disease. [Internet]. 2021 [cited 2021 Jul 15]. Available from: https://goldcopd.org

2. World Health Organization. Global Health Estimates: Life expectancy and leading causes of death and disability [Internet]. [cited 2021 Nov 7]. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates

3. Menezes AMB, Jardim JR, Pérez-Padilla R, Camelier A, Rosa F, Nascimento O, et al. Prevalence of chronic obstructive pulmonary disease and associated factors: the PLATINO Study in São Paulo, Brazil. Cad Saúde Pública. 2005;21(5):1565–73. https://doi.org/10.1590/S0102-311X2005000500030

4. Portaria SAS/MS nº 609, de 6 de junho de 2013 (Brazil). Aprova o Protocolo Clínico e Diretrizes Terapêuticas – Doença Pulmonar Obstrutiva Crônica. [Internet]. Diário Oficial da Nação. 2013 Jun. Available from: http://www.saude.mt.gov.br/arquivo/9751

5. Golpe R, Martín-Robles I, Sanjuán-López P, Cano-Jiménez E, Castro-Añon O, Mengual-Macenlle N, et al. Prevalence of major comorbidities in chronic obstructive pulmonary disease caused by biomass smoke or tobacco. Respiration. 2017;94(1):38–44. https://doi.org/10.1159/000472718

6.Miller J, Edwards LD, Agustí A, Bakke P, Calverley PMA, Celli B, et al. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. Respir Med. 2013;107(9):1376–84. https://doi.org/10.1016/j.rmed.2013.05.001

7. Rubinsztajn R, Przybyłowski T, Grabicki M, Karwat K, Maskey-Warzęchowska M, Batura-Gabryel H, et al. Comorbidities in chronic obstructive pulmonary disease: Results of a national multicenter research project. Adv Clin Exp Med. 2019;28(3):319–24. https://doi.org/10.17219/acem/78024

8. Burney PGJ, Patel J, Newson R, Minelli C, Naghavi M. Global and regional trends in COPD mortality, 1990–2010. 2015;45(5):1239-47. http://dx.doi.org/10.1183/09031936.00142414

9. Westerik JAM, Metting EI, van Boven JFM, Tiersma W, Kocks JWH, Schermer TR. Associations between chronic comorbidity and exacerbation risk in primary care patients with COPD. Respir Res. 2017;18(1):31. https://doi.org/10.1186/s12931-017-0512-2

10. Raherison C, Ouaalaya EH, Bernady A, Casteigt J, Nocent-Eijnani C, Falque L, et al. Comorbidities and COPD severity in a clinic-based cohort. BMC Pulm Med. 2018;18(1):117. https://doi.org/10.1186/s12890-018-0684-7

11. Divo MJ, Casanova C, Marin JM, Pinto-Plata VM, De-Torres JP, Zulueta JJ, et al. COPD comorbidities network. Eur Respir J. 2015;46(3):640–50. https://doi.org/10.1183/09031936.00171614

12. Malfertheiner P, Chan FKL, Mccoll KEL. Peptic ulcer disease. Lancet [Internet]. 2009;374:1449–61. Available from: https://www.jvsmedicscorner.com/Medicine_files/Peptic%20ulcer%20disease%20review_1.pdf

13. Garrow D, Delegge MH. Risk factors for gastrointestinal ulcer disease in the US population. Dig Dis Sci. 2010;55(1):66–72. https://doi.org/10.1007/s10620-008-0708-x

14. Huang KW, Luo JC, Leu HB, Lin HC, Lee FY, Chan WL, et al. Chronic obstructive pulmonary disease: An independent risk factor for peptic ulcer bleeding: A nationwide population-based study. Aliment Pharmacol Ther. 2012;35(7):796–802. https://doi.org/10.1111/j.1365-2036.2012.05028.x

15. Huang KW, Kuan YC, Chi NF, Huang YH, Luo JC, Chien LN. Chronic obstructive pulmonary disease is associated with increased recurrent peptic ulcer bleeding risk. Eur J Intern Med. 2017;37:75–82. https://doi.org/10.1016/j.ejim.2016.09.020

16. Universidade Estadual da Bahia. [Internet]. [cited 2021 Nov 10]. Available from: https://portal.uneb.br/

Annexes

Table 1. Spirometric and clinical classification of the Global Initiative for Obstructive Lung Disease – GOLD (2021)

I: Mild COPD	≥ 80% predicted	At this stage, the patient may not be aware that their lung function is abnormal
II: Moderate COPD	50%≤FEV1 < 80% of predicted	Symptoms progress at this stage, with shortness of breath typically appearing on exertion
III: severe COPD	30% ≤FEV1< 50% of predicted	Shortness of breath typically worsens at this stage and often limits the patient's daily activities. At this stage, exacerbations begin to appear.
IV: very severe COPD	FEV1<30% predicted OR FEV1<50% predicted associated with acute respiratory failure	At this stage, quality of life is appreciably altered, and exacerbations can be life-threatening

Table 2. Classification of COPD according to clinical groups

Risk GOLD		Risk Of Exacerbation
3 e 4	(C) **Less symptoms** **High risk**	(D) **More symptoms** **High risk**
1 e 2	(A) **Less symptoms** **Low risk**	(B) **More symptoms** **Low risk**
	mMRC 0-1 **CAT <10**	**mMRC ≥2** **CAT≥10**
	Symptoms	

http://dx.doi.org/10.17267/2675-021Xevidence.2022.e3984 | ISSN: 2675-021X

Table 3. COPD classification according to clinical group

RESPIRATORY SYMPTOMS - COPD ASSESSMENT TEST (CAT) Score from 0 to 5
01. Do you have a COUGH? I never cough [0] [1] [2] [3] [4] [5] I cough all the time
02. Do you have phlegm? I have none [0] [1] [2] [3] [4] [5] My chest is full of phlegm
03. Do you feel pressure in your chest? I don't have any [0] [1] [2] [3] [4] [5] I feel a lot of pressure in my chest
04. Do you feel short of breath? I do not feel short of breath when going up a slope or a flight of stairs [0] [1] [2] [3] [4] [5] I am very short of breath when going up a slope or a flight of stairs
05. Do you feel limited in household activities? I do not feel any limitation [0] [1] [2] [3] [4] [5] I feel a lot of limitation in my home activities
06. Confidence to leave the house? I feel confident leaving the house despite my lung disease [0] [1] [2] [3] [4] [5] I do not feel confident leaving the house because of my lung disease
07. Quality of sleep I sleep soundly despite my lung disease [0] [1] [2] [3] [4] [5] I don't sleep soundly because of my lung disease
08. Energy I have a lot of energy (I have the energy) [0] [1] [2] [3] [4] [5] I don't have much energy (I don't have the energy)

Score:
6 to 10 points: light
11 to 20 points: moderate
21 to 30 points: serious
31 to 40 points: very severe

Table 4. Modified Medical Research Council Dyspnea Scale, adapted to Portuguese (mMRC)

Degree	
□ 0	Shortness of breath arises when performing intense physical activity (running, swimming, playing sports).
□ I	Shortness of breath arises when hurriedly walking on the level or going uphill
□ II	Walks more slowly than people of the same age due to shortness of breath, or when walking on level ground, at your own pace, you have to stop to breathe.
□ III	After walking a few meters or a few minutes on the level, you have to stop to breathe.
□ IV	Shortness of breath prevents you from leaving your home or shortness of breath occurs when you change clothes.

Subtitle: Modified Medical Research Council dyspnea scale, adapted for the Portuguese language (mMRC).

Table 5. Airway Questionnaire 20 (AQ20)

The following questions concern the effect of your lung disease on your daily life. Please answer □Yes, □ No or □ Not applicable, for each item, by marking with an 'X' in the space provided. Do not leave answers blank.

Question	Yes	No	Not applicable
1. Do you have a coughing attack during the day?			
2. Do you often feel tired because of your lung disease?			
3. Do you feel short of breath when gardening because of your lung disease?			
4. Would you bother going to a friend's house if there was something there that could cause a flare-up of lung symptoms?			
5. Do you have lung symptoms when exposed to strong smells, cigarette smoke or perfume?			
6. Is your partner uncomfortable with your lung disease?			
7. Do you get short of breath while trying to sleep?			
8. Are you worried about the long-term effects on your health caused by the medications you have to take because of your lung disease?			
9. Do your lung symptoms get worse when you are upset?			
10. Are there times when you have difficulty walking around the house because of your lung disease?			
11. Do you feel short of breath for your activities at work because of your lung problems?			
12. Do you feel short of breath when you climb stairs because of your lung disease?			
13. Due to your lung disease, do you feel short of breath to carry out household chores?			
14. Because of your lung disease, do you have to come home earlier than other people after an evening program?			
15. Do you have shortness of breath when laughing because of your lung disease?			
16. Do you often feel impatient because of your lung disease?			
17. Due to your lung disease, do you feel that you cannot fully enjoy your life?			
18. Because of your lung disease, do you feel very weak after a cold?			
19. Do you have a constant feeling of a heaviness in your chest?			
20. Do you worry a lot about your lung disease?			

Score: "Yes" with a value equal to 1 point and "No" and "Does not apply" with a value equal to 0 point
Excellent quality of life: 0 points / Worst quality of life: 100 points

Figure 1. Charlson comorbidity index: weighting of clinical conditions present among secondary diagnoses

Weight	Clinical Condition
1	Myocardial infarction Congestive heart failure Peripheral Vascular Disease Insanity Cerebrovascular disease Chronic lung disease Connective tissue disease Mild, uncomplicated diabetes Peptic ulcer
2	Hemiplegia Moderate or severe kidney disease Diabetes with complication Tumor Leukemia
3	Moderate or severe liver disease
6	Malignant tumor, metastasis AIDS

Flowchart (Study protocol)