ORIGINAL ARTICLE

Mortality predictors in patients with chronic obstructive pulmonary disease in Colombia: A case-control study

Predictores de mortalidad en pacientes con enfermedad pulmonar obstructiva cronica en Colombia: Un estudio de casos y controles

Mariana Blanco-Betancur[1], Natalia Clavijo-Lozano[2,a], Manuel A. Martinez-Muñoz[1], Juan Orozco-Hernandez[1,2,4,b], Manuel Pacheco-Gallego[3], Jose Babativa-Marquez[4], Angela Piamba-Valencia[5], Christian Burbano-Gomez[5], Maria Rey-Guerra[1], Jorge Sanchez-Duque[2,5,c]

[1]Epidemiology, Health and Violence Research Group. Department of Community Medicine, Faculty of Health Sciences, Universidad Tecnologica de Pereira. Pereira, Risaralda, Colombia.
[2]GeriaUNAL Research Group – GREEK. Department of Internal Medicine, Faculty of Medicine, Universidad Nacional de Colombia. Bogota D.C., Colombia.
[3]Division of Pneumology, Comfamiliar Clinic - Department of Internal Medicine, Universidad Tecnologica de Pereira. Pereira, Risaralda, Colombia.
[4]Master's Degree in Epidemiology, Faculty of Health Sciences, Fundación Universitaria del Area Andina. Bogota, Cundinamarca, Colombia.
[5]Health, Family and Society research group. Department of Social Medicine and Family Health, Faculty of Health Sciences, Universidad del Cauca. Popayan, Cauca, Colombia.
[a]Resident of Internal Medicine; [b]Neurology Resident; [c]Geriatric Resident.

Cite as: Blanco-Betancur M, Clavijo-Lozano N, Martinez-Muñoz MA, Orozco-Hernandez J, Pacheco-Gallego M, Babativa-Marquez J, Piamba-Valencia A, Burbano-Gomez C, Rey-Guerra M, Sanchez-Duque J. Predictores de mortalidad en pacientes con enfermedad pulmonar obstructiva cronica en Colombia: un estudio de casos y controles. Rev. Peru. Investig. Salud. [Internet]; 2023; 7(1): 17-25. https://doi.org/10.35839/repis.17.1.1680

Correspondence to: Mariana Blanco Betancur; E-mail: mariana.blanco@utp.edu.co

Orcid: Blanco-Betancur M.: https://orcid.org/0000-0002-0666-8701
Clavijo-Lozano N.: https://orcid.org/0000-0002-3607-3311
Martínez-Muñoz M.A.: https://orcid.org/0000-0001-8690-7794
Orozco-Hernández J.P.: https://orcid.org/0000-0002-7089-7824
Pacheco-Gallego M.C.: https://orcid.org/0000-0001-6783-1608
Babativa-Marquez J.G.: https://orcid.org/0000-0002-4989-7459
Piamba-Valencia A.M.: https://orcid.org/0000-0001-9694-7546
Burbano-Gómez C.E.: https://orcid.org/0000-0001-5499-423X
Rey-Guerra M.A.: https://orcid.org/0000-0003-2787-1466
Sánchez-Duque J.A.: https://orcid.org/0000-0002-8913-7729

Conflict of interest: The author denies conflicts of interest.

Financing: Self-financed.

Editor: Jarvis Raraz, UNHEVAL

Received: december 12, 2022
Approved: february 07, 2023
Online: march 03, 2023

Abstract

Objective. The objective of the study was to explore predictive variables of mortality in patients with COPD in Colombia. **Materials and methods**. Case-control study, in adult patients, diagnosed with COPD, treated at the clínica Comfamiliar, Risaralda, from January 1, 2015 to December 31, 2018. Deceased patients were called cases, and the control group was survivors. A data collection instrument validated by expert judgement was used. A multivariate logistic regression analysis was performed, followed by post-modeling analysis for validation. The analyzes were carried out in Stata 14, official version. It was considered significant with p value <0.05. The project was approved by the bioethics committee of the clínica Comfamiliar. **Results**: 230 patients with a diagnosis of COPD were included. The mortality rate was 10%, for which there were 23 cases. In the multivariate analysis, the predictors of mortality were Chronic Kidney Disease (CKD) (OR: 8.2, CI: 2.3-29.2, p = 0.001), presence of severe exacerbation in the last year (OR: 7.4, CI: 2.6-20.8, p <0.001), and hemoglobin in adequate ranges (Hb>12 in women/hb>13 in men) (OR: 0.82, CI: 0.68-0.99, p = 0.047). **Conclusions**: It was observed that CKD, severe exacerbations in the last year, and low hemoglobin values predict mortality in COPD patients in Colombia.

Keywords: COPD, mortality, prediction, survival, respiratory insufficiency. (Source: MeSH BIREME)

Resumen

Objetivo. El objetivo del estudio fue explorar variables predictivas de mortalidad en pacientes con EPOC de Colombia. **Materiales y métodos**. Estudio de casos y controles, en pacientes mayores de edad, con diagnóstico de EPOC, atendidos en la clínica "Comfamiliar", Risaralda, del 1 de enero de 2015 a 31 de diciembre de 2018. Se denominó caso a pacientes fallecidos y el grupo control fueron los supervivientes. Se utilizó un instrumento de recolección de datos validado por juicio de expertos. Se realizó un análisis multivariado de tipo regresión logística y posteriormente análisis post modelamiento para su validación. Los análisis fueron realizados en Stata 14, versión oficial. Se considero significativo con p valor <0,05. El proyecto fue aprobado por el comité de bioética de la clínica Comfamiliar. **Resultados**. Se incluyeron 230 pacientes con diagnóstico de EPOC. La tasa de mortalidad fue de 10%, por lo que se contó con 23 casos. En el análisis multivariado, los factores predictores de mortalidad fueron la Enfermedad Renal Crónica (ERC) (OR: 8,2, IC: 2,3-29,2, p = 0,001), presencia de exacerbación severa el último año (OR: 7,4, IC: 2,6-20,8, p < 0,001), y la hemoglobina en rangos adecuados (Hb>12 in mujeres/hb>13 in hombres) (OR: 0,82, IC: 0,68-0,99, p = 0,047). **Conclusiones**. Se observó que la ERC, exacerbaciones severas el último año y valores bajos de hemoglobina predicen la mortalidad en el paciente con EPOC en Colombia.

Palabras clave: EPOC, mortalidad, predicción, supervivencia, insuficiencia respiratoria. (Fuente: DeCS BIREME)

https://doi.org/10.35839/repis.17.1.1680

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a prevalent and multifactorial condition, with a high burden of morbidity, mortality, and costs for the healthcare system, often associated with tobacco consumption and environmental pollution[1]. Currently, COPD ranks fifth in terms of disease burden and third in global mortality[1,2].

Given the public health implications attributable to COPD, the global interest in identifying risk factors (predictors) for hospitalization and mortality has led to the description of age[3-5], oxygen therapy[3,5,6], number of exacerbations[4,7-10], presence of comorbidities[7,8], body mass index (BMI)[7,8,11], dyspnea[4], hypoxemia[4,5,6], forced expiratory volume in one second (FEV1)[4,8,12], maximum exercise capacity[8,13], renal function[14], and anemia[15-17] as main predictor factors. Additionally, several clinical prediction rules for mortality or exacerbation have been developed, including the most widely used worldwide, the BODE index, which includes BMI, obstruction, dyspnea, and exercise capacity[18]. Other multidimensional models include the DOSE index[19], ADO[20], and SAFE[21].

However, scientific evidence reports contradictory evidence[22] in the behavior of mortality predictor variables, as well as in the statistical significance of predictor indices[23]. Understanding that Colombia has a prevalence of 8.9% of COPD, that mortality predictor factors may be different in high and low-income countries, and that no studies have been conducted to identify mortality predictor variables in COPD in our population, we decided to conduct this study aimed at developing a mortality prognostic model in patients with COPD in Colombia.

Material y métodos

Study design

An analytical observational study of case-control type was conducted.

Study population

The study population was established based on the following criteria. Inclusion criteria: 1) adult patients, 2) diagnosed with COPD confirmed by spirometry, 3) attended at the Comfamiliar Risaralda clinic, 4) from January 1, 2015, to December 31, 2018. Patients who did not have a complete medical history to extract information were excluded. Patients who died during the study were classified as cases. Hospital death certificates and phone calls were used to obtain information on the cause of death. The control group was formed by those surviving patients during the study period. The research coverage focused on the census of patients with a confirmed diagnosis of COPD at the Comfamiliar Risaralda clinic.

Sample and sampling

A sample size adjusted to the mortality variable was calculated[19] with the following parameters: proportion of cases, 26%; 4 controls per case; odds ratio to detect: 7.0; power, 0.8; confidence, 95%. These calculations identified that 23 cases and 92 controls were required. No randomization mechanisms were applied for the selection of patients. The recommendations of STROBE were used for reporting observational studies[24].

Variables

The following relevant variables were obtained in this population:

- Sociodemographic: age, gender, place of residence (urban or rural), employment status, and marital status.
- Clinical: BMI, severity classification of COPD and group according to GOLD guidelines, number of exacerbations of COPD (last year), number of hospitalizations for exacerbation (last year) for COPD, current smoker, former smoker, second-hand smoking, pack-years, exposure to biomass fuel, type of biomass, years of exposure to smoking, comorbidities, clinical phenotypes (according to proposed definitions, spirometry findings, and mortality from any cause.
- Laboratory: recent blood count (absolute leukocyte count, eosinophils, hemoglobin, and hematocrit), creatinine, glomerular filtration rate (GFR), arterial blood gases, carbon monoxide diffusing capacity (DLCO), end-tidal CO2 (ETCO2), six-minute walk test (6MWT), and immunoglobulin E (IgE).
- Imaging: Findings on chest x-ray and high-resolution computed tomography (HRCT).
- Pharmacological and therapeutic: number of inhalers in use, other treatments for COPD (Roflumilast, N-

acetylcysteine, methylxanthines, and azithromycin), number of current medications, current oxygen therapy, vaccination status for Hib (Haemophilus influenzae type B) and Pneumococcus (Streptococcus pneumoniae).

Procedures

Information was obtained from the digital medical records of patients at the Comfamiliar clinic who were enrolled in the lung disease program and had a COPD diagnosis according to ICD-10 codes. Each medical history was individually analyzed by the research team and cataloged using a data collection sheet to control for selection and information biases. Variables with 20% or more missing data were excluded from the study analysis.

Statistical analysis

Quantitative variables were analyzed by calculating descriptive measures such as mean, median, and interquartile range. For qualitative variables, descriptive statistics were calculated from absolute and relative frequencies. Comparisons between the means of continuous variables were made using the Student t-test according to whether they had a normal distribution according to the Shapiro-Wilk/Kolmogorov Smirnov test. Continuous variables with a non-normal distribution were compared using the median test (Mann Whitney U test). The comparison of proportions was performed with the chi-square test or Fisher's exact test. All comparisons were made with a significance level of 5%.

A logistic regression multivariate model was carried out with the possible predictor factors according to the literature and those with a statistical association in the bivariate analysis with a p-value <0.01, for which the stepwise methodology was used for model adjustment. Likewise, the assumptions of homoscedasticity (Levene's test and residual vs predicted value graphs), normality tests, and independence test (Durbin-Watson, which is interpreted as follows: if d<1.18, H0 is rejected, d>1.4 is not rejected, between 1.18 and 1.4 is inconclusive) were evaluated, while the assumption of multicollinearity was verified using the variance inflation factor (VIF) (greater than 10 defines multicollinearity problem). Odds ratios (OR) and their respective 95% confidence intervals were calculated. In addition, the internal validation of the multivariate model (post-model analysis) was evaluated with the number of correctly classified by the model and the area under the receiver operating characteristic curve (AUC-ROC) to evaluate discrimination, and we also performed the Hosmer-Lemeshow test for calibration. The STATA v.14 statistical package licensed for data analysis was used.

Ethical aspects

This research was approved by the Bioethics Committee of the Comfamiliar Clinic, as a "risk-free" study according to resolution 8430 of 1993 issued by the Ministry of Health of Colombia and in accordance with the Helsinki Declaration.

Results

General description

Two hundred and thirty (n=230) patients diagnosed with COPD were included in the study. Fifty-four percent of the patients were male, and the mean age was 72 ± 10 years with a minimum of 44 years and a maximum of 99 years. A high percentage of patients had no history of smoking (n=58; 25%). The most common type of biomass exposure was wood smoke (n=46; 20%). The majority of patients had ≥3 comorbidities (n=149, 66%), and almost half of the patients were in GOLD C/D group (n=107; 46%). Twenty-three patients (10%) died (cases) while two hundred seven patients (90%) did not have this outcome (controls).

Comparison of numerical variables between cases and controls

Although there were no differences in age between cases and controls (p=0.24), cases had a higher number of severe exacerbations in the last year than controls (1 [exacerbation in cases] vs 0 [exacerbation in controls]; p<0.001), had lower survival (38 vs 53 months; p<0.001), lower peripheral eosinophil count (80 vs 200; p=0.005), lower hemoglobin (12.4 vs 14.0; p=0.005), and a lower percentage of hematocrit (40 vs 42; p=0.037) (Table 1).

https://doi.org/10.35839/repis.17.1.1680

Table 1. Analysis of continuous variables in patients with Chronic Obstructive Pulmonary Disease (comparison of patient characteristics).

	Cases (n=23)	Controls (n=207)	p-value
Age (years), mean (SD)	74 ± 10	72 ± 10	0,243*
Number of overall exacerbations, median (IQR)	1 (0-2)	1 (0-2)	0,214†
Number of severe exacerbations, median (IQR)	1 (0-1)	0 (0-0)	**<0,001†**
Number of comorbidities, median (IQR)	3 (2-6)	3 (2-5)	0,214†
Survival time (months), median (IQR)	38 (29-47)	53 (51-54)	**<0,001†**
BMI, median (IQR)	22 (20-26)	24 (22-28)	0,116†
Pack-years, median (IQR)	40 (30-50)	35 (20-50)	0,393†
Number of inhalers in use, median (IQR)	3 (3-4)	3 (2-4)	0,103†
Number of medications in use, median (IQR)	4 (3-7)	4 (3-6)	0,393
Predicted FEV1 (%), median (IQR)	39 (26-53)	47 (37-61)	0,059†
Predicted FVC (%), median (IQR)	63 (53-67)	70 (56-78)	0,189†
6MWT (meters), mean (SD)	319 ± 96	356 ± 121	0,380*
pO2 (mmHg), median (IQR)	56 (43-65)	58 (46-67)	0,735†
pCO2 (mmHg), median (IQR)	44 (38-69)	41 (36-48)	0,119†
Leukocyte count (cells/mm3), median (IQR)	10100 (7730-13300)	8330 (6990-10110)	0,054†
Eosinophil count (cells/mm3), median (IQR)	80 (10-210)	200 (100-350)	**0,005†**
Hemoglobin (g/dL), median (IQR)	12,4 (9,9-13,9)	14,0 (12,6-15,5)	**0,005†**
Hematocrit (%), median (IQR)	40 (33,4-42,8)	42,5 (38-46.5)	**0,037†**
Creatinine (mg/dL), median (IQR)	0,97 (0,67-1,42)	0,9 (0,74-1,08)	0,337†
Estimated GFR (mL/min/1.73 m2), median (IQR)	82 (51-103)	88 (71-101)	0,468†

* Student's T-test. † Mann Whitney U-test. Abbreviations: IQR: interquartile range; SD: standard deviation; BMI: body mass index; 6MWT: six-minute walk test; pO2: partial pressure of oxygen; pCO2: partial pressure of carbon dioxide; eGFR: estimated glomerular filtration rate. All statistically significant associations are highlighted in bold.

Risk factors for mortality

The following variables were identified as risk factors for mortality: chronic kidney disease (OR: 4.8; CI: 1.3-15.6; p=0.001), very severe classification (OR: 4.1; CI: 1.1-13.3; p=0.005), anemia (OR: 4.1; CI: 1.5-11.1; p<0.001), cardiac arrhythmia (OR: 3.9; CI: 1.1-12.2; p=0.006), need for oxygen therapy (OR: 3.8; CI: 1.4-11.4; p=0.002), heart failure (OR: 3.5; CI: 1.1-9.9; p=0.005), GOLD-D group (OR: 2.8; CI: 1.0-7.6; p=0.018) and GOLD-C group (OR: 2.6; CI: 0.9-7.2; p=0.031) (Table 2).

Table 2. Analysis of categorical variables (risk and protective factors for overall mortality in univariate analysis)

	Cases (n=23), n (%)	Controls (n=207), n (%)	OR	IC 95%	p-value
Protective Factor					
GOLD Group B	2 (9)	72 (34)	0,17	0,01-0,75	0,010
Risk Factor					
Chronic Kidney Disease	6 (26)	14 (7)	4,8	1,34-15,62	0,001
Deep Vein Thrombosis or Pulmonary Embolism	3 (13)	7 (3)	4,2	0,65-20,53	0,031
Very Severe (FEV1 <30% predicted)	6 (26)	17 (8)	4,1	1,16-13,30	0,005
Anemia*	12 (52)	43 (21)	4,1	1,55-11,12	<0,001
Cardiac Arrhythmia	6 (26)	17 (8)	3,9	1,11-12,27	0,006
Supplemental Oxygen	16 (70)	77 (37)	3,8	1,40-11,45	0,002
Heart Failure	8 (34)	27 (13)	3,5	1,17-9,91	0,005
GOLD Group D	10 (43)	46 (22)	2,8	1,02-7,66	0,018
GOLD Group C	9 (39)	42 (20)	2,6	0,92-7,21	0,031
Male Gender	17 (73)	107 (52)	2,6	0,94-8,5	0,042

* Hb<12 in female/hb<13 in male. Abbreviations: OR: odds ratio, CI: confidence interval, FEV1: forced expiratory volume at first second

Protective factors for mortality

Only one protective factor was identified in the analysis: GOLD-B group (OR: 2.6; CI: 0.9-8.5; p=0.042). Other variables analyzed can be seen in Table 3.

Table 3. Other variables analyzed that were not statistically significant

	Cases (n=23), n (%)	Controls (n=207), n (%)	OR	IC 95%	p-value
Rural residence	1 (4)	12 (6)	0,7	0,01-5,41	0,76
Marital status: married	10 (43)	79 (38)	1,08	0,40-2,82	0,86
Marital status: single	8 (35)	41 (20)	1,9	0,66-5,26	0,15
Group GOLD A	1 (4)	41 (20)	0,18	0,004-1,24	0,07
Obesity (BMI≥ 30 kg/m2)	5 (22)	33 (16)	1,4	0,39-4,47	0,47
Malnutrition (BMI<18.5 kg/m2)	3 (13)	8 (4)	3,7	0,58-17,0	0,05
Arterial hypertension	14 (61)	112 (54)	1,3	0,50-3,61	0,53
Diabetes Mellitus Type 2	3 (13)	32 (15)	0,8	0,14-3,01	0,75
Obstructive sleep apnea	1 (4)	29 (14)	0,2	0,006-1,87	0,19
Hypothyroidism	3 (13)	51 (24)	0,4	0,08-1,64	0,21
Dyslipidemia	2 (9)	57 (27)	0,2	0,02-1,08	0,05
Osteoporosis	2 (9)	25 (12)	0,6	0,07-3,13	0,63
Coronary heart disease	6 (26)	28 (14)	2,2	0,66-6,64	0,10
Pulmonary hypertension	3 (13)	10 (5)	2,9	0,48-12,72	0,10
Ischemic cerebrovascular event	1 (4)	6 (3)	1,5	0,03-13,44	0,70
Cancer (any)	4 (17)	17 (8)	2,3	0,52-8,25	0,14
Lung cancer	3 (13)	9 (4)	3,3	0,52-14,59	0,07
Asthma-EPOC syndrome	4 (17)	39 (18)	0,9	0,21-2,94	0,86
Chronic bronchitis (phenotype)	5 (21)	66 (31)	0,5	0,16-1,75	0,31
Emphysema (phenotype)	8 (34)	57 (27)	1,4	0,48-3,75	0,46
Active smoking	4 (17)	31 (15)	1,1	0,27-3,91	0,76
Ex Smoking	21 (91)	151 (73)	3,9	0,89-35,18	0,05
Exposure to biomass smoke	7 (30)	86 (41)	0,6	0,20-1,66	0,30
Abnormal chest x-ray	21 (91)	158 (76)	3,7	0,54-159,29	0,17
Influenza vaccination	13 (56)	118 (57)	0,9	0,36-2,56	0,92
Pneumococcus vaccination	6 (26)	58 (28)	0,9	0,27-2,56	0,84
Eosinophilia (≥300 cells/mL)	4 (17)	62 (29)	0,4	0,11-1,51	0,18
Inhaled Glucocorticoid (ICS)	18 (78)	122 (58)	2,5	0,85-8,94	0,07
ICS + LABA	3 (13)	31 (15)	0,8	0,15-3,13	0,80
LABA+LAMA	4 (17)	53 (25)	0,6	0,14-1,96	0,38

Test used: Chi-square or Fisher's exact test (for n less than 5). Abbreviations: OR: odds ratio; CI: confidence interval; ICS: inhaled glucocorticoid; LABA: long-acting beta agonists; LAMA: long-acting antimuscarinic.

Multivariate analysis

A logistic regression was performed for the previously reported risk factors for mortality and other available variables in the study population. The following variables were included: age, sex, body mass index, number of comorbidities, FEV1, 6MWT, cardiac arrhythmia, deep vein thrombosis and/or pulmonary embolism, oxygen therapy, heart failure, chronic kidney disease, hemoglobin, GOLD classification, and number of severe exacerbations. Three of these variables were associated with mortality: chronic kidney disease (OR: 8.2; CI: 2.3-29.2; p=0.001), severe exacerbation in the last year (OR: 7.4; CI: 2.6-20.8; p<0.001), and hemoglobin within appropriate ranges (OR: 0.82; CI: 0.68-0.99; p=0.047) (Table 4).

https://doi.org/10.35839/repis.17.1.1680

Table 4. Multivariate analysis of predictors of mortality in patients with chronic obstructive pulmonary disease.

	β	Standard error	Wald test	OR, IC 95%	p-value
Chronic Kidney Disease	2,107	0,647	3,26	8,2, (2,3-29,2)	0,001
Severe exacerbation/last year	2,013	0,523	3,85	7,4, (2,6-20,8)	<0,001
Hemoglobin	-0,189	0,095	-1,98	0,82, (0,68-0,99)	0,047

Abbreviations: OR: Odds Ratio; β: Beta coefficient

In this prognostic model, the AUC was 0.83 (95 CI 0.74-0.91), with 82% of patients correctly classified with a specificity of 83%. The Hosmer-Lemeshow test showed no difference between expected and observed data (p = 0.58). There was no absence of data on predictor variables or outcome that could affect the result.

Discussion

To our knowledge, this is the first study to analyze predictors of mortality in this population conducted in Colombia. In this study, we explored the influence of different clinical and sociodemographic characteristics on mortality in COPD patients from a reference center in Colombia, where similar characteristics to those described in the international scientific literature were found.

In our population, pharmacological therapy is optimized in light of current evidence-based guidelines for the treatment of COPD. Non-surviving patients (cases) had a lower peripheral eosinophil count compared to survivors (controls), a finding reported by Rahimi-Rad et al.[25] in 100 patients with exacerbation of COPD, who observed that eosinopenia was associated with higher in-hospital mortality (27% vs. 7%, p = 0.006). It has been proposed that eosinopenia is a result of cell destruction that occurs in sepsis, suppression of eosinophil maturation in the bone marrow, and an increase in hormones such as cortisol and epinephrine[26].

Regarding protective factors for mortality in COPD, our study found that the only associated factor was being classified as GOLD group B, a result consistent with that reported by Gedebjerg et al.[27] who conducted a cohort study of 33,765 COPD patients from hospitals in Denmark, where it was observed that the higher the GOLD group, the greater the risk of mortality, from group A (overall mortality: 10%) to group D (overall mortality: 36.9%). This is evident as it is a classification based on respiratory clinical status and the number of exacerbations the patient has experienced, which have been previously identified as predictors of mortality[8,10,28].

On the other hand, among the identified risk factors for mortality is severe exacerbation, which has been previously reported by other authors. The study by Soler-Cataluña et al.[10] included 304 COPD patients in a prospective cohort study in Spain with a 5-year follow-up, where severe exacerbations (or requiring hospitalization) were identified as an independent predictor of mortality, with the greatest predictor of the analysis being those patients who had three or more severe exacerbations (hazard ratio (HR): 4.13; IC: 1.80-9.4; p = 0.003). Some other studies have supported this association, one of which was the study by Almagro et al.[29], which identified that readmission following hospitalization for COPD was associated with higher mortality, after adjusting for possible confounding variables.

Also, the study by Cardoso et al.[28] with 96 COPD patients in Portugal identified exacerbation history as a predictor of mortality or readmission at 5 years in the multivariate analysis (OR: 2.26; IC: 1.18-4.30; p = 0.013). Likewise, the study by Moll et al.[5] conducted a study using machine learning to establish predictors of mortality in patients from two clinical trials (2632 patients from COPDGene and 1268 from ECLIPSE), where severe exacerbations were identified as an important predictor of this outcome (HR: 1.33; IC: 1.05-1.7). These results provide further support and evidence for exacerbation as a predictor of mortality, with a higher risk if hospitalization is required and if there are a greater number of exacerbations.

Regarding chronic kidney disease, this comorbidity was also identified as an independent predictor of mortality in this study, and has been previously reported as a predictor of mortality of any cause and cardiovascular cause in patients without COPD(30). It is worth noting that several studies on mortality prediction in COPD have not included tests of renal function (creatinine or cystatin C) or comorbidity of kidney disease in their analyses, which has created an information bias[31-33]. Morasert et al.'s retrospective cohort study[14] with 358 patients with exacerbated COPD in Thailand found that creatinine values greater than or equal to 1.5 mg/dL behaved as an independent predictor of in-hospital mortality (HR: 2.08; CI: 1.17-3.70; p=0.013).

Finally, hemoglobin behaved as an independent predictor of mortality in COPD patients, acting as a protective factor with higher levels of hemoglobin present in the patient. This finding is similar to the study by Ittchayen et al.[17], which included 70 Indian patients with exacerbated COPD in the intensive care unit and found that anemia was an independent predictor of mortality (HR: 3.16; CI: 1.51-6.6; p=0.002). Likewise, Cote et al.'s study[16] in a

cohort of 683 COPD patients observed that non-surviving patients had lower hemoglobin levels compared to survivors (14.6 versus 14.2; p=0.002), and anemic patients had a shorter survival time (49 versus 74 months; p<0.01). Polycythemia is a common finding in COPD patients, but anemia has reported higher prevalences of 8-17%(16), with a higher prevalence (31%) in our study. Anemia is a complex finding as it can be multifactorial, due to iron deficiency anemia, vitamin deficiency, chronic illness, comorbidities, and treatment[34,35].

As limitations, this study had selection bias by including patients from a single reference center, which makes it difficult to extrapolate the results. The imbalance between the number of cases and controls is also recognized, which was controlled through multivariate analysis to adjust for known confounders that could affect the reliability of the results. As strengths, we highlight a reduced information bias due to the high quality of the clinical records, a large number of included patients, and the use of robust statistical analysis to control for possible interaction factors, which increases the reliability of our results. We recommend the construction of robust multicenter studies on predictors of mortality and hospitalization that contribute to the construction of follow-up and control programs, not only in patients treated in high complexity services but also in primary care[36-39].

Conclusion

The findings of this study suggest that chronic kidney disease, severe exacerbation, and low hemoglobin are predictors of mortality in COPD patients. Therefore, the timely identification of these predictors by primary care and specialist physicians is ideal to stratify the risk and management of these patients, with the purpose of providing multidisciplinary care, optimizing medical management, and/or performing timely medical interventions according to clinical practice guidelines to reduce the risk of mortality, such as smoking cessation, the use of long-acting inhalers with or without inhaled glucocorticoids, oxygen therapy, lung volume reduction surgery, and lung transplantation, which could increase survival.

Authors' contributions

1. **Conceived the manuscript idea**: Orozco, Pacheco, Babativa, Sanchez.
2. **Conducted the study analyses**: Martinez, Orozco, Pacheco, Babativa, Sanchez.
3. **Wrote the first draft of the article**: Blanco, Clavijo, Orozco, Piamba, Burbano, Rey
4. **Methodology**: Blanco, Clavijo, Martinez, Orozco, Babativa, Sanchez
5. **Data collection**: Blanco, Clavijo, Piamba, Burbano, Rey
6. **Performed critical editing**: Blanco, Clavijo, Martinez, Orozco, Pacheco, Babativa, Piamba, Burbano, Rey.
7. **Approved the final content**: Blanco, Clavijo, Orozco, Martinez, Pacheco, Babativa, Piamba, Burbano, Rey, Sanchez.
8. **Approved version for publication**: Blanco, Clavijo, Martinez, Orozco, Pacheco, Babativa, Piamba, Burbano, Rey, Sanchez.

Acknowledgments

To Clinica Comfamiliar for their non-financial support in carrying out this research work. To Universidad Tecnológica de Pereira and Fundación Universitaria del Área Andina for their support in the statistical part.

References

1. Burney PG, Patel J, Newson R, Minelli C, Naghavi M. Global and regional trends in COPD mortality, 1990-2010. Eur Respir J. 2015; 45(5): 1239-1247. doi: 10.1183/09031936.00142414
2. Ford ES. Trends in mortality from COPD among adults in the United States. Chest. 2015; 148(4): 962-970. doi: 10.1378/chest.14-2311
3. Carone M, Antoniu S, Baiardi P, Digilio VS, Jones PW, Bertolotti G. Predictors of Mortality in Patients with COPD and Chronic Respiratory Failure: The Quality-of-Life Evaluation and Survival Study (QuESS): A Three-Year Study. COPD. 2016; 13(2): 130-138. doi: 10.3109/15412555.2015.1067294
4. Henoch I, Ekberg-Jansson A, Löfdahl CG, Strang P. Early Predictors of Mortality in Patients with COPD, in Relation to Respiratory and Non-Respiratory Causes of Death – A National Register Study. Int J Chron Obstruct Pulmon Dis. 2020; 15: 1495-1505 doi: 10.2147/COPD.S252709
5. Moll M, Qiao D, Regan EA, Hunninghake GM, Make BJ, Tal-Singer R, et al. Machine Learning and Prediction of All-Cause Mortality in COPD. Chest. 2020; 158(3): 952-964. doi: 10.1016/j.chest.2020.02.079
6. Moryson W, Stawinska-Witoszynska B. Premature Mortality Due to Chronic Obstructive Pulmonary Disease (COPD) in Poland. Medicina (Kaunas). 2021; 57(2): 126. doi: 10.3390/medicina57020126
7. Prudente R, Franco EAT, Mesquita CB, Ferrari R, de Godoy I, Tanni SE. Predictors of mortality in patients with COPD after 9 years. International journal of chronic obstructive pulmonary disease. 2018; 13: 3389-3398. doi: 10.2147/COPD.S174665
8. Santibáñez M, Garrastazu R, Ruiz-Nuñez M, Helguera JM, Arenal S, Bonnardeux C, et al. Predictors of

Hospitalized Exacerbations and Mortality in Chronic Obstructive Pulmonary Disease. PLoS One. 2016; 11(6): e0158727. doi: 10.1371/journal.pone.0158727
9. Caballero A, Torres-Duque CA, Jaramillo C, Bolivar F, Sanabria F, Osorio P, et al. Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). Chest. 2008; 133(2): 343-349. doi: 10.1378/chest.07-1361
10. Soler-Cataluña JJ, Martínez-García MA, Román-Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005; 60(11): 925-931. doi: 10.1136/thx.2005.040527
11. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 1999; 160(6): 1856-1861. doi: 10.1164/ajrccm.160.6.9902115
12. Fletcher C, Peto R. The natural history of chronic airflow obstruction. British medical journal. 1977; 1(6077): 1645-1648. doi: 10.1136/bmj.1.6077.1645
13. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. American journal of respiratory and critical care medicine. 2003; 167(4): 544-549. doi: 10.1164/rccm.200206-583OC
14. Morasert T, Jantarapootirat M, Phinyo P, Patumanond J. Prognostic indicators for in-hospital mortality in COPD with acute exacerbation in Thailand: a retrospective cohort study. BMJ open respiratory research. 2020; 7(1): e000488. doi: 10.1136/bmjresp-2019-000488
15. Chambellan A, Chailleux E, Similowski T. Prognostic value of the hematocrit in patients with severe COPD receiving long-term oxygen therapy. Chest. 2005; 128(3): 1201-1208. doi: 10.1378/chest.128.3.1201
16. Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B. Haemoglobin level and its clinical impact in a cohort of patients with COPD. The European respiratory journal. 2007; 29(5): 923-929. doi: 10.1183/09031936.00137106
17. Ittyachen AM, Krishnamoorthy S, Bhatt AN, Abdulla S, Roy JO, Sugathan M, Ambadan K, Kuriakose J. Predictors of outcome in patients admitted with acute exacerbation of chronic obstructive pulmonary disease in a rural Tertiary Care Center. J Family Med Prim Care. 2016; 5(2): 411-415. doi: 10.4103/2249-4863.192365
19. Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, Wedzicha JA, Price D, Hyland ME. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. Am J Respir Crit Care Med. 2009; 180(12): 1189-95. doi: 10.1164/rccm.200902-0271OC
20. Puhan MA, Garcia-Aymerich J, Frey M, ter Riet G, Antó JM, Agustí AG, Gómez FP, Rodríguez-Roisín R, Moons KG, Kessels AG, Held U. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet. 2009; 374(9691): 704-711. doi: 10.1016/S0140-6736(09)61301-5
21. Azarisman MS, Fauzi MA, Faizal MP, Azami Z, Roslina AM, Roslan H. The SAFE (SGRQ score, air-flow limitation and exercise tolerance) Index: a new composite score for the stratification of severity in chronic obstructive pulmonary disease. Postgrad Med J. 2007; 83(981): 492-497. doi: 10.1136/pgmj.2006.052399
22. Celli BR, Cote CG, Lareau SC, Meek PM. Predictors of Survival in COPD: more than just the FEV1. Respiratory medicine. 2008; 102 Suppl 1: S27-35. doi: 10.1016/S0954-6111(08)70005-2
23. Guerra B, Haile SR, Lamprecht B, Ramírez AS, Martinez-Camblor P, Kaiser B, et al. Large-scale external validation and comparison of prognostic models: an application to chronic obstructive pulmonary disease. BMC medicine. 2018; 16(1): 33. doi: 10.1186/s12916-018-1013-y
24. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. International journal of surgery (London, England). 2014; 12 (12): 1495-1499. doi: 10.1016/j.ijsu.2014.07.013
25. Rahimi-Rad MH, Asgari B, Hosseinzadeh N, Eishi A. Eosinopenia as a Marker of Outcome in Acute Exacerbations of Chronic Obstructive Pulmonary Disease. Maedica (Bucur). 2015; 10(1): 10-13. PMID: 26225143
26. Bass DA, Gonwa TA, Szejda P, Cousart MS, DeChatelet LR, McCall CE. Eosinopenia of acute infection: Production of eosinopenia by chemotactic factors of acute inflammation. J Clin Invest. 1980; 65(6): 1265-1271. doi: 10.1172/JCI109789
27. Gedebjerg A, Szépligeti SK, Wackerhausen LH, Horváth-Puhó E, Dahl R, Hansen JG, Sørensen HT, Nørgaard M, Lange P, Thomsen RW. Prediction of mortality in patients with chronic obstructive pulmonary disease with the new Global Initiative for Chronic Obstructive Lung Disease 2017 classification: a cohort study. Lancet Respir Med. 2018; 6(3): 204-212. doi: 10.1016/S2213-2600(18)30002-X
28. Cardoso J, Coelho R, Rocha C, Coelho C, Semedo L, Bugalho Almeida A. Prediction of severe exacerbations and mortality in COPD: the role of exacerbation history and inspiratory capacity/total lung capacity ratio. Int J Chron Obstruct Pulmon Dis. 2018; 13: 1105-1113. doi: 10.2147/COPD.S155848
29. Almagro P, Calbo E, Ochoa de Echagüen A, Barreiro B, Quintana S, Heredia JL, Garau J. Mortality after hospitalization for COPD. Chest. 2002; 121(5): 1441-1448. doi: 10.1378/chest.121.5.1441
30. Fried LF, Katz R, Sarnak MJ, Shlipak MG, Chaves PH, Jenny NS, Stehman-Breen C, Gillen D, Bleyer AJ, Hirsch C, Siscovick D, Newman AB. Kidney function as a predictor of noncardiovascular mortality. J Am Soc

Nephrol. 2005; 16(12): 3728-3735. doi: 10.1681/ASN.2005040384
31. Rodriguez DA, Kortianou EA, Alison JA, Casas A, Giavedoni S, Barberan-Garcia A, et al. Heart Rate Recovery After 6-min Walking Test Predicts Acute Exacerbation in COPD. Lung. 2017; 195(4): 463-467. doi: 10.1007/s00408-017-0027-0
32. Kuzmar I, Giraldo Ospina CE, Acevedo Osorio GO, Rua Salas G. Morbilidad de la Enfermedad Pulmonar Obstructiva Crónica en Colombia. Resultados del Estudio SANEPOC-2. Rev Fac Cien Med Univ Nac Cordoba. 2018; 75(1): 19-24. doi: 10.31053/1853.0605.v75.n1.16617
33. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017; 195(5): 557-582. doi: 10.1164/rccm.201701-0218PP
34. Orozco-Hernández JP, Pacheco-Gallego M, Montoya-Martínez JJ. Update on Clinical Aspects of COPD. N Engl J Med. 2019; 381(25): 2485. doi: 10.1056/NEJMc1914600
35. Celli BR, Wedzicha JA. Update on Clinical Aspects of Chronic Obstructive Pulmonary Disease. N Engl J Med. 2019; 381(13): 1257-1266. doi: 10.1056/NEJMra1900500
36. Sánchez-Duque JA, Muñoz-Marin GA. Ecografía a pie de cama en atención primaria. Aten Primaria. 2022; 54 (11): 102474. doi: 10.1016/j.aprim.2022.102474
37. Blanco-Betancur M, Díez-Concha JF, García-Trochez MF, Zambrano-Pabón LP, Rivera-Eraso VM, Sánchez-Duque JA. Vacunación del adulto en atención primaria: durante y después de pandemia. Rev Peru Investig Salud. 2022; 6 (4): 205 - 213. doi: 10.35839/repis.6.4.1546
38. Solarte-Adrada W, Preciado-Casierra CJ, Galvis-Acevedo S, Sánchez-Duque JA. Determinantes psicosociales y adherencia farmacológica en pacientes geriátricos. Aten Fam. 2022; 29 (2): 126 - 129. doi: 10.22201/fm.14058871p.2022.2.82040
39. Galvis-Acevedo S, Suarez-Orozco L, Blanco-Betancur M, Sánchez-Duque. Medicina Familiar durante y después de la covid-19. Aten Fam. 2021; 28 (4): 280 - 283. doi: 10.22201/fm.14058871p.2021.4.80599