Review

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Prevalence and Impact of Comorbidities in Individuals with Chronic Obstructive Pulmonary Disease: A Systematic Review

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Abstract

This study aimed to describe the prevalence of comorbidities associated with chronic obstructive pulmonary disease (COPD) and their relation with relevant outcomes. A systematic review based on the PRISMA methodology was performed from January 2020 until July 2021. The MEDLINE, Lilacs, and Scielo databases were searched to identify studies related to COPD and its comorbidities. Observational studies on the prevalence of comorbidities in COPD patients and costs with health estimates, reduced quality of life, and mortality were included. Studies that were restricted to one or more COPD pain assessments and only specific comorbidities such as osteoporosis, bronchitis, and asthma were excluded. The initial search identified 1,409 studies and after applying the inclusion and exclusion criteria, 20 studies were finally selected for analysis (comprising data from 447,459 COPD subjects). The most frequent COPD comorbidities were: hypertension (range, 17%–64.7%), coronary artery disease (19.9%–47.8%), diabetes (10.2%–45%), osteoarthritis (18%–43.8%), psychiatric conditions (12.1%–33%), and asthma (14.7%–32.5%). Several comorbidities had an impact on the frequency and severity of COPD exacerbations, quality of life, and mortality risk, in particular malignancies, coronary artery disease, chronic heart failure, and cardiac arrhythmias. Comorbidities, especially cardiovascular diseases and diabetes, are frequent in COPD patients, and some of them are associated with higher mortality.

Keywords: COPD; Comorbidity; Severity; Hospitalization; HealthCare Xosts; Mortality

Introduction

Chronic obstructive pulmonary disease (COPD), a chronic respiratory disease is one of the most prevalent chronic diseases and is the fourth leading cause of mortality worldwide[1]. COPD patients often have comorbidities. which are associated with worse outcomes such as impaired quality of life, increased frequency of hospital admissions, worse therapeutic response, and even increased mortality[2-4].

However, the pathophysiological processes involved in the relationship between COPD and its comorbidities. Probable causes of the high prevalence of comorbidities in COPD patients are hypothesized and generally categorized by: advanced age, physical inactivity, poor diet, smoking, hypoxia, and systemic inflammation[5-10].

Studies describing comorbidities in COPD reported significant variability in not only the prevalence of different comorbidities but also the intensity of asso-

ciation between them[11]. In general, the presence of comorbidities is associated with the worst prognosis, but the impact of different comorbidities on outcomes varies significantly. Identification of the type of comorbidity and the possible clinical impact on the risk of exacerbations, impairment in quality of life, reduction of physical activity, and increased mortality, might help clinicians to improve the care of COPD patients.

This systematic review aimed to describe the estimated prevalence of comorbidities in COPD and their association with the relevant outcomes such as the use of health resources, quality of life, symptoms, exercise capacity, exacerbations, and mortality. To accomplish this, exploratory and quantity methodologies were applied.

Materials and Methods

This systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA)[12] protocol. The studies were searched in the electronic databases MEDLINE-PubMed (Medical Literature Analysis and Retrieval System Online), Lilacs (Latin Literature and the Caribbean of Ciencias de la Salud), and Scielo (Scientific Electronic Library Online) - by the Virtual Health Library Brazil. To construct this research, the Patient, Intervention, Comparison, and Outcome (PICOS) strategy was required as an acronym for Population (individuals with COPD) and Intervention - or Exposure, for observational studies (comorbidities), Comparison (individuals without COPD), "Outcomes" - outcomes (exacerbations, hospitalizations, health costs, reduced quality of life and mortality), and "Study design" - study design (observational studies)[13]. The following keywords were used: pulmonary disease, chronic obstructive; comorbidity; observational studies as a topic, synonyms, and related words added by the Boolean operators "AND" and "OR" (Supplementary Table S1). No search strategies from the previous reviews were used. The period full search for the articles was carried out from January 2020 to July 2021, using the words found in the titles and article's abstracts.

The relevant articles, collected through database searches, were selected by their main titles (first stage), abstracts (second stage), and complete and full reading of the selected material (third stage). An exploratory reading of all the selected materials was made, and, later, a selection and more analytical reading of the parts that were the most relevant for the review. Observational studies that estimated the prevalence of comorbidities in individuals with COPD and associated with exacerbations, hospitalizations, healthcare costs, reduced quality of life, and mortality were included. Articles that used primary or secondary data, published between 2003 and 2020, and that were available in English, Portuguese, or Spanish were also included in the data collection and added to the reading references for this study.

Studies that were restricted to evaluating individuals with COPD and only one more specific comorbidity such as osteoporosis, bronchiectasis, asthma, or pain were excluded. The other exclusion criteria followed the PRISMA methodology: duplicate studies which were removed and also the ones that described the same or very similar results from the same database. In addition, studies that did not list the comorbidities or their frequencies and studies that evaluated patients with respiratory diseases other than COPD[12] were excluded. Mendeley - Reference Management Software was used to deduplicate records from several database searches.

All the results related to outcomes were presented, even if they came from the same database, and this circumstance was indicated in the results. We opted to select all the results related to the outcomes, including those from the same database. Nevertheless, their circumstances are quoted in the results of the present study.

The process of identifying the methodological aspects and extracting data from the articles was accomplished by two independent reviewers (N.C.S. and F.W.R.C.). When there was any disagreement between them, the reviewers read the entire article again for reassessment. When there was a disagreement, a third independent reviewer evaluated the article and made the final decision.

After the article was completed, the search was last updated in December 2021, using the publication date filter present in the databases. This way, it was possible to evaluate the articles published after the analysis of the previous articles.

The quality of the included studies was elaborated using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[14]. The protocol for the construction stages of this systematic review was published in the International Prospective Register of Systematic Reviews (PROSPERO), under registration no. CRD42018081641.

Results

The initial search resulted in 1,409 articles (MEDLINE, 1,348; Lilacs, 35; Scielo, 26), and later 1,406 records

after removing the duplicated ones. In these studies, 60 articles were selected by title screening. Twelve of the 60 were excluded because the abstract did not fit the selection criteria, leaving 48 articles for a full reading. Of the 48, 28 of them did not meet all the inclusion criteria, resulting in the final selection of 20 articles as shown in Figure 1.

1. Characteristics of the studies

The characteristics of the 20 articles selected are presented in Table 1. Of the 20 articles, most of them were cohort studies, with 11 retrospective and three prospective, four cross-sectional observational and two case- control[11,15-33]. Data from 637,827 subjects were included. Only one study did not show the number of participants, with the number of admissions as a sample (47,404,700)[15].

2. Used instruments

In the 20 articles, the researchers evaluated medical records while the others used different instruments. In one of these articles, a list of the comorbidities of interest was produced[19], while seven others used the COPD specific comorbidity test (COTE Index)[16], Charlson Comorbidity Index[19,21,24,27,32]. Five of these studies[11,18,22,23,27] used other instruments that were not designed to assess comorbidities such as the Modified Medical Research Council, mMRC[18,23] (dyspnea assessment); the St George's Respiratory Questionnaire for COPD patients, SGRQ-C[18,23] (quality of life); Health-related quality of life - HRQoL-15D[22] (quality of life); Airways questionnaire 20, AQ20[22] (quality of life); Hospital Anxiety and Depression Scale, HADS[27] (emotional state); Body mass index, Airway Obstruction, Dyspnea, and Exercise capacity, BODE[16,18,23] (health status and risk of death); and 6-minute walk test, 6MWT[11,18,23] (functional capacity).

3. Methodological quality

All the selected articles presented the research question or objective clearly, the population was well defined and the participation rate of the eligible people

Figure 1. Research flow diagram. COPD: chronic obstructive pulmonary disease.

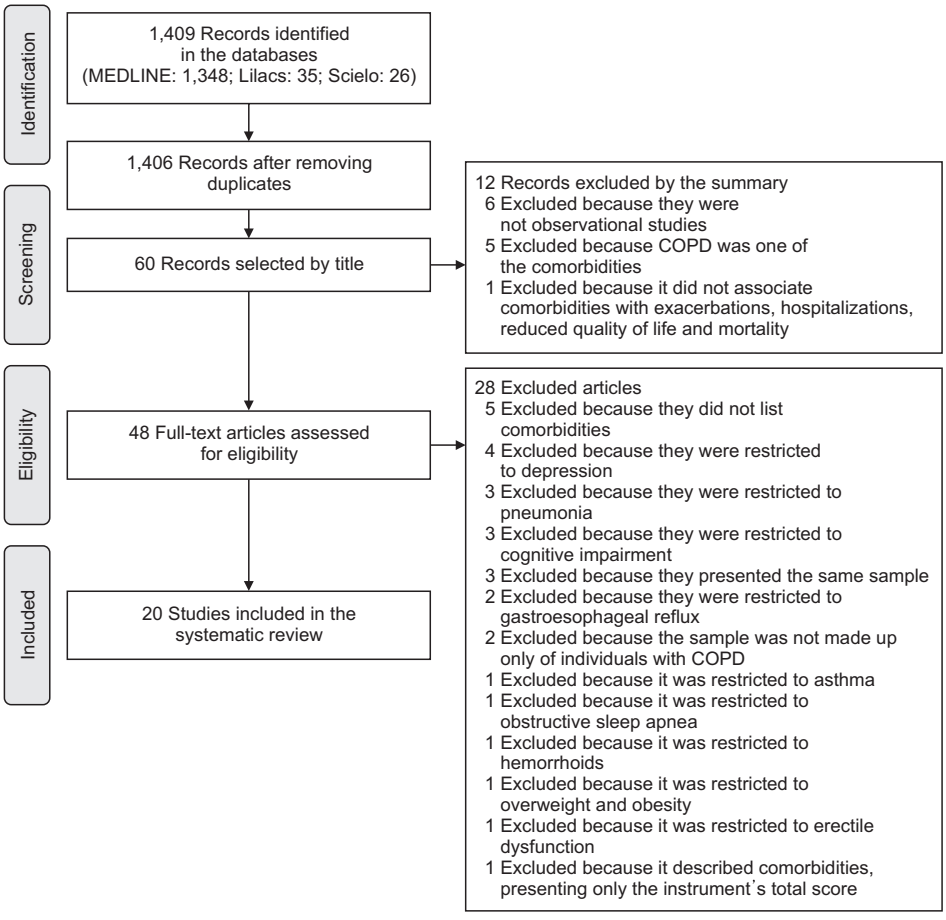

Table 1. Main characteristics of the selected studies

Study	Objective	Kind of study	Sample	Country, source (period)	Outcomes	Assessment tool	Evaluated comorbidities
Holguin (2005)[15]	To analyze the prevalence of comorbidities and mortality in patients with COPD	Retrospective cohort study	47,404,700 Hospitalizations of individuals over the age of 25 years	USA; National Hospital Discharge Survey (1979–2001)	Prevalence of comorbidities and mortality	Evaluation of medical records	Pneumonia; hypertension; diabetes; congestive heart failure; ischemic heart disease; pulmonary vascular disease; acute kidney injury; chronic kidney failure; thoracic malignancies; respiratory failure; human immunodeficiency virus; stroke; and gastrointestinal bleeding
Divo (2012)[16]	Prospectively assess COPD comorbidities and mortality risk	Prospective cohort, multicenter study	1,664 Individuals	USA and spain; Pneumology outpatient clinics (1997–2010)	Prevalence of comorbidity and risk of death	COTE index, medical records assessment, and other comorbidities listed in the interviews	Oncological (lung, pancreatic, esophageal, breast cancer); pulmonary (pulmonary fibrosis); cardiac (atrial/flutter fibrillation, congestive heart failure, and coronary artery disease); gastrointestinal (gastric/duodenal ulcers, liver cirrhosis); endocrine (diabetes with neuropathy); psychiatric (anxiety)
Baty (2013)[17]	Analyze the prevalence and prognostic relevance of specific COPD comorbidities	Case-control study	340,948 Hospitalizations of 160,317 individuals over the age of 40 years	Switzerland; Swiss Federal Statistics Office database with all hospital registrations (2002–2010)	Prevalence of comorbidities, time of internment, and mortality	Charlson's comorbidity index and medical records evaluation	Neoplasms; psychological disorders; atherosclerosis; tobacco/alcohol addiction; heart diseases; hypertension; other lung diseases; osteoporosis; kidney disease; diabetes; obesity; congestive heart failure; sleep apnea; candidiasis; anemia; cachexia; senile cataract; meniscus disorder; dependence on a mechanical ventilation, extreme obesity with alveolar hypoventilation; pneumonia due to pseudomonas; secondary polycythemia

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Table 1. Continued

Study	Objective	Kind of study	Sample	Country, source (period)	Outcomes	Assessment tool	Evaluated comorbidities
Miller (2013)[18]	Establish the type and proportion of patients with comorbidities and explore their characteristics in relation to systemic inflammation and measures of clinical outcome	Prospective cohort study	2,164 Individuals aged between 40 and 75 years	46 Centers in 12 countries; Data from Longitudinally Identify Predictive Surrogate Endpoints – ECLIPSE (3 years)	Prevalence of comorbidity, mortality, distance covered, and dyspnea	Evaluation of medical records, mMRC, SGRQ-C, BODE index, and 6MWT	Self-reported osteoporosis; anxiety/panic attacks; peptic ulcer, depression; diabetes; intestinal disorders; rheumatoid arthritis; reflux/heartburn; hypertension; heart attack; congestive heart failure; ischemic heart disease; arrhythmia; stroke and heart problems
Echave-Sustaeta (2014)[19]	Established the prevalence of comorbidities and investigate whether it is related to the severity of the disease	Multicenter cross-sectional study	200 Individuals in stage I or II, 400 in stage III, and 400 in stage IV	Spain; Data from several Centers in the country (period not informed)	Prevalence of comorbidities and disease severity	Predetermined list of 24 diseases, medical records evaluation, and the Charlson index	Hypertension; hypercholesterolemia; diabetes; congestive heart failure and atrial fibrillation, cataracts; arthrosis; anxiety and depression; anemia; renal insufficiency; digestive disease; liver disease; peripheral vascular disease; ischemic heart disease; cancer and pneumonia
Ongel (2014)[20]	Set if comorbidities and clinical variables of intensive care unit admission are predictive of mortality	Retrospective cohort study	1,013 Individuals (749 men with an average age of 70±10 years)	Turkey; Kartal Lutfi Kirdar Teaching and Research Hospital, Istanbul (2008–2012)	Prevalence of comorbidity and mortality in the intensive care unit	Evaluation of medical records	Arrhythmia; hypertension; coronary artery disease; depression; congestive heart failure; pneumonia; lower respiratory tract infection; lung cancer; severe sepsis/septic shock; bankruptcy of several organs; myocardial infarction and pulmonary embolism
Diez-Manglano (2014)[21]	Discuss the relationship between clinical characteristics and metabolic equivalents task units in patients with COPD	Cross-sectional and multicenter study	375 Individuals	Spain; 26 Hospital centers (2007–2008)	Prevalence of comorbidities	Charlson's comorbidity index and medical records evaluation	Diabetes; osteoporosis; coronary artery disease; congestive heart failure; myocardial infarction; chronic kidney failure; insanity; alcoholism; anemia; hypertension; dyslipidemia

Table 1. Continued

Study	Objective	Kind of study	Sample	Country, source (period)	Outcomes	Assessment tool	Evaluated comorbidities
Koskela (2014)[22]	Estimate the contribution of common comorbidities on self-reported Quality of Life-Related to Health in patients with COPD	Retrospective cohort study	739 Individuals	Finland; Database of Heart and Lung Center at Hospitals at the University of Helsinki and Turku (2005–2007)	Prevalence of comorbidities and quality of life	Evaluation of medical records, generic instruments (HRQoL-15D), and specific respiratory instruments (AQ20)	Coronary heart disease: myocardial infarction, acute coronary artery syndrome; Cerebrovascular diseases: stroke and ischemic attacks; Cardiovascular diseases: coronary heart disease, cerebrovascular disease, chronic atrial fibrillation, type 1 and 2 diabetes; Alcohol abuse: chronic alcoholism; Psychiatric condition: psychotic disorders, depression and anxiety; Cancer: solid malignant tumors and malignant hematological diseases
Divo (2014)[23]	To assess the prevalence of COPD-related comorbidities in different body mass index (BMI) categories and their possible association with risk of death	Prospective multicenter cohort study	1,659 Individuals. BMI<21 (n=254) 21<BMI<25 (n=295) 25<BMI<30 (n=622) 30<BMI<35 (n=332) BMI>35 (n=156)	USA and spain; Database of five study centers for individuals attending pulmonology clinics	Prevalence of comorbidity and risk of death	Evaluation of medical records, BODE index, mMRC, SGRQ, and 6MWT	Abdominal aortic aneurysm; substance abuse; osteoporosis; peripheral arterial disease; prostate cancer; systemic arterial hypertension; hyperlipidemia; sleep apnea; diabetes mellitus; chronic renal failure; congestive heart failure; gout; venous insufficiency; degenerative joint; pulmonary hypertension; erectile dysfunction; atrial fibrillation; pulmonary fibrosis; cancer; and gastric/duodenal ulcer
Dal Negro (2015)[24]	To discuss the prevalence of the main comorbidities by sex and disease severity	Cross-sectional study	1,216 Individuals over the age of 40 years	Italy; Specialist medical center lung unit database (2012–2015)	Prevalence of comorbidities by sex and disease severity	Charlson's comorbidity index and medical records evaluation	Cardiovascular disorders; respiratory; metabolic; digestive; oncological; neurological/ psychiatric and osteoarticular
Battaglia (2015)[25]	To investigate if there is a prevalence of COPD comorbidities and their relationship with the severity of the disease	Retrospective cohort study	326 Individuals aged 71.8±9.2 years	Italy; Respiratory disease clinic Palermo University (period not informed)	Prevalence of comorbidities and disease severity	Evaluation of medical records	Arrhythmias; congestive heart failure; coronary artery disease; hypertension; cerebrovascular disease; diabetes; chronic kidney disease; depression (requiring treatment)

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Table 1. Continued

Study	Objective	Kind of study	Sample	Country, source (period)	Outcomes	Assessment tool	Evaluated comorbidities
Mannino (2015)[26]	Evaluate and quantify the impact of comorbidities on the costs associated with COPD in a large data set of administrative claims	Retrospective cohort study	183,681 Individuals aged between 40 and 90 years	USA; Truven Health MarketScan Commercial Claims database and supplementary databases for MarketScan Medicare (2009–2012)	Prevalence of comorbidities and costs	Evaluation of medical records	Chronic kidney disease; cardiovascular disease, including congestive heart failure, stroke, acute myocardial infarction, and peripheral vascular disease; asthma; depression; diabetes; osteoporosis; and anemia
Caram (2016)[27]	To assess the prevalence of comorbidities and risk factors of cardiovascular disease in COPD according to the severity of the disease	Cross-sectional descriptive study	25 Individuals with mild /moderate COPD and 25 severe/very severe	Brazil; Pulmonology Outpatient Clinic of Botucatu's *Hospital das Clínicas* (period not informed)	Prevalence of comorbidity, risk factors for cardiovascular disease, and disease severity	Charlson's comorbidity index, medical records evaluation, clinical evaluation, and HADS	Depression; dyslipidemia; diabetes; hypertension; alcoholism, smoking, ischemic heart disease, and congestive heart failure
Jeong (2016)[28]	Investigate factors associated with frequent severe exacerbations in patients with COPD	Retrospective cohort study	77 Individuals who had severe exacerbations	South Korea; Samsung Medical Center Hospital (2012–2014)	Prevalence of comorbidity, severe and frequent exacerbations	Evaluation of medical records	Ischemic heart disease; hypertension; disseminated intravascular coagulation; congestive heart failure; cerebrovascular disease; cor pulmonale; diabetes; neoplasms; asthma; demyelinating tumefactive lesions; chronic liver disease; chronic kidney disease
Deniz (2016)[29]	Evaluate the effects of COPD comorbidities on costs and investigate the relationship between comorbidities and clinical variables	Retrospective cohort study	3,095 Individuals who were hospitalized for exacerbations over the age of 40 years	Turkey; Database of all hospitals in the state of Aydin (Jan 2014–Dec 2014)	Prevalence of comorbidity, exacerbations, and costs of hospitalizations	Evaluation of medical records	Hypertension; congestive heart failure; coronary artery disease; diabetes; anemia; gastroesophageal reflux; anxiety/depression; arrhythmia; lung cancer; pulmonary thromboembolism; chronic kidney failure; cachexia; obesity; and osteoporosis

Table 1. Continued

Study	Objective	Kind of study	Sample	Country, source (period)	Outcomes	Assessment tool	Evaluated comorbidities
Liao (2016)[30]	Examine the incidence of site-specific fracture in patients with COPD	Retrospective cohort study	11,312 Individuals over the age of 40 years	Taiwan; Longitudinal Health Insurance Database (2001–2013)	Prevalence of comorbidity and most frequent fractures	Evaluation of medical records	Cardiovascular diseases; cerebrovascular diseases; chronic kidney disease; liver disease; diabetes; vertebral fractures; femoral; rib and forearm
Westerik (2017)[31]	Explore associations between a wide range of chronic comorbid conditions and risk of exacerbation	Retrospective cohort study	170 Individuals over the age of 40 years	Netherlands; Department of Primary and Community Care at Radboud University Medical Center, Nijmegen (2012–2013)	Prevalence of frequent comorbidities and exacerbations	Evaluation of medical records	Hypertension; coronary heart disease; osteoarthritis; diabetes; peripheral vascular disease; congestive heart failure; blindness and low vision; lung cancer; depression; prostate disease; asthma; osteoporosis, dyspepsia; and other chronic respiratory diseases
Schwab (2017)[32]	Describe the comorbidity profiles of patients with COPD and examine the associations between the presence of comorbidities and healthcare resource utilization or health care costs	Retrospective cohort study	52,643 Individuals aged between 40 and 89 years	USA; Database of administrative claims for a major national health plan (2008–2012)	Prevalence of comorbidity, hospitalizations, costs	Charlson's comorbidity index and medical records evaluation	Obesity; anxiety disorders; depressive disorders; coronary artery disease; congestive heart failure; cerebrovascular disease; stroke; chronic kidney disease includes end-stage kidney disease; osteoarthritis; osteoporosis; diabetes and sleep apnea

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Table 1. Continued

Study	Objective	Kind of study	Sample	Country, source (period)	Outcomes	Assessment tool	Evaluated comorbidities
Divo (2018)[33]	To assess whether individuals with COPD have a higher number of comorbidities characteristically seen in older individuals and whether they are detected at a younger age	COPD cases and controls selected from the EpiChron Cohort	27,617 Individuals over the age of 40 years	Spain; Electronic medical records of the inhabitants of the Spanish autonomous community of Aragon (2011)	Prevalence of comorbidity and time of diagnosis	Evaluation of medical records	Aortic aneurysm; benign prostatic hypertrophy; coronary artery disease; congestive heart failure; chronic kidney failure; stroke; cerebrovascular syndrome; degenerative joint disease; diabetes; endocrinopathy; anemia; gastroesophageal reflux; hematological disorder; hypertension; another neurological disorder; other respiratory disorders; hypertension; depression; obesity; varicose veins; hypothyroidism; urinary incontinence; atherosclerosis; osteoporosis
Maselli (2019)[11]	Summarize the main advances in the clinical epidemiology of COPD in the first 10 years of the COPDGene study	Retrospective cohort study	8,078 Individuals	USA; COPDGene database (10 years)	Risk of presenting comorbidities	Evaluation of medical records and 6MWT	High cholesterol; congestive heart failure; obesity; osteoporosis; stroke; peripheral vascular disease; gastroesophageal reflux; sleep apnea; coronary artery disease; hypertension; stomach ulcers; allergic rhinitis; diabetes mellitus; osteoarthritis; and arthrosis

COPD: chronic obstructive pulmonary disease; COTE: COPD specific comorbidity test; mMRC: modified Medical Research Council; SGRQ-C: St George's Respiratory Questionnaire for COPD patients; BODE: Body-mass index, airflow Obstruction, Dyspnea, and Exercise; 6MWT: 6-minute walk test; HRQoL: health-related quality of life; AQ20: Airways questionnaire 20; HADS: Hospital Anxiety and Depression Scale.

Table 2. Quality assessment of the reviewed articles

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality
Holguin (2005)[15]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Divo (2012)[16]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Good
Baty (2013)[17]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Miller (2013)[18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Echave-Sustaeta (2014)[19]	Y	Y	Y	NR	Y	Y	NR	Y	Y	N	Y	N	NA	Y	Regular
Ongel (2014)[20]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Diez-Manglano (2014)[21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Koskela (2014)[22]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Divo (2014)[23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Good
Dal Negro (2015)[24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Battaglia (2015)[25]	Y	Y	Y	NR	Y	Y	NR	Y	Y	N	Y	N	NA	Y	Regular
Mannino (2015)[26]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Caram (2016)[27]	Y	Y	Y	NR	Y	Y	NR	Y	Y	N	Y	N	Y	Y	Regular
Jeong (2016)[28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Deniz (2016)[29]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Liao (2016)[30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Westerik (2017)[31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Schwab (2017)[32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Divo (2018)[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Good
Maselli (2019)[11]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Good

1. Was the research question or objective in this article clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of the eligible people or at least 50% of them?
4. Have all subjects been selected or recruited from the same or similar populations (including the same period of time)? Were the inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all the participants?
5. Has a sample size justification, description of potency or variation, and effect estimates been provided?
6. For the analyses in this article, were the exposure(s) of interest measured before the result(s) to be quantified?
7. Was the time enough to reasonably expect an association between exposure and outcome if it existed?
8. For exposures that may vary in quantity or level, did the study examine different levels of exposure as related to the outcome (for example, categories of exposure or exposure measured as a continuous variable)?
9. Were exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently in all study participants?
10. Has the exposure(s) been evaluated more than once through the period of time presented?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently in all the study participants?
12. Were the outcome assessors blinded to the participants' exposure status?
13. Was the loss to follow-up after baseline 20% or less than that?
14. Were the main confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and result(s)?

Y: yes; N: no; CD: can't determine; NA: not applicable; NR: not reported.

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was at least 50%. In all the studies, the measures of exposure and results were clearly defined, valid, reliable, and implemented consistently. The main variables were measured and adjusted statistically for their impact on the relationship between exposure and outcome in all the studies, as shown in Table 2.

Only three articles did not report the period of selection and recruitment of the participants[19,25,27], and it was also not possible to understand whether the period was long enough to reasonably expect an association between exposure and outcome. Four articles evaluated exposure more than once through time[11,16,23,33]. In one of the studies, the evaluators of the results were blinded to the exposure status of the participants[23] and only one showed loss to follow-up[27]. Seventeen studies were classified as good methodological quality and three as regular (Table 2).

4. Comorbidities and outcomes

The prevalence of comorbidities in COPD patients are shown in Table 3. The most prevalent were hypertension (17%–64.7%), coronary artery disease (19.9%–47.8%), and diabetes mellitus (10.2%–45%).

Six studies[15-18,20,23] showed increased mortality based on the presence of comorbidities, in particular malignancies, coronary artery disease, and cardiac arrhythmia. Four studies[28,29,31,32] indicated a role of comorbidities in the frequency and severity of exacerbations and one of them demonstrated a longer length of hospital stay for an exacerbation in patients with comorbidities[17]. Four studies showed an increased severity of COPD associated with more frequent comorbidities[19,24,25,27]. In general, the Charlson comorbidity index was higher in patients with more severe COPD. Two studies suggested an impact of comorbidities on quality of life[18,22], specifically, cardiovascular and psychiatric comorbidities. Lastly, three studies[26,29,32] indicated that healthcare costs were higher in patients with comorbidities. The impact of comorbidities on outcomes of COPD is summarized in Table 4.

Discussion

Our systematic review results showed that COPD patients are frequently affected by comorbidities and the most common are: cardiovascular diseases[11,15-17,22-26,28-33] (mainly hypertension, coronary artery disease, chronic heart failure, peripheral arterial disease, arrhythmia, and atrial fibrillation), metabolic diseases[15,17-19,21-28,32,33] (diabetes, hyperlipidemia, chronic kidney disease, and obesity), osteoarticular[11,18,23,24,26,28-33] (osteoarthritis and osteoporosis), respiratory[11,15,16,24,26,28,29,32] (obstructive sleep apnea and asthma), psychiatric conditions[17,18,20,22,26,29,32,33], and gastroesophageal reflux[11,18,29,33]. The presence of comorbidities in COPD subjects influences their clinical outcomes, demonstrated by increased frequency and severity of exacerbations, impairment in quality of life, and eventually an increased mortality[34,35]. The presence of comorbidities is essential in designing individualized treatment plans for COPD patients that enable better symptom control, better health-related quality of life, and improved survival.

Table 3. Most frequent comorbidities based on selected studies

Comorbidity	Prevalence (%) (minimum–maximum)	Study
Hypertension	17–64.7	Holguin (2005)[15], Battaglia (2015)[25]
Coronary artery disease	19.9–47.8	Battaglia (2015)[25], Schwab (2017)[32]
Diabetes	10.2–45	Baty (2013)[17], Dal Negro (2015)[24]
Osteoarthritis	18–43.8	Westerik (2017)[31], Schwab (2017)[32]
Psychiatric conditions	12.1–33	Baty (2013)[17], Koskela (2014)[22]
Asthma	14.7–32.5	Mannino (2015)[26], Jeong (2016)[28]
Gastroesophageal reflux disease	11.2–28	Miller (2013)[18], Deniz (2016)[29]
Chronic heart failure	7.8–27.6	Jeong (2016)[28], Schwab (2017)[32]
Chronic kidney disease	9.9–25.8	Mannino (2015)[26], Schwab (2017)[32]
Arrhythmia	14.4–24	Ongel (2014)[20], Divo (2018)[33]
Osteoporosis	6.9–20.1	Mannino (2015)[26], Schwab (2017)[32]
Obesity	2.8–20	Diez-Manglano (2014)[21], Deniz (2016)[29]
Atrial fibrillation	9.7–13	Divo (2012)[16], Baty (2013)[17]

Table 4. Main outcomes of selected articles

Outcome	Study	Result
Mortality	Holguin (2005)[15]	Higher mortality (p<0.01): respiratory failure (37%), pneumonia (25%), congestive heart failure (24%), ischemic heart disease (18%), hypertension (14%), chest malignancies (13%), diabetes (12%), and pulmonary vascular disease (5%).
	Divo (2012)[16]	Risk of death: lung cancer (p<0.001), atrial fibrillation/flutter (p<0.001), pulmonary fibrosis (p=0.006), anxiety (p=0.006), coronary artery disease (p=0.01), pancreatic cancer (p=0.02), esophageal cancer (p=0.02), congestive heart failure (p=0.02), gastric/duodenal ulcers (p=0.02), and liver cirrhosis (p=0.02). The COPD specific comorbidity test (COTE Index) were associated with an increased risk of death from COPD (HR, 1.13; 95% CI, 1.08–1.18; p<0.001) and non-COPD causes (HR, 1.18; 95% CI, 1.15–1.21; p<0.001). The BODE index and COTE Index were associated with increased risk of death. A COTE score of greater than or equal to 4 points increased by 2.2-fold the risk of death (HR, 2.26–2.68; p<0.001) in all BODE quartile.
	Baty (2013)[17]	Risk of in-hospital death (p<0.001): lung neoplasm; pulmonary heart disease, atrial fibrillation, and congestive heart failure
	Miller (2013)[18]	Higher mortality (p<0.01): heart problems, congestive heart failure, ischemic heart disease, heart disease, and diabetes. COPD and cardiovascular disease were associated with higher mMRC dyspnea scores, reduced 6MWT, and higher BODE index scores. Osteoporosis, hypertension, and diabetes were associated with higher MRC dyspnea scores and reduced 6MWT.
	Ongel (2014)[20]	Risk of death: pneumonia (p<0.001), chronic hypoxia (p<0.001), coronary artery disease (p<0.001), arrhythmia (p=0.003), and hypertension (p<0.008).
	Divo (2014)[23]	Coronary artery disease (p=0.05) and atrial fibrillation (p=0.01) in the group BMI ≤21 kg/m^2; and lung cancer (p<0.0001), diabetes mellitus (p=0.04), pulmonary hypertension (p=0.019), and pulmonary fibrosis (p=0.04) in the group BMI ≥30 kg/m^2. The BMI was inversely related to the ratio of FEV_1 to FVC, BODE index and hyperinflation.
Exacerbations	Jeong (2016)[28]	Coexisting asthma (p=0.016), home oxygen therapy (p=0.013), and C-reactive protein (p=0.036) were associated with frequent severe exacerbations.
	Deniz (2016)[29]	In 73.1% of exacerbations, at least one comorbid disease was recorded.
	Westerik (2017)[31]	Patients with one or more comorbid conditions had more than 2 exacerbations/year compared to patients without any comorbidity (p=0.001).
Hospitalizations	Schwab (2017)[32]	Association with hospitalizations (p<0.0001): congestive heart failure, coronary artery disease, and cerebrovascular disease. Association with COPD-related hospitalizations (p<0.0001): congestive heart failure, anxiety, and sleep apnea.
Hospital stay length	Baty (2013)[17]	Longer hospital stay (p<0.001): candidiasis, anemia, depressive disorder, atrial fibrillation, congestive heart failure, asthma, respiratory failure, and cachexia.
Disease severity	Echave-Sustaeta (2014)[19]	Association with severity: diabetes, hypercholesterolemia, congestive heart failure, and atrial fibrillation. The Charlson comorbidity index score, increased with the severity of the disease (p=0.013) between stages I and IV. The mean (SD) Charlson score was 2.2 (2.2) for stage I, 2.3 (1.5) for stage II, 2.5 (1.6) for stage III, and 2.7 (1.8) for stage IV (p=0.013 between stage I and IV groups), independent predictors of Charlson score were age, smoking history (pack-years), the hemoglobin level, and dyspnea, but not GOLD stage.
	Dal Negro (2015)[24]	All the comorbidities increased their prevalence progressively until the last stage of COPD, except for cardiovascular and metabolic ones that fell in stage IV GOLD (p=0.02 and p<0.05, respectively).
	Battaglia (2015)[25]	None of the analyzed comorbidities showed a tendency to increase the prevalence of COPD severity, except for nutritional problems (p=0.039).
	Caram (2016)[27]	Current smoking, depression, and dyslipidemia were more prevalent in patients with mild to moderate COPD than in those with severe to very severe (p<0.001, p=0.008, respectively). The Charlson index and HADS scores did not differ between the groups.

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Table 4. Continued

Outcome	Study	Result
Quality of life	Miller (2013)[18]	COPD and cardiovascular disease were associated with poorer quality of life (p<0.001).
	Koskela (2014)[22]	The significant determinants of the HRQoL-15D scores: psychiatric conditions, FEV_1, alcohol abuse (p≤0.001), diabetes (p=0.007), cardiovascular diseases (p=0.006), and hypertension (p=0.04). Psychiatric conditions and alcohol abuse were the strongest determinants of HRQoL in COPD and could be detected by both 15D (OR, 4.7 and 2.3 respectively) and AQ20 (OR, 2.0 and 3.0) instruments. FEV_1 was a strong determinant of HRQoL only at more severe stages of disease (FEV_1 <40% of predicted). Poor HRQoL also predicted death during the next 5 years.
Healthcare costs	Mannino (2015)[26]	Costs were higher for patients with chronic kidney disease ($ 41,288) and anemia ($ 38,870).
	Deniz (2016)[29]	The cost of each exacerbation was US$ 1,014.9 in patients with at least one comorbidity, and US$ 233.6 in patients without comorbidity (p<0.001).
	Schwab (2017)[32]	All the evaluated comorbidities (except obesity and chronic renal insufficiency) were associated with higher costs (p<0.0001).

COPD: chronic obstructive pulmonary disease; COTE: COPD specific comorbidity test; HR: harzad ratio (a measure of an effect of an intervention on an outcome of interest over time); CI: confidence interval; BODE: Body-mass index, airflow Obstruction, Dyspnea, and Exercise; mMRC: modified Medical Research Council; 6MWT: 6-minute walk test; BMI: body mass index; FEV_1: ratio of forced expiratory volume in second; FVC: forced vital capacity; SD: standard deviation; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HADS: Hospital Anxiety and Depression Scale; HRQoL-15D: health-related quality of life; AQ20: Airways questionnaire 20; OR: odds ratio (a measure of the association between an exposure and an outcome).

1. Frequency of comorbidities in COPD

It is well known that the existence of comorbidities increases with age in the general population. However, COPD patients appear to have comorbidities earlier in life compared to non-COPD subjects[33]. Mechanisms explaining the higher frequency of comorbidities in COPD include the premature aging process, possibly due to high oxidative stress levels, reduction in endogenous antiaging molecules, and cellular senescence, among other factors[33,36].

However, accelerated aging does not explain the variability observed in the prevalence of comorbidities in different studies. For example, in the study by Schwab et al.[32] the prevalence of coronary artery disease was 19.9% among COPD patients with a mean age of 70.6 years, compared to 47.8% in the Battaglia et al.'s study[25] in patients in the same age group (mean age, 71.8 years). Other pathophysiological mechanisms may be involved in the development of comorbidities, as systemic inflammation is associated with smoking or the inhalation of noxious environmental particles. This systemic inflammation has been associated with the development of cardiovascular diseases, neoplasms, or skeletal muscle dysfuncion[37].

Variability in the prevalence of comorbidities is also probably related to the characteristics of the studied population. Some studies analyzed comorbidities in patients admitted to hospital for COPD exacerbations, while others analyzed ambulatory, and therefore, milder COPD patients. To illustrate these differences, the presence of comorbid asthma in a large administrative health claims dataset was 14.7%[26], whereas it rose to 32.5% in COPD patients from a referral hospital in South Korea[28]. In addition to the different severity of COPD, different aspects like the genetic background of the populations and different environmental exposures may partly account for the differences in the prevalence of some comorbidities[38].

The two most frequent comorbidities in COPD are hypertension and coronary artery disease, but chronic heart failure, arrhythmia, and atrial fibrillation are also among the 13 most frequent comorbidities. Therefore, it is not surprising that the main cause of death in patients with mild to moderate COPD is cardiovascular disease. The high prevalence and impact of cardiovascular comorbidity in COPD justify the systematic evaluation of cardiovascular diseases in these patients. The link between COPD and cardiovascular disease is not completely clear. They share important etiologic factors (for example, smoking) and the systemic inflammation, the lung hyperinflation, the reduced oxygenation and associated factors like sedentarism and obesity may

explain the high frequency of cardiovascular comorbidities in COPD[17,34,39].

2. Impact of comorbidities in COPD

Not all comorbidities have demonstrated an association with poor outcomes in COPD patients, which may have implications for clinical practice. Divo et al.[34] developed the concept of the comorbidome taking into account the frequency and impact on mortality in a series of 78 comorbidities found in COPD patients from the BODe cohort. Among them, only 12 comorbidities were associated with increased mortality in COPD; similarly, only six of the most frequent comorbidities identified in our systematic review showed a significant association with increased mortality: coronary artery disease, diabetes, psychiatric disorders, chronic heart failure, atrial fibrillation, and other arrhythmias.

Nevertheless, other comorbidities may be associated with different outcomes in COPD. In the large longitudinal ECLIPSE study, self-reported gastroesophageal reflux was associated with an increased risk of COPD exacerbations and hospitalizations[40]. Interestedly, cardiovascular diseases, like congestive heart failure and coronary artery disease are relevantly associated with increased risk of exacerbations and hospitalizations and a prolonged length of hospital stay.

Asthma is also significantly associated with more frequent COPD exacerbations. Asthma may coexist in up to 25% of COPD patients and this correlation implies more severe respiratory symptoms, more frequent exacerbations, and significantly impaired quality of life compared with COPD alone[41-44]. It is important to recognize the coexistence of asthma because it has therapeutic implications due to inhaled corticosteroids.

The coexistence of cardiovascular disease and COPD results in a significantly impaired quality of life. This impairment may be partly due to the limited exercise capacity caused by an imbalance in the oxygen transportation, alterations in perfusion, and diffusion of the cardiopulmonary system, among other pathophysiological mechanisms[45]. The coexistence of chronic heart failure and COPD may produce severe dyspnea on exertion and it might limit performance in the daily activities[45]. Finally, these alterations may be complicated by psychological distress[46].

Despite the frequency and impact of the coexistence of chronic heart failure and COPD, some studies have demonstrated that treatment for these patients does not always follow the existing guidelines. In particular, there is a low level of prescription of cardioselective beta-blockers, which may have a negative impact on the disease progression in these patients[47,48].

3. Limitations

Therefore, the present systematic review presented important data on the most prevalent comorbidities in COPD patients and their main associations with important clinical outcomes. However, the review was based only on studies from the MEDLINE, Lilacs, and Scielo databases. This limited search strategy can lead to publication bias and decrease the likelihood of finding relevant studies.

Conclusion

Comorbidities are frequent in individuals with COPD although their prevalence varies according to patient characteristics and different study designs. Comorbidities do have a negative impact on several outcomes in COPD, including the symptoms, exercise capacity, quality of life, and survival among others. It is essential to understand the repercussions of each comorbidity in COPD, in order to design more personalized and effective treatments approaches.

Authors' Contributions

Conceptualization: dos Santos NC, Miravitlles M, de Almeida VDC, Camelier FWR. Methodology: dos Santos NC, Camelier AA, Maciel RRBT, Camelier FWR. Formal analysis: dos Santos NC, Miravitlles M, de Almeida VDC, Camelier FWR. Data curation: dos Santos NC, Camelier AA, Maciel RRBT, Camelier FWR. Software: dos Santos NC, Maciel RRBT, Camelier FWR. Validation: Miravitlles M, de Almeida VDC, Camelier AA, Maciel RRBT, Camelier FWR. Investigation: dos Santos NC, Miravitlles M, Camelier FWR. Writing - original draft preparation: dos Santos NC, Miravitlles M, Camelier AA, de Almeida VDC, Camelier FWR. Writing - review and editing: dos Santos NC, Miravitlles M, Camelier AA, de Almeida VDC, Camelier FWR. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).
Supplementary Table S1. Keywords used in the electronic search with the Boolean operators "AND" and "OR".

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