




# A Systematic Literature Review of the Humanistic Burden of COPD

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**Background:** Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, causing substantial economic and social burden.

**Objective:** This review assessed the patient-reported humanistic burden associated with moderate to very severe COPD, specifically the impact on health-related quality of life (HRQoL), symptoms, limitations in daily life, and emotional implications, through the use of HRQoL instruments.

**Methods:** A systematic review was conducted to retrieve relevant clinical data from published literature using a representative sample of countries where healthcare systems provide wide availability of COPD medications and/or universal coverage includes respiratory medicines (Australia, Canada, China, France, Germany, Italy, Spain, the UK, and the USA). The primary inclusion criteria were patients with moderate to very severe COPD. HRQoL was quantified with non-disease-specific and disease-specific questionnaires.

**Results:** In total, 82 studies from 95 publications presented HRQoL data from patients with moderate to very severe COPD. Patient-reported HRQoL declined with worsening airflow limitation, advancing GOLD group, and increasing exacerbation frequency. Both increasing frequency of hospitalization for COPD exacerbations and recurrent hospitalization adversely impacted HRQoL. Comorbidity incidence was higher in patients with increased airflow limitation. It was associated with a further decline in HRQoL and increased depression and anxiety, particularly as disease-associated pain worsened. Physical activity improved HRQoL over time.

**Conclusion:** This review highlighted the impact of exacerbations and associated hospitalizations on the humanistic burden of COPD. These findings underline the importance of managing COPD actively, including prompt and appropriate use of pharmacological and non-pharmacological therapies that can improve symptoms and reduce the risk of exacerbations, thereby lessening the humanistic burden. Future reviews could consider a broader range of countries and publications to further assess the humanistic impact of COPD in low- and middle-income economies.

**Keywords:** chronic obstructive pulmonary disease, quality of life, humanistic burden, patient-reported outcomes

## Background

Persistent respiratory symptoms and airflow limitation characterize chronic obstructive pulmonary disease (COPD).<sup>1</sup> It is a leading cause of both morbidity and mortality worldwide, which leads to a substantial economic and social burden.<sup>1,2</sup> In 2017, there were approximately 300 million cases of COPD reported globally,<sup>3</sup> with approximately 3.2 million COPD-related deaths,<sup>4</sup> ranking the disease seventh

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in a global list of causes of disability,<sup>4</sup> and third in the leading global causes of death.<sup>5</sup>

Risk factors for COPD include tobacco smoking, environmental factors (such as air pollution and a reduction in air quality due to the burning of biomass fuels), and genetic susceptibility.<sup>6,7</sup> The burden of COPD is projected to increase in the coming decades due to continued exposure to environmental COPD risk factors and an aging population.<sup>8</sup>

Currently available treatments are directed toward improving symptoms, functional capacity, and quality of life while reducing the COPD exacerbation risk. Stable COPD is typically managed using non-pharmacological means, including smoking cessation, increasing physical activity (including pulmonary rehabilitation), other lifestyle changes, and pharmacological therapy.<sup>1</sup>

The cornerstones of pharmacological therapy for COPD are long-acting bronchodilators (long-acting muscarinic antagonists and long-acting  $\beta_2$  agonists), which function to relax the smooth muscle of the airways and reduce lung hyperinflation. Together, these can be used individually or in combination with inhaled corticosteroids (ICS) as dual or triple therapy.<sup>1</sup> ICS target the inflammatory aspects of COPD, and the magnitude of their effect can be predicted by measuring blood eosinophil levels. Triple therapy is typically reserved for patients with a high symptom burden and a high risk of exacerbations despite previous combination therapies.<sup>1,9</sup>

The objective of this systematic literature review (SLR) was to further the understanding of the humanistic burden of moderate to very severe COPD, with no restrictions on interventions or comparators, using health-related quality of life (HRQoL) instruments, and examining the impact of symptoms, limitations in daily life, emotional implications, and stress on individuals affected. The SLR was based on data from non-interventional, cohort, case-control and registry/database studies conducted in nine countries (Australia, Canada, China, France, Germany, Italy, Spain, the UK, and the USA).

## Methods

### Identification of Studies

An SLR was conducted to retrieve relevant clinical data from published literature. Searches of Embase<sup>®</sup>, MEDLINE<sup>®</sup>, and MEDLINE<sup>®</sup> In-Process were run from January 1 2006 until March 30 2020; only articles published in English were included. Bibliographic searching

of selected Cochrane reviews and/or systematic reviews, identified during the screening, was conducted to identify any additional published literature not retrieved through previous database searches. The search strategies are shown in [Tables S1–3](#).

Additionally, abstracts from the American College of Chest Physicians, the American Thoracic Society, the European Respiratory Society, the International Society for Quality of Life Research, and the International Society for Pharmacoeconomics and Outcomes Research conference proceedings from 2018 to 2020 were hand searched.

Due to the large amount of data identified, the studies included in the SLR were limited to nine countries; Australia, Canada, China, France, Germany, Italy, Spain, the UK, and the USA. These countries were selected to provide a representative sample of countries across Europe, Asia and North America. A further criterium for inclusion was that the country's healthcare system provides wide access to COPD medications and/or has universal healthcare coverage that includes respiratory medicines.

Studies examined included patients  $\geq 40$  years of age with moderate to very severe COPD (% predicted forced expiratory volume in 1 second [FEV<sub>1</sub>]  $\leq 80\%$ ), with no restrictions on sex, race, interventions, or comparators; data for patients with mild COPD were excluded. The selection criteria of the studies are summarized in [Table 1](#). Literature reviews and previous systematic reviews were excluded in order to focus solely on primary data sources.

### Data Collection and Extraction Phase

For the first pass, citations were screened by a single reviewer based on the abstract supplied with each citation; an independent reviewer conducted a quality check (QC). Citations that did not match the eligibility criteria were excluded; where unclear, citations were included. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded.

For the second pass, the eligibility criteria were applied to the full-text citations. Each full-text was screened by a single reviewer, followed by an independent QC. The data presented in the studies included after this stage were extracted to data extraction grids by a single reviewer to ensure that data were extracted uniformly and were comparable across trials. A further independent QC was then conducted. Where a single study was described by more than one publication, the data were compiled into a single entry in the data extraction sheet to avoid duplication.

**Table 1** PICOS for the Inclusion of Studies in the Humanistic Burden Review

Criteria	Inclusion Criteria	Exclusion Criteria	Rationale for Exclusion
Patient population	Age: adults (≥40 years) Sex: any Race: any Disease: patients with moderate to very severe COPD (% predicted FEV <sub>1</sub> : ≤80%)	Patient population with mild COPD Children	Limit review to core population impacted by COPD exacerbations
Interventions	Studies assessing the overall humanistic burden of COPD without the impact of an intervention were included	Studies assessing intervention impact	Focus on overall humanistic burden
Comparators	No restriction on comparators	NA	NA
Study designs	Non-interventional studies Cohort studies Case-control Registry/database studies	Case studies, case series, case reports, and literature review, and systematic reviews	Limit review inputs to controlled studies and primary sources
Publication timeframe	January 1 2006 to March 30 2020	Studies prior to 2006	Focus on recent data to reflect current situation
Countries	Australia Canada China France Germany Italy Spain UK USA	Other countries	Limit review to representative country sample across Europe, Asia, North America and Australia
Language	Studies published in the English language	Studies not published in the English language	Focus on data published via international platforms

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in one second; NA, not applicable; PICOS, Population, Intervention, Comparator, Outcomes, Study design.

## Appraisal/Grading of Included Studies

A critical appraisal was conducted using 10 criteria previously described by Gill and Feinstein<sup>10</sup> and further modified by Moons et al.<sup>11</sup> The number of studies complying with each specific criterion was counted. A summary score (number of criteria fulfilled/total number of criteria) was calculated, indicating how well each study performed on the respective criteria, ranging from 0 (complying with

none of the criteria) to 100 (complying with all the criteria). This information is summarized in [Table S5](#).

## HRQoL and Symptoms Questionnaires

The included studies used a range of patient-reported HRQoL data ([Table 2](#)) from the disease-specific St. George's Respiratory Questionnaire (SGRQ), the COPD Assessment Test™ (CAT), the Clinical COPD

**Table 2** Tools Used to Assess the HRQoL Across Included Studies

	Non-Specific			Specific						
	EQ-5D VAS	SF-36	SF-12	SGRQ	CAT	MRC	mMRC	CRQ	CCQ	EXACT
<b>No. of studies</b>	9	9	12	34	20	6	12	7	4	1

**Abbreviations:** CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; CRQ, Chronic Respiratory Questionnaire; EQ-5D VAS, EuroQol five dimensions questionnaire visual analog scale; EXACT, EXacerbations of Chronic pulmonary disease Tool; HRQoL, health-related quality of life; MRC, Medical Research Council Dyspnea scale; mMRC, modified Medical Research Council Dyspnea Scale; SF-12, 12-item short-form survey; SF-36, 36-item short-form survey; SGRQ, St. George's Respiratory Questionnaire.

Questionnaire (CCQ), the Chronic Respiratory Disease Questionnaire (CRQ), the Medical Research Council dyspnea scale (MRC), and the Exacerbations of Chronic Pulmonary Disease Tool (EXACT). Additionally, several non-disease-specific questionnaires reported HRQoL data (Table 2): the 36-item short-form survey (SF-36), 12-item short-form survey (SF-12), and EuroQol five dimensions visual analog scale (EQ-5D VAS).

## Assessments

Disease severity was assessed based on airflow limitation, exacerbations, physical activity, and comorbidities.

### Airflow Limitation

Disease severity in COPD is most commonly defined by the degree of airflow limitation, measured by the percentage of predicted post-bronchodilator FEV<sub>1</sub>, and is classified into four stages by GOLD.<sup>1</sup>

### COPD Stratified by GOLD Groups A–D

GOLD groups A–D are used to classify patients based on symptom burden (through the assessment of dyspnea using a modified MRC scale [mMRC] or symptoms using CAT) and exacerbation history (previous history of moderate or severe exacerbations) to aid treatment decisions. Symptom burden is lower in GOLD groups A and C (mMRC 0–1, CAT <10) compared with GOLD groups B and D (mMRC ≥2, CAT ≥10), and exacerbation risk is lower in GOLD groups A and B (0/1 exacerbation event) compared with GOLD groups C and D (≥1 exacerbation event leading to hospitalization or ≥2 that did not).<sup>1</sup>

### Exacerbations and Hospitalization

The most recent GOLD report defines COPD exacerbations as an acute worsening of respiratory symptoms that requires additional therapy and categorizes them as mild, moderate, or severe.<sup>1</sup> Mild exacerbation events may be managed with an increase in short-acting rescue medication but are often not reported in clinical practice or clinical trials; moderate exacerbations require treatment with short-acting rescue medication plus antibiotics and/or oral steroids, and severe exacerbations require treatment in the emergency room or hospitalization (and may lead to death).<sup>12</sup>

### Physical Activity

Physical activity was commonly measured as the physical component of non-disease-specific questionnaires such as the SF-36 and SF-12, where a physical health composite

score (PCS) can be determined from the individual domains.

### Comorbidities

Physical comorbid diseases were measured similarly to physical activity, as the PCS of non-disease-specific questionnaires, and mental comorbidities used the mental health composite score (MCS) of non-disease-specific questionnaires.

## Results

### Study Selection

The initial database searches identified 17,708 publications, of which 2740 were subsequently removed due to duplication. Screening of article titles and abstracts reduced the number of eligible publications to 2874, and bibliographic searching identified a further two citations; following review of the full articles, a further 2754 publications were excluded. In total, 122 studies were identified and, after linking, 95 publications reporting data from 82 studies were included in the review (Figure 1).

### Study Characteristics

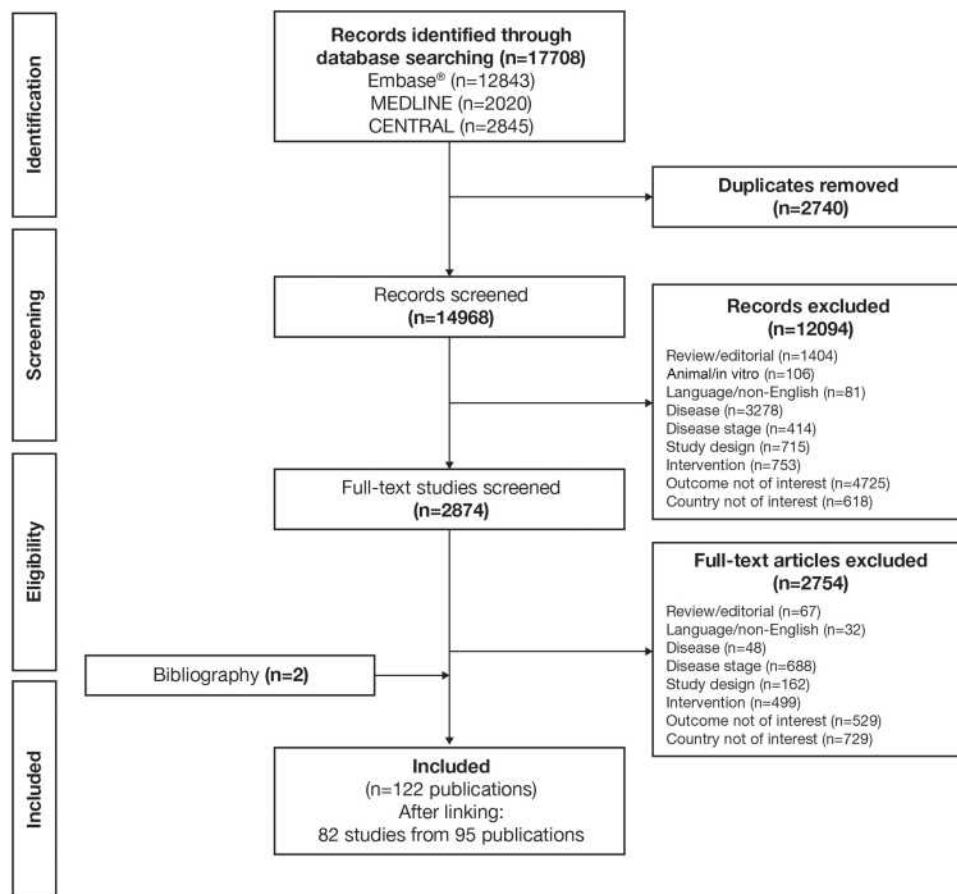
The studies included either non-disease-specific or disease-specific HRQoL data. The data were predominantly reported in cross-sectional (40 studies) or prospective observational studies (33 studies); 50 studies were multi-center, 18 studies were single-center, and the setting could not be ascertained in the remaining 14 studies.

The majority of studies in the review were conducted in the USA and Spain (19 studies each), followed by the UK and China (11 studies each). Studies included in the review reported HRQoL primarily using SGRQ followed by CAT, MRC/mMRC, SF-12, SF-36, and EQ-5D VAS (Table 2). The patient numbers varied widely between studies ranging from 14–10,711 patients<sup>13,14</sup> (Table S4).

The mean age of patients was reported by 65 studies and ranged from 57 to 76 years of age. Patient characteristics are summarized in Table S4.

### Critical Appraisal of Studies

Only 6 studies (7%) provided a definition of quality of life (QoL, Table 3), while 72 studies (88%) explicitly stated the domains constituting QoL. Thirteen studies (16%) reported why the specific measurement was chosen. Forty-seven studies (57%) assessed QoL with a single-item instrument or with a composite score of multiple-item tools to provide an overall score. Five



**Figure 1** Flow of studies through the humanistic burden SLR.  
**Abbreviation:** SLR, systematic literature review.

studies (6%) allowed patients to self-rate their perceived QoL. Seven studies (9%) distinguished between overall QoL and HRQoL. None of the studies included provided a way for the respondents to select supplemental items important to them. However, one study (1%) used an instrument allowing respondents to rate the importance of respective items in the instrument. Summary scores for individual studies ranged from 0 to 62.5, with a median score of 25 (quartile 1=12.5; quartile 3=25). A score of 100 indicated compliance with all ten criteria. Only 4 studies had a summary score of 50 or higher.

## Airflow Limitation

Studies reported the effects of airflow limitation on HRQoL using both disease-specific and non-disease-specific questionnaires, primarily using SGRQ followed by CAT, mMRC, SF-12, SF-36, and EQ-5D-VAS (Table 2).<sup>15–37</sup> Overall, the highest SGRQ values (greatest impairment) were reported in patients with severe/very severe airflow limitation compared with other patients.<sup>20,24,35</sup> Vaz Fragoso

et al showed SGRQ total score was higher in patients with severe COPD compared with patients with moderate COPD (41.8 [95% confidence interval (CI) 39.0–44.7] vs 30.0 [95% CI 26.6–33.3]).<sup>24</sup> Further data revealed a weak positive correlation between CAT score and severity of airflow obstruction.<sup>15,26,28</sup>

A large body of evidence across all nine countries and all instruments showed that, in general, the HRQoL of patients with COPD deteriorated with increased severity of airflow limitation. However, there was a wide variation between individual patients.<sup>18,19,25,27,38–40</sup>

## COPD Stratified by GOLD Groups A–D

A study by Lopez-Campos used GOLD groups defined by MRC dyspnea score to study the relationship between the GOLD group and HRQoL (CAT score).<sup>41</sup> CAT score was highest for GOLD D patients (high symptom burden/high exacerbation risk, 21.8), followed by GOLD B (high symptom burden/low exacerbation risk, 18.2;  $p < 0.001$  vs GOLD D), GOLD C (low symptom burden/high

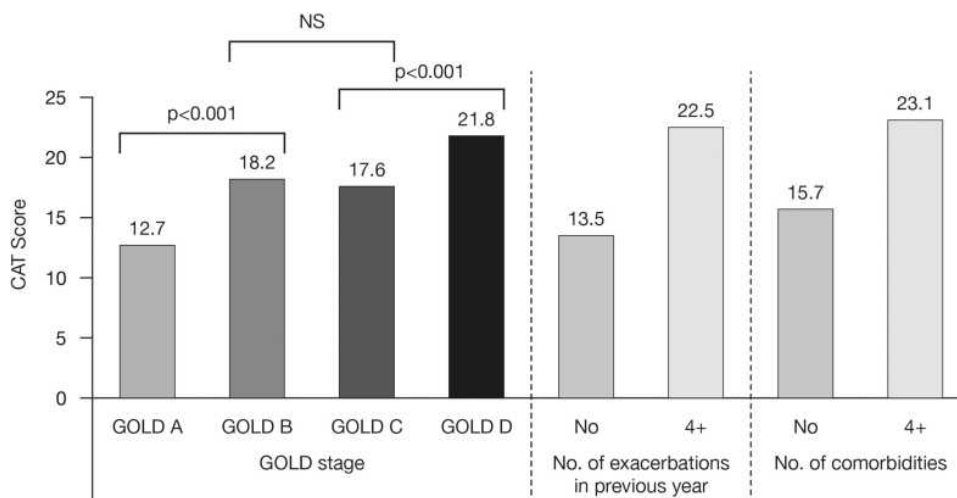
**Table 3** Summary of Studies Meeting and Adhering to HRQoL Criteria

Criteria	Studies Meeting Criteria, n (%)
Did the investigator give a definition of quality of life?	6 (7)
Did the investigators state the domains they will measure as components of quality of life?	72 (88)
Did the investigators give reasons for choosing the instrument they used?	13 (16)
Did the investigator aggregate results from multiple items, domains or instruments into a single composite score for quality of life?	47 (57)
Were patients asked to give their own global rating for quality of life?	5 (6)
Was overall quality of life distinguished from health-related quality of life?	7 (9)
Were the patients invited to supplement the items listed in the instruments offered by the investigators that they considered relevant for their quality of life?	0 (0)
If so, were these supplemental items incorporated into the final rating?	0 (0)
Were patients allowed to indicate which items were personally important to them?	1 (1)
If so, were the importance ratings incorporated into the final rating?	0 (0)

**Note:** Studies could be counted in more than one category.

exacerbation risk, 17.6) then GOLD A (low symptom burden/low exacerbation risk, 12.7;  $p < 0.001$  vs GOLD B; [Figure 2](#)); this indicated that both symptom burden and exacerbation risk had a negative impact on HRQoL.<sup>41</sup> Patients who moved from GOLD B to D had significantly higher SGRQ total score and CAT score at baseline than patients who remained in GOLD group B at follow-up (SGRQ total score 50.0 vs 40.1,  $p = 0.019$ ; CAT score 21.0 vs 14.0,  $p = 0.006$ ), indicating a worsening in HRQoL. At 1-year follow-up, patients who had

experienced a moderate to severe exacerbation and progressed to GOLD D reported significantly worse CAT score than those who had not (20.0 vs 15.5,  $p = 0.018$ ), suggesting that exacerbations increase symptom burden and reduce HRQoL.<sup>42</sup> Patients categorized as having a high symptom burden (GOLD B and D) had higher SGRQ total scores than those with a low symptom burden (GOLD A and C), highlighting the impact on HRQoL.<sup>43</sup> Further to this, when assessed using CRQ, HRQoL was significantly better for patients in GOLD A and



**Figure 2** Mean CAT scores segregated according to GOLD stage, exacerbation history, and comorbidities. Adapted from Lopez-Campos JL, et al. Evaluation of the COPD Assessment Test and GOLD patient types: a cross-sectional analysis. *Int J Chron Obstruct Pulmon Dis.* 2015;10:975–984. Dove Medical Press Limited.<sup>41</sup>

**Abbreviations:** CAT, COPD Assessment Test; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NS, not significant.

C compared with GOLD B and D.<sup>44</sup> GOLD B patients have also been shown to have lower mean SF-36 PCS and MCS compared with GOLD C patients,<sup>45</sup> providing further evidence that symptomatic patients have a reduced HRQoL compared with patients with a low symptom burden.

The included studies showed that the greatest impact on HRQoL was in patients with high symptom burden and, in particular, patients categorized as GOLD D.

## Exacerbations and Hospitalization

CAT scores were strongly associated with annual exacerbation frequency<sup>46</sup> and increased as the number of exacerbations increased (Figure 2).<sup>41</sup> However, the CAT score was not associated with increased hospitalization risk.<sup>47</sup> The baseline severity of airflow limitation was an independent determinant for increased CAT score during severe exacerbation ( $p=0.013$ ). Patients with recurrent hospitalizations showed slower recovery compared with patients hospitalized less frequently over a 3-month observational period.<sup>48</sup> Fernández-García et al reported that patients with a hospital stay of  $\geq 7$  days had worse CAT scores than patients with a hospital stay of  $< 7$  days ( $20.1$  vs  $18$ ;  $p=0.02$ ).<sup>32</sup>

Bourbeau et al assessed patients with moderate to very severe COPD (mean pre-bronchodilator FEV<sub>1</sub> of 45% predicted) to evaluate the impact of exacerbations upon HRQoL.<sup>38</sup> Exacerbation events of any severity were associated with statistically significant decreases in the mean changes in SGRQ activity and impact domains at onset, during the first and second weeks post-exacerbation. A clinically significant deterioration in SGRQ impact scores (an increase in score of  $\geq 4$  from baseline) was seen in 71% of patients at the onset of an exacerbation, decreasing to 55% at 1 week post-exacerbation and again to 37% at 2 weeks post-exacerbation.<sup>38</sup>

Assessment of patients over 6 months indicated that the number of exacerbations was associated with HRQoL. Improvements in HRQoL were reported in patients who had experienced either no exacerbations (SGRQ total score mean change of  $-6.2$  at 1 month and  $-6.9$  at 6 months after initiating treatment) or only one exacerbation (SGRQ total score mean change of  $-4.7$  at 1 month and  $-4.2$  at 6 months after initiating treatment). In contrast, HRQoL did not improve in patients who experienced  $\geq 2$  exacerbations. However, these patients' health status remained unchanged during the 6-month study period.<sup>38</sup> A cross-sectional study reported significantly higher SGRQ-C (a shorter, COPD-

specific form of the SGRQ questionnaire) total scores in patients with recent severe vs moderate exacerbation ( $70.3 \pm 19.9$  vs  $61.7 \pm 20.1$ ,  $p<0.001$ ). SGRQ-C was also significantly higher in patients with very severe vs severe exacerbation ( $70.1 \pm 21.3$  vs  $61.1 \pm 19.0$ ,  $p<0.001$ ). Thus, increased exacerbation severity negatively affected the HRQoL.<sup>49</sup>

The frequency of hospitalization has been related to a reduction in HRQoL reported by both disease-specific and non-disease-specific questionnaires. SGRQ score was strongly associated with the number of hospitalizations, with lower scores correlating to fewer hospitalizations in the previous year.<sup>50</sup> In a 5-year study, no changes in HRQoL were observed among patients not hospitalized for COPD exacerbations.<sup>19</sup> In contrast, a significant decline in HRQoL was observed in patients with  $\geq 3$  hospitalizations due to an exacerbation during 5 years of follow-up.<sup>51</sup> Similarly, the largest changes were observed among patients with  $\geq 3$  hospitalizations, determined by a large decrease in the SF-36 PCS score. However, hospitalization following an exacerbation resulted in a decline in HRQoL over the study period regardless of the initial severity of the disease.<sup>51</sup> In terms of mortality, patients who did not survive the 5-year follow-up period (27.2%) had a higher SGRQ total score (mean  $47.3 \pm 16.1$  vs  $38.2 \pm 18.2$ ,  $p<0.0001$ ) and higher incidence of severe airflow limitation (15.7% vs 3.2%) at baseline compared with patients who survived.<sup>51</sup>

Following adjustment by percentage predicted FEV<sub>1</sub>, age, comorbidities, and baseline HRQoL, a multivariate analysis found that hospitalizations were an independent predictor of the change in HRQoL when assessed by SGRQ total score ( $4.9$  [1–2 hospitalizations,  $p=0.01$ ] vs  $15.3$  [ $\geq 3$  hospitalizations,  $p<0.0001$ ]). When using the SF-36 questionnaire, the decline in physical component was independently associated with hospital admission ( $-2.7$  with 1–2 hospitalizations [ $p=0.004$ ];  $-5.2$  with  $\geq 3$  hospitalizations [ $p=0.0005$ ] vs no hospitalizations), whereas a decline in the mental component was only an independent predictor in patients experiencing  $\geq 3$  hospitalizations ( $-5.0$  vs no hospitalizations,  $p=0.01$ ).<sup>51</sup>

Data collated in this review indicate that patients who experienced moderate to severe exacerbations, or had a history of exacerbations, had worse HRQoL than patients with stable COPD not experiencing these events. Furthermore, the number of exacerbations experienced by

a patient and hospitalization frequency were correlated with a worsening in HRQoL.

## Physical Activity

Changes in HRQoL in association with physical activity were reported in seven publications using SGRQ, CAT, SF-12, CCQ, and SF-36.<sup>19,34–37,51–53</sup> A strong relationship was reported between physical activity and HRQoL, as determined by the association with the number of steps/day and SGRQ activity scores in patients who were physically active compared with those who were not.<sup>52</sup> Ramon et al performed a pooled analysis investigating the usefulness of self-reported walking time to identify patients with COPD at high risk of inactivity and determined that self-reported walking time decreased with an increase in CAT score.<sup>53</sup>

The physical function and physical role scores of SF-36 have been shown to decrease with improved airflow limitation, indicating an improvement in HRQoL. SF-36 PCS and MCS scores declined in all categories over time, regardless of physical activity. However, the largest decline in HRQoL was observed in those patients who reported a decrease in physical activity at the 5-year follow-up.<sup>51</sup>

Overall, the body of evidence showed that increased airflow limitation is associated with greater physical overall decline. Higher levels of physical activity are associated with a positive impact on HRQoL in patients with COPD.

## Comorbidities

Patients with physical comorbidities such as heart disease, diabetes,<sup>14</sup> or anaemia,<sup>54</sup> showed significantly impaired HRQoL compared with patients without the comorbid disease, as indicated by a decrease in the PCS of both SF-12 and SF-36, but not the MCS.<sup>14,54</sup> An increase in CAT score was positively correlated with the number of comorbidities (15.7 with no comorbidities vs 23.1 for those patients with  $\geq 4$  comorbidities; Figure 2).<sup>41</sup>

Mental health status deteriorates with increased COPD severity;<sup>55</sup> patients with moderate to very severe airflow limitation and comorbid mental disorders, such as depression or anxiety, had reduced HRQoL compared with patients with airflow limitation but without comorbid disease.<sup>56</sup> Patients with greater bodily pain reported a lower HRQoL than patients with little pain (mean SF-12 MCS score 46.4 vs 54.2,  $p < 0.0001$ ).<sup>57</sup> Patients with comorbid depression and anxiety have demonstrated

significantly greater SGRQ total scores (55.3 for comorbid depression vs 40.4 for those without, and 61.5 for comorbid anxiety vs 40.6 for those without,  $p < 0.05$ ) across all sub-domains of the questionnaire.<sup>58</sup>

Two studies reported the relationship between HRQoL, airflow limitation, and sleep quality in patients with COPD. Dignani et al determined that sleep quality is associated with HRQoL and worsened with airflow limitation.<sup>18</sup> Furthermore, Shah et al reported that sleep disturbances can lead to increased exacerbation frequency and healthcare resource utilization.<sup>59</sup>

In summary, the data found during this review indicated that comorbidities were associated with a reduction in HRQoL. In particular, mental health-related comorbidities were increasingly cited as airflow limitation severity increased, further decreasing HRQoL in patients with COPD.

## Strengths and Limitations

To provide a representative sample of the worldwide burden of COPD while restricting the data to a manageable volume, the review focused on nine countries from Europe, Asia, Australasia and North America. Each included country was required to have a healthcare system that provided wide access to available COPD treatments and/or a universal coverage that included respiratory medicines. While country-specific or cultural differences were beyond the scope of the review, this is an area that could be explored with further research. China is classified by the World Bank as an upper middle-income economy, which distinguishes it from the other high-income economies in this review.<sup>60</sup> China was included based on ongoing changes to its healthcare system such as increased public health insurance coverage.<sup>61</sup> Inclusion was also in consideration of the exposure of individuals in China to important COPD risk factors such as tobacco smoking and air pollution related to biomass fuel usage.<sup>62</sup> Focusing the scope of the review on specific countries potentially eliminated important data, but it also meant that the review could not report the humanistic burden in low-/middle-income countries, where the World Health Organization reports that approximately 90% of COPD-related deaths occur per annum.<sup>63</sup> Also, only English language studies published from 2006 onwards were investigated, which may have eliminated important data from studies in other languages. Studies from prior to 2006 were deemed to be less relevant and, therefore, beyond the scope of this analysis.



There were wide variations regarding study size, COPD severity definitions, study design, and HRQoL instruments used. In addition, there may have been differences in cultural attitudes to COPD across the countries included that could have affected the assessment and reporting of HRQoL. While this makes direct comparisons difficult, all the data agree that increased COPD severity negatively impacts HRQoL.

## Discussion and Conclusions

This review demonstrated that moderate to very severe COPD has a significant impact on HRQoL through increased COPD symptoms, daily life limitations, worsening mental health, and reduction in physical activity and sleep quality, resulting in a considerable humanistic burden. Moreover, a progressive increase of COPD-associated pain (potentially manifesting as comorbid depression) is likely to lead to a further decline in HRQoL,<sup>57</sup> and patients with comorbid heart disease or diabetes had significantly impaired HRQoL when compared with patients without comorbid disease.<sup>14</sup> Exacerbations and a decline in lung function represent a large component of the humanistic burden and require specific management to prevent and control their occurrence. Patients with lower symptom burden in GOLD A and C reported a better HRQoL than patients in GOLD B and D, who are defined as having a higher symptom burden. Subsequently, patients in GOLD D had the worst HRQoL of any GOLD group.

As there is currently no way to reverse established pathology in COPD, disease management aims to reduce the symptom burden and the risk of exacerbations and mortality, all of which have been shown to impact HRQoL negatively. Both pharmacological and non-pharmacological therapies are vital in the management of COPD. The active management of COPD can prevent exacerbation events.

This review highlights the importance of active management for patients with COPD, along with treatments that reduce the risk of exacerbations and the rate of decline in lung function while improving symptoms. Active management should be individualized to specific patient needs, and focus on both COPD and its associated comorbidities, which have an important impact on HRQoL. Pulmonary rehabilitation and lifestyle intervention, including increasing physical activity, are also a critical consideration to reduce the humanistic burden of COPD. Prompt and appropriate use of pharmacological and non-pharmacological therapies have the potential to reduce

the cumulative long-term effects of exacerbations and the impact of COPD, thereby improving patient HRQoL and reducing the humanistic burden.

Future research may consider in more detail the impact of specific non-pharmacological interventions on HRQoL in COPD such as pulmonary rehabilitation, smoking cessation, domiciliary oxygen therapy, influenza/pneumococcal vaccinations and community-based multidisciplinary care, in addition to pharmacological interventions. As well as examining differences by country, expanding the scope to consider low- and middle-income economies could provide additional insights into differences in the humanistic burden of COPD that could further guide active COPD management in clinical practice.

## Abbreviations

CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; EQ-5D VAS, EuroQol five dimensions questionnaire visual analog scale; EXACT, EXAcerbations of Chronic pulmonary disease Tool; FEV<sub>1</sub>, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; ICS, with inhaled corticosteroids; mMRC, modified Medical Research Council Dyspnea Scale; MRC, Medical Research Council Dyspnea scale; NA, not applicable; NS, not significant; PICOS, Population, Intervention, Comparator, Outcomes, Study design; QC, quality check; SF-12, 12-item short-form survey; SF-36, 36-item short-form survey; SGRQ, St. George's Respiratory Questionnaire; SLR, systematic literature review.

## Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Consent for Publication

All authors provide consent for publication.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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