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SYSTEMATIC REVIEW

Systematic Review of Humanistic and Economic Burden of Symptomatic Chronic Obstructive Pulmonary Disease

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Abstract

Background An understanding of the humanistic and economic burden of individuals with symptomatic chronic obstructive pulmonary disease (COPD) is required to inform payers and healthcare professionals about the disease burden.

Objectives The aim of this systematic review was to identify and present humanistic [health-related quality of life (HRQoL)] and economic burdens of symptomatic COPD.

Methods A comprehensive search of online databases (reimbursement or claims databases/other databases), abstracts from conference proceedings, published literature, clinical trials, medical records, health ministries, financial reports, registries, and other sources was conducted. Adult patients of any race or gender with symptomatic COPD were included. Humanistic and economic burdens included studies evaluating HRQoL and cost and resource use, respectively, associated with symptomatic COPD.

Results Thirty-two studies reporting humanistic burden and 74 economic studies were identified. Symptomatic COPD led to impairment in the health state of patients, as assessed by HRQoL instruments. It was also associated with high economic burden across all countries. The overall, direct, and indirect costs per patient increased with an increase in symptoms, dyspnoea severity, and duration of disease. Across countries, the annual societal costs associated with symptomatic COPD were higher among patients with comorbidities.

Conclusions Symptomatic COPD is associated with a substantial economic burden. The HRQoL of patients with symptomatic COPD is, in general, low and influenced by dyspnoea.

Key Points for Decision Makers

Symptomatic chronic obstructive pulmonary disease (COPD) leads to impairment in the health state of patients.

Symptomatic COPD was associated with high economic burden across all countries. It influenced both direct and indirect costs associated with symptoms, dyspnoea severity, and duration of disease.

The health-related quality of life of patients with symptomatic COPD is, in general, low and influenced by multifactorial causality.

1 Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by varying degrees of airflow obstruction that reflect the severity of symptoms such as breathlessness, chronic cough, and wheeze [1]. It is the leading cause of morbidity and mortality across all countries with varying financial status [2] and thus imposes a challenging problem

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to the healthcare system [3]. Although the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends routine use of the modified Medical Research Council (mMRC) and COPD Assessment Test (CAT) to assess and treat COPD symptoms, symptomatic COPD has not been defined adequately in the published literature [1]. Increases in the number and severity of general symptoms and in the disease severity of COPD are associated with a humanistic and economic burden [4–10]. Furthermore, various comorbid conditions such as cardiac disorders, diabetes, obesity, osteoporosis, lung cancer, pneumonia, and psychological disorders may further impact the disease process [11–13]. Taken together, COPD has a high-level impact on health-related quality of life (HRQoL) and healthcare resource utilisation [14].

Patients with COPD usually suffer from a marked deterioration in HRQoL [15]. This impact on HRQoL can be measured in terms of general health status, mental health, functional status, fatigue, and quality of sleep [16, 17]. The findings of these HRQoL instruments, which provide non-invasive patient-centered monitoring, reflect the humanistic burden of COPD [14]. Similarly, there exists a strong correlation between disease severity and economic burden [18]. The main focus of COPD treatment has been on the reduction and prevention of exacerbations [19], which are costly to treat and exert a negative impact on the HRQoL of the affected individuals [20]. Thus, patients with no or very few exacerbations also incur significant costs through repeated general practitioner (GP) visits and associated healthcare contact for their symptoms, in addition to a compromised HRQoL, indicating that symptomatic COPD is associated with high economic and humanistic burdens [10].

The objective of this systematic review was to identify and evaluate humanistic (HRQoL) and economic burdens among symptomatic patients with COPD.

2 Methods

2.1 Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. It evaluated published evidence of humanistic burden of symptomatic COPD, as measured by HRQoL indices. The economic burden was assessed from cost-of-illness and resource use studies in patients with symptomatic COPD.

2.2 Information Sources

A comprehensive search of Excerpta Medica Database (EMBASE®), Medical Literature Analysis and Retrieval System Online (MEDLINE®), MEDLINE® In-Process, Cochrane Central Trials Register, Cochrane National Health Service Economic Evaluation Database (NHS EED), EconLit®, and Literatura Latino Americana em Ciências da Saúde (LILACS®) was performed from 2003 to 31 May 2013. In addition to database searching, abstracts from conference proceedings from the American Thoracic Society (ATS), American College of Chest Physicians (ACCP), European Respiratory Society (ERS), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) were hand searched from 2010 to 2013. A comprehensive search strategy was designed to retrieve relevant clinical data from published literature. An example of the search strategy is presented in detail in electronic supplementary Table S1.

The searches were restricted to include studies published in the English language, with the exception of LILACS®, which was not restricted to English articles. Relevant data from all included studies were extracted by a single reviewer, using a pre-defined extraction grid, which was subsequently validated by an independent reviewer. Thereafter, studies meeting the eligibility criteria were critically appraised using the Downs and Black checklist [22] for the humanistic burden, and the Drummond and Jefferson checklist for the economic burden [23].

2.3 Eligibility Criteria

The patient population of interest comprised adults of any race or gender with symptomatic COPD. Considerable variability in the definition of symptomatic COPD suggests that it is poorly defined in the clinical literature [1]. Therefore, in line with the GOLD guidelines, patients with one or more symptoms such as cough, breathlessness, sputum production, wheeze, and chest tightness were considered symptomatic [24]. Based on these recommendations, symptoms were also considered for evaluation in situations where they were based on physicians' discretion only. Furthermore, the burden of symptomatic COPD patients in early stages might be higher than for non-symptomatic patients in slightly advanced disease, making quantification of this disease burden even more challenging. The GOLD guidelines have defined dyspnoea as a sense of increased effort to breathe, heaviness, air hunger, or gasping. In addition to the above mentioned criteria, the GOLD guidelines have recommended the mMRC scale and CAT for assessing COPD symptoms. An mMRC score $\geq$2 (breathlessness) and a CAT score $\geq$10 (high level of symptoms) represents patients with high symptoms [1]. Thus, patients with an mMRC score $\geq$2 and a CAT score $\geq$10 were also included in the review.

The humanistic burden was restricted to include cohort/longitudinal, case–control, cross–sectional, single-arm, and

utility studies along with analyses of hospital records/databases and surveys. The outcomes of interest were patient-reported outcomes/HRQoL measures. Randomized controlled trials (RCTs) were excluded as they primarily focus on the assessment of efficacy and safety on a highly selective patient population rather than burden observed in clinical practice. Studies evaluating the impact of pharmacological or non-pharmacological interventions on improvement/deterioration of HRQoL were also excluded.

The economic burden was restricted to include cost studies/surveys/analysis and resource use studies in adult patients with symptomatic COPD, irrespective of the type of treatment investigated. As economic models present data for costs or cost effectiveness related to specific interventions under investigation, economic evaluations from modeling studies were excluded. The outcomes of interest were cost (direct, indirect, or total) and resource use associated with symptomatic COPD care.

2.4 Humanistic Assessments

The humanistic burden of illness (e.g. COPD) is characterised by the impact of illness on health and consequences of treatment, including impact on HRQoL or the relationship between various HRQoL scales and symptomatic COPD, loss of productivity and absenteeism, and frequency of clinical events (i.e. exacerbations, severity of symptoms). The complete list of HRQoL scales included in this review is available in electronic supplementary Table S2. Moreover, the relationship between patients' demographic and comorbid characteristics (age, gender, body mass index [BMI], smoking status, comorbid conditions, etc.) and their humanistic burden was also evaluated.

2.5 Cost Assessments

The economic burden was characterised by the estimation of cost-of-illness (direct, indirect, and total) required for treating the COPD cohort of interest. These included costs associated with symptoms (severity and frequency) and dyspnoea care (based on the MRC dyspnoea scale score), and costs related to comorbidity.

3 Results

3.1 Study Characteristics

A total of 32 studies reporting humanistic burden and 74 economic studies specifically reporting cost and resource use involving patients with symptomatic COPD were included. Six studies reported both humanistic and economic impact of COPD. Figure 1 shows the study selection process, in line with PRISMA guidelines. The characteristics of patients and studies included in the humanistic burden review are presented in Table 1. The impact of varying levels of symptoms on the humanistic burden in patients with symptomatic COPD is presented in electronic supplementary Table S3.

3.2 Humanistic Burden

3.2.1 Impact of Demographic Factors on Humanistic Burden of Symptomatic Chronic Obstructive Pulmonary Disease

Mollaoglu and colleagues observed that with advancing age (age groups 65–69, 70–74, and ≥75 years), elderly patients with symptomatic COPD demonstrated a trend towards increasing fatigue, disability, and overall decrease in energy ($p > 0.05$). Moreover, females were associated with higher fatigue and low energy levels compared with males, which was attributed to traditional female responsibilities within a family; however, the association was not statistically significant. Married patients had significantly increased fatigue compared with their single counterparts ($p = 0.02$). Furthermore, lower education level and employment (housewives and full-time employees) were associated with lower overall HRQoL ($p > 0.05$) [25].

3.2.2 Impact of Respiratory Symptoms and Dyspnoea

An increase in the severity of respiratory symptoms was associated with a corresponding decline in the HRQoL of patients [4, 5, 25–28].

Antoniu and colleagues evaluated HRQoL by categorising patients on the basis of symptom levels (mild, moderate, and severe). Patients experiencing severe sputum and cough had significantly higher fatigue and disability levels and significantly lower energy levels compared with patients with mild symptoms [28]. In contrast, a study by Al Moamary and colleagues revealed no significant differences in HRQoL in patients experiencing cough and wheezing evaluated using CAT and Chronic Respiratory Questionnaire–Self-Administered Standardized (CRQ-SAS) scores [4].

Based on the AQ20 score, patients reporting frequent cough, breathlessness during domestic work, and chest problems experienced limitation in full enjoyment of their life, whereas patients who did not present any respiratory symptoms scored the best possible result (score 0) [29]. Another study by Bellas and colleagues evaluated the relationship between cough and HRQoL in patients with COPD by using the CAT and the Leicester Cough Questionnaire (LCQ) as a cough-specific HRQoL measure. It

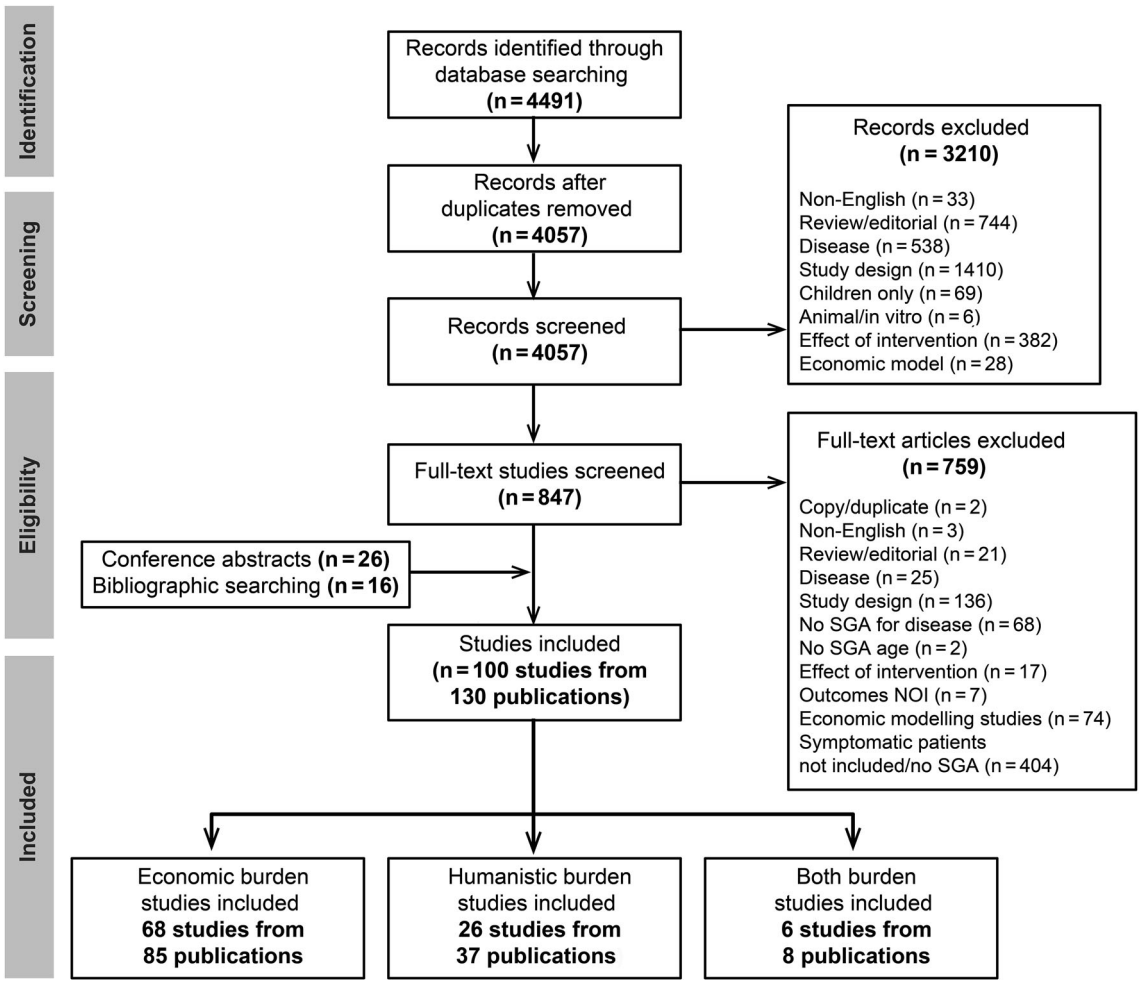

Fig. 1 Study selection process, in line with the PRISMA guidelines. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *NOI* Not of Interest, *SGA* Subgroup Analysis

was observed that increasing cough severity was associated with greater impairments in HRQoL [5].

This was also reflected in a significantly high mean of poor self-rated sleep quality [Pittsburgh Sleep Quality Index (PSQI)] in patients with a higher frequency of nocturnal wheezing, worrying, and uncontrolled thoughts. Other specific respiratory symptoms, not significant but associated with poor sleep quality, included cough, dyspnoea, chest pain, heartburn, and palpitations [30].

The association of dyspnoea with humanistic burden of symptomatic COPD was assessed in six studies. An increase in MRC scores from 0 to 4 was associated with worsening of HRQoL [4, 25, 27, 31–33]. Punekar and colleagues demonstrated a greater impairment in HRQoL with higher levels of dyspnoea, such that EuroQol (EQ-5D) utilities ranged from 0.88 to 0.17 in the primary care physician (PCP) cohort and 0.88 to 0.29 in the respiratory specialist cohort, with MRC score increasing from 0 to 4 [33]. Furthermore, among elderly patients, an increase in the severity of dyspnoea from mild to severe was associated with an increase in fatigue and disability and decrease in energy levels [25]. In a cross-sectional survey by Al Moamary and colleagues, patients with shortness of breath had significantly lower HRQoL compared with patients with no symptoms of shortness of breath on using the CAT score in contrast to the CRQ-SAS score, where association was negative but statistically non-significant [4]. Furthermore, using Short Form-12 (SF-12), the questionnaire-based 'symptom of grade 2 dyspnoea' reported the lowest mean Physical Component Summary (PCS), whereas dyspnoea attacks had the lowest mean Mental Component Summary (MCS). Both scores decreased significantly with increasing number of symptoms; however, this was more evident for physical than mental scores. The larger impact of dyspnoea on these scores could be attributed to other disease conditions such as heart disease [27].

Table 1 Characteristics of patients and studies included in the humanistic burden review

References	Treatment setting	Study country	Disease severity	Study size (*N*)	Age [years; mean (SD)]	Females (%)	Disease duration [years; mean (SD)]	BMI [kg/m^2; mean (SD)]	Current smokers (%)
Al Moamary et al. [4]	Outpatient	Kingdom of Saudi Arabia (Riyadh, Dammam, and Jeddah), Kuwait, Bahrain, UAE	NR	120	63.3 (7.3)	19.17	11.5 (7.8)	29.9 (7.7)	75.83
Almagro et al. [66]	Inpatient	Spain	NR	129	72 (9.2)	7	–	–	17.83
Antoniu et al. [28]	Inpatient	Romania	NR	72			–	–	–
Bellas et al. [5]	Outpatient	NR	Moderate to severe	40	65.2 (11.9)	45	–	–	–
Bentsen et al. [6]	Outpatient	Norway	Moderate to very severe	100	66.1 (8.3)	49	–	–	–
Boros and Lubinski [7]	Outpatient	Poland	Mild to very severe	8,537	64.41 (9.86)	36	8.95 (6.87) (range 0–61)	–	46
Cai et al. [55][a]	Outpatient	USA	NR	752	60.2 (8)	60.5	–	–	–
Diamantea et al. [64]	Inpatient	NR	NR	31	69.5 (7.8)	35.48	–	–	–
Elmariami et al. [67]	Inpatient	Libya	NR				–	–	–
Carvounis et al. (EPIPTOSI study) [36]	Outpatient	Greece	Mild to severe	927	64.95 (10.78) (*N* = 921)	33.5	–	27.64 (3.92) (*N* = 904)	49.78 (*N* = 912)
Llor et al. (EVOCA study) [68]	Outpatient	Spain	Mild to very severe	136	70 (9.7)	3.7	11.7 (8.1)	–	26.47
Goossens et al. [69]	Inpatient	USA	Mild to very severe	59	61.1 (10.4)	67.8	–	–	54.24
Jones et al. (HEED study) [31]	Outpatient	Belgium, France, Germany, Italy, The Netherlands, Spain, UK	Mild to very severe				–	–	–
Hens et al. [26]	Outpatient	Belgium	NR	31	65.7 (1.7)	13	–	–	29.03
Hernandez et al. [58][a]	Inpatient	Spain	NR	222	70.8 (9.7)	3.2	–	–	23
Lopez Jove et al. [32]	NR	NR	Mild to very severe	107	63.1 (8.3)	28.9	–	26.9 (4.7)	18.69
Loh et al. [70]	Inpatient	Malaysia	NR	52	67 (95 % CI 63–70)	13.5	–	–	17.31
Lu et al. [35]	Outpatient	Singapore	NR	136	73.19 (5.87)	57.4	–	–	–
Mazur et al. [29]	NR	Finland	NR	739	64 (6.8)	35.99	–	–	–
Mocarski et al. [71]	Outpatient	North America	Mild to very severe				–	–	–
Mollaoglu et al. [25]	Inpatient	Turkey	NR	98	72 (13.47) (range 65–83)	36.7	–	–	–

Table 1 continued

References	Treatment setting	Study country	Disease severity	Study size (*N*)	Age [years; mean (SD)]	Females (%)	Disease duration [years; mean (SD)]	BMI [kg/m^2; mean (SD)]	Current smokers (%)
Stridsman et al. (OLIN-COPD study) [59]	Outpatient	Sweden, Spain	Mild to very severe	564	67.5 (10)	46.5	–	26.9 (4.4)	–
Partridge et al. [72]	Outpatient	NR	Severe	2,441	67.3	–	–	–	–
Punekar et al. [33]	Outpatient	France, Italy, Spain, UK, Germany, USA	Mild to severe	–	–	–	–	–	–
Aimonino Ricauda et al. [60]	Inpatient	Italy	NR	–	–	–	–	–	–
Bridevaux et al. (SAPALDIA study) [8]	Outpatient	Switzerland	Mild to very severe	–	–	–	–	–	–
Scharf et al. [30]	Outpatient	Israel	Mild to very severe	180	65.9 (11.7); 66.7 (IQR 59.5–73.2)[b]	22.2	–	27.3 (5.5); 26.6 (IQR 23.5–30.1)[b]	–
Shafiq et al. [73]	Inpatient	NR	NR	102	71.2	41.18	–	–	–
Solem et al. [74]	Inpatient	NR	Severe to very severe	206	67.7 (10.2)	48	–	–	31.07
Trappenburg et al. [75]	Mixed	The Netherlands	Mild to very severe						
Voll-Anaerud et al. [27]	Outpatient	Norway	Mild to very severe	2,306	Females: 50.6 (15.3) Males: 48.8 (14.4) ($p = 0.003$)	51.73	–	–	32.35
Wang and Bourbeau [20]	Inpatient	Canada	Moderate to severe	282	71.2 (9.9)	58.9	–	–	30.14

BMI body mass index, *CI* confidence interval, *IQR* interquartile range, *NR* not reported, *SD* standard deviation, *UAE* United Arab Emirates

[a] Represents primary studies which include secondary studies from which data were extracted and evaluated

[b] Median value reported

3.2.3 Impact of Time to Occurrence of Symptoms

Patients with symptomatic COPD experiencing daytime as well as night-time symptoms had lower HRQoL compared with patients with either or none of the symptoms [33, 34]. Multivariate analysis demonstrated significant impact of both symptoms on HRQoL after controlling for age, comorbidities, country, and treatment setting measured using the EQ-5D [33]. Sullivan and colleagues showed that compared with patients without symptoms, those with both or either (night-time/early morning) symptoms reported worse HRQoL and dyspnoea, as indicated by significantly lower SF-12 PCS and MCS mean scores ($p < 0.01$), as well as higher CAT and mMRC mean scores ($p < 0.01$) [34].

3.2.4 Impact of Comorbidities

Life-event stress is associated with depressive symptoms and worse HRQoL in elderly individuals with COPD. It was observed that life-event stress was associated with more depressive symptoms and worse QoL in individuals with symptomatic COPD [35]. Carvounis and colleagues also showed that the mean Geriatric Depression Scale (GDS) score for patients >65 years was low (7.8 ± 0.9), indicating mild depression. These patients also presented with a higher risk of exacerbations [36].

3.3 Economic Burden

Results from the published studies reporting cost and healthcare resource use were variable and could be attributed to a number of influencing parameters (country, patient characteristics, disease severity, and the cost/resource item). Characteristics of patients and studies included in the economic review are presented in Table 2. The economic burden of symptomatic COPD is presented in electronic supplementary Tables S4 and S5.

3.3.1 Resource Use and Direct Costs

Two global surveys provided comprehensive evidence on the economic burden of COPD across countries. Symptomatic COPD was associated with high economic burden across all countries studied in these two surveys [37, 38]. The Confronting COPD survey was a large-scale international survey conducted across eight countries in Europe and North America (between August 2000 and January 2001). The annual direct costs of COPD for the year 2002 ranged from US$522 in France to US$4119 in the US. The composition of direct costs differed between countries, with more than 50 % of direct costs resulting from inpatient admissions in Canada, Italy, Spain, the UK, and the US, and almost 50 % due to regularly prescribed medicines in The Netherlands [38]. In the US, the mean direct annual per patient costs of PCP visits, specialist visits, and emergency room (ER) visits for the year 2002 were US$225.19, US$150.20, and US$289.10, respectively (data evaluated between August 2000 and January 2001). Patients in the US also reported the maximum specialist visits, with a mean of 1.8 visits per patient in the past year [39]. The costs were lowest in France, with oxygen therapy accounting for 25 % of the total direct costs [38, 39].

Another large survey (the BREATHE study, conducted between June 2010 and December 2011) was conducted in 2012 in 11 countries of the Middle East and North Africa. Physician consultations were the most frequently utilised resource, followed by ER visits and hospitalisations. Resource use was significantly higher in subjects with more symptoms (CAT score ≥10) compared with those with fewer symptoms ($p < 0.0001$) [37]. Murtagh and colleagues reported that using a random sample of the Northern Ireland population (for the year 2000), the mean direct healthcare cost for each COPD patient was estimated at £171.69 (US$309) per annum, as per the year 2000 estimates [40].

Dalal and colleagues evaluated the direct healthcare costs (data evaluated between 1 January 2005 and 30 September 2008) associated with COPD care during 2008 in a hospital setting among COPD patients aged ≥40 years. The mean costs for emergency department (ED) visits were US$647 (SD US$445), simple admissions were US$7,242 (SD US$7,987), and complex admissions (intensive care unit [ICU; general, surgical, or medical] or intubation) were US$20,757 (SD US$41,370). Complex admissions accounted for 20.9 % of the total costs for COPD management in a hospital setting [41].

3.3.2 Impact of Demographic Characteristics

An association between age of patients with COPD and increase in healthcare resource utilisation was observed, whereas gender was not considered as an independent predictor of healthcare resource utilisation [42–45]. Readmission at least twice in the first year of follow-up was observed among 9 % of total patients with COPD studied and was related to increasing age and male gender [46]. However, Berkius and colleagues observed that although the majority of readmissions were observed in women, female gender was not an independent determinant of readmission [odds ratio (OR) 0.97; 95 % confidence interval (CI) 0.75–1.25]. Age was observed to be independently associated with readmissions, with older patients demonstrating less chance of being readmitted (OR 0.68; 95 % CI 0.59–0.79 per 10-year increase in age) [42]. Furthermore, with an increase in years of schooling, a fall

Table 2 Characteristics of studies included in the economic review

References	Country	Treatment setting	Source of cost data/Resource use data	Study size (*N*)	Age [years; mean (SD)]	Females (%)	BMI [kg/m^2; mean (SD)]	Cardiovascular comorbidities (%)	Current smokers (%)
Al Moamary et al. [4]	Saudi Arabia	Inpatient and outpatient	NA/medical charts of patients	50	66 (11.9)	46	–	–	–
Almagro et al. [66]	Spain	Inpatient	NA/NR	129	72 (9.2)	7	–	–	17.8
Andreassen et al. [76]	Sweden, Norway	Inpatient	NA/admissions were identified from patient administrative systems	–	–	–	–	–	–
Asai et al. [77]	Japan	Inpatient	NR/NR	–	–	–	–	–	–
Bahadori et al. [78]	Canada	Inpatient	NA/patients' charts	310	74 (12)	46	–	41	–
Bakerly et al. [79]	UK	Inpatient/ outpatient/ retrospective data	NHS cost/NHS national tariff 2007/2008 and PSSRU, Kent 2006	–	–	–	–	–	–
Ban et al. [80]	Malaysia	Inpatient	NA/follow-up	193	68.48 (8.84)	13	24.4[b] (range 20.9–27.2)	HT: 47.2 IHD: 26.9 Dyslipid.: 24.9	11.40
Berkius et al. [42]	Sweden	Inpatient	NA/APACHE II registry	1,009	70.2 (9.1)	61.5	–	–	–
Bertolini et al. [81]	Italy	Inpatient	Retail price of drugs (the rebate companies apply to hospitals in Italy), cost estimation for all other items required ad hoc data collection/data were prospectively collected from hospital	–	–	–	–	–	–
Bingol et al. [82]	Turkey	Inpatients/oral prednisolone	NA/follow-up	20	63.7 (6.22)	25	–	40	–
Boros and Lubinski [7]	Poland	Outpatient	NA/NR	88,537	64.41 (9.86)	36	–	–	46
Polatli et al. (BREATHE Study) [37][a]	Algeria, Egypt, Jordan, Lebanon, Morocco, Pakistan, Saudi Arabia, Syria, Tunisia, Turkey, UAE	Unclear	NA/questionnaires; recent national censuses	1,392	–	24.4	–	24.71	49.93
Cai et al. [55][a]	USA	NR	NR/NA	437	58.2 (6.7)	54.2	–	–	–
Camp et al. [83]	North America	Inpatient	NA/hospital records	–	–	–	–	–	–
Chandra et al. [84]	Canada	Inpatient	NA/Multicenter Airway Research Collaboration study	–	–	–	–	–	–

Table 2 continued

References	Country	Treatment setting	Source of cost data/Resource use data	Study size (*N*)	Age [years; mean (SD)]	Females (%)	BMI [kg/m^2; mean (SD)]	Cardiovascular comorbidities (%)	Current smokers (%)
Chen et al. [85]	China	Inpatient	NR/NR	439	73.4 (9.8)	33	–	CBVD: 70 HT: 231 CHD: 123	–
Chen et al. [86]	China	NR	NR/NR						
Chmielowicz et al. [87]	Poland	Inpatient	NA/NR	34	71 (6.5)	23.5	–	–	–
Wouters (Confronting COPD survey) [38][a]	Global	Inpatient and outpatient	Local unit costs were applied to estimate the direct, indirect, and total societal costs of COPD/clinical outcomes; patient responses were used to derive measures of healthcare resource utilisation (including inpatient hospitalisations, ER visits, contacts with healthcare professionals, treatment and laboratory investigations), and lost productivity due to COPD	–	–	–	–	–	–
Dal Negro et al. [88]	Italy	Outpatient	NA/Institutional Health Services database	–	–	–	–	–	–
Dal Negro et al. [56]	Italy	Unclear	Healthcare interventions (e.g. visits, hospital admissions, etc.) were valued and corresponding real costs attributed; literature; indirect costs were calculated after referring to the patients' job and considered the average daily wage that such activity implies/Centralised institutional database	–	–	–	–	–	–
Dalal et al. [41][a]	USA	Inpatient	Premier Perspective^{TM} database (Premier, Inc., Charlotte, NC, USA)	71,493 encounters	67.5 (12.3)	56.4	–	50.88	–
Dalal et al. [89]	USA	Inpatient and outpatient	COPD-related costs were estimated using the allowed payment for all COPD-related medical and pharmacy services/NA	21,524	57.4 (11.2)	56.8	–	–	–
De Jong et al. [90]	The Netherlands	Inpatient	NA/follow-up	–	–	–	–	–	–
de Miguel-Diez et al. [91]	Spain	Inpatient	Other sources (diagnosis-related groups)/NR	215,835	–	13.7	–	–	–
Drescher et al. [92]	USA	Inpatient	Medical records, discharge summaries, information from the Washington Hospital Centre clinical documentation database	–	–	–	–	–	–

Table 2 continued

References	Country	Treatment setting	Source of cost data/Resource use data	Study size (*N*)	Age [years; mean (SD)]	Females (%)	BMI [kg/m^2; mean (SD)]	Cardiovascular comorbidities (%)	Current smokers (%)
Eaton et al. [93]	New Zealand	Inpatient and outpatient	NA/follow-up	–	–	–	–	–	–
Edelman et al. [94]	USA	Inpatient	NR/NR	14	66 (13)	29	–	HT: 71 CAD: 57	100
Fuhrman et al. [43]	France	Inpatient	NA/French hospital discharge database	–	–	–	–	–	–
Gabriel et al. [53]	Romania	NR	NA/NR	–	–	–	–	–	–
Geitona et al. [95]	Greece	Inpatient	Cost analysis was based on the estimation of patients' actual and nominal costs. Actual cost refers to the resources patients consumed during their hospital stay. Nominal cost refers to a fixed amount for each day of hospitalisation reimbursed by the social security funds (per diem payment) in all NHS hospitals, irrespective of patients' diagnosis, disease severity, and resource consumption/UTHA. Clinical and epidemiological data were collected using patient records. Utilisation data consisted of (a) resource consumption, including supplies, medication, laboratory, and imaging testing; (b) operational and other overhead costs; and (c) personnel costs	142	71.2 (8.4)	7	–	–	61
George et al. [96][a]	UK	Inpatient	NA/NHS organisation of care and management hospital	–	–	–	–	–	–
Golmohammadi et al. [97]	Canada	Outpatient	The costs of the program were calculated based on the portion of total expenditures allocated to the rehabilitation program by the Center for Lung Health. These included costs for administration, respiratory therapists, aides, supplies, rental fee for space, and physician services. Since the rehabilitation program provides services to persons with respiratory conditions other than COPD, costs were prorated of the total costs based on the proportion of COPD patients enrolled in the program	210	68.5 (8.5)	50.5	–	–	–

Table 2 continued

References	Country	Treatment setting	Source of cost data/Resource use data	Study size (*N*)	Age [years; mean (SD)]	Females (%)	BMI [kg/m^2; mean (SD)]	Cardiovascular comorbidities (%)	Current smokers (%)
Hernandez et al. [58][a]	Spain	Inpatients and outpatients (home hospitalised)	Average specifically-observed tariffs for COPD patients in a public insurance company covering the civil servants of the City Council of Barcelona (PAMEM)/follow-up	–	–	–	–	–	–
Hutchinson et al. [98]	Australia	Inpatient	Direct hospital costs were derived using transition II, an activity-based costing system/NR	80	73 (range 54–88)	41.3	–	–	21.25
Johannesdottir et al. [46][a]	Denmark	Inpatient	Danish National Patient Registry	3,176	71.1 (9.11); 72.1[b] (IQR 65.2–77.7)	55.2	–	–	–
Kruavit and Thien [99]	Australia	Inpatient	NR/NA	–	–	–	–	–	–
Lampela et al. [44]	Finland	Inpatient	NA/Finnish National Research and Development Centre for Welfare and Health	–	–	–	–	–	–
Lerikou et al. [100]	Greece	NR	NA/NR	–	–	–	–	–	–
Limsuwat et al. [101]	USA	Inpatient	NA/Medical records	–	66.9 (10.9)	55.5	–	–	–
Lindenauer et al. [102]	USA	Inpatient	Perspective database report/perspective database and discharge file	–	–	–	–	–	–
Martinez et al. [103]	USA	Unclear	NA/national survey of patients with COPD conducted in 2007–2008	–	–	–	–	–	–
Monteiro et al. [104]	Portugal	Inpatient	NA/Respiratory ICU, Hospital Santa Maria, Portugal	136	70 (10)	24	–	–	–
Murtagh et al. [40]	Ireland	Unclear	Health care costs were calculated using standard references, i.e. unit costs of health and social care in respect of the various services utilised (e.g. general practitioner visits and hospital visits). The BNF was used in respect of prescribed medications. The same descriptive statistics were calculated regarding the various health services used/Published literature	49	58.02 (7.91)	28.6	27.86 (4.58)	–	86.00
Nangia and Gandhi [105]	India	Inpatient	NA/follow-up	–	–	–	–	–	–

Table 2 continued

References	Country	Treatment setting	Source of cost data/Resource use data	Study size (*N*)	Age [years; mean (SD)]	Females (%)	BMI [kg/m^2; mean (SD)]	Cardiovascular comorbidities (%)	Current smokers (%)
Nasciben [106]	Brazil	Inpatient	For physician fees, procedure reimbursement, inpatient costs, and drug costs were gathered from public lists (CBHPM 5th, Kairos, PROHASA) that are the base for negotiations between providers and payers/UPLIFT1A study	–	–	–	–	–	–
Nielsen et al. [107]	Norway	Outpatient	NA/questionnaires						
Nikolakopoulou et al. [108]	Greece	Inpatient	NA/NR	80	69.82 (9.67)	31	30.97 (6.80)	–	–
Nishimura et al. [109]	Japan	Inpatient	NA/Hospital record data	–	–	–	–	–	–
Ornek et al. [110]	Turkey	Inpatient	Bills were evaluated in two categories, as ward bills and ICU bills. Ward bills were examined in four categories consisting of laboratory, disbursement, drug, and clinical (diagnostic procedures, interventions, and oxygen therapy) procedures. Since the study was performed in a university hospital, prices of all expenditures were determined by the state. Expenditures associated with the ICU were not subdivided into categories since these expenditures determined by the state were at fixed prices according to disease severity and number of days of hospitalisation	242	70.35 (10.65)	30.6	–	–	8.4
Overbeek et al. [111]	The Netherlands	NR	NA/The PHARMO RLS, an administrative database network	886	66 (11)	47	–	IHD: 122 CD: 83 CHF: 61	–
Ozkaya et al. [112]	Turkey	Inpatient	Medical records	7,832	64.6 (19.8)	19.8	–	–	–
Perera et al. [54][a]	USA	Inpatient	Inpatient discharge records from the AHRQ HCUP NIS for 2006 were used	1,254,703	70.6 (11.9)	52.8	–	CA: 25.2	–
Punekar et al. [52]	UK	NR	The costs associated with the estimated resource use were calculated using NHS reference costs for 2010–2011/NR	7,881	67.2	45	–	–	–

Table 2 continued

References	Country	Treatment setting	Source of cost data/Resource use data	Study size (*N*)	Age [years; mean (SD)]	Females (%)	BMI [kg/m^2; mean (SD)]	Cardiovascular comorbidities (%)	Current smokers (%)
Ramanath and Sabith [113]	India	Inpatient	By using patient case note/prescription, all medicine costs were noted and day-to-day follow-up was done while attending the ward rounds. The direct medical costs were obtained from patient direct enquiry and hospital pharmacy slips, laboratory reports and laboratory bills, and hospital charges. The cost of each medicine was taken from the latest editions of tertiary sources, enquiries from hospital pharmacy/community pharmacy, and also from medicine strips/Follow-up	50	64.16 (9.92)	16	–	–	12
Aimonino Ricauda et al. [60]	Italy	Inpatient	Hospital costs were collected from the official hospital medical cost database, including direct medical costs for beds. Costs for hospital-at-home patients were obtained in a similar manner, except that costs for hospital-at-home patients did not include costs for food, laundry, heating, or lighting. Costs for ED care were included for both patient groups/NR	–	–	–	–	–	–
Roberts et al. [114]	USA	Inpatient	NR/database	–	–	–	–	–	–
Romagnoli et al. [115]	Italy	Inpatient	NA/follow-up	–	–	–	–	–	–
Rosychuk et al. [116]				38,638	72 (10.1)	50.3	–	–	–
Rowe et al. [117][a]	Canada and USA	Inpatient	NA/Alberta Ambulatory Care Classification System for Canada patients and NHAMCS data for USA patients	–	–	–	–	–	–
Mittmann et al. (RUSIC Study) [118][a]	Canada	Inpatient and outpatient	Provincial sources, hospital databases, and published sources (Ontario Case Costing Initiative, Ontario Schedule of Benefits, Ontario Drug Benefit Formulary, published literature)/follow-up. Records of patients who experienced an exacerbation were reviewed and medications and outcomes were documented	609	68.6 (9.4)	41.7	–	–	–

Table 2 continued

References	Country	Treatment setting	Source of cost data/Resource use data	Study size (*N*)	Age [years; mean (SD)]	Females (%)	BMI [kg/m^2; mean (SD)]	Cardiovascular comorbidities (%)	Current smokers (%)
Shen [119]	China	Inpatient	NR/Peking University Third Hospital	199	77.4 (7.8)	–	–	–	–
Silver et al. [120]	USA	Inpatient	NR/Premier's perspective comparative database	69,841	–	56.2	–	HT: 52.4 IHD: 31.7 CD: 24.4	–
Simoens et al. [121]	Belgium	Inpatient	IMS Health; patient invoices; data on unit costs were based on official reimbursement tariffs and patient co-payments applicable in Belgium/data on antimicrobial therapy in ambulatory care in Belgium were derived from IMS Health	267	70 [range 38–92]	24	–	–	–
Sridhar et al. [122]	UK	Inpatient	NR/NR	–	–	–	–	–	–
Stein et al. [123]	USA	Inpatient	Hospital charges for the years 2000–2005 were converted to 2006 US$ using the consumer price index for medical care; different algorithms were used from different data sources/hospital discharge weights included in the NIS were used to develop national estimates for the number of hospitalisations. Different algorithms were used from different data sources	–	–	–	–	–	–
Tanriverdi et al. [124]	Turkey	Inpatient	Hospital automation system	–	–	–	–	–	–
Tsai et al. [125][a]	USA	Inpatient	Nationwide EDs	27,770	68	56	–	–	–
Varol et al.[45]	Turkey	Inpatient	Cost data were taken from budget application instructions of the Turkish Ministry of Health/data were retrospectively collected from hospital	376	65.31 (10.32)	17.4	–	–	–

Table 2 continued

References	Country	Treatment setting	Source of cost data/Resource use data	Study size (*N*)	Age [years; mean (SD)]	Females (%)	BMI [kg/m^2; mean (SD)]	Cardiovascular comorbidities (%)	Current smokers (%)
Veettil et al. [126]	India	Inpatient	The unit cost for inpatient treatment per bed per day was calculated on the basis of budget allocation of the institution for the year 2006. The cost of the drugs was calculated as per the Central Purchase Committee list of the Government of Kerala. The cost of the drugs not included in the official list was calculated based on the average wholesale price given in the monthly index of medical specialties. The laboratory investigation costs were as per the costs in the manual of the ACRL of the institution. The indirect costs due to lost work days, lost productivity, travel time, and waiting time were calculated by interviewing both patients and their bystanders/NA	120	66 (11)	12.5	–	CAD: 10	42.50
Vitacca et al. [127]	Italy	Outpatient	Single drug piece cost was derived from the current marketed costs; final costs (both for acute exacerbations and usual chronic therapy) were computed by multiplying the number of inhalers used for the unitary cost per piece/NR	–	–	–	–	–	–
Vitacca et al. [128]	Italy	Outpatient	The unit cost per event was derived using Medicare diagnosis-related group reimbursement values. Costs for drugs and transportation were directly calculated using information about market prices/Follow-up	–	–	–	–	–	–
Wang and Bourbeau [20]	Canada	Unclear	Medical charts, questionnaire survey/NR	282	71.2 (9.9)	58.9	–	–	30.14
Wang et al. [129]	Norway	Inpatient	NA/Oslo University Hospital	145	–	51	–	–	–

Table 2 continued

References	Country	Treatment setting	Source of cost data/Resource use data	Study size (*N*)	Age [years; mean (SD)]	Females (%)	BMI [kg/m^2; mean (SD)]	Cardiovascular comorbidities (%)	Current smokers (%)
Yang et al. [130]	China	Inpatient	Tianjin UEBMI database	1,321	71.1	41.3	–	–	–

Rosychuk et al. [116] and Rowe et al. [117] are linked studies; therefore, the studies add up to 75

ACRL Association of College and Research Libraries, *AHRQ HCUP* Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project, *APACHE* Acute Physiology and Chronic Health Evaluation II system, *BNF* British National Formulary, *BMI* body mass index, *CBHPM* Classificação Brasileira Hierarquizada de Procedimentos Médicos, *CA* cardiac arrhythmia, *CAD* coronary artery disease, *CBVD* cerebrovascular disease, *CD* cardiac dysrhythmia, *CHD* coronary heart disease, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *dyslipid.* dyslipidemia, *ED* emergency department, *ER* emergency room, *HT* hypertension, *ICU* intensive care unit, *IHD* ischemic heart disease, *IQR* interquartile range, *NA* not applicable, *NHS* National Health Service, *NHAMCS* National Hospital Ambulatory Medical Care Survey, *NIS* national (nationwide) inpatient sample, *NR* not reported, *PAMEM* Institut de Prestacions d'Assistència Mèdica al Personal Municipal, *PSSRU* personal and social services research unit, *RLS* record linkage system, *SD* standard deviation, *UAE* United Arab Emirates, *UEBMI* Urban Employee Basic Medical Insurance, *UTHA* University Teaching Hospital of Alexandroupolis

[a] Represents primary studies that include secondary studies from which data were extracted and evaluated

[b] Median value reported

in direct medical costs associated with COPD was observed [40].

3.3.3 Impact of Respiratory Symptoms and Dyspnoea

In multiple studies across several countries evaluating data from the Confronting COPD survey, costs were higher in patients with severe dyspnoea [MRC dyspnoea scale (dyspnoea score 5)] compared with those with mild (dyspnoea score 0–2) and moderate (dyspnoea score 3–4) dyspnoea [9, 39, 47–51]. In the UK, costs ranged from €590 (direct cost €395; indirect cost €195) in patients with mild dyspnoea, to €4,670 (direct cost €3,036; indirect cost €1,634) in those with severe dyspnoea in the Confronting COPD survey [9]. In Italy, the corresponding costs ranged from €441 in patients with mild dyspnoea to €6,365 in those with severe dyspnoea in the Confronting COPD survey [48].

The annual costs per patient increased with an increase in dyspnoea severity (according to the mMRC criteria) and duration of the disease (higher cost in the second year). However, it was observed that with the exclusion of medication costs, the costs 2 years post-diagnosis decreased compared with the costs 1 year post-diagnosis (£2,499.85 and £3,149.53, respectively). This could be attributed to better symptom control and disease management strategies in the primary care setting [52]. Gabriel and colleagues reported that COPD patients with chronic symptoms of airflow obstruction were associated with a higher rate of hospital service utilisation (1000/year) (19.6, 95 % CI 8.8–43.7 vs. 3.3, 95 % CI 0.8–13.2) compared with those without chronic symptoms [53].

3.3.4 Impact of Comorbid Conditions

Across countries, the annual societal costs associated with symptomatic COPD were higher among patients with comorbidities compared with those without any comorbidity [9, 39, 41, 47–51]. The rate of hospital admissions, ER visits, and physician consultations was higher among patients with comorbidities [37]. Perera and colleagues [54] reported that comorbidities were associated with significantly higher hospitalisation costs in the US ($p < 0.001$).

3.3.5 Indirect Cost

Very few studies have examined the impact of symptomatic COPD on indirect costs, despite the fact that these are quite substantial. In the US, productivity loss was significantly higher in patients with both night-time and early morning symptoms compared with those without symptoms [55]. The Confronting COPD survey estimated the

average indirect costs among US participants at 27 % of the total societal costs [39]. In Italy, costs due to absenteeism from work decreased significantly over a period of time due to the substantial decline in the number of exacerbations experienced by patients with COPD [56]. These observations were in line with those of an analysis based on an RCT in patients with COPD in which the increased cost of treatment was offset by indirect cost savings as a result of a decrease in the frequency of exacerbations [57].

4 Discussion

The current systematic literature review was undertaken to establish evidence on humanistic burden (based on HRQoL parameters) and economic burden in patients with symptomatic COPD.

4.1 Humanistic Burden

The results of humanistic burden showed variability in the inclusion criteria based on disease severity evaluated by using spirometry (mild, moderate, severe, and very severe) at the time of diagnosis. The evaluated studies included patients aged ≥40 years, with few studies particularly focussing on geriatric patients (>65 years of age) [25, 35, 58–60]. Patients with symptomatic COPD were associated with impaired HRQoL. These findings are in line with the findings from Jones and colleagues who reported impaired HRQoL in patients with a CAT score ≥10 [61].

Demographic factors such as age and gender, and other factors such as marital status, education level, or employment status, were found to have an impact on the humanistic burden of the disease. An association between advancing age and deteriorating HRQoL was reported in a majority of the studies (n = 17). In addition, duration of illness was the disease-driven factor, while severity of dyspnoea and time of symptoms (daytime or night-time symptoms) were disease-specific factors affecting the humanistic burden of the disease [4, 30, 33, 36, 62]. These findings are in line with the findings of the systematic review conducted by Tsiligianni and colleagues [63], where gender, BMI, smoking, symptoms, comorbidity, depression, anxiety, and exacerbations were reported as important parameters impacting the HRQoL of patients with COPD. Therefore, treatment strategies should also influence modifiable demographic factors to improve HRQoL in the COPD patient population.

Disease-specific symptoms such as dyspnoea considerably influenced the health of patients with COPD [31, 32, 63]. A longer duration of illness, longer hospital stay, and higher number of hospitalisations were other important factors influencing HRQoL in patients with symptomatic COPD [25, 28, 63, 64]. HRQoL also deteriorated with an increase in general respiratory symptoms and their severity. The symptoms evaluated in these studies included breathlessness or shortness of breath while walking, cough, sputum, wheeze, fatigue, and disability [4–6, 8, 25–27, 29, 63]. Therefore, a symptom-oriented approach involving treatment strategies aimed at severity of dyspnoea and exacerbations may improve HRQoL of COPD patients.

4.2 Economic Burden

Respiratory diseases are major causes of mortality and morbidity, and consume a considerable amount of healthcare resources. Among chronic respiratory diseases, COPD is associated with more healthcare consumption than other chronic diseases, and accounts for around five times as many hospital admissions in the UK compared with asthma [65]. A majority of included studies utilised reimbursement/claims/other databases as the sources of cost and resource use data. Variation in terms of country of study, year, currency, analysis perspective, disease severity, and cost/resource item under evaluation was observed in the published economic burden studies, making it difficult to compare across different health economies. Overall, both modifiable and non-modifiable demographic risk factors such as low education status, increasing age, and female gender were associated with greater annual societal costs. Higher societal costs were incurred for patients with increasing comorbidities, disease severity, frequency and severity of exacerbation, and symptoms. These factors directly influenced treatments administered, equipment used, labour, diagnosis, hospital admissions, PCP visits, specialist visits, ER visits, etc., thus, increasing the total direct costs across all the studies. Furthermore, indirect costs of absenteeism from work also suggest that a cost-effective treatment should focus on all aspects of the response to the disease per se, its consequence, and its progression.

4.3 Limitations

This systematic review is a qualitative evaluation of available evidence in symptomatic COPD; therefore, it does not provide a complete picture of COPD burden. Although better and reliable associations of various factors with symptomatic COPD can be achieved through quantitative analysis of HRQoL data, it was not conducted for the current review. Vague definitions of symptomatic COPD across studies made evidence generation a challenging task. In many studies, generic questionnaires [EQ-5D, SF-12, SF-36, and Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–F)] were used to measure HRQoL, which

are less sensitive when compared with disease-specific tools for COPD (Clinical COPD Questionnaire (CCQ), St. George's Respiratory Questionnaire (SGRQ), Sino-Nasal Outcome Test-22 (SNOT-22), CAT, CRQ-SAS). Also, a majority of the studies (>50 %) recruited patients with symptomatic COPD from an outpatient setting, mostly primary care centres; therefore, they may not represent the COPD population at large. The HRQoL component of the review focused on studies published in English only. Non–English language studies meeting the inclusion criteria of the review were included only from the LILACS® database. Nearly 30 % of the included studies on humanistic and economic burden were published as conference abstracts. Very few studies presented evidence on indirect costs associated with symptomatic COPD, although indirect costs are a major contributor to the overall economic burden of symptomatic COPD. This could be attributed to the fact that symptoms act as triggers that generate indirect costs followed by direct costs from clinical evaluation and treatment. Therefore, a better understanding of symptoms and symptom control should be the primary focus of future research.

5 Conclusions

HRQoL among patients with symptomatic COPD, as well as management of the disease, were associated with a substantial burden, especially in the developed nations of Europe and North America. This is particularly relevant because the burden of symptomatic COPD patients in the early stages might be higher than for non-symptomatic patients in slightly advanced disease. Therefore, this review attempted to better understand and quantify this difficult-to-define symptomatic COPD. HRQoL in patients with symptomatic COPD was influenced by various factors, of which dyspnoea was the most important determinant. In terms of economic burden, after excluding increase in disease severity and exacerbations, the presence of comorbidities, increasing age, and female gender were the critical parameters associated with an increase in the societal burden of symptomatic COPD. Future COPD cost-of-illness studies should take into account all types of costs incurred by patients, including indirect costs, to determine the most appropriate estimation of economic burden of the disease. In addition, early diagnosis and better treatment and disease management strategies should be undertaken to further curtail the economic burden of symptomatic COPD on patients, especially in the developed nations of the world.

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