

Chronic Obstructive Pulmonary Disease Symptom Cluster Composition, Associated Factors, and Methodologies: A Systematic Review

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Abstract

This systematic review details symptom clusters, their compositions, and associated factors and appraises the methodologies of studies that reported symptom clusters in patients with chronic obstructive pulmonary disease (COPD). Ten studies were eligible for inclusion in this study. Four common symptom clusters were identified. Two theoretical frameworks, four statistical methods, and various symptom assessment tools were used to identify symptom clusters. Factors associated with symptom clusters included demographic, clinical, and biological factors. No studies examined the subjective experiences of symptom clusters. Overall, inconsistencies were identified in the composition of symptom clusters across studies. This may be due to variations in study design, assessment tools, and statistical methods. Future studies should attempt to arrive at a common definition, especially that is theoretically derived, for symptom clusters, standardize the criteria for symptoms for inclusion in the clusters, and focus on patients' subjective experience to inform which clusters are clinically relevant.

Keywords

chronic obstructive pulmonary disease, symptom clusters, nursing, theoretical frameworks, symptom assessment tools

Chronic obstructive pulmonary disease (COPD) is a chronic disabling lung condition characterized by airflow limitation (COPD Working Group, 2012). It is anticipated to become the third leading cause of death by 2030 (Quaderi & Hurst, 2018). COPD principally occurs as a result of tobacco smoking and long-term exposure to harmful fumes or dust, or, more rarely, a consequence of a rare genetic problem, resulting in severe lung damage (Moore et al., 2016). Patients with COPD experience multiple distressing somatic and psychological symptoms, including breathlessness, fatigue, anorexia, pain, depression, anxiety, cough, daytime sleepiness and insomnia, dry mouth, and sexual dysfunction (Maddocks et al., 2017). Moreover, patients with COPD experience recurrent exacerbations associated with a decline in exercise capacity, quality of life, and self-efficacy (Greulich et al., 2014). The final years for patients with advanced COPD are characterized by frequent exacerbations, progressive functional decline, and increased dependency on informal caregivers and the health care system (Yohannes & Alexopoulos, 2014).

Strategies for symptom management in people with COPD involve pharmacological and non-pharmacological methods (Khakban et al., 2017). An increasing number of studies have

investigated the effectiveness of different strategies for treating different symptoms. A key management strategy for breathlessness is pulmonary rehabilitation, which represents a multidisciplinary program of care, involving self-management educational training and exercise training (McCarthy et al., 2015). Strategies for fatigue management involve activity pacing, good sleep hygiene, self-management education programs, and pulmonary rehabilitation (Baltzan et al., 2011; Lewko et al., 2012). Strategies for managing psychological symptoms, including depression and anxiety, involve exercise, cognitive behavioral techniques, dignity therapy, and spiritual support (Chochinov et al., 2011; Kunik et al., 2008). It appears that single strategies may be used to alleviate more

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than one symptom. For example, pulmonary rehabilitation may be used to manage breathlessness and fatigue (Corhay et al., 2014).

While some people with COPD may experience only a single symptom, a large proportion of people experience multiple concurrent symptoms. This is more common in individuals with advanced disease who present up to seven symptoms per day as reported in a study (Eckerblad et al., 2014). Previous studies concerning symptoms among patients with COPD have mainly focused on isolated or single symptoms and their associated factors (Knorst et al., 2019; Lim et al., 2019; Sharma & Sharma, 2019). Although this method has created a specific perception of each symptom, its main limitation is that many people with COPD experience multiple and concurrent symptoms. In addition, Lenz pointed out that interventions considering diverse concurrent symptoms are more effective than independent interventions focusing on single symptoms (Lenz, 2018).

The concept of the symptom cluster first appeared in the fields of psychiatry and psychology before it was incorporated into general medicine (Aktas et al., 2010). The term symptom cluster was first proposed by Dodd et al., who defined it as *three or more concurrent symptoms that are related to each other but are not required to have the same aetiology* (Dodd et al., 2001b). In 2005, Kim et al. revised the definition of symptom clusters as “two or more concurrent symptoms as constituting a symptom cluster that are related to one another and are relatively independent of other symptom clusters” (Kim et al., 2005). Therefore, the science of symptom management has emphasized the conversion from a focus of targeting single symptom to exploring symptom clusters that may improve symptom management by focusing on multiple symptoms at the same time (Miaskowski et al., 2004). Comprehensive understanding of the phenomenon of symptom clusters in people with COPD allows for more thorough symptom assessment and conduct strategies for targeted symptom management to improve patient-centered outcomes and satisfied experiences of care (Kwekkeboom, 2016; Morjaria & Polosa, 2010). A growing number of robust studies have identified, investigated, evaluated, and explored symptom clusters among patients with cancer (Aktas, 2013), and these clusters have expanded to other chronic conditions such as cardiovascular disease (DeVon et al., 2017), chronic kidney disease (Lockwood et al., 2019), and human immunodeficiency virus (Zhu et al., 2019).

In the clinical setting, nurses play a prominent role in the assessment of symptoms. If nurses possess knowledge of symptoms that typically occur concurrently, then they will be able to anticipate and investigate further into other potentially related symptoms (Lacasse & Beck, 2007). This may result in more efficient use of limited patient-provider time and potentially uncover symptoms that might, otherwise, have been overlooked (Kwekkeboom, 2016). Moreover, through a holistic approach, nurses may more easily be able to identify the presence of a cluster and then develop effective symptom

management strategies or self-management intervention programs to improve the quality of life of COPD patients (Lim et al., 2017). The organizations of the National Institute of Nursing Research and Palliative Medicine and the American Academy of Hospice have proposed symptom management as a focus for research, thereby devoting financial resources and education in this area (Coyné et al., 2018). Therefore, it seems intuitively reasonable that nurses are able to recognize the co-occurrence of specific symptoms, which leads to the development of more efficient and effective symptom management strategies and the development of clinical guidelines (Dunn et al., 2018).

To date, there is little consensus on the definition of symptom clusters, either methodologically or conceptually, both in clinical practice and in research (Miaskowski et al., 2017). Validation of the concept of symptom clusters is complicated and difficult because evaluating symptom interrelationships involves many methodological challenges, specifically the study design, theoretical framework, measurement tools, symptom dimensions (severity vs. intensity vs. distress vs. prevalence), statistical methods to identify the cluster, statistical “cut-off” points to define clusters, and characteristics of study samples, which may contribute to these inconsistencies of symptom clusters (Xiao, 2010). To date, there has been only one literature review examining symptom clusters among COPD patients. This review therefore focuses on studies published in English between 2005 and 2018 (Jenkins et al., 2019). The review summarized the compositions of COPD symptom clusters and examined statistical techniques and instruments for symptom cluster formation. However, it did not critically report the presence of theoretical frameworks that guided research in symptom clusters, synthesize the approaches used to select symptoms, and the statistical methods adopted to identify symptom clusters and examine factors associated with symptom clusters in people with COPD. In addition, because of language limitation, the study by Jenkins et al. may have omitted some studies meeting the inclusion criteria, such as Chinese studies. Accordingly, the composition of symptom clusters summarized in the study may not be comprehensive enough. Therefore, it is vital to address these outstanding concerns by rigorous appraisal, including the composition of symptom clusters, the methodologies applied in previous studies to identify symptom clusters, and the factors associated with symptom clusters in people with COPD.

In this study, we aimed to identify, systematically appraise, and synthesize available evidence on symptom clusters in people with COPD, specifically focusing on the following objectives: (a) investigate the composition of common symptom clusters in COPD; (b) critically review the methodological elements of COPD symptom cluster papers, including theoretical frameworks, approach to symptom selection, common symptom assessment instruments, symptom dimensions, and statistical methods used to derive symptom clusters and (c) examine the factors associated with symptom clusters.

Methods

Design

We conducted a systematic review to identify published studies on symptom cluster among patients with COPD. We followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al., 2009).

Search Methods

We searched the databases MEDLINE (Ovid), EMBASE (Ovid), CINAHL(EBSCO), PsycInfo, Web of Science, and China National Knowledge Infrastructure. The search results were limited to articles published from database inception to the present day. The language of publication was limited to English and Chinese.

In MEDLINE, we searched articles using the following Mesh terms: (“Pulmonary Disease, Chronic Obstructive” OR “Lung Diseases, Obstructive”) OR key words [chronic obstructive pulmonary disease OR COPD OR Obstructive Lung Disease OR Obstructive Lung Diseases OR Obstructive Pulmonary Disease OR Obstructive Pulmonary Diseases OR Acute exacerbation of COPD OR acute exacerbation of chronic obstructive pulmonary disease OR AECB OR COAD OR Restrictive Lung Disease OR airways obstruction OR chronic obstructive airways disease OR emphysema OR bronchitis] AND (Mesh terms [Syndrome] OR keywords [(symptom* adj2 cluster*) OR (multiple adj2 symptom*) OR (symptom* adj2 constellation*) OR (concurrent adj2 symptom*) OR (symptom* adj2 combination*) OR (symptom* adj2 co-occurrence) OR (synchro* adj2 symptom*)]). An example of the full search strategy used in the MEDLINE database is presented in Table 1.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) quantitative studies (primary and secondary analyses of dataset) aimed at identifying symptom clusters or interrelations between two or more symptoms in people with COPD, or quantitative studies tested statistically for a symptom cluster within a set of symptoms, and (b) qualitative studies aimed at exploring symptom clusters or interrelations between two or more symptoms in people with COPD. Any type of medical setting was eligible for inclusion. Theoretical articles, editorials, commentary/discussion articles, review articles, methodology articles, abstracts, and articles focusing on one specific symptom were excluded.

Titles and abstracts were screened based on the inclusion and exclusion criteria. All identified citations were imported into EndNote X9, and duplicates were removed. Screening and selection were independently conducted by two reviewers. Discrepancies were resolved through discussion between the two reviewers until a consensus was reached.

Quality Appraisal

Study quality was assessed using the Appraisal tool for Cross-Sectional Studies (AXIS tool) (Downes et al., 2016). This scale is designed for nonexperimental research and includes 20 items that measure aspects of study quality. Each study was assigned a score from 0 to 20, with higher scores indicating a lower risk of bias (higher study quality). Two reviewers independently conducted the assessments. When there was a divergence in scoring, the reviewers discussed the item further until a consensus was reached; if necessary, a third reviewer was consulted.

Data Abstraction

The two reviewers independently extracted information from the included studies, including data on authors' names, year, location, primary aims, design, theoretical foundation, sample, symptom assessment instrument, analytic technique, number of symptom clusters, specific symptoms within each cluster, additional findings, and limitations. Discrepancies were resolved through discussion between the two reviewers.

Synthesis

In this review, we were unable to synthesize outcomes in a meta-analysis because of the heterogeneity in sample characteristics, research designs, and outcomes. Therefore, this review represents a narrative synthesis, which refers to “an approach to the systematic review and synthesis of findings from multiple studies that relies primarily on the use of words and text to summarize and explain the findings of the synthesis” (Popay et al., 2006). We reviewed the matrix tables to synthesize the data from the included studies and to identify consistencies and inconsistencies across studies.

Results

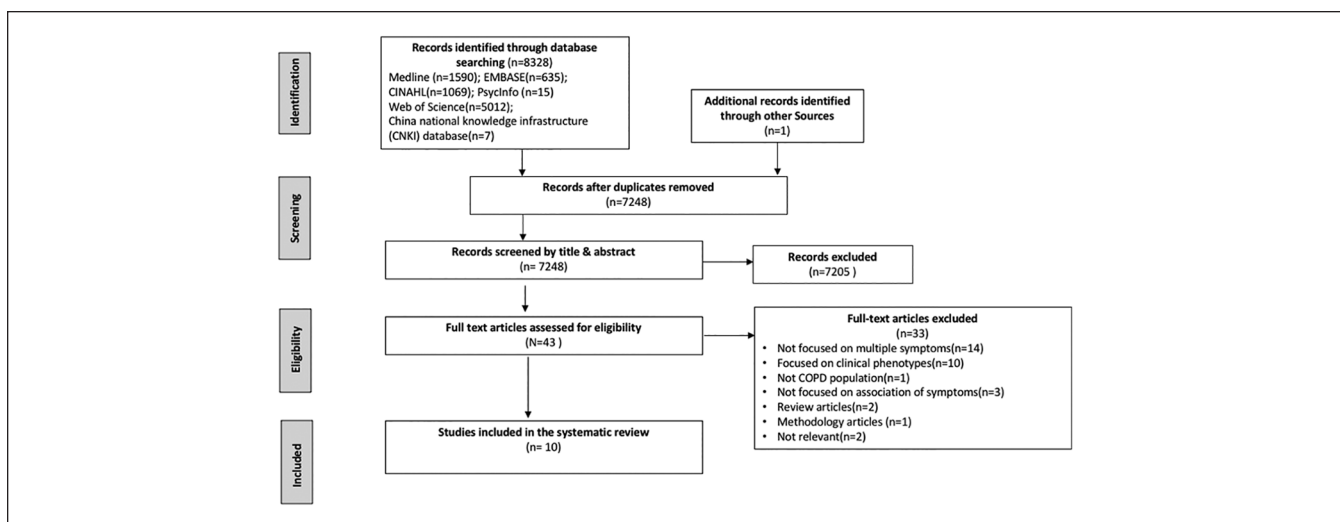
Search Outcome

Figure 1 shows the PRISMA flowchart for the article retrieval process. The search was conducted in six databases, and additional sources yielded 8,329 articles. After removing duplicate articles, 7,248 remained and were entered into the screening process. We excluded 7,205 articles after reading the titles and abstracts and further excluded 33 articles based on a review of the full text. Consequently, 10 articles were included in this narrative review as summarized in Table 2. Overall, 9 of the 10 studies were cross-sectional (Breland et al., 2015; Li et al., 2013; Lim et al., 2017; Park & Larson, 2014; Park et al., 2012; 2013; Srirat et al., 2014; Wu et al., 2020; Yang et al., 2020), one of which used a longitudinal design (Srirat et al., 2015). No qualitative study explored patient experience of symptom clusters. Articles were

Table 1. Search Strategy Example: Ovid (MEDLINE).

Search Terms

#1 exp Lung Diseases, Obstructive/
 #2 exp Pulmonary Disease, Chronic Obstructive/
 #3 (chronic obstructive pulmonary disease OR COPD OR Obstructive Lung Disease OR Obstructive Lung Diseases OR Obstructive Pulmonary Disease OR Obstructive Pulmonary Diseases OR Acute exacerbation of COPD OR acute exacerbation of chronic obstructive pulmonary disease OR AECB OR COAD OR Restrictive Lung Disease OR airways obstruction OR chronic obstructive airways disease OR emphysema OR bronchitis).mp.
 #4 1 OR 2 OR 3
 #5 exp syndrome/
 #6 ((symptom* adj2 cluster*) OR (multiple adj2 symptom*) OR (symptom* adj2 constellation*) OR (concurrent adj2 symptom*) OR (symptom* adj2 combination*) OR (symptom* adj2 co-occurrence) OR (synchron* adj2 symptom*)).mp.
 #7 Search #5 OR #6
 #8 Search #4 AND #7

**Figure 1.** PRISMA flow diagram of potential studies through eligibility determinations.

published between 2012 and 2020; nine were written in English, and one was written in Chinese (Li et al., 2013).

Quality of Studies

The results of the quality assessment of 10 eligible studies using the AXIS tool (Downes et al., 2016) are presented in Table 3. AXIS is used for assessing the quality of a study, but it is not an implicit measure of study bias (Downes et al., 2016). The mean total quality score was 16.3 (range 11–19). Our analysis revealed that all included studies had clear study objectives and employed an appropriate study design related to the objectives. Only four studies (Park & Larson, 2014; Park et al., 2013; Srirat et al., 2014, 2015) reported an estimated sample size using appropriate statistical methods. Eight studies (Lim et al., 2017; Park & Larson, 2014; Park et al., 2012, 2013; Srirat et al., 2014, 2015; Wu et al., 2020; Yang et al., 2020) clearly defined the target/reference population and had an appropriate sampling frame. Two studies (Breland et al., 2015; Li et al., 2013) had no selection

process. Five studies (Park & Larson, 2014; Park et al., 2012, 2013; Srirat et al., 2015; Yang et al., 2020) addressed and categorized nonresponders. All the studies that included risk factors and measured outcomes were appropriate to the aims of their study. Two studies (Li et al., 2013; Srirat et al., 2015) did not present the statistical significance of the key variables. All studies sufficiently described the methodology so that it could be repeated. All studies presented adequate data of basic characteristics and described their results completely. However, only one study (Yang et al., 2020) categorized nonresponders and reported profiles of nonrespondents to the survey. Except for one study (Li et al., 2013), all others provided information about methodological limitations. Two studies (Li et al., 2013; Park et al., 2013) did not provide information on ethical approval.

Sample Characteristics

Studies were usually conducted across four countries, namely China (Li et al., 2013; Wu et al., 2020; Yang et al., 2020),

Table 2. Characteristics of the Included Studies.

Author (Year), Location	Primary Aim and Design	Sample	Approaches for Symptom Selection	Assessment Instrument(s) and Analytic Technique	Number of Symptom Clusters Specific Symptoms Within Each Cluster	Additional Findings	Limitations
Yang et al. (2020), China	Aim: (a) Investigate SCs; (b) explore influencing factors associated with SCs; and (c) explore relationship between SCs and inflammatory biomarkers. Design: Cross-sectional	AECOPD N = 151 Male = 84.8% Mean age = 67.26 Gold stage: I: 17 (11.2%) II: 30 (19.9%) III: 55 (36.4%) IV: 49 (32.5%)	All-possible symptom approach	Instrument(s): Sociodemographic and disease information questionnaires, CCI, mMRC, RMSAS Analysis: EFA and LRA	Two symptom clusters identified Cluster 1: Emotional cluster Feeling nervous, feeling sad, feeling irritable, worrying, difficulty sleeping, difficulty in concentrating, and I don't like myself Cluster 2: Respiratory functional cluster Shortness of breath, dry mouth, lack of energy, cough, and feeling drowsy	Emotional SC was associated with CCI and mMRC scores Respiratory functional SC was related to low BMI, non-usage of inhaled drugs, and lax inhaled drug therapy The significant association between the emotional cluster and CRP represented the biological mechanism or etiology of this cluster	Limitations: Only provided a relatively stable pattern, but variability also existed within each SC; identified SCs using the dimension of symptom severity; only examined the relationships between SCs and CRP and PCT levels
Wu et al. (2020), China	Aim: (a) identify SCs; (b) examine the relationship between SCs and HRQoL. Design: Cross-sectional	COPD N = 154 Mean age = 69.2 ± 9.7 (range 41–93 years) Male = 55.2%	All-possible symptom approach	Instrument(s): CCI, MSAS, patient demographics, clinical traits, and CCO Analysis: EFA and MRA	Five symptom clusters identified Cluster 1: Psychological symptom feeling nervous, feeling sad, and worrying Cluster 2: Pain and fatigue Lack of energy, pain, and feeling drowsy Cluster 3: Disturbed sleep Difficulty sleeping and cough Cluster 4: GI Lack of appetite and dry mouth Cluster 5: Dyspnea—Sweat shortness of breath, and sweating	Symptom clusters had negative effects on quality of life in people with COPD	Limitations: The MSAS instrument: Lack of some COPD-related symptoms; the sample: Lack of representation and findings for forced expiratory volume in one second were not available
Lim et al. (2017), South Korea	Aim: (a) identify SCs; (b) investigate the relationship between SCs and clinical characteristics; (c) explore the effects of SCs on QoL. Design: Cross-sectional	COPD N = 130 Mean age = 69.5 ± 8.7 years Male = 86.2% Gold stage: I: 5 (3.8%) II: 36 (27.7%) III: 68 (52.3%) IV: 21 (16.2%)	Most-common symptom approach	Instrument(s): Borg scale, FACITF, BDI, SAI, Korean Sleep Scale A, visual analogue scale, KPS, patient demographics, clinical traits, C and CQ Analysis: PCA, K-means cluster analysis	Three symptom clusters identified Cluster 1: Respiratory-functional cluster dyspnea, physical functional status, and dry mouth Cluster 2: Mood cluster Anxiety and depression Cluster 3: Fatigue-sleep cluster Sleep disorder and fatigue	Two distinct subgroups emerged, identified as low-symptom subgroup and high-symptom subgroup The symptom clusters differed significantly, depending on the age, educational level, and monthly income, and had a negative impact on subjects with COPD	Limitations: The numbers of female subjects and subjects with GOLD 4 were small; did not identify longitudinal changes in symptom clusters associated with COPD; and the Cronbach alpha for the QoL scale mental state was low

(continued)

Table 2. (continued)

Author (Year), Location	Primary Aim and Design	Sample	Approaches for Symptom Selection	Assessment Instrument(s) and Analytic Technique	Number of Symptom Clusters Specific Symptoms Within Each Cluster	Additional Findings	Limitations
Srirat et al. (2015), Thailand	Aim: explore SCs in severity and distress dimensions as well as similarity and stability Design: Longitudinal	COPD N = 250 Mean age = 71.03 ± 7.16 years Male = 67.2% Gold stage: I: 19(7.6%) II: 114(45.6%) III: 108(43.2%) IV: 9 (3.6%)	All-possible symptom approach	Instrument(s): BESC, PIQ Analysis: PCA	Cluster at time 1 (symptom distress) Seven symptom clusters identified Cluster 1: Emotional problems Cluster 2: Memory function decline Cluster 3: Respiration difficulty Cluster 4: Fatigue-related distress Cluster 5: Sleep alteration Cluster 6: Pain and unpleasant sensation Cluster 7: Respiratory muscle weakness Cluster at time 2 (symptom distress) Five symptom clusters identified Cluster 1: Emotional problems Cluster 2: Memory function decline Cluster 3: Respiration difficulty Cluster 4: Sleep alteration Cluster 5: Pain and unpleasant sensation	At time 1, the similarity rate of both dimension (severity and distress) in each cluster ranges from 75% to 100% At time 2, the similarity rate of both dimensions in each cluster ranges from 95.4% to 100% The replication rate in each distress cluster ranged from 66.7% to 100% The replication rate in each severity cluster ranged from 50% to 100% Respiration difficulty had the lowest of replication rate Back-and-forth transitions between psychological and physical symptoms within clusters over time were observed	Limitations: The sample: Lack of representation
Breland et al. (2015), USA	Aim: (a) Identify anxiety SCs and (b) access the association of SCs with COPD-related quality of life Design: Cross-sectional	COPD N = 162 Mean age = 66.46 ± 8.94 years Male = 94%	All-possible symptom approach	Instrument(s): BAI and model prediction for quality-of-life domains: CRQ, MRC, and PHQ-9 Analysis: PCA and MLR	Four symptom clusters identified Cluster 1: General somatic distress Dizziness or lightheadedness, fainting episode, unsteady, wobbliness in legs, and heart pounding or racing Cluster 2: Fear Scared, fear of dying, terrified, fear of worst happening, and fear of losing control Cluster 3: Nervousness Shaky, hand trembling, nervous, and unable to relax Cluster 4: Respiratory-related distress Feeling of choking, indigestion, or discomfort in the abdomen, face flushed, difficulty breathing, numbness or tingling, feeling hot, and sweating (not due to heat)	Fear cluster, depression symptoms, and COPD functional impairment revealed a negative association with mastery over COPD Severity of functional impairment predicted worse dyspnea-related quality of life Higher depression symptoms predicted worse fatigue-related quality of life	Limitations: Additional work is needed to confirm and extend the present findings; the sample: Lack of representation; and reports of COPD-related impairment may be inflated.

(continued)

Table 2. (continued)

Author (Year), Location	Primary Aim and Design	Sample	Approaches for Symptom Selection	Assessment Instrument(s) and Analytic Technique	Number of Symptom Clusters Specific Symptoms Within Each Cluster	Additional Findings	Limitations
Park and Larson (2014), USA	<i>Aim: Determine how subgroups differed on health care use and mortality.</i> <i>Design: Cross-sectional secondary analysis</i>	COPD N = 597 Mean age = 65.93 ± 10.21 Male = 63.5% All severe airflow obstruction	Most common symptom approach	<i>Instrument(s):</i> SOBQ, STAI, BDI, and MOS-36 <i>Analysis:</i> HCA and Multivariate logistic regression	One large symptom cluster identified Dyspnea-anxiety-depression-fatigue Three subgroup clusters identified (subgroup clusters emerged based on four symptom ratings) Cluster 1: All high levels of symptoms Cluster 2: All moderate levels of symptoms Cluster 3: All low levels of symptoms	Quality of life differed significantly between subgroups. Participants with high levels of symptoms used health care services more and were more likely to have died at the 5-year follow-up than those with low levels of symptoms Symptom cluster subgroups had more significant relationship with mortality than single symptoms	<i>Limitations:</i> No data for comorbidity were available; detailed information was unable to be obtained on the reasons for health care use; and findings may not be generalizable to people with mild-to-moderate COPD
Srirot et al. (2014), Thailand	<i>Aim: Explore symptom distress, SCs, and effective management strategies used for each cluster</i> <i>Design: Cross-sectional</i>	COPD N = 250 Mean age = 71.03 ± 7.16 years Male = 67.2% Gold stage: I: 19 (7.6%) II: 114 (45.6%) III: 108 (43.2%) IV: 9 (3.6%)	All-possible symptom approach	<i>Instrument(s):</i> BESQ, PIQ, and SMSQ <i>Analysis:</i> PCA	Seven symptom clusters identified Cluster 1: Emotional problems Cluster 2: Memory function decline Cluster 3: Respiratory difficulty Cluster 4: Fatigue-related distress Cluster 5: Sleep alteration Cluster 6: Pain and unpleasant sensation Cluster 7: Respiratory muscle weakness	Clusters and best treatments Cluster 3: Taking bronchodilator and mucolytic drugs, inhaling corticosteroid, using the pursed lip technique, effective coughing, and deep breathing exercise Cluster 4: Taking a bronchodilator, reducing activities, shortening of distance, and general exercise. Cluster 5: Taking alprazolam, listening to songs or music, practicing meditation or praying or performing religious activities, and reading books. Cluster 6: Taking nonsteroidal inflammatory drugs (NSAIDs) and paracetamol	<i>Limitations:</i> Findings may not be generalizable to Thais with COPD in other regions of the country and complete questionnaires might be too long
Li et al. (2013), China	<i>Aim: (a) Identify SCs and (b) examine the relationship between SCs and functional performance</i> <i>Design: Cross-sectional</i>	COPD N = 106 Mean age = 71.23 ± 4.64 years Male = 62.3%	All-possible symptom approach	<i>Instrument(s):</i> MMRC, MSAS, POMS-SF, and FPL-SF <i>Analysis:</i> EFA, HCA, and MLR	Three symptom clusters identified (based on factor analysis) Cluster 1: Seven symptoms Pain, feeling nervous, numbness/tingling in hands/feet, difficulty sleeping, shortness of breath, feeling sad, and worrying Cluster 2: Seven symptoms Lack of energy, cough, dry mouth, feeling drowsy, feeling bloated, sweats, and dizziness Cluster 3: Two symptoms Problems with urination and constipation	Functional performance was most related to MSAS total score, symptoms of MSAS and mean severity score of the cluster 1 Age, mean severity score of seven symptoms (cluster 1), emotional status, and level of education explained significant variance (29.29%) in functional performance	<i>Limitations:</i> Cannot provide a definite measure for the severity of diseases

(continued)

Table 2. (continued)

Author (Year), Location	Primary Aim and Design	Sample	Approaches for Symptom Selection	Assessment Instrument(s) and Analytic Technique	Number of Symptom Clusters Specific Symptoms Within Each Cluster	Additional Findings	Limitations
Park et al. (2013), USA	Aim: (a) Identify subgroups and (b) explore the differences of subgroups in characteristics; functioning, exercise capacity, and physical activity Design: Cross-sectional secondary analysis	COPD N = 596 Mean age = 65.93 ± 10.21 years Male = 63.6% All severe airflow obstruction	Most common symptom approach	Instrument(s): SOBO, STAI, BDI, MOS-36, and 6WMT Analysis: HCA, T-test or chi-square test and HMR	One large symptom cluster identified Dyspnea-anxiety-depression-fatigue Two subgroup clusters identified (subgroup clusters emerged based on four symptom ratings) Cluster 1: All high levels of symptoms Cluster 2: All low levels of symptoms	Mean age and the proportion of participants with higher education and income levels, and using oxygen at rest were significantly different between subgroups Participants with high levels of symptoms had lower functioning and decreased exercise capacity Symptom cluster subgroups were significantly associated with social functioning	Limitations: The results cannot be generalized to patients with milder COPD; assessment of fatigue; Lack of structured instruments and findings may be affected by different dimensions of symptoms
Park et al. (2012), USA	Aim: Examine concurrent symptoms, SCs, and the effects of symptoms on functional performance Design: Cross-sectional	COPD N = 54 Mean age = 75.0 ± 7.1 years Male = 90.7%	All-possible symptom approach	Instrument(s): VAS, MSAS, POMS-SF, mMOS-SS, SL-ASIA, and FPI-SF Analysis: EFA, HCA, and MLR	Three symptom clusters identified Cluster 1: Seven symptoms Pain, feeling nervous, numbness/tingling, difficulty sleeping, shortness of breath, feeling sad, and worrying Cluster 2: Seven symptoms Lack of energy, cough, dry mouth, feeling drowsy, feeling bloated, sweats, and dizziness Cluster 3: Two symptoms Problems with urination and constipation	Functional performance was most related with dyspnea alone in the MSAS total score, symptoms of MSAS; MMRC, and VAS, $r = -0.29$, $r = -0.27$, $r = -0.43$, and $r = -0.27$, respectively.	Limitations: Study does not provide a definite measure for the severity of diseases; specific symptoms of asthma was not added and assessed in the MSAS.

Note: AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BESS: Bronchitis Emphysema Symptom Checklist; BMI: Body mass index; CCI: Charlson comorbidity index; CCO: Clinical COPD Questionnaire; COPD: Chronic obstructive pulmonary disease; CRQ: Chronic Respiratory Disease Questionnaire; EFA: Exploratory factor analysis; FACITF: Functional Assessment of Chronic Illness Therapy—Fatigue; FPI-SF: Functional Performance Inventory—Short Form; HCA: Hierarchical cluster analysis; HMR: Hierarchical multiple regression; HRQoL: Health-related quality of life; KPS: Karnofsky Performance Scale; LRA: Logistic regression analysis; MLR: multiple linear regression; mMOS-SS: Modified Medical Outcomes Study Social Support Survey; mMRC: Modified Medical Research Council Dyspnea Scale; MOS-36: Medical Outcomes Study 36-Item Short-Form Health Survey; MRA: multivariate regression analyses; MRC: Medical Research Council Dyspnea Scale; MSAS: Memorial Symptom Assessment Scale; PCA: Principal component analysis; PCT: Procalcitonin; PHQ-9: Patient Health Questionnaire-9; PIQ: Personal Information Questionnaire; POMS-SF: Profile of Mood States—Short Form; QoL: Quality of life; R/MSAS: Memorial Symptom Assessment Scale; SAI: Spielberger Anxiety Inventory; SCs: Symptom clusters; SL-ASIA: Suijin-Lew Asian Self-Identity Acculturation Scale; SMSQ: Symptom Management Strategies Questionnaire; SOBQ: Shortness of Breath Questionnaire; STAI: State-trait Anxiety Inventory; VAS: Dyspnea Visual Analogue Scale; and 6WMT: Six minutes walking test.

Table 3. Assessment of the Included Studies' Quality Using AXIS Tool.

Questions	Yang et al. (2020)	Wu et al. (2020)	Lim et al. (2017)	Srirat et al. (2015)	Breland et al. (2015)	Park et al. (2014)	Srirat et al. (2014)	Li et al. (2013)	Park et al. (2013)	Park et al. (2012)
1. Were the aims/objectives of the study clear?	1	1	1	1	1	1	1	1	1	1
2. Was the study design appropriate for the stated aim(s)?	1	1	1	1	1	1	1	1	1	1
3. Was the sample size justified?	0	0	0	1	0	1	1	0	1	0
4. Was the target/reference population clearly defined? (Is it clear who the research was about?)	1	1	1	1	0	1	1	0	1	1
5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	1	1	1	1	0	1	1	0	1	1
6. Was the selection process likely to select subjects/participants who were representative of the target/reference population under investigation?	1	1	1	1	0	1	1	0	1	1
7. Were measures undertaken to address and categorize nonresponders?	1	0	0	1	0	1	0	0	1	1
8. Were the risk factor and outcome variables measured appropriate to the aims of the study?	1	1	1	1	1	1	1	1	1	1
9. Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialed, piloted, or published previously?	1	1	1	1	1	1	1	1	1	1
10. Is it clear what was used to determine statistical significance and/or precision estimates? (e.g., p-values, CIs)	1	1	1	0	1	1	1	0	1	1
11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	1	1	1	1	1	1	1	1	1	1
12. Were the basic data adequately described?	1	1	1	1	1	1	1	1	1	1
13. Does the response rate raise concerns about nonresponse bias?	1	0	0	1	0	0	1	1	0	0
14. If appropriate, was information about nonresponders described?	1	0	0	0	0	0	0	0	0	0
15. Were the results internally consistent?	1	1	1	1	1	1	1	1	1	1
16. Were the results for the analyses described in the methods presented?	1	1	1	1	1	1	1	1	1	1
17. Were the authors' discussions and conclusions justified by the results?	1	1	1	1	1	1	1	1	1	1
18. Were the limitations of the study discussed?	1	1	1	1	1	1	1	0	1	1
19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	1	1	1	1	1	1	1	1	1	1
20. Was ethical approval or consent of participants attained?	1	1	1	1	1	1	1	0	0	1
Total score	19	16	16	18	13	18	18	11	17	17

South Korea (Lim et al., 2017), Thailand (Srirat et al., 2014, 2015), and the United States (Breland et al., 2015; Park & Larson, 2014; Park et al., 2012, 2013). The recruited participants had a mean age, ranging from 65.9 years to 75.0 years. Males were predominant among the enrolled participants, ranging from 55.2% to 94.0%. Four studies examined symptom clusters in people with COPD stages 1–4, based on spirometry results, rated as being “mild” to “very severe” (Lim et al., 2017; Srirat et al., 2014, 2015; Yang et al., 2020); two articles included patients with severe airflow obstruction (Park & Larson, 2014; Park et al., 2013); four studies (Breland et al., 2015; Park et al., 2012; Wu et al., 2020; Li et al., 2013) did not report the data about forced expiratory volume in one second. Consequently, these studies could not provide a definite measure for the severity of COPD (Breland et al., 2015; Li et al., 2013; Park et al., 2012; Wu et al., 2020). We did not identify any studies that investigated the pediatric patient populations.

Theoretical Frameworks

Two studies used the Symptom Management Theory (SMT) as a theoretical framework (Srirat et al., 2014, 2015), and one study used the theory of unpleasant symptoms (TOUS) as a theoretical framework (Park et al., 2012). The remaining seven studies did not identify theoretical frameworks in their studies.

Approaches for Symptom Selection in Cluster Identification

Two approaches of symptom selection in cluster identification were first proposed by Xiao (2010): the “most common symptom approach” and the “all-possible symptom approach.” The “most common symptom approach” is known as “a priori” cluster identification, wherein researchers first selected several commonly experienced symptoms, assuming that these most common symptoms could be grouped as a cluster (Xiao, 2010). Generally, the number of symptoms in a cluster is small, with most having two–four symptoms (Given et al., 2001; Miaskowski & Lee, 1999; Reyes-Gibby et al., 2006; So et al., 2009). In this approach, the biggest limitation was whether it was sufficient to select only the most common symptoms in cluster identification (Xiao, 2010). In this systematic review, Lim et al. adopted this approach to select symptoms for cluster identification. Additionally, they selected the most common symptoms such as dyspnea, depression, anxiety, fatigue, sleep disturbance, dry mouth, and decreased physical function in the Korean COPD population, and these symptoms were categorized into symptom clusters (Lim et al., 2017). In addition, Park and Larson (2014) selected four main symptoms, namely dyspnea, anxiety, depression, and fatigue experienced by patients with COPD in their cluster identification. Park et al. (2013) similarly adopted this approach to select

the most common symptoms, namely dyspnea, anxiety, depression, and fatigue, in determining symptom clusters in patients with severe COPD.

Compared with the “most common symptom approach,” the “all-possible symptom approach,” which was used in 7 (Breland et al., 2015; Li et al., 2013; Park et al., 2012; Srirat et al., 2014, 2015; Wu et al., 2020; Yang et al., 2020) of the 10 studies reviewed, targets all potential symptoms that patients with COPD might experience when identifying clusters. Rather than simply selecting the most common symptoms, it yields the results of symptom clusters after statistical analysis rather than assuming clusters before empirical methods (Xiao, 2010). The number of symptoms in a cluster and the number of symptom clusters were more than those in the “most common symptom approach,” wherein the number of symptom clusters exceeded more than three in several studies (Jarden et al., 2009; Kim et al., 2009; Molassiotis et al., 2010).

Symptom Measurement

Table 4 shows the symptom measures of the included studies. A total of four of the 10 studies used the Memorial Symptom Assessment Scale (MSAS) to assess symptoms (Li et al., 2013; Park et al., 2012; Wu et al., 2020; Yang et al., 2020); 2 of the 10 studies used the Bronchitis Emphysema Symptom Checklist (BESC) to assess symptoms (Srirat et al., 2014, 2015). Only one study used the Beck Anxiety Inventory to examine anxiety symptoms in the COPD population (Breland et al., 2015). Lim et al. used more than one instrument (seven) for symptom cluster analysis among the Borg scale, the Functional Assessment of Chronic Illness Therapy–Fatigue, the Beck Depression Inventory (BDI), the Spielberger Anxiety Inventory (SAI), the Sleep Scale A, the visual analogue scale for dry mouth, and the Karnofsky Performance Scale (KFS) (Lim et al., 2017).

Two studies (Park & Larson, 2014; Park et al., 2013) used the same four instruments to measure symptoms. Specifically, the Shortness of Breath Questionnaire was used to measure dyspnea; the State-Trait Anxiety Inventory was used to assess anxiety; the BDI was used to evaluate depression; and the vitality subscale of the Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-36) was used to assess fatigue.

Dimension. Detailed information on symptom dimensions is shown in Table 4. Four studies evaluated symptom-related severity (Li et al., 2013; Park et al., 2012; Srirat et al., 2015; Yang et al., 2020), three studies measured distress of symptoms (Breland et al., 2015; Srirat et al., 2014, 2015), and three studies evaluated symptom intensity (Lim et al., 2017; Park & Larson, 2014; Park et al., 2013). Symptom intensity is an evaluation of the perceived severity of symptoms (Armstrong, 2003); therefore, these studies measured the same symptom dimension. Two studies were multidimensional,

Table 4. Summary of Measures.

Study	Assessment Tool	Description	Dimensions
Yang et al. (2020), China	Charlson comorbidity index (CCI); Modified Medical Research Council; Dyspnea Scale (MMRC); and Memory Symptom Assessment Scale (RMSAS)	CCI: 19 comorbidities. Six-point scale MMRC: Five correlated questions about dyspnea are evaluated from Grade 0 to Grade 4 MSAS: 32 symptoms with three dimensions. Frequency—four-point Likert scale (1 = rarely to 4 = almost constantly); Severity—four-point Likert scale (1 = slight to 4 = very severe); and Distress—five-point Likert scale (0 = not at all to 4 = very much)	Severity symptoms presented in >25% of the patients were subjected to exploratory factor analyses
Wu et al. (2020), China	Charlson comorbidity index (CCI) and Memory Symptom Assessment Scale (MSAS);	CCI: 19 comorbidities. Six-point scale MSAS: 32 symptoms with three dimensions. Frequency—four-point Likert scale (1 = rarely to 4 = almost constantly); Severity—four-point Likert scale (1 = slight to 4 = very severe); Distress—five-point Likert scale (0=not at all to 4=very much).	Average of frequency, severity, and distress scores and symptoms presented in >30% of the patients who were subjected to exploratory factor analyses
Lim et al. (2017), South Korea	Borg scale; Korean version of Functional Assessment of Chronic Illness Therapy—Fatigue (FACITF); Beck Depression Inventory (BDI); Korean version of the Spielberger Anxiety Inventory (SAI); Korean Sleep Scale A; visual analogue scale; and Karnofsky Performance Scale (KPS) Questionnaire	Borg scale: One item to measure subjective respiratory difficulty. Eleven-point scale; from 0 points (no dyspnea) to 10 points (the most severe dyspnea) FACITF: 13 questions; Four-point Likert scale BDI: 21 questions; Four-point Likert scale SAI: 20 questions; Four-point Likert scale—from 1 (almost never) to 4 (almost always) Korean Sleep Scale: 15 questions; Four-point Likert scale Visual analogue scale scores the intensity of dry mouth, ranging from 0 (no dry mouth) to 10 (the most severe dry mouth) KPS: 11 levels, ranging from 0 (dead) to 10 (normal function). Korean version of the Clinical COPD Questionnaire: 10 items with 3 domains: symptom (4 items), functional state (4 items), and mental state (2 items); Six-point Likert scale	Intensity
Srirat et al. (2015), Thailand	Bronchitis Emphysema Symptom Checklist (BESC)	BESC (Thai version): 54 items with three dimensions; Five-point scale; symptom frequency (0 = never to 4= always), symptom severity (1 = very slight to 5 = very severe), and symptom distress (1 = not at all to 5 = very much).	Severity and distress
Breland et al. (2015), USA	Beck Anxiety Inventory (BAI); Chronic Respiratory Disease Questionnaire (CRQ); Medical Research Council Dyspnea Scale (MRC); and Patient Health Questionnaire-9(PHQ-9)	BAI: 21-item measure of anxiety symptoms; Four-point scale—from 0 (not at all) to 3 (severely—it bothers me a lot) CRQ: 20-item measure of dyspnea, fatigue, and mastery; Six-point scale MRC: 5 questions. Five grades of COPD-related functional impairment (range I–V) PHQ-9: 9-item measure of depressive symptoms; Four-point scale—from 0 (not at all) to 3 (severely—it bothers me a lot)	Distress

(continued)

Table 4. (continued)

Study	Assessment Tool	Description	Dimensions
Park et al. (2014), USA	Shortness of Breath Questionnaire (SOBQ); State-Trait Anxiety Inventory (STAI); Beck Depression Inventory (BDI); and The vitality subscale of Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-36)	SOBQ: 24-item measure of shortness of breath associated with 21 daily activities and limitations in daily life; Six-point scale—from 0 (none at all) to 5 (maximal or unable to do because of breathlessness) STAI: 20 questions; Four-point Likert scale—from 1 (almost never) to 4 (almost always) BDI: 21 questions; Four-point Likert scale The vitality subscale of MOS-36: 4 questions about fatigue; Six-point scale—from 1 ("all the time") to 6 ("none of the time").	Intensity
Sriat et al. (2014), Thailand	Bronchitis Emphysema Symptom Checklist (BESC)	BESC (Thai version): 54 items and three dimensions; Five-point scale; symptom frequency (0 = never to 4 = always), symptom severity (1 = very slight to 5 = very severe), and symptom distress (1 = not at all to 5 = very much)	Distress
Li et al. (2013), China	Modified Medical Research Council Dyspnea Scale (MMRC) and Memorial Symptom Assessment Scale (MSAS) Profile of Mood States—short form (POMS-SF)	MMRC: 5 correlated questions about dyspnea are evaluated from Grade 0 to Grade 4. MSAS: 32 symptoms with three dimensions. Frequency—four-point Likert scale (1 = rarely to 4 = almost constantly); severity—four-point Likert scale (1 = slight to 4 = very severe); distress—five-point Likert scale (0 = not at all to 4 = very much) POMS-SF: 30 adjectives; 5-point rating scales—from 0 (not at all) to 4 (extremely)	Severity symptoms presented in >30% of the patients were subjected to exploratory factor analyses
Park et al. (2013), USA	Shortness of Breath Questionnaire (SOBQ); State-Trait Anxiety Inventory (STAI); Beck Depression Inventory (BDI); and Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-36)	SOBQ: 24-item measure of shortness of breath associated with 21 daily activities and limitations in daily life; 6-point scale—from 0 (none at all) to 5 (maximal or unable to do because of breathlessness) STAI: 20 questions; Four-point Likert scale—from 1 (almost never) to 4 (almost always) BDI: 21 questions; Four-point Likert scale MOS-36: 36-item measure of eight distinct dimensions of health; Six-point scale,—from 1 ("all the time") to 6 ("none of the time").	Intensity
Park et al. (2012), USA	Visual Analogue Scale (VAS); Modified Medical Research Council (MMRC); Memorial Symptom Assessment Scale (MSAS); and Profile of Mood States—short form (POMS-SF)	VAS: Description of usual intensity of dyspnea. A vertical 100-mm line anchored at 1 end with the words "no breathlessness" and at the other end with "worst imaginable breathlessness." MMRC: 5 correlated questions about dyspnea are evaluated from Grade 0 to Grade 4. MSAS: 32 symptoms with three dimensions; frequency—four-point Likert scale (1 = rarely to 4 = almost constantly); severity—four-point Likert scale (1 = slight to 4 = very severe); distress—five-point Likert scale (0 = not at all to 4 = very much) POMS-SF: 30 adjectives; Five-point rating scales—from 0 (not at all) to 4 (extremely).	Severity symptoms presented in >30% of the patients were subjected to exploratory factor analyses

one assessed two dimensions (severity and distress) (Srirat et al., 2015) and the other assessed three dimensions (severity, frequency, and distress) (Wu et al., 2020).

Statistical Methods for Identifying Symptom Clusters

In the previous section, “most common symptom approach” and “all-possible symptom approach” were proposed to select symptoms. The “most common symptom approach” and “all-possible symptom approach” adopted their own statistical methods for cluster identification.

The statistical method used most in the “most common symptom approach” was “clustering by a correlation between symptoms: (Chan et al., 2005; So et al., 2009). Lim et al. used this statistical approach to identify symptom clusters that examined the inter-item correlation between these symptoms, using the Spearman rank correlation (Lim et al., 2017). An alternative statistical method in the most common symptom approach involves identifying subgroups of people with similar symptom experiences based on a specific symptom cluster (Meeusen et al., 2018; Miaskowski et al., 2017; Xiao, 2010). Two studies used this statistical method to identify subgroups of people based on a specific symptom cluster (dyspnea–anxiety–depression–fatigue) (Park & Larson, 2014; Park et al., 2013). Specifically, Park et al. identified subgroups of patients with COPD, using hierarchical cluster analysis methods associated with four symptoms (dyspnea–anxiety–depression–fatigue) and examined their effect on mortality and health care use (Park & Larson, 2014). In addition, Park and colleagues identified two subgroups of people with COPD: High levels of symptoms and low levels of symptoms (Park et al., 2013).

The statistical methods used to identify symptom clusters in the “all-possible symptom approach” varied across the seven studies (Breland et al., 2015; Li et al., 2013; Park et al., 2012; Srirat et al., 2014, 2015; Wu et al., 2020; Yang et al., 2020). Three studies used principal component analysis (PCA) (Breland et al., 2015; Srirat et al., 2014, 2015), and four studies used exploratory factor analysis (EFA) (Li et al., 2013; Park et al., 2012; Wu et al., 2020; Yang et al., 2020). Furthermore, two studies used EFA in conjunction with hierarchical cluster analysis to identify symptom clusters (Li et al., 2013; Park et al., 2012).

Symptom Clusters

The four main symptom groupings reported in the 10 studies are as follows: (a) respiratory-related symptom cluster (short of breath/dyspnea/shallow breathing/difficulty breathing/feeling of choking + lack of energy/feeling drowsy/fatigue + dry mouth + sweat); (b) emotional cluster (anxiety/feeling irritable/feeling nervous + depression/feeling worried/

feeling sad/I don’t like myself/feel like a cripple); (c) disturbed sleep-related cluster (pain/numbness/pins and needles feelings/cough + difficulty sleeping/disturbed sleep); (d) urination–constipation cluster (problems with urination + constipation). Further details are shown in Table 5.

The general symptoms of respiratory-related symptom clusters have been reported in 10 studies (Breland et al., 2015; Li et al., 2013; Lim et al., 2017; Park & Larson, 2014; Park et al., 2012, 2013; Srirat et al., 2014, 2015; Wu et al., 2020; Yang et al., 2020). Eight studies reported that this cluster coexisted with additional symptoms of physical functional status, mucus congestion, numbness, indigestion or discomfort in the abdomen, anxiety, depression, feeling bloated, and dizziness (Breland et al., 2015; Li et al., 2013; Lim et al., 2017; Park & Larson, 2014; Park et al., 2012, 2013; Srirat et al., 2014, 2015). The emotional cluster was reported in eight studies (Breland et al., 2015; Lim et al., 2017; Park & Larson, 2014; Park et al., 2013; Srirat et al., 2014, 2015; Wu et al., 2020; Yang et al., 2020). Of these studies, five identified this cluster to occur independently (Breland et al., 2015; Lim et al., 2017; Srirat et al., 2014, 2015; Wu et al., 2020), and three identified the additional symptoms that were present within this cluster, including difficulty in sleeping, difficulty in concentrating, dyspnea, and fatigue (Park & Larson, 2014; Park et al., 2012, 2013). Disturbed sleep-related clusters were reported in four studies (Li et al., 2013; Park et al., 2012; Srirat et al., 2014; Wu et al., 2020), with only one study identifying that it occurred independently (Wu et al., 2020). Moreover, two studies reported a urination–constipation cluster experienced by COPD patients (Li et al., 2013; Park et al., 2012), which occurred independently of other studies (Li et al., 2013; Park et al., 2012).

Factors Associated with Symptom Clusters

Across 10 studies, articles investigated factors associated with symptom clusters, including demographic factors (e.g., age, gender, and marital status), clinical factors (e.g., COPD stage and comorbidities), and biological factors. Among the demographic factors, older age and low income were positively associated with the “respiratory–functional cluster” (Lim et al., 2017); older age, lower monthly income, and lower educational level were positively associated with the “fatigue–sleep cluster” (Lim et al., 2017). Low body mass index, nonuse of inhaled drugs, and lax inhaled drug therapy were significantly associated with the “respiratory functional cluster” (Yang et al., 2020). Among the clinical factors, mMRC scores (severity of dyspnea) and comorbidity index (CCI) were significantly associated with the “emotional cluster” (Yang et al., 2020). The inflammatory biomarker C-reactive protein (CRP) is a biological factor significantly associated with the “emotional cluster” (Yang et al., 2020).

Table 5. Most Commonly Occurring Symptom Combinations.

Author (year), Location	Respiratory-Related Cluster (short of breath/dyspnea/shallow breathing/difficulty breathing/feeling of choking + lack of energy/feeling drowsy/fatigue + dry mouth + sweat)	Emotional Cluster (anxiety/ feeling irritable/feeling nervous + depression/feeling worried/ feeling sad/I don't like myself/ feel like a cripple)	Disturbed Sleep-Related Cluster (pain/numbness/pins and needles feelings + cough + difficulty sleeping/disturbed sleep)	Urination- constipation Cluster (problems with urination + constipation)	Other Clusters
Yang et al. (2020), China	Yes -Cough and sweat	Yes + Difficulty sleeping and difficulty in concentrating	Yes		
Wu et al. (2020), China	Yes -Lack of energy and dry mouth	Yes			Pain and Fatigue cluster: Lack of energy, pain, and feeling drowsy GI cluster: Lack of appetite, and dry mouth Fatigue-sleep cluster: Sleep disorder and fatigue
Lim et al. (2017), South Korea	Yes + Physical functional status -Lack of energy and sweat	Yes			Memory function decline cluster: forget recent things, forgetful, poor memory, difficulty remembering, get confused, and coughing
Srirat et al. (2015), Thailand	Yes + Mucus congestion, numbness -Lack of energy, dry mouth, and sweat	Yes			Disease-related fatigue cluster: fatigue, exhaustion, and no energy Sleep alteration cluster: Poor sleep, trouble falling asleep, and disturbed sleep Pain and unpleasant sensation cluster: Leg aches, cramps, pins and needles feelings, and pain in other regions Respiratory muscle weakness cluster: Weak, tingling in arms and legs, and chest filled up General somatic distress cluster: Dizziness or lightheaded, faint, unsteady, wobbliness in legs, and heart pounding or racing Nervousness cluster: Shaky, hand trembling, nervous, unable to relax
Breiland et al. (2015), USA	Yes + Indigestion or discomfort in the abdomen, numbness, or tingling -Lack of energy and dry mouth	Yes			

(continued)

Table 5. (continued)

Author (year), Location	Respiratory-Related Cluster (short of breath/dyspnea/shallow breathing/difficulty breathing/feeling of choking + lack of energy/feeling drowsy/fatigue + dry mouth + sweat)	Emotional Cluster (anxiety/ feeling irritable/feeling nervous + depression/feeling worried/ feeling sad/I don't like myself/ feel like a cripple)	Disturbed Sleep-Related Cluster (pain/numbness/pins and needles feelings + cough + difficulty sleeping/disturbed sleep)	Urination- constipation Cluster (problems with urination + constipation)	Other Clusters
Park et al. (2014), USA	Yes + Anxiety and depression -Dry mouth	Yes + dyspnea and fatigue			No other clusters
Srirat et al. (2014), Thailand	Yes + Mucus congestion and numbness -Lack of energy, dry mouth, and sweat	Yes	Yes + Forget recent things, poor memory, forgetful, difficulty remembering, and get confused		Fatigue-related distress cluster: Fatigue, exhaustion, and no energy Sleep alteration cluster: Poor sleep, trouble falling asleep, and disturbed sleep Pain and unpleasant sensation cluster: Leg aches, cramps, pins and needles feelings, and pain in other regions Respiratory muscle weakness cluster: Weak, tingling in arms and legs, and chest filled up No other clusters
Li et al. (2013), China	Yes + Feeling bloated and dizziness -Dyspnea and cough		Yes + Feeling nervous, shortness of breath, feeling sad, and worrying	Yes	No other clusters
Park et al. (2013), USA	Yes + Anxiety and depression -Dry mouth and sweat	Yes + Dyspnea and fatigue			No other clusters
Park et al. (2012), USA	Yes + Feeling bloated and dizziness -Dyspnea and cough		Yes + Feeling nervous, dyspnea, feeling sad, and worrying	Yes	No other clusters

Discussion

In this review, we systematically identified, summarized for the first time, and critically appraised the composition of symptom clusters among patients with COPD, the underlying theoretical frameworks associated with the approaches that have been used to explain and classify these clusters, assessment instruments to quantify symptoms, statistical methods to identify symptom clusters, and factors associated with symptom clusters. We reviewed 10 studies and identified that symptom clusters varied considerably, depending on their combination. Differences in methodology and symptom assessment tools were the main issues that limit the inferences that can be drawn from the findings we present.

In this review, TOUS and SMT were utilized as COPD symptom cluster theoretical frameworks. Specifically, TOUS has three major components: (a) influencing factors, (b) symptoms, and (c) performance. In the TOUS framework, symptoms can occur as separate entities or concurrently as a symptom cluster and include four dimensions: timing, intensity, quality, and distress (Lenz et al., 1997). The main aim of the TOUS model was to improve the understanding of the symptom experience as being in a multidimensional, contextual way and to assist in providing information for developing a means to manage or prevent unpleasant symptoms and reduce their negative effects (Corwin et al., 2014). Underpinning this theory, Park et al. (2012) specified the key variables of influencing factors associated with the COPD symptom cluster. However, there are controversies related to this theory. First, some investigators suggest that this theory does not include an intervention component within the model (Lenz, 2018). Instead, it is assumed that many of the components and relationships in the TOUS could be used for targeted interventions. Second, based on the linear presentation of influencing factors, symptoms, and outcomes, this theory does not demonstrate a time component because the symptoms associated with COPD may vary considerably over time, and the variability in one symptom may interact or influence others (Barsevick, 2016). Third, the ways of treating psychological factors have caused some conceptual confusion (Almutary et al., 2017). For example, some researchers considered symptoms such as depression and anxiety to be influencing factors (Tankumpuan et al., 2015), while others viewed anxiety and/or depression as a symptom itself (Herr et al., 2015).

The SMT includes three interactive components of symptom management: Symptom experience, symptom management strategies, and symptom outcomes. Dodd and his colleagues subsequently revised this model to focus on symptom management within the wider nursing context, which includes the following interrelated domains: Person–environment–health and illness (Dodd et al., 2001a). The SMT identifies explicit phenomena, proposes specific relationships between concepts, and provides a comprehensive framework for considering interventions and outcomes

(Hockenberry, 2004). In this review, two studies adopted the SMT theory to guide the selection of symptom dimensions (Srirat et al., 2014, 2015). However, a growing number of researchers have recently introduced the concept of “symptom clusters” into the SMT model, in which the connections between these multiple symptoms in a cluster are not specifically illustrated. For example, which groups of symptoms should be categorized as symptom clusters, how to identify which of the multiple symptoms are part of a cluster, and which symptoms are considered to be more or less important (Dodd et al., 2010). Additionally, this model does not specifically consider other dimensions associated with symptom experience, such as the importance and meaning attributed to multiple symptoms. Moreover, the relationships between multiple symptom experiences and patient-centered outcomes have not been delineated. However, outcome variables within this model mirror the TOUS model, for example, quality of life. While these two models focus on symptom clusters, the relationships among these symptom clusters are not clearly illustrated. Therefore, limitations remain in relation to these frameworks, and there is a need to develop and test a more comprehensive theoretical model specific to COPD-related symptoms.

The most frequently used instrument was the MSAS, which was used in 40.0% of the reviewed studies. The original version of the MSAS was developed to measure 32 cancer-related symptoms (Portenoy et al., 1994a, 1994b). It evaluates multiple dimensions of the symptom experience, such as frequency, occurrence, severity, and distress (Portenoy et al., 1994b). Of the four studies that used the MSAS, one study identified five symptom clusters (Wu et al., 2020), two studies identified three symptom clusters (Li et al., 2013; Park et al., 2012), and one study identified two symptom clusters (Yang et al., 2020). The “respiratory-related cluster” was identified in four studies (Li et al., 2013; Park et al., 2012; Wu et al., 2020; Yang et al., 2020). The inconsistency in the number of symptom clusters and the composition within each cluster in these four studies may be due to the heterogeneity of patients recruited in these studies. BESC, BDI, SAI, Korean Sleep Scale A, and visual analogue scale were used to measure symptoms in other studies, which yielded inconsistent symptom clusters. Thus far, no “gold standard” assessment tool is available to evaluate symptom clusters in patients with chronic conditions (Miaskowski et al., 2017). In this review, half of the included studies measured symptom severity. However, a report from an expert panel called for comprehensive evaluation of symptom clusters and stated that there is currently no clear answer about which symptom dimension is most useful for advancing symptom cluster science (Miaskowski et al., 2017). Moreover, cutoffs used to determine whether symptoms had sufficient prevalence to be included in symptom clusters were also inconsistent.

This review examined two approaches to symptom selection for cluster identification in people with COPD. The

“all-possible symptom approach” included any potential symptoms that people living with COPD experience. Most studies (Breland et al., 2015; Li et al., 2013; Park et al., 2012; Srirat et al., 2014, 2015; Wu et al., 2020; Yang et al., 2020) have used this approach. However, a limitation of this approach is that it lacks an explanation of the clinical meaning of symptom clusters identified by statistical methods (Ward Sullivan et al., 2018). While the “most common symptom approach” represents a way to identify symptom clusters, the main limitation is whether it is reasonable or reliable, or sufficient to select only the most common COPD symptoms present in the cluster identification (Xiao, 2010). Therefore, researchers must determine which approach should be adopted based on their study objectives.

The studies included in this review indicated that EFA and PCA, based on clustering symptoms by underlying factors and components, are the most common analytical methods. However, there were inconsistent symptom cluster results across the seven studies (Breland et al., 2015; Li et al., 2013; Park et al., 2012; Srirat et al., 2014, 2015; Wu et al., 2020; Yang et al., 2020) because of different patient populations, assessment instruments, and statistical methods. In addition, it is possible that the identified symptom clusters might not have a rational explanation because the reported clusters depend only on the components or factors from the statistical procedures. For example, only one study (Wu et al., 2020) identified the “GI” symptom cluster in this review, which was not defined in other studies that aimed to identify symptom clusters in people with COPD (Breland et al., 2015; Li et al., 2013; Lim et al., 2017; Park & Larson, 2014; Park et al., 2012, 2013; Srirat et al., 2014, 2015; Yang et al., 2020). The “GI” symptom cluster was the most common symptom cluster identified in cancer patients (Huang et al., 2016; Molassiotis et al., 2010; Yates et al., 2015). Specifically, the composition of “GI” symptom cluster in this review included lack of appetite, and dry mouth was the common symptom in people with COPD (Maddocks et al., 2017). Although this is an initiation in defining the “optimal” method, such as EFA and PCA, there is still a lack of consensus on which statistical method should be used to identify symptom clusters in this field (Miaskowski et al., 2017).

Cluster analysis was used to identify subgroups of people with similar experiences based on a specific symptom cluster. This method may be clinically intuitive because it translates these findings into clinical practice, and people with a similar symptom profile can be more easily identified and interpreted (Miaskowski et al., 2006). Park et al. (2013, 2014) used this statistical method to identify subgroups based on four symptom ratings. Recent research has focused on COPD phenotype, which refers to a single or a combination of disease attributes that describe differences between COPD patients based on clinically significant parameters such as symptoms, exacerbation, response to treatment, rate of disease progression, and mortality (Christensen et al., 2016). Based on our current knowledge, we believe that

there is evidence for an overlap between COPD phenotypes and symptom cluster research. In our opinion, subgroup identification based on symptom ratings is equal to the COPD symptom phenotypes. Therefore, we assume that studies that use statistical methods to identify subgroups based on symptom ratings could be included in the field of symptom cluster research.

To date, no qualitative studies have been conducted to examine patients’ subjective experiences, meanings, and the impacts of symptom clusters among people living with COPD. Studies of this nature, which look beyond symptom associations, and explore in detail the perspectives of people’s lived experiences of their symptom clusters, may help in forming a stronger conceptual basis for existing symptom clusters (Bennion & Molassiotis, 2013). Meanwhile, the composition of symptom clusters may or may not be stable through the trajectory of the disease (Dodd et al., 2001a). Kirkova et al. highlighted the notion that the cross-sectional study design limited the accuracy of examining the variability in symptom interrelationships (Kirkova et al., 2010). Consequently, longitudinal study designs are required to explore the stability of symptom clusters over the disease course.

Surprisingly, only few demographic and clinical factors associated with symptom clusters were identified in this review, where only age and monthly income were observed as being significantly associated with the “respiratory–functional cluster”; age, educational level, and monthly income were related to “fatigue–sleep cluster”; and mMRC scores and comorbidity index were significantly associated with the “emotional cluster.” This is consistent with the findings of oncology studies (Gwede et al., 2008; Miaskowski et al., 2006; Pud et al., 2008). The heterogeneity of patients recruited to studies and the inconsistent statistical methods used may contribute to the absence of more clinically meaningful factors. Only one study in this review used linear regression analysis to examine the relationship between the biological factors and symptom clusters in people with COPD, specifically identifying that the CRP level was significantly associated with the “emotional cluster” (Yang et al., 2020). Dodd and colleagues identified that the coexisting symptoms might share common biological underpinnings (Dodd et al., 2001a). Moreover, inflammatory pathways have been postulated to explain the biology of clustering of symptoms in clinical populations (Kelly et al., 2016). Understanding the biological mechanisms associated with symptom clusters may inform the future development and evaluation of targeted therapeutics and personalized interventions to mitigate COPD-related symptoms (Kim & Malone, 2019). Therefore, it is vital to explore the biological basis of clustering of COPD-related symptoms in more studies that are adequately powered. In addition, conducting more longitudinal studies would inform and validate the relationship between symptom clusters and specific biomarkers (Miaskowski & Aouizerat, 2007). The knowledge

gained from these findings will critically inform relevant health care providers and improve the health-related quality of life of patients with COPD (Cazzola & Novelli, 2010).

Beyond the limitations already discussed, the items and dimensions of symptom assessment tools varied considerably across the 10 studies that may influence cluster composition. In addition, notably, only two studies (Wu et al., 2020; Yang et al., 2020) in this review reported data associated with comorbidities in people with COPD. The absence of this information is critical because it has the potential to influence a range of symptoms associated with these conditions and should therefore be viewed as a confounding factor in symptom experience (Fan et al., 2007).

In conclusion, this review identified inconsistencies in the composition of symptom clusters across studies due to variations in study design, assessment tools, and statistical methods. Future studies should attempt to arrive at a common definition of symptom clusters that are theoretically derived and standardize the criteria for symptoms to be included in the clusters. In addition, there is an urgent need to conduct qualitative studies in this research field that will provide a deeper patient-centered perspective into the living experience of multiple symptoms present in people with COPD. This review also provides information about the associated factors and biomarker CRP linked with COPD symptom clusters. The associated factors found in this review may help nurses identify at-risk patients and guide their patients for treatment-seeking and symptom self-management behaviors. Future investigations are warranted to identify and validate potential factors and plan optimal interventions to advance science.

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References

Aktas, A. (2013). Cancer symptom clusters: Current concepts and controversies. *Current Opinion in Supportive and Palliative Care*, 7(1), 38–44. <https://doi.org/10.1097/SPC.0b013e32835def5b>

Aktas, A., Walsh, D., & Rybicki, L. (2010). Symptom clusters: Myth or reality? *Palliative Medicine*, 24(4), 373–385. <https://doi.org/10.1177/0269216310367842>

Almutary, H., Douglas, C., & Bonner, A. (2017). Towards a symptom cluster model in chronic kidney disease: A structural

equation approach. *Journal of Advanced Nursing*, 73(10), 2450–2461. <https://doi.org/10.1111/jan.13303>

Armstrong, T. S. (2003). Symptoms experience: A concept analysis. *Oncology Nursing Society*, 30(4), 601–612. <https://doi.org/10.1188/03.ONF.601-606>

Baltzan, M. A., Scott, A. S., Wolkove, N., Bailes, S., Bernard, S., Bourbeau, J., & Maltais, F., Canadian COPD Pulmonary Rehabilitation Research Group. (2011). Fatigue in COPD: Prevalence and effect on outcomes in pulmonary rehabilitation. *Chronic Respiratory Disease*, 8(2), 119–128. <https://doi.org/10.1177/1479972310396737>

Barsevick, A. (2016). Defining the symptom cluster: How far have we come? *Seminars in Oncology Nursing*, 32(4), 334–350. <https://doi.org/10.1016/j.soncn.2016.08.001>

Bennion, A., & Molassiotis, A. (2013). Qualitative research into the symptom experiences of adult cancer patients after treatments: A systematic review and meta-synthesis. *Supportive Care in Cancer*, 21(1), 9–25. <https://doi.org/10.1007/s00520-012-1573-x>

Breland, J. Y., Hundt, N. E., Barrera, T. L., Mignogna, J., Petersen, N. J., Stanley, M. A., & Cully, J. A. (2015). Identification of anxiety symptom clusters in people with COPD: Implications for assessment and treatment. *International Journal of Behavioral Medicine*, 22(5), 590–596. <https://doi.org/10.1007/s12529-014-9450-2>

Cazzola, M., & Novelli, G. (2010). Biomarkers in COPD. *Pulmonary Pharmacology & Therapeutics*, 23(6), 493–500. <https://doi.org/10.1016/j.pupt.2010.05.001>

Chan, C. W., Richardson, A., & Richardson, J. (2005). A study to assess the existence of the symptom cluster of breathlessness, fatigue and anxiety in patients with advanced lung cancer. *European Journal of Oncology Nursing*, 9(4), 325–333. <https://doi.org/10.1016/j.ejon.2005.02.003>

Chochinov, H. M., Kristjanson, L. J., Breitbart, W., McClement, S., Hack, T. F., Hassard, T., & Harlos, M. (2011). Effect of dignity therapy on distress and end-of-life experience in terminally ill patients: A randomised controlled trial. *The Lancet Oncology*, 12(8), 753–762. [https://doi.org/10.1016/S1470-2045\(11\)70153-X](https://doi.org/10.1016/S1470-2045(11)70153-X)

Christensen, V. L., Rustøen, T., Cooper, B. A., Miaskowski, C., Henriksen, A. H., Bentsen, S. B., & Holm, A. M. (2016). Distinct symptom experiences in subgroups of patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 11, 1801–1809. <https://doi.org/10.2147/COPD.S105299>

COPD Working Group. (2012). Pulmonary rehabilitation for patients with chronic pulmonary disease (COPD): An evidence-based analysis. *Ontario Health Technology Assessment Series*, 12(6), 1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3384375/>

Corhay, J.-L., Dang, D. N., Van Cauwenberge, H., & Louis, R. (2014). Pulmonary rehabilitation and COPD: Providing patients a good environment for optimizing therapy. *International Journal of Chronic Obstructive Pulmonary Disease*, 9, 27. <https://doi.org/10.2147/COPD.S52012>

Corwin, E. J., Berg, J. A., Armstrong, T. S., Dabbs, A. D., Lee, K. A., Meek, P., & Redeker, N. (2014). Envisioning the future in symptom science. *Nursing Outlook*, 62(5), 346–351. <https://doi.org/10.1016/j.outlook.2014.06.006>

Coyne, P., Mulvenon, C., & Paice, J. A. (2018). American society for pain management nursing and hospice and palliative

- nurses association position statement: Pain management at the end of life. *Pain Management Nursing*, 19(1), 3–7. <https://doi.org/10.1016/j.pmn.2017.10.019>
- DeVon, H. A., Vuckovic, K., Ryan, C. J., Barnason, S., Zerwic, J. J., Pozehl, B., Schulz, P., Seo, Y., & Zimmerman, L. (2017). Systematic review of symptom clusters in cardiovascular disease. *European Journal of Cardiovascular Nursing*, 16(1), 6–17. <https://doi.org/10.1177/1474515116642594>
- Dodd, M. J., Miaskowski, C., & Paul, S. M. (2001a). Symptom clusters and their effect on the functional status of patients with cancer. *Oncology Nursing Forum*, 28(3), 465–470.
- Dodd, M. J., Cho, M. H., Cooper, B. A., & Miaskowski, C. (2010). The effect of symptom clusters on functional status and quality of life in women with breast cancer. *European Journal of Oncology Nursing*, 14(2), 101–110. <https://doi.org/10.1016/j.ejon.2009.09.005>
- Dodd, M., Janson, S., Facione, N., Faucett, J., Froelicher, E. S., Humphreys, J., Lee, K., Miaskowski, C., Puntillo, K., Rankin, S., & Taylor, D. (2001b). Advancing the science of symptom management. *Journal of Advanced Nursing*, 33(5), 668–676. <https://doi.org/10.1046/j.1365-2648.2001.01697.x>
- Downes, M. J., Brennan, M. L., Williams, H. C., & Dean, R. S. (2016). Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open*, 6(12), e011458. <https://doi.org/10.1136/bmjopen-2016-011458>
- Dunn, H., Quinn, L., Corbridge, S. J., Eldeirawi, K., Kapella, M., & Collins, E. G. (2018). Cluster analysis in nursing research: An introduction, historical perspective, and future directions. *Western Journal of Nursing Research*, 40(11), 1658–1676. <https://doi.org/10.1177/0193945917707705>
- Eckerblad, J., Tödt, K., Jakobsson, P., Unosson, M., Skargren, E., Kentsson, M., & Theander, K. (2014). Symptom burden in stable COPD patients with moderate or severe airflow limitation. *Heart & Lung*, 43(4), 351–357. <https://doi.org/10.1016/j.hrtlng.2014.04.004>
- Fan, G., Filipczak, L., & Chow, E. (2007). Symptom clusters in cancer patients: A review of the literature. *Current Oncology*, 14(5), 173. <https://doi.org/10.3747/co.2007.145>
- Given, C. W., Given, B., Azzouz, F., Kozachik, S., & Stommel, M. (2001). Predictors of pain and fatigue in the year following diagnosis among elderly cancer patients. *Journal of Pain and Symptom Management*, 21(6), 456–466. [https://doi.org/10.1016/s0885-3924\(01\)00284-6](https://doi.org/10.1016/s0885-3924(01)00284-6)
- Greulich, T., Nell, C., Koepke, J., Fectel, J., Franke, M., Schmeck, B., Haid, D., Apelt, S., Filipovic, S., Kenn, K., Janciauskiene, S., Vogelmeier, C., & Koczulla, A. R. (2014). Benefits of whole body vibration training in patients hospitalised for COPD exacerbations—a randomized clinical trial. *BMC Pulmonary Medicine*, 14(1), 60. <https://doi.org/10.1186/1471-2466-14-60>
- Gwede, C. K., Small, B. J., Munster, P. N., Andrykowski, M. A., & Jacobsen, P. B. (2008). Exploring the differential experience of breast cancer treatment-related symptoms: A cluster analytic approach. *Supportive Care in Cancer*, 16(8), 925–933. <https://doi.org/10.1007/s00520-007-0364-2>
- Herr, J. K., Salyer, J., Flattery, M., Goodloe, L., Lyon, D. E., Kabban, C. S., & Clement, D. G. (2015). Heart failure symptom clusters and functional status—a cross-sectional study. *Journal of Advanced Nursing*, 71(6), 1274–1287. <https://doi.org/10.1111/jan.12596>
- Hockenberry, M. (2004). Symptom management research in children with cancer. *Journal of Pediatric Oncology Nursing*, 21(3), 132–136. <https://doi.org/10.1177/1043454204264387>
- Huang, J., Gu, L., Zhang, L., Lu, X., Zhuang, W., & Yang, Y. (2016). Symptom clusters in ovarian cancer patients with chemotherapy after surgery: A longitudinal survey. *Cancer Nursing*, 39(2), 106–116. <https://doi.org/10.1097/NCC.0000000000000252>
- Jarden, M., Nelausen, K., Hovgaard, D., Boesen, E., & Adamsen, L. (2009). The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: A randomized controlled trial. *Journal of Pain and Symptom Management*, 38(2), 174–190. <https://doi.org/10.1016/j.jpainsymman.2008.09.005>
- Jenkins, B. A., Athilingam, P., & Jenkins, R. A. (2019). Symptom clusters in chronic obstructive pulmonary disease: A systematic review. *Applied Nursing Research*, 45, 23–29. <https://doi.org/10.1016/j.apnr.2018.11.003>
- Kelly, D. L., Dickinson, K., Hsiao, C.-P., Lukkahatai, N., Gonzalez-Marrero, V., McCabe, M., & Saligan, L. N. (2016). Biological basis for the clustering of symptoms. *Oncology Nursing*, 32(4), 351–360. <https://doi.org/10.1016/j.soncn.2016.08.002>
- Khakban, A., Sin, D. D., FitzGerald, J. M., McManus, B. M., Ng, R., Hollander, Z., & Sadatsafavi, M. (2017). The projected epidemic of chronic obstructive pulmonary disease hospitalizations over the next 15 years. A population-based perspective. *American Journal of Respiratory and Critical Care Medicine*, 195(3), 287–291. <https://doi.org/10.1164/rccm.201606-1162PP>
- Kim, H.-J., & Malone, P. S. (2019). Roles of biological and psychosocial factors in experiencing a psychoneurological symptom cluster in cancer patients. *European Journal of Oncology Nursing*, 42, 97–102. <https://doi.org/10.1016/j.ejon.2019.08.005>
- Kim, H.-J., McGuire, D. B., Tulman, L., & Barsevick, A. M. (2005). Symptom clusters: Concept analysis and clinical implications for cancer nursing. *Cancer Nursing*, 28(4), 270–282. <https://doi.org/10.1097/00002820-200507000-00005>
- Kim, E., Jahan, T., Aouizerat, B. E., Dodd, M. J., Cooper, B. A., Paul, S. M., West, C., Lee, K., Swift, P. S., Wara, W., & Miaskowski, C. (2009). Differences in symptom clusters identified using occurrence rates versus symptom severity ratings in patients at the end of radiation therapy. *Cancer Nursing*, 32(6), 429. <https://doi.org/10.1097/NCC.0b013e3181b046ad>
- Kirkova, J., Walsh, D., Aktas, A., & Davis, M. P. (2010). Cancer symptom clusters: Old concept but new data. *American Journal of Hospice and Palliative Medicine*, 27(4), 282–288. <https://doi.org/10.1177/1049909110364048>
- Knorst, M. M., Coertjens, P. C., Coertjens, M., & Coelho, A. C. (2019). Factors associated with fatigue in chronic obstructive pulmonary disease: A cross-sectional study. *European Respiratory Journal*, 54, PA3987. <https://doi.org/10.1183/13993003.congress-2019.PA3987>
- Kunik, M. E., Veazey, C., Cully, J. A., Soucek, J., Graham, D. P., Hopko, D., Carter, R., Sharafkhaneh, A., Goepfert, E. J., Wray, N., & Stanley, M. A. (2008). COPD education and cognitive behavioral therapy group treatment for clinically significant symptoms of depression and anxiety in COPD patients: A randomized controlled trial. *Psychological Medicine*, 38(3), 385–396. <https://doi.org/10.1017/S0033291707001687>

- Kwekkeboom, K. L. (2016). Cancer symptom cluster management. *Seminars in Oncology Nursing, 32*(4), 373–382. <https://doi.org/10.1016/j.soncn.2016.08.004>
- Lacasse, C., & Beck, S. L. (2007). Clinical assessment of symptom clusters. *Seminars in Oncology Nursing, 23*(2), 106–112. <https://doi.org/10.1016/j.soncn.2007.01.007>
- Lenz, E. R. (2018). Application of the theory of unpleasant symptoms in practice: A challenge for nursing. *Investigación en Enfermería: Imagen y Desarrollo, 20*(1). [https://revistas.javeriana.edu.co/files-articulos/IE/20-1%20\(2018-I\)/145254388001/](https://revistas.javeriana.edu.co/files-articulos/IE/20-1%20(2018-I)/145254388001/)
- Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: An update. *Advances in Nursing Science, 19*(3), 14–27. <https://doi.org/10.1097/00012272-199703000-00003>
- Lewko, A., Bidgood, P., Jewell, A., & Garrod, R. (2012). A comprehensive literature review of COPD-related fatigue. *Current Respiratory Medicine Reviews, 8*(5), 370–382. <https://doi.org/10.2174/157339812803832476>
- Li, Y., Chen, L., Shi, L., Wang, Y., & Zhang, H. (2013). Symptom clusters and functional status in Chinese old patients with chronic obstructive pulmonary disease. *Guangdong Medical Journal, 34*(21), 3319–3322 (In Chinese).
- Lim, K. E., Kim, S. R., Kim, H. K., & Kim, S. R. (2017). Symptom clusters and quality of life in subjects with COPD. *Respiratory Care, 62*(9), 1203–1211. <https://doi.org/10.4187/respcare.05374>
- Lim, J. U., Park, C. K., Kim, T. H., Jang, A. S., Park, Y. B., Rhee, C. K., Jung, K. S., Yoo, K. H., Lee, W. Y., & Yoon, H. K. (2019). The difficulty of improving quality of life in COPD patients with depression and associated factors. *International Journal of Chronic Obstructive Pulmonary Disease, 14*, 2331–2341. <https://doi.org/10.2147/COPD.S216746>
- Lockwood, M. B., Chung, S., Puzantian, H., Bronas, U. G., Ryan, C. J., Park, C., & DeVon, H. A. (2019). Symptom cluster science in chronic kidney disease: A literature review. *Western Journal of Nursing Research, 41*(7), 1056–1091. <https://doi.org/10.1177/0193945918808766>
- Maddocks, M., Lovell, N., Booth, S., Man, W. D., & Higginson, I. J. (2017). Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *The Lancet, 390*(10098), 988–1002. [https://doi.org/10.1016/S0140-6736\(17\)32127-X](https://doi.org/10.1016/S0140-6736(17)32127-X)
- McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., & Lacasse, Y. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews, 2*. <https://doi.org/10.1002/14651858.CD003793.pub3>
- Meeusen, C., Meuleman, B., Abts, K., & Bergh, R. (2018). Comparing a variable-centered and a person-centered approach to the structure of prejudice. *Social Psychological and Personality Science, 9*(6), 645–655. <https://doi.org/10.1177/1948550617720273>
- Miaskowski, C., & Auizerat, B. E. (2007). Is there a biological basis for the clustering of symptoms? *Seminars in Oncology Nursing, 23*(2), 99–105. <https://doi.org/10.1016/j.soncn.2007.01.008>
- Miaskowski, C., & Lee, K. A. (1999). Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: A pilot study. *Journal of Pain and Symptom Management, 17*(5), 320–332. [https://doi.org/10.1016/s0885-3924\(99\)00008-1](https://doi.org/10.1016/s0885-3924(99)00008-1)
- Miaskowski, C., Dodd, M., & Lee, K. (2004). Symptom clusters: The new frontier in symptom management research. *Journal of the National Cancer Institute Monographs, 2004*(32), 17–21. <https://doi.org/10.1093/jncimonographs/lgh023>
- Miaskowski, C., Cooper, B. A., Paul, S. M., Dodd, M., Lee, K., Auizerat, B. E., West, C., Cho, M., & Bank, A. (2006). Subgroups of patients with cancer with different symptom experiences and quality-of-life outcomes: A cluster analysis. *Oncology Nursing Forum, 33*(5), e79–e89. <https://doi.org/10.1188/06.ONF.E79-E89>
- Miaskowski, C., Barsevick, A., Berger, A., Casagrande, R., Grady, P. A., Jacobsen, P., Kutner, J., Patrick, D., Zimmerman, L., Xiao, C., Matocha, M., & Marden, S. (2017). Advancing symptom science through symptom cluster research: Expert panel proceedings and recommendations. *Journal of the National Cancer Institute, 109*(4), djw253. <https://doi.org/10.1093/jnci/djw253>
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine, 6*(7), e1000097. <https://doi.org/10.1371/journal.pmed.1000097>
- Molassiotis, A., Wengström, Y., & Kearney, N. (2010). Symptom cluster patterns during the first year after diagnosis with cancer. *Journal of Pain and Symptom Management, 39*(5), 847–858. <https://doi.org/10.1016/j.jpainsymman.2009.09.012>
- Moore, E., Palmer, T., Newson, R., Majeed, A., Quint, J. K., & Soljak, M. A. (2016). Pulmonary rehabilitation as a mechanism to reduce hospitalizations for acute exacerbations of COPD: A systematic review and meta-analysis. *Chest, 150*(4), 837–859. <https://doi.org/10.1016/j.chest.2016.05.038>
- Morjaria, J. B., & Polosa, R. (2010). The holistic perspective of chronic obstructive pulmonary disease: Doubt some more. *Therapeutic Advances Chronic Disease, 1*(2), 37–41. <https://doi.org/10.1177/2040622310373959>
- Park, S. K., & Larson, J. L. (2014). Symptom cluster, healthcare use and mortality in patients with severe chronic obstructive pulmonary disease. *Journal of Clinical Nursing, 23*(17–18), 2658–2671. <https://doi.org/10.1111/jocn.12526>
- Park, S. K., Meldrum, C. A., & Larson, J. L. (2013). Subgroup analysis of symptoms and their effect on functioning, exercise capacity, and physical activity in patients with severe chronic obstructive pulmonary disease. *Heart & Lung, 42*(6), 465–472. <https://doi.org/10.1016/j.hrtlng.2013.08.008>
- Park, S. K., Stotts, N. A., Douglas, M. K., Donesky-Cuenco, D., & Carrieri-Kohlman, V. (2012). Symptoms and functional performance in Korean immigrants with asthma or chronic obstructive pulmonary disease. *Heart & Lung, 41*(3), 226–237. <https://doi.org/10.1016/j.hrtlng.2011.09.014>
- Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., Britten, N., Roen, K., & Duffy, S. (2006). Guidance on the conduct of narrative synthesis in systematic reviews. *A Product from the ESRC Methods Programme Version, 1*, b92. https://www.researchgate.net/profile/Mark_Rodgers4/publication/233866356_Guidance_on_the_conduct_of_narrative_synthesis_in_systematic_reviews_A_product_from_the_ESRC_Methods_Programme/links/02e7e5231e8f3a6183000000/Guidance-on-the-conduct

- of-narrative-synthesis-in-systematic-reviews-A-product-from-the-ESRC-Methods-Programme.pdf
- Portenoy, R. K., Thaler, H. T., Kornblith, A. B., Lepore, J. M., Friedlander-Klar, H., Coyle, N., & Scher, H. (1994a). Symptom prevalence, characteristics and distress in a cancer population. *Quality of Life Research*, 3(3), 183–189. <https://doi.org/10.1007/BF00435383>
- Portenoy, R. K., Thaler, H. T., Kornblith, A. B., Lepore, J. M., Friedlander-Klar, H., Kiyasu, E., & Scher, H. (1994b). The Memorial Symptom Assessment Scale: An instrument for the evaluation of symptom prevalence, characteristics and distress. *European Journal of Cancer*, 30(9), 1326–1336. [https://doi.org/10.1016/0959-8049\(94\)90182-1](https://doi.org/10.1016/0959-8049(94)90182-1)
- Pud, D., Ami, S. B., Cooper, B. A., Aouizerat, B. E., Cohen, D., Radiano, R., Naveh, P., Nikkhou-Abeles, R., Hagbi, V., Kachta, O., Yaffe, A., & Miaskowski, C. (2008). The symptom experience of oncology outpatients has a different impact on quality-of-life outcomes. *Journal of Pain and Symptom Management*, 35(2), 162–170. <https://doi.org/10.1016/j.jpainsymman.2007.03.010>
- Quaderi, S., & Hurst, J. (2018). The unmet global burden of COPD. *Global Health, Epidemiology and Genomics*, 3, e4. <https://doi.org/10.1017/ghg.2018.1>
- Reyes-Gibby, C. C., Aday, L. A., Anderson, K. O., Mendoza, T. R., & Cleeland, C. S. (2006). Pain, depression, and fatigue in community-dwelling adults with and without a history of cancer. *Journal of Pain and Symptom Management*, 32(2), 118–128. <https://doi.org/10.1016/j.jpainsymman.2006.01.008>
- Sharma, S., & Sharma, P. (2019). Prevalence of dyspnea and its associated factors in patients with chronic obstructive pulmonary disease. *Indian Journal of Respiratory Care*, 8(1), 36. https://doi.org/10.4103/ijrc.ijrc_21_18
- So, W. K., Marsh, G., Ling, W., Leung, F., Lo, J. C., Yeung, M., & Li, G. K. (2009). The symptom cluster of fatigue, pain, anxiety, and depression and the effect on the quality of life of women receiving treatment for breast cancer: A multicenter study. *Oncology Nursing Forum*, 36(4), e205–e14. <https://doi.org/10.1188/09.ONF.E205-E214>
- Srirat, C., Hanucharunkul, S., Aree-Ue, S., & Junda, T. (2015). Similarity and stability of symptom cluster in severity and distress among persons with chronic obstructive pulmonary disease. *Pacific Rim International Journal of Nursing Research*, 19(2), 89–106. <https://he02.tci-thaijo.org/index.php/PRIJNR/article/view/22473>
- Srirat, C., Hanucharunkul, S., Aree-Ue, S., Viwatwongkasem, C., & Junda, T. (2014). Symptom distress, cluster, and management in Thais with COPD. *Pacific Rim International Journal of Nursing Research*, 18(3), 244–262. <https://he02.tci-thaijo.org/index.php/PRIJNR/article/view/17413>
- Tankumpuan, T., Utriyaprasit, K., Chayaput, P., & Itthimathin, P. (2015). Predictors of physical functioning in postoperative brain tumor patients. *Journal of Neuroscience Nursing*, 47(1), E11–E21. <https://doi.org/10.1097/JNN.0000000000000113>
- Ward Sullivan, C., Leutwyler, H., Dunn, L. B., & Miaskowski, C. (2018). A review of the literature on symptom clusters in studies that included oncology patients receiving primary or adjuvant chemotherapy. *Journal of Clinical Nursing*, 27(3–4), 516–545. <https://doi.org/10.1111/jocn.14057>
- Wu, M., Zan, T., Zhao, Q., Ge, S., Li, K., & Li, J. (2020). Symptom clusters and health-related quality of life in Chinese patients with chronic obstructive pulmonary disease. *Western Journal of Nursing Research*, 42(6), 437–445. <https://doi.org/10.1177/0193945919866475>
- Xiao, C. (2010). The state of science in the study of cancer symptom clusters. *European Journal of Oncology Nursing*, 14(5), 417–434. <https://doi.org/10.1016/j.ejon.2010.05.011>
- Yang, Z., Cui, M., Zhang, X., Bai, J., Tang, L., Tan, G., & Jiang, Y. (2020). Identification of symptom clusters and their influencing factors in subgroups of patients with acute exacerbation of chronic obstructive pulmonary disease in a Chinese population. *Journal of Pain and Symptom Management*, 60(3), 559–567. <https://doi.org/10.1016/j.jpainsymman.2020.03.037>
- Yates, P., Miaskowski, C., Cataldo, J. K., Paul, S. M., Cooper, B. A., Alexander, K., Aouizerat, B., Dunn, L., Ritchie, C., McCarthy, A., & Skerman, H. (2015). Differences in composition of symptom clusters between older and younger oncology patients. *Journal of Pain and Symptom Management*, 49(6), 1025–1034. <https://doi.org/10.1016/j.jpainsymman.2014.11.296>
- Yohannes, A. M., & Alexopoulos, G. S. (2014). Depression and anxiety in people with COPD. *European Respiratory Review*, 23(133), 345–349. <https://doi.org/10.1183/09059180.00007813>
- Zhu, Z., Zhao, R., & Hu, Y. (2019). Symptom clusters in people living with HIV: A systematic review. *Journal of Pain and Symptom Management*, 58(1), 115–133. <https://doi.org/10.1016/j.jpainsymman.2019.03.018>