

# Exploring Symptom Clusters and Their Measurements in Patients With Lung Cancer: A Scoping Review for Practice and Research

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**PROBLEM IDENTIFICATION:** This scoping review aimed to explore symptom clusters (SCs) in patients with lung cancer and how included symptoms and symptom dimensions are measured.

**LITERATURE SEARCH:** PubMed®, CINAHL®, Scopus®, and Cochrane Library were searched for studies published until December 31, 2021. Fifty-three articles were included.

**DATA EVALUATION:** Data extracted included descriptive items and SC constellations. Patient-reported outcome instruments and measured symptom dimensions were described according to the middle-range theory of unpleasant symptoms.

**SYNTHESIS:** 13 articles investigated SCs a priori and 40 de novo. Thirty-six instruments were used, mostly measuring intensity alone or in combination with timing. Qualitative articles (n = 6) provided rich descriptions within the distress, timing, and quality dimensions.

**IMPLICATIONS FOR RESEARCH:** Fatigue was the symptom found to most frequently co-occur with other symptoms in SCs. Fatigue, psychological symptoms, and nutritional aspects are emphasized as important areas for oncology nursing practice and further research to improve SC management for patients with lung cancer.

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**KEYWORDS** lung cancer; symptom cluster; symptom dimensions; patient-reported outcome instruments  
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Despite the many advances in cancer treatment options and the increasing number of cancer survivors, patients with lung cancer continue to experience significant symptom burden and distress (Siegel et al., 2020; Sung et al., 2017). Patients with lung cancer often experience multiple side effects from treatment and symptoms from the disease itself (Bouazza et al., 2017), affecting their functional status, general health perception, and overall health-related quality of life (Ferrans et al., 2005). Systematic use of patient-reported outcome measures (PROMs) during treatment and follow-up is fundamental in the era of person-centered care, and symptom assessment is the first step of the symptom management process. Using PROMs is one method to improve symptom management, enhance quality of care, and promote patient satisfaction for patients with cancer (Graupner et al., 2021). Within oncology nursing, continuous symptom management, including assessment, is critical in providing holistic person-centered care of high quality.

## Symptom Clusters in the Oncologic Setting

In clinical practice and research, symptoms occurring in clusters have a synergistic and cumulative effect on patient outcomes compared with single symptoms, hence having important implications for clinical practice (Miaskowski et al., 2017). Research has focused on single symptoms, and most patients with cancer experience multiple co-occurring, related symptoms (Dodd, Miaskowski, & Paul, 2001; Kim et al., 2005). The present study relies on the symptom cluster definition by Kim et al. (2005) as established groups of symptoms (two or more)

related to each other and relatively independent of other clusters revealing specific underlying concepts of symptoms and that may share the same etiology. Symptom clusters have been identified in qualitative and quantitative research by exploring nonpredefined clusters de novo (Chen & Tseng, 2006; Walsh & Rybicki, 2006) or predefined clusters a priori (Gift et al., 2003; Hammer et al., 2022; Miaskowski et al., 2006). The de novo approach means that relationships between many symptoms are explored and clusters consisting of a varied number of symptoms are identified. The a priori approach denotes that symptom clusters, generally consisting of two to three symptoms, are investigated based on a beforehand assumed relationship (Xiao, 2010). The number and specific symptoms within each symptom cluster and symptom dimensions measured have been found to be highly variable (Ward Sullivan et al., 2018), and the constellations depend on patient characteristics, disease stage, treatment, time frame of the measuring instrument, and statistical method used (Fan et al., 2007; Kim et al., 2009; Kirkova et al., 2010).

The middle-range theory of unpleasant symptoms (TOUS) (Lenz et al., 1997) has been applied in research within the oncology setting regarding multiple symptoms (Chan et al., 2005; Fox & Lyon, 2007; Gift et al., 2004; Hoffman et al., 2007; Kim et al., 2015; Wu et al., 2015; Xiao et al., 2021). TOUS has the following three main reciprocal components: the multidimensional symptom experience, the influencing factors, and performance (outcome). The conceptualized symptom experience includes four symptom dimensions as follows: intensity (strength or severity), timing (duration and/or frequency of occurrence), distress (level of discomfort), and quality (specific perceptions experienced with the symptom). Factors influencing the symptom experience are important in symptom assessment and management, including physiologic, psychological, and situational antecedents, which can interact. Performance is the result of the symptom experience, including functional and cognitive activities (Lenz et al., 1997), and quality of life may be recognized as an outcome of the symptom experience (Lenz & Pugh, 2014).

The instruments used in symptom research within the oncologic context evaluate different symptom dimensions, sometimes combined with outcomes regarding function. They are cancer-specific, disease-specific, or symptom-specific instruments designed for self- or interviewer administration, and minor cultural adaptations may apply. Symptom instruments may include single or multiple symptoms,

varying between either single or multiple items per symptom. A wide variety of 18 symptom and functional assessment tools were used in symptom cluster research (Xiao, 2010). When searching for comparable health-related quality-of-life parameters among patients with lung cancer, 17 different instruments were identified (Damm et al., 2013). A more detailed description of symptom assessment instruments and the symptom dimensions creating the symptom cluster was reported by Ward Sullivan et al. (2018), where the MD Anderson Symptom Inventory (MDASI) (Cleeland et al., 2000) and Memorial Symptom Assessment Scale (Portenoy et al., 1994) were the most commonly used. Although instruments may measure several dimensions of the symptom experience, composite indexes are presented in the results, and symptom dimensions have been sparingly used as outcomes (Hench et al., 2018).

Many issues remain in symptom cluster research (Miaskowski et al., 2017; Ward Sullivan et al., 2018), such as whether the number and varieties of symptom clusters differ based on the dimensions used to create the cluster and how cluster symptoms are related (Miaskowski, 2016; Miaskowski et al., 2017).

It is essential to have a relevant scope of the literature within the field of interest to ensure that data can be presented for comparison to develop symptom management interventions. Hence, the present scoping review maps findings from symptom cluster research within the specific context of lung cancer and the oncologic setting to help clinical healthcare personnel and researchers. The aim is to explore symptom clusters in patients with lung cancer, describing how included symptoms and symptom dimensions are measured.

## Methods

### Study Design

A scoping review methodology was chosen because the intention was to map the knowledge regarding the contents and measurements of symptom clusters. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) was used (Tricco et al., 2018). The scoping review followed the five stages proposed by Arksey and O'Malley (2005) and the updates regarding alignment with the PRISMA-ScR (Peters et al., 2020) and the clarification and enhancement of each stage (Levac et al., 2010): (a) identifying the research question, (b) finding relevant studies, (c) selecting studies, (d) charting the data, and (e) collating, summarizing, and reporting the results. The optional sixth

stage—consulting with the reference group—was not used.

### Research Questions

The research questions were as follows:

- Which symptom clusters exist in lung cancer research?
- How do the de novo and a priori clusters differ in symptom constellation?
- Which instruments are used in symptom cluster research (i.e., how are the symptoms measured)?
- How are the symptom dimensions (intensity, timing, distress, and quality) made evident in quantitative and qualitative research?

### Search Strategy

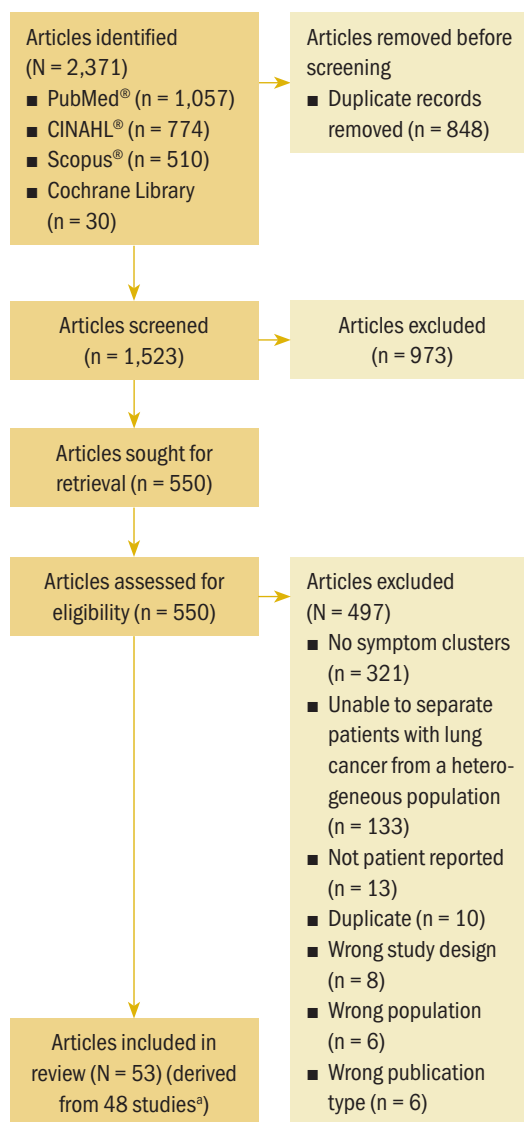
The key search terms were arranged (Peters et al., 2020) by defining the population (patients with lung cancer), concept (symptom clusters and symptom dimensions), and context (oncologic setting) and comprised the following: *lung cancer* OR *lung neoplasm* AND *patient experiences* OR *patient descriptions* OR *patient reported outcomes* AND *symptoms* OR *symptom cluster* OR *multiple symptoms* OR *symptom distress* OR *symptom burden* OR *symptom dimensions* OR *symptom intensity* OR *symptom quality* OR *symptom severity* OR *symptom frequency* OR *meaning*. Searches were performed in PubMed®, CINAHL®, Scopus®, and the Cochrane Library. Specific headings, MeSH (Medical Subject Headings) terms, and keywords were used in combination with free-text search terms by using Boolean operators adapted to the specific databases to obtain breadth and depth. Searches were conducted with no limitation as to the earliest year of publication, and the searches ended at December 31, 2021.

### Study Selection and Eligibility Criteria

Eligibility criteria guiding study selection were discussed until consensus was reached. Studies published in English in peer-reviewed journals concerning self-reported experiences of multiple co-occurring symptoms in a population of adult patients with lung cancer at or after the time of diagnosis were considered for selection. The selection process is presented in a PRISMA-ScR flow diagram (Page et al., 2021) (see Figure 1). The first author performed the database searches, with guidance from an experienced librarian. Selected articles (n = 2,371) were exported to EndNote X8/X9 for sorting and removing duplicates (n = 848), and the Rayyan QCRI software was used for further review processing. Through Rayyan, 1,523

articles were screened for inclusion. The eligibility criteria were used to screen the title/abstract, resulting in the exclusion of 973 articles. Following full-text screening (n = 550), 53 articles from 48 studies met the eligibility criteria. The screening was blinded and conducted by a minimum of two authors for each article. Any discrepancies were discussed within the author team until consensus was reached.

**FIGURE 1. PRISMA-ScR Flow Diagram of the Selection Process**



\*5 pairs of articles involved the same participants; therefore, the total number of studies was 48.  
PRISMA-ScR—Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

All included articles were screened for ethical approval, and a quality appraisal was performed (Daudt et al., 2013) using the Mixed Methods Appraisal Tool (Hong et al., 2018). The Mixed Methods Appraisal Tool includes five domains that vary depending on study design. Each assessment was scored from 0 to 100, with a higher score indicating higher quality. The quality appraisal was performed by the first author and then discussed and verified by another author.

### Charting the Data

An extraction template consistent with the aim and research questions was developed to organize the data extraction. The symptom dimension-related data were identified using the TOUS (Lenz et al., 1997) for guidance regarding the specific inference of each dimension.

### Collating, Summarizing, and Reporting the Results

The initial analysis divided the articles by their methodology, some investigating a priori symptom clusters and others de novo symptom clusters. The de novo section was arranged into two parts, when applicable, according to whether the included article had a distinct study aim to explore symptom clusters. All identified symptom clusters were charted per article. The most prevalent symptoms among the symptom clusters were identified. A comparison was also made regarding which other symptoms these prevalent symptoms were inclined to cluster with depending on methodology.

Because of the vast variety of obtainable symptom items from the variety of assessment scales used in the included articles, related individual symptom items were combined and further sorted into seven symptom categories to make comparisons possible. For example, the breathing-related symptoms dyspnea, difficulty breathing, shortness of breath, and breathlessness were combined into “dyspnea symptoms” as a part of the “respiratory symptoms.” “Pain symptoms” include the symptom items pain, neuropathy, numbness, and tingling.

## Results

### Sample Characteristics

The final sample included 53 articles (see Tables 1 and 2). Overall, the sample represented 11,948 participants with lung cancer who, in terms of their cancer care trajectory, were recently diagnosed, were currently undergoing treatment, or had finished treatment, and were as many as five years after diagnosis, with

a mean age ranging from 54 to 72.8 years. Six articles had a qualitative design and 47 a quantitative design; one was a mixed-methods study from 15 different countries. The years of publication ranged from 1993 to 2021. Because one study may yield articles with both a priori and de novo methodology, the included records are referred to as articles instead of studies.

The quality assessment showed an overall moderate to high quality score in 46 studies, with a score of 80–100, and 7 scoring 40–60 (range = 0–100). The main area producing a lower score was the assessment regarding the risk of nonbias because the information was lacking or indicated high nonresponse bias.

### Research Questions 1 and 2

The total number of symptom clusters in the final sample of 53 articles was 289. Reoccurring symptom clusters were fatigue and depression, fatigue and dyspnea, fatigue and cough, and dyspnea and cough.

### A Priori and De Novo Symptom Clusters

A total of 19 a priori defined symptom clusters were investigated in 13 articles (Chan et al., 2011, 2013; Cheville et al., 2011a, 2011b; Fox & Lyon, 2006; Gift et al., 2003; Henoch & Lövgren, 2014; Hoffman et al., 2007; Lee, 2020; Molassiotis et al., 2021; Reyes-Gibby et al., 2013; Steffen et al., 2020; Wang et al., 2014). Three clusters—fatigue, anxiety, and breathlessness; fatigue and pain; and fatigue, dyspnea, and cough—were described in more than one article, making the total number of unique clusters 15.

The prevalence of some symptoms was more evident than others. Fatigue was the prevailing symptom, being present in all articles and in 11 different clusters. Dyspnea symptoms were the second most common, being present in eight articles and four different clusters, followed by pain in seven articles and five unique clusters, and depression in four studies and five clusters. Cough was present in three studies but only two clusters.

These most prevalent symptoms in a priori clusters were found to cluster with specific symptom categories. Fatigue is clustered commonly with psychological and nutritional impact symptoms. Dyspnea, pain, and depression had a similar pattern of clustering most often with fatigue and psychological symptoms. Cough was found only in clusters with other respiratory symptoms and/or fatigue. Few clusters included the nutritional impact symptoms, elimination/abdominal symptoms, or the body/hair/skin-related symptoms.

**TABLE 1. Descriptive Results: Included Articles With A Priori Methodology (N = 13)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Chan et al., 2011 (Hong Kong)	<ul style="list-style-type: none"> <li>■ Patients with advanced lung cancer receiving palliative RT on an outpatient unit of a public hospital</li> <li>■ Mean age = 63.5 years; SD = 11.9</li> <li>■ N = 140</li> </ul>	To examine the effectiveness of a psychoeducational intervention for relief of an SC of anxiety, breathlessness, and fatigue compared with usual care	<ul style="list-style-type: none"> <li>■ Quantitative RCT</li> <li>■ Pre-/post-test, 2-group RCT</li> </ul>	A significant difference over time between the psychoeducational intervention and usual care control group on the pattern of change of the SC was found. Significant effects on the patterns of changes in breathlessness, fatigue, anxiety, and functional ability were also found.	60
Chan et al., 2013 (Hong Kong)	<ul style="list-style-type: none"> <li>■ Patients with advanced lung cancer (stage III or IV) receiving palliative RT on an outpatient unit of a public hospital</li> <li>■ Mean age = 63.5 years; SD = 11.9</li> <li>■ N = 140</li> </ul>	To examine the prevalence and intensity of individual symptoms, the association between individual symptoms, and the pattern of association in symptom intensity over time	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Longitudinal design, secondary analysis of data from an RCT (same population as Chan et al., 2011)</li> </ul>	64%–73% of patients experienced all 3 symptoms concurrently across time. The prevalence of anxiety, breathlessness, and fatigue ranged from 65% to 97%. Intensities of breathlessness and fatigue were highest at time 1. Significant correlations between the 3 symptoms were moderate across time.	40
Cheville et al., 2011a (United States)	<ul style="list-style-type: none"> <li>■ Lung cancer (stage I–IV) survivors at 1 cancer clinic, providing a self-reported annual follow-up within 6 months of diagnosis and until death</li> <li>■ Mean age = 65.9 years; SD = 10.79 at year ≥ 1 of survival</li> <li>■ N = 2,405</li> </ul>	To characterize the SC containing fatigue, dyspnea, and cough, and its predictive value for important outcomes relative to these symptoms	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Prospective cohort study</li> </ul>	The SC, as well as its individual symptoms and symptom pairs, were all negatively associated with survival in years 1–3 after diagnosis. Only in year 3 did the SC prognosticate survival marginally better; fatigue was strongly associated with survival at all time points. The SC was not predictive of participants' employment status, physical activity, or QOL, whereas the presence of fatigue, dyspnea, or their combination was strongly associated with these outcomes.	100

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**TABLE 1. Descriptive Results: Included Articles With A Priori Methodology (N = 13) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Cheville et al., 2011b (United States)	<ul style="list-style-type: none"> <li>■ Lung cancer (stage I–IV) survivors at 1 cancer clinic providing a self-reported annual follow-up within 6 months of diagnosis and until death</li> <li>■ Mean age = 65.9 years; SD = 10.79 at year ≥ 1 of survival</li> <li>■ N = 2,405</li> </ul>	To describe SCs in lung cancer survivors as many as 5 years after diagnosis, investigate their stability over time, and identify determinants of SC development and resolution	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Prospective cohort study (same population as Cheville et al., 2011a)</li> </ul>	A single robust SC of fatigue, cough, and dyspnea was identified. Those with the SC were more likely to die; this diminished over time. Persistence varied, with more than 40% of surviving patients annually transitioning to or from the SC state until year 4, after which it became increasingly stable. The SC was more likely to develop among male survivors who underwent surgery, received RT, and were current smokers.	100
Fox & Lyon, 2006 (United States)	<ul style="list-style-type: none"> <li>■ Patients diagnosed with lung cancer (any stage) recruited from an online lung cancer support group, in which 94% of the sample had some form of treatment prior to the study</li> <li>■ Mean age = 56.9 years; SD = 7.85</li> <li>■ N = 51</li> </ul>	To explore possible SCs in patients with lung cancer and their relationship to QOL, specifically to explore the prevalence and intensity of depression, fatigue, and pain; to examine the relationship of simultaneously occurring or clustered symptoms with each other; and to examine the relationship of the SC with QOL	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Secondary analysis data</li> </ul>	Depression, fatigue, and pain were found in a majority of survivors, with pain being the least common symptom. Fatigue was the most intense of the 3 symptoms. 2 significantly correlated symptoms were depression and fatigue. The cluster explained 29% of the variance in QOL in the lung cancer survivors.	40
Gift et al., 2003 (United States)	<ul style="list-style-type: none"> <li>■ Patients at 24 sites (community hospitals and medical, oncology, and RT clinics) newly diagnosed with lung cancer (any stage)</li> <li>■ Mean age = 72 years; SD = 4.9</li> <li>■ N = 112</li> </ul>	To determine whether the SC identified at diagnosis remained 3 and 6 months later and whether there was a difference in mean number of symptoms and mean symptom severity over time, and to determine whether physiologic factors predict number of cluster symptoms reported and whether severity is predictive of death	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ A secondary analysis of data collected as part of a larger study</li> </ul>	The cluster of 7 symptoms had internal consistency that remained at 3 and 6 months. The mean symptom severity and number of symptoms at diagnosis were correlated with later ratings but decreased in severity over time. A similar decrease in severity rating was seen for the individual symptoms in the SC.	60

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**TABLE 1. Descriptive Results: Included Articles With A Priori Methodology (N = 13) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Henoch & Lövgren, 2014 (Sweden)	<ul style="list-style-type: none"> <li>■ Patients with inoperable lung cancer at the lung medicine departments of 2 university hospitals</li> <li>■ Mean age = 64.5 years; SD = 10.5</li> <li>■ N = 400</li> </ul>	To explore the influence of SCs and the most distressing concerns on global rating of QOL among patients with inoperable lung cancer during a 3-month period following diagnosis	<ul style="list-style-type: none"> <li>■ Mixed methods</li> <li>■ Cross-sectional, using data from a longitudinal study (same population as Henoch et al., 2009)</li> </ul>	The pain, mood, and respiratory clusters were identified in the original study. In this study, all 3 SCs predicted QOL at each time point. Close to diagnosis, none of the dimensions of most distressing concerns predicted QOL, and the bodily distress dimension was a significant predictor of QOL after 1 month.	100
Hoffman et al., 2007 (United States)	<ul style="list-style-type: none"> <li>■ Patients newly diagnosed with lung cancer (stage II–IV) and receiving oncologic treatment at 4 sites: 2 clinical community oncology programs and 2 comprehensive cancer centers</li> <li>■ Mean age = 63 years; SD = 9</li> <li>■ N = 80</li> </ul>	To examine the relationships among pain, fatigue, insomnia, and gender while controlling for age, comorbidities, and stage of cancer in patients newly diagnosed with lung cancer within 56 days of receiving chemotherapy	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Secondary analysis of data from a single-blinded, randomized clinical intervention trial</li> </ul>	Fatigue (97%) and pain (69%) were the most frequently occurring symptoms; insomnia occurred 51% of the time. A model containing all main effects was a good fit to the data. Gender did not make a difference. Age, comorbidities, and stage of cancer were not significant covariates.	100
Lee, 2020 (South Korea)	<ul style="list-style-type: none"> <li>■ Patients with NSCLC, mostly undergoing chemotherapy, at a single tertiary institution</li> <li>■ Mean age = 66 years; SD not available</li> <li>■ N = 135</li> </ul>	To describe the symptoms experienced by patients with NSCLC, examine whether different symptom groups significantly affected functioning domains, and determine the effect of the symptom groups on the functioning domains of HRQOL	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Cross-sectional</li> </ul>	The most common symptoms were fatigue (69%), pain (47%), dyspnea (38%), and lack of appetite (36%). The pain group was negatively associated with physical, emotional, cognitive, and role functioning. The lack of energy group was negatively associated with physical, role, emotional, social, and cognitive functioning, and explained the most variance for physical and role functioning. The pain group explained the most variance for emotional functioning.	100

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**TABLE 1. Descriptive Results: Included Articles With A Priori Methodology (N = 13) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Molassiotis et al., 2021 (Vietnam)	<ul style="list-style-type: none"> <li>■ Patients with invasive lung cancer randomized to Qigong group (n = 78) (mean age = 57.6 years; SD = 9.6) or a waitlist control group (n = 78) (mean age = 56.1 years; SD = 9.25)</li> <li>■ N = 156</li> </ul>	To assess the effect of Qigong on managing dyspnea, fatigue, and anxiety (as a cluster) in patients with lung cancer and to explore the effect of Qigong on cough and QOL dimensions	<ul style="list-style-type: none"> <li>■ Quantitative RCT</li> </ul>	No significant interaction effect between group and time for the SC overall and for fatigue and anxiety; a significant trend toward improvement was observed on fatigue, dyspnea, and anxiety in the Qigong group. Improvements in dyspnea and cough, global health status, functional well-being, and QOL were statistically significant.	80
Reyes-Gibby et al., 2013 (United States)	<ul style="list-style-type: none"> <li>■ Patients newly diagnosed with NSCLC (participants in another epidemiologic study) at 1 cancer center</li> <li>■ Mean age = 61 years; SD = 12</li> <li>■ N = 599</li> </ul>	To assess the extent to which 55 SNPs in immune response genes may serve as biomarkers for SCs of pain, depressed mood, and fatigue and to test the a priori hypothesis that SNPs in immune response genes may help in identifying patients with severe versus nonsevere clusters	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	2 homogenous clusters were identified. 19% of patients reported severe SCs, with high intensity of pain, depressed mood, and fatigue; 30% of patients reported low intensity. Using Bayesian model averaging methodology, of the 55 SNPs assessed, an additive effect of mutant alleles in 5 SNPs was predictive for SCs.	100
Steffen et al., 2020 (United States)	<ul style="list-style-type: none"> <li>■ Ambulatory patients with advanced NSCLC undergoing treatment at an outpatient cancer center</li> <li>■ Mean age = 68.7 years; SD = 8.8</li> <li>■ N = 50</li> </ul>	To test whether between- and within-person variation in aspects of hope agency and pathways thinking was related to patients' daily experiences of fatigue and pain and functional concerns (i.e., perceived burden, usefulness, and independence)	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> </ul>	Within-person increases in pathways thinking were associated with less daily fatigue, pain, and functional concern; within-person increases in agency thinking were associated with less daily fatigue and pain. Models examining symptoms and concerns as predictors of hope suggested within-person increases in functional concern and fatigue and pain were related to lower agency and pathways thinking.	100

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**TABLE 1. Descriptive Results: Included Articles With A Priori Methodology (N = 13) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Wang et al., 2014 (Taiwan)	<ul style="list-style-type: none"> <li>■ Patients with advanced NSCLC at assessed pretreatment and at 1 month, 3 months, and 6 months after gefitinib treatment</li> <li>■ Mean age = 62.3 years; SD = 12.61</li> <li>■ N = 57</li> </ul>	To analyze the relationships between single symptoms/SCs and cytokines in patients with advanced NSCLC after receiving gefitinib treatment	<ul style="list-style-type: none"> <li>■ Quantitative</li> <li>■ Longitudinal feasibility study</li> </ul>	Positive relationships were found between IL-2 and nausea, distress, drowsiness, lack of appetite, sum of symptom severity scores, and a GI SC. Positive relationships between IL-6 and sadness, lack of appetite, and pain and a negative relationship between IL-6 and difficulty remembering were also observed. Positive relationships were observed between IL-10 and fatigue, lack of appetite, drowsiness, sadness, sum of symptom severity scores, and a general SC.	60

GI—gastrointestinal; HRQOL—health-related quality of life; IL—interleukin; MMAT—Mixed Methods Appraisal Tool; NSCLC—non-small cell lung cancer; QOL—quality of life; RCT—randomized controlled trial; RT—radiation therapy; SC—symptom cluster; SNPs—single nucleotide polymorphisms

A total number of 270 de novo symptom clusters were identified in 40 articles, where 15 (Brown et al., 2011; Choi & Ryu, 2018; DeClue et al., 2020; Gift et al., 2004; Hamada et al., 2016; Henocho et al., 2009; Khamboon et al., 2015; Li, Li, et al., 2021; Li, Wu, et al., 2021; Liu, Liu, et al., 2021; Maguire et al., 2014; Sarna & Brecht, 1997; Wang & Fu, 2014; Wang et al., 2006, 2008) described an intention in their methodology to investigate symptom clusters de novo (hereby defined as “with cluster aim”). The other 25 articles (Andersen et al., 2020; Belqaid et al., 2016, 2018; Chien et al., 2021; Henocho et al., 2008; Kiteley & Fitch, 2006; Kuo & Ma, 2002; Lavdaniti et al., 2021; Lee, 2021; Liu, Hou, et al., 2021; Lowe & Molassiotis, 2011; Maguire et al., 2019; Maric et al., 2010; McFarland et al., 2020; Mody et al., 2021; Molassiotis, Lowe, Blackhall, & Lorigan, 2011; Molassiotis, Lowe, Ellis, et al., 2011; Morrison et al., 2017; Nishiura et al., 2015; Okuyama et al., 2001; Reyes-Gibby et al., 2007; Sarna, 1993; Tanaka et al., 2002; Tchekmedyan et al., 2003; Turcott et al., 2020) did not do this as a part of their aim (hereby defined as “without cluster aim”), but the results have presented patient-reported co-occurring symptoms—that is,

symptom clusters. The number of symptom clusters varied from 1 to 49 variations per article.

Among the 15 articles with a cluster aim, the most prevalent symptoms were fatigue in all 15 articles (Brown et al., 2011; Choi & Ryu, 2018; DeClue et al., 2020; Gift et al., 2004; Hamada et al., 2016; Henocho et al., 2009; Khamboon et al., 2015; Li, Li, et al., 2021; Li, Wu, et al., 2021; Liu, Liu, et al., 2021; Maguire et al., 2014; Sarna & Brecht, 1997; Wang & Fu, 2014; Wang et al., 2006, 2008), followed by pain in 13 (Brown et al., 2011; Choi & Ryu, 2018; DeClue et al., 2020; Hamada et al., 2016; Henocho et al., 2009; Khamboon et al., 2015; Li, Li, et al., 2021; Li, Wu, et al., 2021; Maguire et al., 2014; Sarna & Brecht, 1997; Wang & Fu, 2014; Wang et al., 2006, 2008), depression (n = 12) (Choi & Ryu, 2018; DeClue et al., 2020; Hamada et al., 2016; Henocho et al., 2009; Khamboon et al., 2015; Li, Li, et al., 2021; Li, Wu, et al., 2021; Liu, Liu, et al., 2021; Sarna & Brecht, 1997; Wang & Fu, 2014; Wang et al., 2006, 2008), appetite loss (n = 12) (Choi & Ryu, 2018; Gift et al., 2004; Hamada et al., 2016; Henocho et al., 2009; Khamboon et al., 2015; Li, Li, et al., 2021; Li, Wu, et al., 2021; Liu, Liu, et al., 2021; Maguire et al.,

**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Andersen et al., 2020 (United States)	<ul style="list-style-type: none"> <li>■ Newly diagnosed patients with stage IV NSCLC at thoracic oncology clinics of a comprehensive cancer center</li> <li>■ Mean age = 62.5 years; SD = 11.7</li> <li>■ N = 186</li> </ul>	To identify those with moderate to severe depressive symptoms and to provide a clinical description of the multiple co-occurring psychological and behavioral difficulties and physical symptoms that potentially exacerbate and maintain depressive symptoms	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Observational study</li> </ul>	Patients with severe depressive symptoms reported concomitant feelings of hopelessness, anxiety symptoms suggestive of GAD, and traumatic, cancer-specific stress. Pain and multiple severe symptoms were present along with substantial functional impairment. Patients with moderate depressive symptoms had generally lower levels of disturbance, but these were still substantial.	100
Belqaid et al., 2016 (Sweden)	<ul style="list-style-type: none"> <li>■ Patients with primary LC receiving systemic or localized treatment at a university hospital</li> <li>■ Mean age = 66.8 years; SD = 8.7</li> <li>■ N = 52</li> </ul>	To explore and describe how characteristics of self-reported taste and smell alterations change in individuals with LC over time	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Longitudinal and multiple case study</li> </ul>	There is a large diversity of characteristics of TSAs between patients treated for primary LC; also, the characteristics of TSAs change over time within many patients. The individual experiences of TSAs and the impact of these symptoms on daily life may be influenced by individual and contextual factors.	80
Belqaid et al., 2018 (Sweden)	<ul style="list-style-type: none"> <li>■ Patients with LC (10 in treatment/7 finished or on a break from treatment) at a university hospital</li> <li>■ Age range = 48–77 years; mean and SD N/A</li> <li>■ N = 17</li> </ul>	To investigate how people with experience from LC-related TSAs reason about the resources and strategies offered and used to manage these symptoms	<ul style="list-style-type: none"> <li>■ Qualitative</li> </ul>	TSAs led to 2 overarching challenges in daily life. The participants engaged in various activities to adjust to their altered sense of taste and/or smell and underwent a process of coming to terms with TSAs as a feature of having LC. Limited support was received from healthcare professionals but was still significant.	100

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Brown et al., 2011 (United States)	<ul style="list-style-type: none"> <li>■ Women with NSCLC, 6 months to 5 years after diagnosis, at multiple clinical sites in 5 states, with 13% currently receiving treatment</li> <li>■ Mean age = 65.4 years; SD = 11.4</li> <li>■ N = 196</li> </ul>	To describe the occurrence, severity, SCs, and relationships of demographic and clinical characteristics, health status factors, and meaning of illness with symptom experience and SCs and determine whether a co-occurring sentinel symptom was associated with the presence of SCs	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Prospective, correlational study</li> </ul>	About 98% of women experienced 3 or more symptoms in the past day. The most common symptoms reported by more than 80% were fatigue, shortness of breath, anorexia, cough, and pain, with fatigue and shortness of breath rated as the most severe.	100
Chien et al., 2021 (Taiwan)	<ul style="list-style-type: none"> <li>■ Patients newly diagnosed with LC receiving oncologic treatment at a medical center hospital</li> <li>■ Mean age = 60.8 years; SD = 1.3</li> <li>■ N = 120</li> </ul>	To identify distinct subgroups of patients newly diagnosed with LC over time and to explore predictors of distinct trajectories of symptom and fatigue distress	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Longitudinal, prospective study</li> </ul>	The linear 3-trajectory model had the best model fit for symptom and fatigue distress. Symptom and fatigue distress improved with time, except for patients with increasing trajectories. Pain, lower functional status, total symptom score, and depression affected trajectories of symptom and fatigue distress.	80
Choi & Ryu, 2018 (South Korea)	<ul style="list-style-type: none"> <li>■ Patients with advanced LC at the National Cancer Center in Korea</li> <li>■ Mean age = 54 years; SD = 8.7</li> <li>■ N = 178</li> </ul>	To identify the symptoms experienced by patients with advanced LC and classify them into SCs, identify the presence of depression in patients, and compare to other symptoms and QOL and the factors influencing the effects of depression and SCs on the QOL	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Cross-sectional</li> </ul>	Almost all (98%) presented with at least 4 concurrent symptoms. The 5 most common were fatigue, distress, feeling sad, drowsiness, and dry mouth. Distress was perceived to be most severe, followed by fatigue, feeling sad, disturbed sleep, and lack of appetite. 3 SCs were identified: treatment associated, LC, and psychological. The regression model found a significant negative impact on QOL for depression and the LC SC.	100

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
DeClue et al., 2020 (United States)	<ul style="list-style-type: none"> <li>■ Patients with metastatic NSCLC who had received cancer treatment within 3 months prior to the survey date</li> <li>■ Mean age = 72.8 years; SD = 6.7</li> <li>■ N = 698</li> </ul>	To establish a claims-based mechanism for identifying patients with metastatic NSCLC and high levels of patient-reported cancer-related symptoms who could benefit from engagement with healthcare programs	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Cross-sectional</li> </ul>	2 distinct SCs were identified: less severe (38.4%) and more severe (61.6%). Those in the more severe cluster were younger, were more frequently dually eligible for Medicare and Medicaid, and more frequently had prescription fills for opioids. Claims-based factors associated with the more severe cluster included 2 or more 30-day fills for opioids in the prior 6 months, age younger than 75 years, depression diagnosis or antidepressants, bone metastases, and pain-related outpatient visits.	100
Gift et al., 2004 (United States)	<ul style="list-style-type: none"> <li>■ Patients at 24 sites (community hospitals and medical, oncology, and radiation clinics) newly diagnosed with LC (any stage)</li> <li>■ Mean age = 72 years; SD = 5.02</li> <li>■ N = 220</li> </ul>	To determine whether symptoms co-occur in patients newly diagnosed with LC; whether symptoms vary according to the stage of disease, comorbidities, treatment provided, or gender; and whether those co-occurring symptoms affect patients' performance, such as their perceptions of their limitations or their self-reported functional status	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ A secondary analysis of data collected as part of a larger study (same population as Gift et al., 2003)</li> </ul>	Patients reported multiple distressing symptoms related to symptom severity and limitations. Factor analysis found that fatigue, nausea, weakness, appetite loss, weight loss, altered taste, and vomiting form an SC. Initial staging of cancer, the number of comorbid conditions, and being treated with chemotherapy emerged as significant predictors of symptoms reported. Few differences were noted between men and women. A correlation was found among the numbers of symptoms reported, symptom severity, and limitations attributed to symptoms.	80

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Hamada et al., 2016 (Japan)	<ul style="list-style-type: none"> <li>■ Patients with advanced NSCLC receiving standard therapy at 1 regional university hospital and 1 general hospital</li> <li>■ Mean age = 64.3 years; SD = 11.4</li> <li>■ N = 60</li> </ul>	To identify SCs based on symptoms experienced by patients with advanced NSCLC and examine the relationship between the SCs and impairment in everyday life and QOL	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	Identified 3 SCs comprising 3–5 symptoms each; severity was mild and reported at 1 point in time. The 3 SCs were identified as fatigue/anorexia, pain, and numbness. The pain SC had the strongest influence on daily life, and the numbness SC most strongly affected walking. The fatigue/anorexia cluster explained 22.7% of role function variance.	100
Henoch et al., 2008 (Sweden)	<ul style="list-style-type: none"> <li>■ Patients with LC, not amenable for further treatment with curative or life-prolonging intent, at a university hospital</li> <li>■ Mean age = 69 years; SD N/A</li> <li>■ N = 105</li> </ul>	To describe and analyze the dimensionality of dyspnea experience and to examine the relations with other symptoms and personal and health-related factors	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	More than half perceived dyspnea. Coping capacity, performance status, and other symptoms correlated with different aspects of dyspnea experience. Dyspnea dimensions and activity-related dyspnea correlated with anxiety, depression, fatigue, and cough, as well as negatively with coping capacity.	80
Henoch et al., 2009 (Sweden)	<ul style="list-style-type: none"> <li>■ Patients with inoperable LC at the lung medicine departments of 2 university hospitals</li> <li>■ Mean age = 64.5 years; SD = 10.5</li> <li>■ N = 400</li> </ul>	To inductively explore the existence of SCs among a homogenous group of patients with inoperable LC close to diagnosis and to explore whether the SCs are consistent when examined with different instruments and analytical methods	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	3 SCs were found to be notably consistent across instruments and analyses. A pain SC consisting of pain, nausea, bowel issues, appetite loss, and fatigue; a mood SC consisting of mood, outlook, concentration, and insomnia; and a respiratory SC consisting of breathing and cough, with fatigue and appetite loss closely related to more than 1 SC in several analyses.	80

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Khamboon et al., 2015 (Thailand)	<ul style="list-style-type: none"> <li>■ Patients with advanced-stage LC receiving chemotherapy on 1 outpatient unit and at a cancer institute</li> <li>■ Mean age = 61.4 years; SD = 10.3</li> <li>■ N = 300</li> </ul>	To identify the symptoms experienced by patients with advanced LC and identify and compare the SCs in the severity and distress dimensions	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	Participants experienced multiple symptoms simultaneously. A lack of appetite was rated as the most prevalent and severe. Problems with urination was rated the most frequent and constipation as the most distressing. 5 SCs existed in both dimensions of symptom severity and distress.	80
Kiteley et al., 2006 (Canada)	<ul style="list-style-type: none"> <li>■ Patients newly diagnosed with LC at a regional cancer clinic; 4 had treatment prior to the first interview, and 14 received treatment between interviews.</li> <li>■ Mean age = 66.5 years; SD = 10.1</li> <li>■ N = 16</li> </ul>	To describe the patients' perceptions about their symptoms over the course of their illness to better understand which symptoms patients experience, which they find most troublesome, and the strategies they use to manage the symptoms	<ul style="list-style-type: none"> <li>■ Qualitative</li> </ul>	The most commonly identified symptoms were fatigue and pain. Participants described coping with multiple symptoms simultaneously, how the symptoms intensified over time, and using very few strategies. Participants described symptoms as troublesome; fatigue was reported most frequently as troublesome.	100
Kuo & Ma, 2002 (Taiwan)	<ul style="list-style-type: none"> <li>■ Patients with NSCLC, 42 receiving chemotherapy and 31 receiving RT, at the cancer center or ward in the 2 medical centers in northern Taiwan</li> <li>■ Age range = 39–84 years (mean and SD N/A)</li> <li>■ N = 73</li> </ul>	To understand the correlation of symptom distresses and coping strategies of patients with LC	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	The degree of symptom distress during the therapeutic period was mild to moderate. Patients combined problem- and emotion-focused coping strategies. The distress of tension–anxiety and age explained 39.4% of variance in physical symptom distresses. The physical symptom distresses and frequency of emotion-focused coping strategy explained 48.8% of variance in the psychological symptom distresses.	100

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Lavdaniti et al., 2021 (Greece)	<ul style="list-style-type: none"> <li>■ Patients with LC at the oncology department of a general hospital, not undergoing concomitant chemotherapy/RT or RT</li> <li>■ Mean age = 67.1 years; SD = 7.8</li> <li>■ N = 76</li> </ul>	To assess the perceived symptoms, depression, and QOL in patients with advanced LC undergoing chemotherapy	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Cross-sectional</li> </ul>	The most frequently observed symptoms were tiredness, shortness of breath, anxiety, and well-being. Gender affected level of depression, and type of LC affected depression. Type of treatment influenced the score of global health status, role functioning, and social functioning. Predictors for QOL were pain and tiredness, and type of lung cancer, type of insurance, and type of treatment influenced depression.	80
Lee, 2021 (South Korea)	<ul style="list-style-type: none"> <li>■ Patients undergoing chemotherapy, RT, or concurrent chemotherapy/RT for NSCLC at a university hospital</li> <li>■ Mean age = 66 years; SD = 9.1</li> <li>■ N = 132</li> </ul>	To investigate the relationship of spiritual well-being and QOL in patients undergoing treatment for NSCLC and to identify the role of appetite loss, dyspnea, pain, and fatigue in mediating this relationship	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	Spiritual well-being directly affected QOL. A serial multiple mediation model showed causal relationships of spiritual well-being on appetite loss, appetite loss on dyspnea, dyspnea on pain, pain on fatigue, and fatigue on QOL.	100
Li, Li, et al., 2021 (China)	<ul style="list-style-type: none"> <li>■ Patients with LC receiving surgical treatment at a tertiary hospital</li> <li>■ Mean age = 59.8 years; SD = 10.5</li> <li>■ N = 217</li> </ul>	To describe the trajectory, number, and types of SCs at 3 time points (i.e., day of admission, 2–4 days postoperatively, and 1 month postoperatively) using ratings of symptom occurrence and severity and to identify the changes in these SCs over time	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Secondary analysis of data obtained from a descriptive, longitudinal study</li> </ul>	7 SCs were identified across symptom dimensions. However, only 3 of them (i.e., lung cancer-specific, sleep disturbance, and nervous system) were relatively stable across dimensions and time. 2 SCs varied over time but not with dimensions (nutritional and GI). The other 2 SCs (psychological and respiratory) differed in terms of time and dimensions.	80

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Li, Wu, et al., 2021 (China)	<ul style="list-style-type: none"> <li>■ Patients with NSCLC, mainly stages III and IV, at 2 hospitals</li> <li>■ Mean age = 62.7 years; SD = 7.79</li> <li>■ N = 144</li> </ul>	To determine types and components of SCs according to severity dimension and to understand how they change during chemotherapy in a homogeneous population of patients with LC	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Longitudinal study</li> </ul>	6 SCs were identified by exploratory factor analysis at 3 time points. Among 6 SCs, 3 remained stable at all time points; differences were found in SCs before and after chemotherapy.	60
Liu, Hou, et al., 2021 (United States)	<ul style="list-style-type: none"> <li>■ Patients with LC and a Karnofsky Performance Status Scale score of 60 or greater at an oncology clinic at 1 academic cancer center</li> <li>■ Mean age = 62.9 years; SD = 10.9</li> <li>■ N = 288</li> </ul>	To quantify symptom burden and the factors associated with willingness to participate in herbal clinical trials among patients with LC	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	The most commonly reported moderate to severe symptoms were fatigue (57%), drowsiness (44%), disturbed sleep (43%), distress (42%), and dyspnea (36%). Higher education was significantly associated with willingness to participate in herbal studies.	100
Liu, Liu, et al., 2021 (China)	<ul style="list-style-type: none"> <li>■ Patients with NSCLC undergoing chemotherapy at a university general hospital</li> <li>■ Age range = 39–80 years; mean and SD N/A</li> <li>■ N = 127</li> </ul>	To explore the most common side effects to evaluate their trajectories and interrelation and to assess the impact of prolonging the use of low-dosage dexamethasone on alleviating the symptom burden of chemotherapy	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Prospective cross-sectional</li> </ul>	The most frequent symptoms were fatigue, insomnia, cough and sputum, appetite loss, and hypodipsia. A statistically significant difference was found between the intervention group and control group.	100
Lowe & Molassiotis, 2011 (United Kingdom)	<ul style="list-style-type: none"> <li>■ Patients with inoperable primary LC receiving palliative treatment at a specialist cancer hospital</li> <li>■ Mean age = 66.7 years; SD N/A</li> <li>■ N = 16</li> </ul>	To examine the patients' symptom experiences and the explanatory models used by patients (and their caregivers) as a way to expand understanding of patient symptom experiences and distress across the disease trajectory of LC	<ul style="list-style-type: none"> <li>■ Qualitative</li> </ul>	Factors influencing degree of distress were symptom anticipation, symptom novelty, symptom impact on daily life, previous experience with symptoms, and causal reasoning. The relationship between symptom characteristics and patient distress is unlikely to be static because patient anticipation is certain to evolve over time.	100

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Maguire et al., 2014 (Scotland)	<ul style="list-style-type: none"> <li>■ Patients with advanced LC stage IIIb–IV who were experiencing 3 or more concurrent symptoms</li> <li>■ Mean age = 63 years; SD N/A</li> <li>■ N = 10</li> </ul>	To explore the lived experience of multiple concurrent symptoms in people with advanced LC to contribute to the understanding of the experience of SCs	<ul style="list-style-type: none"> <li>■ Qualitative</li> </ul>	Participants experienced 4–11 concurrent symptoms, with fatigue, cough, pain, and breathlessness featured prominently. Participants commonly identified associations between the symptoms they experienced, with the occurrence of 1 symptom often used to explain the occurrence of another. Reductions in physical and social functioning were often associated with the experience of multiple concurrent symptoms, particularly at times of high symptom severity.	100
Maguire et al., 2019 (United Kingdom)	<ul style="list-style-type: none"> <li>■ Patients with LC, various stages and treatment modalities, at 6 regional hospitals</li> <li>■ Mean age = 69.2 years; SD = 9.1</li> <li>■ N = 201</li> </ul>	To investigate the prevalence of patient-perceived LCS and its relationships to symptom burden and severity, depression, and deficits in HRQOL	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Observational, cross-sectional study</li> </ul>	LCS was significantly correlated with younger age, greater social deprivation, being unemployed, depression, symptom burden, and HRQOL deficits. Symptom burden explained 18% of variance in LCS. LCS explained 8.5% and 14.3% of the variance in depression and HRQOL, respectively.	80
Maric et al., 2010 (Serbia)	<ul style="list-style-type: none"> <li>■ Patients with advanced NSCLC and Karnofsky index 70% or greater, 31% newly diagnosed, and 69% having treatment as in- and outpatients in 1 clinical center</li> <li>■ Mean age = 58.5 years; SD = 8.3</li> <li>■ N = 100</li> </ul>	To assess self-reported HRQOL and to analyze whether HRQOL dimensions were associated with treatment, side effects of treatment, and socioeconomic characteristics	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> </ul>	Highly educated patients reported significantly worse social functioning and higher degree of financial difficulties than less educated patients. Unemployed patients had significantly better HRQOL in all domains and significantly lower symptom distress.	100

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
McFarland et al., 2020 (United States)	<ul style="list-style-type: none"> <li>■ Patients with stage IV LC during treatment at an outpatient clinic</li> <li>■ Mean age = 65.9 years; SD = 9.3</li> <li>■ N = 116</li> </ul>	To evaluate self-reported physical symptom burden by using the physical problem list of the NCCN Distress Thermometer and Problem List and to assess whether physical symptoms identified accurately reflect the most common physical symptoms in patients with LC; and to examine whether physical symptom burdens vary systematically by patient demographic, medical characteristics, and psychological state	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	The average number of physical problems was 4.7 (SD = 3.8), and the median was 3. Fatigue, sleep, pain, and breathing problems were most common. Physical symptom burden was associated with non-married/partnered status and depression on multivariate analysis, accounting for 43% of physical symptom burden variance. A greater number of physical symptoms and lower BMI were associated with worsened survival.	80
Mody et al., 2021 (United States)	<ul style="list-style-type: none"> <li>■ Patients receiving treatment for advanced or metastatic LC at several community sites</li> <li>■ Mean age = 64.6 years; SD = 9.9</li> <li>■ N = 118</li> </ul>	To determine feasibility of electronic PRO monitoring in patients with LC receiving treatment in community settings	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Prospective trial with data from the larger parent PROTECT Study</li> </ul>	Patients with LC participating in electronic PROs were older, had worse performance status, had more comorbidities, and had less technology experience than those with other cancers. Nearly all patients reported concerning symptoms. Pain was the most frequent and longest lasting symptom.	80
Molassiotis, Lowe, Blackhall, & Lorigan, 2011 (United Kingdom)	<ul style="list-style-type: none"> <li>■ Patients with inoperable primary LC receiving treatment at a large specialist cancer hospital</li> <li>■ Mean age = 66.7 years; SD = 12.6</li> <li>■ N = 17</li> </ul>	To explore the symptom experience of patients with cancer during a 1-year period from the patient and informal caregiver perspectives	<ul style="list-style-type: none"> <li>■ Qualitative (same population as Lowe &amp; Molassiotis, 2011)</li> </ul>	3 themes emerged from accounts of respiratory symptom experiences: (a) breadth and dynamic nature of patients' symptom experiences; (b) symptom interrelationships; and (c) symptom identification. Findings indicate that a cluster of interacting respiratory symptoms play a central role in patients' symptom experiences within the LC population.	100

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Molassiotis, Lowe, Ellis, et al., 2011 (United Kingdom)	<ul style="list-style-type: none"> <li>■ Patients with LC, in treatment or after completed curative or palliative treatment, at a specialist cancer hospital and 2 district general hospitals</li> <li>■ Mean age = 70.2 years; SD = 10</li> <li>■ N = 26</li> </ul>	To explore the experience of cough and its impact on life in a group of patients with cancer known to be particularly affected by coughing	<ul style="list-style-type: none"> <li>■ Qualitative</li> </ul>	A theme around descriptions of cough suggests typically a dry, tickly cough and highlights mechanical and environmental triggers. The theme around the effects of cough in daily life shows the impact of cough in socializing. The last theme focuses on strategies for coping with and managing cough, showing the perceived ineffectiveness of current antitussives and patients' use of a variety of approaches.	100
Morrison et al., 2017 (United States)	<ul style="list-style-type: none"> <li>■ Patients with primary LC who provided self-report information on emotional problems at the time diagnosis</li> <li>■ Mean age = 66.5 years; SD = 10.5</li> <li>■ N = 2,205</li> </ul>	To identify the patient and disease characteristics of patients with LC experiencing emotional problems and to examine how emotional problems relate to QOL and symptom burden	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	Emotional problems at diagnosis were associated with younger age, female gender, current cigarette smoking, current employment, advanced LC disease, surgical or chemotherapy treatment, and a lower ECOG performance score. Strong associations were found between greater severity of emotional problems, lower QOL, and greater symptom burden.	80
Nishiura et al., 2015 (Japan)	<ul style="list-style-type: none"> <li>■ Of patients with LC, more than half were receiving chemotherapy as in- or outpatients at 1 national hospital</li> <li>■ Mean age = 71.8 years; SD = 3.5</li> <li>■ N = 50</li> </ul>	To evaluate the prevalence of sleep disturbance and compare patients with and without sleep disturbance concerning psychological distress, QOL, pain, and fatigue and to examine the association between sleep disturbance and psychological distress, QOL, pain, and fatigue.	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Cross-sectional</li> </ul>	Patients with LC experienced combined symptoms related to sleep. Sleeping pills improved sleep induction but were not sufficient to provide sleep quality and prevent daytime dysfunction. Daytime dysfunction was specifically associated with psychological distress.	100

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Okuyama et al., 2001 (Japan)	<ul style="list-style-type: none"> <li>■ Ambulatory patients with advanced LC; no treatment in the preceding 4 weeks; 2 National Cancer Center hospitals</li> <li>■ Mean age = 63.1 years; SD = 9.4</li> <li>■ N = 157</li> </ul>	To determine the prevalence of patients who had interference with daily activity because of fatigue, the correlated factors, and methods to detect such patients	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	Fatigue is a frequent and important symptom and is associated with physical and psychological distress. More than half had experienced clinical fatigue, defined as fatigue that interfered with any daily activities.	100
Reyes-Gibby et al., 2007 (United States)	<ul style="list-style-type: none"> <li>■ Patients with newly diagnosed LC at 1 cancer center before starting oncologic therapy; the study sample was drawn from another ongoing case control study.</li> <li>■ Age N/A</li> <li>■ N = 695</li> </ul>	To explore whether polymorphisms in cytokine genes could explain variability in self-reported pain in patients with LC of all stages	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	More AA patients reported severe pain relative to Hispanic and White patients. No significant association between genotypes in TNF-alpha, IL-6, and IL-8 and severe pain for AA or Hispanic patients was observed. IL-8 was significantly associated with severe pain among White patients.	60
Sarna, 1993 (United States)	<ul style="list-style-type: none"> <li>■ Women with primary or recurrent LC of all stages at 1 university medical center and private medical offices</li> <li>■ Mean age = 61 years; SD = 11</li> <li>■ N = 69</li> </ul>	To explore and describe symptom distress and its correlates, with symptom distress viewed as related to functional status and overall QOL	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional pilot study</li> </ul>	The most prevalent and distressing symptoms were fatigue, frequent pain, and insomnia. Poor outlook, dyspnea, and appetite disruptions were other common distressing problems. Distress was strongly correlated to QOL and functional status.	100
Sarna & Brecht, 1997 (United States)	<ul style="list-style-type: none"> <li>■ 40 women with advanced disease from a previous study and 20 women in a current longitudinal trial; participants from oncology clinics, private practices, and oncology units</li> <li>■ Mean age = 58.3 years; SD = 9.7</li> <li>■ N = 60</li> </ul>	To explore the underlying constellation of distressing symptoms in women with advanced LC and to investigate the differences in symptoms among clinical and demographic variables	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Exploratory study using secondary analysis data from 2 studies</li> </ul>	Fatigue, outlook disruptions, frequent pain, and difficulties sleeping were the most distressing and prevalent serious disruptions. A 4-factor solution for symptom distress ratings revealed groups of items representing emotional and physical suffering, GI distress, respiratory distress, and malaise.	80

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**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Tanaka et al., 2002 (Japan)	<ul style="list-style-type: none"> <li>■ Outpatients with advanced LC at 2 National Cancer Center hospitals; 76% had previous anticancer treatment.</li> <li>■ Mean age = 63 years; SD = 9.3</li> <li>■ N = 171</li> </ul>	To identify factors correlated with dyspnea in patients with cancer among a broad range of medical, psychological, and sociodemographic factors	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	Results revealed that psychological distress, presence of organic causes, cough, and pain were significantly correlated with dyspnea, confirming that dyspnea is multifactorial and that a beneficial therapeutic strategy may include an intervention for psychological distress and pain.	100
Tchekmedyan et al., 2003 (United States)	<ul style="list-style-type: none"> <li>■ Patients with LC and anemia receiving chemotherapy, in a multinational, randomized, double-blinded, placebo-controlled trial</li> <li>■ Mean age = 61.4 years; SD = 9</li> <li>■ N = 250</li> </ul>	To examine the relationship between changes in depression and anxiety	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	At baseline, 25% and 35% of patients reported high levels of anxiety and depression, respectively. Correlations of changes in normed BSI Anxiety and Depression subscale scores with changes in FACT-F scores were statistically significant. In the multiple regression models, change in the FACT-F score was the only significant explanatory variable. For every unit improvement in FACT-F score, there was a corresponding improvement of 0.7 points and 0.8 points in anxiety and depression levels, respectively.	80
Turcott et al., 2020 (Mexico)	<ul style="list-style-type: none"> <li>■ Newly diagnosed patients with stage IIIB/IV NSCLC on 1 thoracic oncology unit at the National Cancer Institute of Mexico</li> <li>■ Mean age = 58.7 years; SD = 14.1</li> <li>■ N = 65</li> </ul>	To quantify dysgeusia in patients with NSCLC before chemotherapy treatment and to identify its association with nutritional parameters and HRQOL	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	Patients with dysgeusia presented significantly less lean body mass and higher fat mass and had significantly more GI symptoms. Dysgeusia was associated with less food consumption. Patients with dysgeusia had clinically significant alterations in HRQOL scales.	80

*Continued on the next page*

**TABLE 2. Descriptive Results: Included Articles With De Novo Methodology (N = 40) (Continued)**

Study (Country)	Patient Characteristics	Aim	Design and Methods	Summary of Key Findings	MMAT Quality Appraisal Score
Wang & Fu, 2014 (China)	<ul style="list-style-type: none"> <li>■ Patients with stage II–IV LC receiving chemotherapy at 3 public hospitals</li> <li>■ Mean age = 58.3 years; SD = 10.3</li> <li>■ N = 183</li> </ul>	To explore the SCs and QOL in patients with LC undergoing chemotherapy	<ul style="list-style-type: none"> <li>■ Quantitative descriptive</li> <li>■ Cross-sectional</li> </ul>	Functioning subscale QOL scores were lowest; family subscale QOL scores were highest. 3 SCs were identified: GI, emotional, and fatigue related. There was a negative relationship between SCs and multiple QOL dimensions.	80
Wang et al., 2006 (United States)	<ul style="list-style-type: none"> <li>■ Patients with locally advanced inoperable (stage III) NSCLC scheduled for curative chemotherapy/RT at a university cancer center</li> <li>■ Age range = 42.5–78.3 years; mean = 63.4 years; SD N/A</li> <li>■ N = 64</li> </ul>	To determine the levels of prevalence, severity, and longitudinal patterns of dynamic change in physical and psychological symptoms that were present before, during, and after chemotherapy/RT, and to assess how each symptom affected the patient's daily activities	<ul style="list-style-type: none"> <li>■ Quantitative nonrandomized</li> <li>■ Cross-sectional, prospective</li> </ul>	63% of patients experienced moderate to severe levels of multiple symptoms by the end of chemotherapy/RT, with fatigue being the most severe symptom throughout. SCs with 4 development patterns appeared over time. All symptoms had a significant impact on the level of interference. Fatigue, distress, and sadness were the strongest predictors of total symptom interference.	80
Wang et al., 2008 (Taiwan)	<ul style="list-style-type: none"> <li>■ Patients with LC at various stages and most having treatment on the oncology in- and outpatient units at 2 medical centers and a teaching hospital</li> <li>■ Mean age = 67.5 years; SD = 10.5</li> <li>■ N = 108</li> </ul>	To explore the phenomenon of symptom distress, to investigate the presence of SCs, and to examine the relationship of SCs to symptom interference with daily life	<ul style="list-style-type: none"> <li>■ Quantitative prospective</li> <li>■ Cross-sectional</li> </ul>	The 5 most severe symptoms were fatigue, sleep disturbance, lack of appetite, shortness of breath, and general distress. Factor analysis generated a 2-factor solution (general and GI symptoms) for symptom severity items. Both SCs were significantly correlated with symptom interference items, but the general SC presented higher correlation coefficients.	80

AA—African American; BMI—body mass index; BSI—Brief Symptom Inventory; ECOG—Eastern Cooperative Oncology Group; FACT-F—Functional Assessment of Cancer Therapy—Fatigue; GAD—generalized anxiety disorder; GI—gastrointestinal; HRQOL—health-related quality of life; IL—interleukin; LC—lung cancer; LCS—lung cancer stigma; MMAT—Mixed Methods Appraisal Tool; N/A—not available; NCCN—National Comprehensive Cancer Network; NSCLC—non-small cell lung cancer; PRO—patient-reported outcome; QOL—quality of life; RT—radiation therapy; SC—symptom cluster; TNF—tumor necrosis factor; TSAs—taste and smell alterations

2014; Sarna & Brecht, 1997; Wang et al., 2006, 2008), cough (n = 10) (Brown et al., 2011; Choi & Ryu, 2018; Hensch et al., 2009; Khamboon et al., 2015; Li, Li, et al., 2021; Li, Wu, et al., 2021; Liu, Liu, et al., 2021; Maguire et al., 2014; Sarna & Brecht, 1997; Wang et al., 2006), and dyspnea (n = 10) (Brown et al., 2011; Choi & Ryu, 2018; Hensch et al., 2009; Khamboon et al., 2015; Li, Li, et al., 2021; Li, Wu, et al., 2021; Maguire et al., 2014; Sarna & Brecht, 1997; Wang et al., 2006, 2008). These symptoms clustered with the following symptom categories: fatigue and pain with nutritional and psychological symptoms. Depression was usually present in constellations with other psychological symptoms and fatigue, and appetite loss with other nutritional impact symptoms and fatigue. Cough was present mostly along with dyspnea and psychological symptoms, and dyspnea clustered mostly with other respiratory symptoms, pain, and psychological symptoms.

Among the 25 articles without a cluster aim, fatigue was the most prevalent symptom, being present in 19 articles (Andersen et al., 2020; Belqaid et al., 2016; Chien et al., 2021; Hensch et al., 2008; Kiteley & Fitch, 2006; Kuo & Ma, 2002; Lee, 2021; Liu, Hou, et al., 2021; Lowe & Molassiotis, 2011; Maric et al., 2010; McFarland et al., 2020; Molassiotis, Lowe, Blackhall, & Lorigan, 2011; Molassiotis, Lowe, Ellis, et al., 2011; Morrison et al., 2017; Nishiura et al., 2015; Okuyama et al., 2001; Reyes-Gibby et al., 2007; Sarna, 1993; Tchekmedyan et al., 2003), followed by dyspnea symptoms (n = 18) (Andersen et al., 2020; Belqaid et al., 2016; Hensch et al., 2008; Kiteley & Fitch, 2006; Kuo & Ma, 2002; Lavdaniti et al., 2021; Lee, 2021; Li, Li, et al., 2021; Liu, Hou, et al., 2021; Lowe & Molassiotis, 2011; Maguire et al., 2019; McFarland et al., 2020; Molassiotis, Lowe, Blackhall, & Lorigan, 2011; Molassiotis, Lowe, Ellis, et al., 2011; Morrison et al., 2017; Okuyama et al., 2001; Sarna, 1993; Tanaka et al., 2002), pain (n = 15) (Andersen et al., 2020; Belqaid et al., 2016; Chien et al., 2021; Kuo & Ma, 2002; Lavdaniti et al., 2021; Lee, 2021; Lowe & Molassiotis, 2011; Maguire et al., 2014; McFarland et al., 2020; Molassiotis, Lowe, Blackhall, & Lorigan, 2011; Morrison et al., 2017; Nishiura et al., 2015; Reyes-Gibby et al., 2007; Sarna, 1993; Turcott et al., 2020), depression (n = 14) (Andersen et al., 2020; Belqaid et al., 2016; Chien et al., 2021; Hensch et al., 2008; Kuo & Ma, 2002; Lavdaniti et al., 2021; Liu, Hou, et al., 2021; Maguire et al., 2019; McFarland et al., 2020; Nishiura et al., 2015; Okuyama et al., 2001; Reyes-Gibby et al., 2007; Tanaka et al., 2002; Tchekmedyan et al., 2003), appetite loss (n = 11) (Belqaid et al., 2018; Kiteley & Fitch, 2006; Kuo & Ma, 2002; Lavdaniti et al., 2021; Lee, 2021; Lowe &

Molassiotis, 2011; Maguire et al., 2019; Maric et al., 2010; Mody et al., 2021; Okuyama et al., 2001; Sarna, 1993), and cough (n = 10) (Belqaid et al., 2016; Kiteley & Fitch, 2006; Kuo & Ma, 2002; Maguire et al., 2019; Molassiotis, Lowe, Blackhall, & Lorigan, 2011; Molassiotis, Lowe, Ellis, et al., 2011; Morrison et al., 2017; Okuyama et al., 2001; Sarna, 1993; Tanaka et al., 2002).

These most prevalent symptoms clustered with various symptom categories. Fatigue was commonly clustered with psychological and respiratory symptoms. Dyspnea and pain clustered mostly with psychological symptoms and fatigue. Depression clustered commonly with fatigue and other psychological symptoms. Appetite loss mostly co-occurred with other nutritional impact symptoms and fatigue. Cough was likely to cluster with dyspnea and fatigue.

As with the a priori cluster findings, the analysis of the de novo constellations revealed that few constellations included the elimination/abdominal or the body/hair/skin-related symptoms.

Comparisons are made between the prevalent symptoms and symptom cluster constellations (see Figure 2).

## Research Questions 3 and 4

### Symptom Measurement Instruments

Overall, 36 different validated instruments containing symptom measurements were identified within the 47 included articles with quantitative and mixed-methods designs. In addition, there were some variations in the numeric rating scale items because this scale was used for several symptoms, such as dyspnea, pain, nausea, and fatigue. In addition, there were some nonconventional author-developed symptom scales in seven articles.

The instruments were cancer, disease, or symptom specific. The instruments mainly used were cancer specific, such as the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 (EORTC QLQ-C30) or the MDASI questionnaire, and disease specific, like the lung cancer modules of these instruments along with the Lung Cancer Symptom Scale. Some instruments were symptom specific, such as the Cancer Dyspnea Scale, Hospital Anxiety and Depression Scale, or Center for Epidemiological Studies-Depression.

The most frequently used instrument was the EORTC QLQ-C30 (n = 12), a general questionnaire developed for populations of patients with cancer (Aaronson et al., 1993). This 30-item instrument contains four domains, where the symptom items constitute half the questionnaire. The supplementary

lung cancer-specific module LC13 with 13 additional symptom items (Bergman et al., 1994) was also used frequently (n = 6), as well as the MDASI (n = 8), which contains 13 core cancer symptom items (Lin et al., 2007).

Among the symptom-specific questionnaires, the most frequently used was the Hospital Anxiety and Depression Scale (n = 7), either in covering all 14 items or the depression subscale only (Zigmond & Snaith, 1983), the 12-item Cancer Dyspnoea Scale (n = 3) (Tanaka et al., 2000), and the 10- to 20-item (depending on version) Center for Epidemiological Studies–Depression (n = 3) (Radloff, 1977).

### Symptom Dimensions Measured in Quantitative Studies and Described in Qualitative Studies

The author-developed symptom scales measured either intensity or timing. The validated instruments measured mainly intensity and/or timing, with only a few containing the distress and quality dimensions. The qualitative studies provided several descriptions within the distress, timing, and quality dimensions but less of intensity.

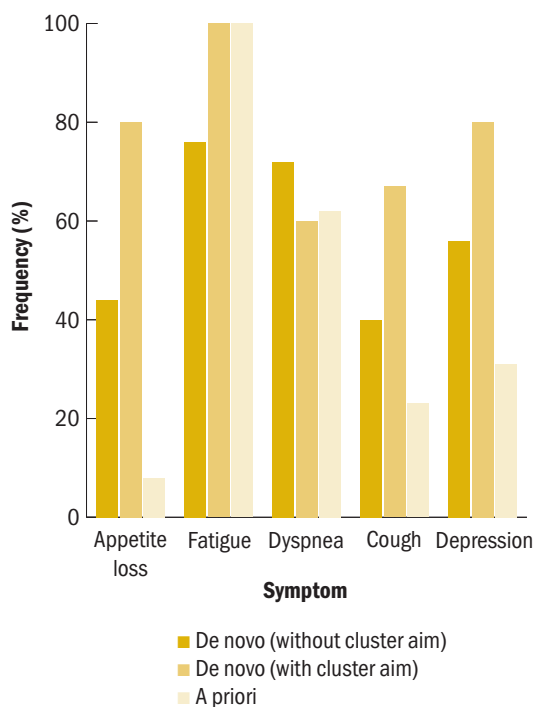
**Intensity:** Intensity was the most frequently measured dimension, existing in 15 instruments as the

solitary measured dimension. The MDASI, EORTC scales, and SF-36® are examples. Intensity and timing are present in nine instruments, such as the Memorial Symptom Assessment Scale and Symptom Distress Scale; intensity and distress in four instruments, the Brief Fatigue Inventory, Brief Pain Inventory, Functional Assessment of Cancer Therapy–Fatigue, and Cancer Fatigue Scale. One instrument, the Cancer Dyspnea Scale, measures intensity and quality.

The intensity dimension was not as prominent in the qualitative studies. Because qualitative data do not provide a severity grading in numbers, the intensity dimension is explained in other terms, such as being bothersome, offensive, or unbearable. This dimension is also explained through relationships between symptoms, such as the presence of one symptom was the reason another symptom worsened (Belqaid et al., 2018; Kiteley & Fitch, 2006) or that symptom severity was graded compared with other physical problems (Kiteley & Fitch, 2006). The severity dimension was also partially related to illness status because disease progression intensified some symptoms. Noticeably, co-occurring symptoms that individually have relatively low severity appear to have a cumulative impact on patients and may cause higher distress (Kiteley & Fitch, 2006; Molassiotis, Lowe, Blackhall, & Lorigan, 2011).

**Distress:** Four instruments, the Brief Fatigue Inventory, Brief Pain Inventory, Cancer Fatigue Scale, and Functional Assessment of Cancer Therapy–Fatigue, measured the intensity and distress dimension. In the qualitative studies, the distress dimension was commonly described as highly dependent on the patients’ experience and knowledge of the symptoms. Insecurity and novelty of symptoms increase distress, and experience, acceptance, and knowledge infer lower distress. Patients also described how the level of distress was related to how the symptoms affected their daily life. A higher interference causes more distress (Belqaid et al., 2018; Kiteley & Fitch, 2006; Maguire et al., 2014; Molassiotis, Lowe, Blackhall, & Lorigan, 2011; Molassiotis, Lowe, Ellis, et al., 2011). Also, symptoms possibly related to disease progression or treatment not working would cause higher distress for some (Molassiotis, Lowe, Ellis, et al., 2011) but be of less importance to others (Molassiotis, Lowe, Blackhall, & Lorigan, 2011). Similar to intensity, the distress dimension involved descriptions of the additive effects of multiple symptoms (Maguire et al., 2014; Molassiotis, Lowe, Blackhall, & Lorigan, 2011; Molassiotis, Lowe, Ellis, et al., 2011). The level of distress may vary depending on setting but can differ in

**FIGURE 2. Comparing Frequent Symptoms Among De Novo and A Priori Symptom Clusters**



descriptions between studies. For example, cough was described as being particularly prominent and causing a higher level of distress because of the association with visibility and embarrassment in public or disturbing family members (Maguire et al., 2014; Molassiotis, Lowe, Ellis, et al., 2011), but also as not being particularly bothersome to others because many were former smokers and had previous experience of cough in the past (Molassiotis, Lowe, Blackhall, & Lorigan, 2011). The symptoms perceived as most distressing would change during the course of their illness trajectory (Molassiotis, Lowe, Blackhall, & Lorigan, 2011). Not being met with respect and understanding for bothersome symptoms and lack of emotional support were described as causing increased distress (Belqaid et al., 2018; Molassiotis, Lowe, Ellis, et al., 2011).

**Timing:** Six instruments, including the Hospital Anxiety and Depression Scale and Center for Epidemiological Studies–Depression, measured the timing dimension. In the qualitative articles, symptoms were described as having unpredictable timing (Belqaid et al., 2018) and being long-lasting and ever present (Belqaid et al., 2018; Molassiotis, Lowe, Blackhall, & Lorigan, 2011) and related to certain activities and time points (Belqaid et al., 2018; Maguire et al., 2014; Molassiotis, Lowe, Ellis, et al., 2011). Some symptoms could increase at a specific time related to oncologic treatment, such as anxiety building up in the days before a chemotherapy cycle or aggravated cough because of radiation therapy treatment (Molassiotis, Lowe, Blackhall, & Lorigan, 2011). Patients described symptoms such as fatigue and pain in relation to how much they needed to rest and how they felt before and after their rest (Kiteley & Fitch, 2006). Several descriptions described the occurrence of one symptom attributing to the onset of another (Belqaid et al., 2018; Maguire et al., 2014; Molassiotis, Lowe, Ellis, et al., 2011), and symptoms induced or intensified by being in a certain environment (Belqaid et al., 2018; Molassiotis, Lowe, Ellis, et al., 2011).

**Quality:** Only one instrument, the Cancer Dyspnea Scale, was used to assess the quality dimension. Narratives regarding the quality dimension were sensory and location descriptions related to the symptoms (Belqaid et al., 2018; Kiteley & Fitch, 2006; Maguire et al., 2014; Molassiotis, Lowe, Ellis, et al., 2011) and bodily perceptions (Kiteley & Fitch, 2006; Maguire et al., 2014), particularly when describing how the symptoms made them feel. Some described how symptoms responded to interventions (Belqaid et al., 2018; Molassiotis, Lowe, Ellis, et al., 2011). There were patients who struggled to find the right

words to explain the sensation but knew that something had changed (Belqaid et al., 2018; Molassiotis, Lowe, Ellis, et al., 2011).

## Discussion

### Results

A large diversity of cluster constellations appeared in the 53 articles. Most studies (40 of 53) explored symptom clusters *de novo* and the rest *a priori*, differing in content regarding symptoms and number of symptoms in their constellations. Additional comparisons between *a priori* and *de novo* approaches are necessary for understanding symptom clusters (Xiao, 2010), and further considerations may be needed when selecting *a priori* clusters. Fatigue was the predominant symptom across all studies, and other commonly occurring symptoms in clusters were dyspnea, pain, depression, and cough. In *de novo* clusters, there was a greater occurrence of nutritional impact symptoms.

Forty-seven articles used quantitative/mixed methods with a large number of different symptom assessment instruments, and a few nonconventional authors developed instruments for measuring intensity alone or in combination with timing. Six were qualitative articles describing distress, timing, and quality dimensions but had fewer accounts of the intensity dimension. Because the findings indicate cluster differences depending on the methodology, there is a need to refine how symptom clusters are measured and managed, where fatigue and nutritional aspects stand out. It is likely that nausea and vomiting are temporary and treatment related; therefore, appetite loss was selected as the nutritional symptom for comparison because it may affect the patients during a greater part of the cancer care continuum. Symptoms affecting nutritional intake and development of malnutrition in patients with lung cancer affecting health-related outcomes have been identified (Kiss, 2016; Polański et al., 2021). Across a variety of treatment modalities and disease stages, malnutrition ranges from 45% to 69% (Kiss et al., 2014). Nutritional screening and supportive care are likely significant in symptom management because patients experience better health-related quality of life, lower overall symptom burden, and better prognosis (Gul et al., 2021; Polański et al., 2017).

Fatigue has a range of causes and coexists with many other symptoms; therefore, treatment requires an interprofessional effort with medication, exercise, nutrition, and other therapeutic approaches (Stone et al., 2023). A multimodal symptom management intervention targeting exercise and nutrition can



improve PROMs and symptom burden in patients with advanced lung cancer (Ester et al., 2021). Relative to depression and anxiety, fatigue yields a more negative effect on lung cancer survivors' health-related quality of life (Jung et al., 2018), but exercise has been shown to improve capacity and health-related quality of life in cancer survivors (Peddle-McIntyre et al., 2019). There is also a challenge in considering fatigue as one symptom or as two separate phenomena: physical fatigue and mental fatigue (de Raaf et al., 2013). In this review, multidimensional aspects of fatigue have been considered, but it is defined as one symptom. Regarding measurement of cancer-related fatigue, European Society for Medical Oncology guidelines suggest a 10-point numeric rating scale for fatigue as the best screening tool. However, using a more specific questionnaire, such as the Brief Fatigue Inventory, to assess moderate to severe fatigue could be necessary. Because fatigue often occurs with related symptoms, a screening tool that captures multiple symptoms may also be of clinical value. There is no clear recommendation regarding the most appropriate subjective measure, so there is a need for comparable data to reliably detect changes over time (Fabi et al., 2020).

Patients with lung cancer experience a large diversity of symptom cluster constellations that fluctuate and vary in intensity, timing, distress, and quality over time. "Unpleasant symptoms, in all their synergy, interaction, and complexity, are what the whole patient presents" (Lenz et al., 1997, p. 25). This complex multidimensional symptom experience is important to consider when measuring symptoms, for example, because a patient may score high on intensity but may not be so bothered by that symptom because the timing dimension may be limited or their knowledge and coping skills make it manageable. Conversely, a lower-intensity symptom may be more incapacitating because of the quality aspects or meaning for the patient. The intensity dimension was the most commonly measured dimension among the quantitative studies. However, intensity was not the most prominent dimension from the patients' perspective in the qualitative studies, but rather distress, timing, and quality. The TOUS can provide a clinically relevant conceptual mapping of the symptom dimensions and suggest how and why they are important to measure and a selection of variables for clinically useful research. The restriction of measuring an individual dimension is considered inadequate, and it is recommended that each symptom be measured separately with multidimensional measures (Lenz et al., 1997). Symptom

dimensions should be important when developing and evaluating symptom management strategies, not just for the assessment itself (Dodd, Janson, et al., 2001; Humphreys et al., 2014). When and by which instrument a symptom assessment is conducted will affect the accuracy and relevance of that measurement. Using multidimensional scales to measure the complex nature of a symptom cluster was suggested by Barsevick et al. in 2006, but this scoping review indicates the methodologic issues in measurement and comparison of symptom items and dimensions because of the vast number of instruments used and absence of multidimensional assessments within the lung cancer context alone. There is a need to further evaluate the validity, reliability, and responsiveness of PROMs instruments in symptom cluster research (Miaskowski et al., 2017) because this stringency is still missing.

## Method

The scoping review gives width and possibilities in the searches but is a challenge when summarizing the large amount of data collected. The authors' original plans for the review process developed into dividing their research questions into two parts. Part 1 has been presented in this scoping review, and part 2 will be presented as a separate study (in manuscript) as an integrative review with the same sample but other specific research questions linked to the theoretical framework as stated in the authors' protocol (Karlsson et al., 2020). Part 2 aims to explore how influencing factors affect the patients' experience of symptom clusters and the consequences in their daily life. An option could have been to deselect the *de novo* articles without a cluster aim to render a smaller final sample with a full focus on explicit symptom cluster research. No limitation was set regarding earliest year of publication because co-occurring related symptoms have been investigated before the concept of symptom clusters was introduced. A limitation to more current years could have also decreased the final sample but then omitted important findings.

Although lung cancer is a divided group of molecularly and histologically heterogeneous subtypes (Travis et al., 2015), and the incidence, mortality, and therapy options vary between subtypes (Howlader et al., 2020), this review included a wide population with varying subtypes and in various phases of the cancer care continuum: before, during, or after treatment. This may affect the occurrence of specific symptom clusters, depending on when the symptoms have been measured and dimensions measured. For example, nausea



and vomiting are symptoms more likely to occur during chemotherapy than at diagnosis, and the presence of cough may decrease as treatment decreases the tumor burden or increase as a side effect of treatment. As reported by Kalantari et al. (2022), changes occur in the relationships and interconnections between and among symptom clusters, depending on the time point in the treatment period and type of cancer. Therefore, these results should be interpreted with caution regarding specific treatments, such as immunotherapy that has a different action mechanism and side effects compared with standard chemotherapy or radiation therapy or subgroups of patients who may have a different symptomology. However, the key symptoms of fatigue, distress, and appetite loss appeared among the five symptom clusters (general, immunotherapy related, pulmonary, gastrointestinal, and neural) discovered in a study of symptom clusters in patients with lung cancer who were treated with programmed cell death protein 1 immunotherapy (Zhang et al., 2022) were comparable to the current results. In the study by Zhang et al. (2022), five symptom clusters were identified as follows: (a) the general cluster, (b) the immunotherapy-related cluster, (c) the pulmonary cluster, (d) the gastrointestinal cluster, and (e) the neural cluster.

The authors did not analyze the methodologic approaches regarding statistical methods used, which may have provided additional knowledge regarding the most appropriate analytical method to create symptom clusters and awareness concerning common and unique underlying mechanisms of symptom clusters (Ward Sullivan et al., 2018). The authors did not limit the inclusion related to a specific level of correlation of symptoms in a cluster regarding the p value, which contributed to the large number of individual clusters.

Methodologic rigor was shaped by involving two to five team members in the five steps (Arksey & O'Malley, 2005), supporting a systematic and transparent review process.

The theoretical framework provided direction regarding the categorization of symptom dimensions in the PROMs instruments, but the authors' interpretation of the dimensions may not equate to others' interpretations.

### Implications for Nursing

Symptom clusters among patients with lung cancer are numerous and with varied symptom patterns, some more common than others. Fatigue is the most prevalent symptom among the many symptom

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### KNOWLEDGE TRANSLATION

- The symptom clusters defined a priori and explored de novo differ in content regarding symptoms and number of symptoms in their constellations.
  - Fatigue is the overall most prevalent symptom in clusters, indicating a specific area of concern in symptom management because fatigue may significantly impair health-related quality of life.
  - Fatigue, psychological symptoms, and nutritional impact symptoms often co-occur and are an important area of interest for oncology nursing practice, symptom management interventions, and further symptom cluster research.
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clusters, and it is essential for oncology nurses to perform timely assessments, ensure that person-centered supportive care is provided to reduce fatigue, and continuously evaluate patients' needs. Compassionate nursing and patient education regarding symptom management is recommended to reduce distress, as well as psychosocial interventions and individually adapted physical activity. If patients' fatigue-related distress is addressed, it may also positively affect the presence of related psychological symptoms. Because nutritional impact symptoms are highlighted in this population, interventions and symptom management to improve nutritional status and reduce symptom burden are important and may also reduce fatigue and psychological symptoms.

In clinical practice, the patient–nurse relationship enables assessment of multiple symptom dimensions by the use of appropriate instruments in combination with person-centered communication. Influencing factors need to be considered when assessments are made and interventions proposed. Having access to the advanced expertise and continuity of high-quality care provided by an oncology nurse specialist may be vital for this population.

Because patients with lung cancer are not always capable of engaging in the recommended moderate to high levels of physical activity because of fatigue-, dyspnea- and nutrition-related problems, the authors recommend a team approach involving oncology nurses, dietitians, physicians, and other healthcare professionals to develop, support, and follow up on individual person-centered rehabilitation plans.

The symptom assessments and interventions need to be performed with patients' life expectancy in mind because not all patients would benefit from the same types of interventions.

## Conclusion

This scoping review shows an abundant variety of symptom clusters among patients with lung cancer. The symptoms occurring in clusters vary if researchers have defined the clusters in advance (a priori) or not (de novo). Overall, fatigue is the symptom found to most frequently co-occur with other symptoms in clusters.

Noticeably, the a priori clusters contain dyspnea more often, and the de novo clusters contain pain, cough, depression, and nutritional symptoms more often. Because of the differences between symptom clusters related to the a priori or de novo approach, future symptom cluster research should consider this.

The qualitative studies, although being quite few, complement the findings from the quantitative studies in this sample, endorsing the presence of clinically significant symptom clusters among patients with lung cancer, and contribute evidence regarding the quality dimension that is missing in most symptom assessment instruments.

The importance of considering the multidimensional aspects of the symptom cluster experience is vital in future research and clinical practice to sustain the holistic approach to patient-centered care.

Because certain symptoms are more likely to cluster than others, future research regarding a potential underlying biologic etiology by measuring specific biomarkers could be valuable.

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Karlsson completed the data collection. All authors contributed to the conceptualization and design, provided the analysis, and contributed to the manuscript preparation.

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