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Review Article

Nonpharmacological Interventions for Managing the Dyspnea-Fatigue-Physical/Role Functioning Symptom Cluster in Lung Cancer Patients: A Systematic Review

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Objective. Lung cancer (LC) patients suffer from multiple cooccurring symptoms. Interventions that have the potential to impact more than one symptom within a symptom cluster should be identified. The aim of this review was to examine nonpharmacological interventions that were effective in the management of one or more of the following symptoms in LC patients: dyspnea, fatigue, physical functioning (PF), and role functioning (RF). *Methods*. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used for reporting this systematic review. The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (using the PubMed interface), Embase (using the embase.com interface), and Web of Science were used as electronic databases. Randomized controlled studies were included if they assessed the effects of nonpharmacological interventions on dyspnea, fatigue, PF, and/or RF in patients with LC. Studies were evaluated with the Cochrane risk of bias tool, and relevant data were extracted and narratively summarized. *Results and Conclusions*. In total, 89 articles were included. Search results (until April 2023) show that most evidence was found for exercise interventions, followed by multicomponent, psychoeducational, diet, acupuncture, and other interventions. Studies that had an effect on multiple symptoms were observed to have the most frequent instances of positively affecting dyspnea, followed by PF, fatigue, and RF.

1. Introduction

Lung cancer (LC) is one of the leading causes of global cancer incidence and mortality. Worldwide, an estimated 2.21 million new LC cases and 1.8 million deaths occurred in 2020. In most countries, the 5-year survival rate of LC ranges from 10% to 20% [1]. LC patients often experience a variety of symptoms as a result of their disease and treatments, which affect their overall health-related quality of life (HRQoL) [2, 3]. Literature shows that the most common symptoms in LC patients include coughing, dyspnea, fatigue, insomnia, pain, and anxiety [4–7]. In addition, LC patients often suffer from multiple cooccurring symptoms at the same time, referred to as "symptom clusters (SCs)" [2].

SCs are generally defined as "two or more symptoms that are related to each other and that occur together" [8]. SCs may share a common underlying etiology or mechanism [9], and symptoms within a cluster can reinforce or weaken each other. Consequently, the presence of SCs has a worse impact on the patients' general HRQoL compared to single symptoms [9]. Currently, interventions to improve HRQoL are mainly focused on individual symptoms rather than

focusing on multiple coexisting symptoms leading to a multitude of interventions and thus a significant overload and burden of care for patients [9]. Ideally, interventions to improve HRQoL in LC patients should aim at targeting multiple symptoms within an SC by addressing one or two symptoms and therefore alleviating the severity of other symptoms within that SC. This way, greater gains in a patients' HRQoL can potentially be achieved, and patient care can be simplified. Furthermore, identifying SCs is important to anticipate on other symptoms within a cluster and to uncover possibly overlooked symptoms.

A previous study by our research team performed machine learning analyses on the REQUITE database to build a prediction model for SCs along the LC trajectory in patients receiving radiotherapy [10]. This study showed that the SC with the highest prevalence across timepoints and the worst impact on the patients' HRQoL included the following dimensions: dyspnea, fatigue, physical functioning, and role functioning (respectively, PF and RF) [11]. Hence, it is important to tackle one or two symptoms within that cluster to potentially alleviate the burden of other symptoms within that cluster and consequently improve the HRQoL of LC patients. For the purpose of this review, the authors refer to dyspnea, fatigue, PF, and RF as symptoms, acknowledging that PF and RF are, however, not symptoms but domains of functioning.

Evidence in the literature suggests that nonpharmacological interventions such as exercise or psychosocial interventions have a positive impact on symptoms within the dyspnea, fatigue, PF, and RF cluster [12, 13]. However, it is important to identify which interventions have the potential to impact more than one symptom within that SC. To date, it is not clear which nonpharmacological interventions have an impact on multiple symptoms within the dyspnea, fatigue, PF, and RF cluster in LC patients. Therefore, the purpose of this review is to systematically review nonpharmacological interventions that have shown to be effective in the management of one or more of the following symptoms in LC patients: dyspnea, fatigue, PF, and RF.

2. Methods

2.1. Protocol and Registration. The methodology and reporting were based on recommendations from the Cochrane Collaboration [14] and the preferred reporting items for systematic reviews and meta-analysis statement (PRISMA [15]). This review was conducted according to the protocol previously published in the PROSPERO register (registration number CRD42021291926).

2.2. Search Strategy. We searched for studies published from inception until April 18, 2023. The following electronic databases were searched: the Cochrane Central Register of Controlled Trails (CENTRAL), MEDLINE (using the PubMed interface), Embase (using the embase.com interface), and Web of Science. Only articles with full texts in English were considered for this systematic review. The search strategies are presented in Supplementary File 1. Search terms combined "lung cancer," "RCT," and one or more symptoms of the SC.

2.3. Screening and Selection of Studies. The PICO(S) framework was used to select eligible studies [16]. Eligible study designs were randomized controlled studies (RCTs) to assess the effects of nonpharmacological interventions on dyspnea, fatigue, PF, and/or RF before, during, and after LC treatment. We included studies with adults (>18 years of age) with medically confirmed diagnosis of any type of LC and receiving any type of LC treatment. Although the SC being investigated was chosen based on a previous study in LC patients treated with radiotherapy only, symptoms within that cluster are common across different treatment types. Studies involving participants with a range of cancers and separately reported results for patients with LC were also included. The interventions had to be compared with a control group (e.g., no intervention, standard of care, or a waiting list control). Studies were included if they measured the following patient- or clinician-reported outcomes: dyspnea, fatigue, PF, and/or RF. Outcomes could be measured with any validated or nonvalidated questionnaire, objective measurement tool, or physical test.

2.4. Data Extraction. All references found through the search process were transferred to EndNote. After removing duplicates, all references were imported into Rayyan for screening purposes. Irrelevant studies, based on title and abstract, were excluded by two review authors (ER and LP). The same review authors assessed full-text reports for eligibility. Data extraction was performed by two review authors (EB and ER) with a modified Effective Practice and Organisation of Care (EPOC) data collection form of the Cochrane collaboration [17]. Discrepancies were resolved through consensus. The data collection form was pilot-tested with three of the included studies.

2.5. Critical Appraisal and Data Synthesis. Risk of bias was assessed with at least two authors using the Cochrane Collaboration's tool for assessing risk of bias 2.0 (EB and two master students) which scores six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias [18]. Only the findings from the included studies which have a statistically significant impact on multiple symptoms within the dyspnea-fatigue-PF-RF cluster are summarized in the main results section as the focus of this systematic review is to investigate which interventions are effective on more than one symptom. Studies showing a significant impact on only one or none of the symptoms within the SC are presented in Supplementary files 2–4.

3. Results

A total of 5375 articles were identified through the database search. After the removal of duplicates, 3259 articles were screened for eligibility. Following the screening of the

abstracts, 2990 articles were excluded. Full-text screening was carried out for 282 articles, out of which 89 studies were selected for final synthesis. The PRISMA diagram for the study selection process is shown in Figure 1.

3.1. Study Characteristics. The sample sizes of the included studies ranged from 11 [19] to 549 patients [20]. Most study participants across studies were older adults and male patients. The treatments consisted of surgery [21–45], radiation [46], chemo [47–67], targeted therapy [68–70], or a mix of therapies [20, 56, 57, 59–61, 64, 65, 71–92]. A detailed overview of the study and participant characteristics is shown in Table 1 (i.e., only studies with significant effects on more than one symptom) and Supplementary File 2 (i.e., all included studies).

Most of the included studies conducted an exercise intervention ($n = 31$). Twenty-two studies conducted a psychoeducational intervention, six studies used acupuncture/acupressure, six studies implemented a nutritional intervention, and 19 studies combined different (one or more) types of interventions (multicomponent interventions). Five articles conducted an intervention type that we could not classify into one of the previous categories. A detailed overview of the intervention regimens is shown in Table 2 (i.e., only studies with significant effects on more than one symptom) and Supplementary File 3 (i.e., all included studies). Figure 2 shows the significantly improved symptoms for each intervention type (only studies with significant effects on more than one symptom).

Of the 89 included studies, 33 (37%) studies measured only one symptom of the SC, 34 (38%) studies measured two symptoms of the SCs, and 10 (11%) studies measured three symptoms of the SC. Twelve studies (13%) measured all four of the symptoms within the SC.

3.2. Exercise Interventions. 31 of 89 included articles conducted an exercise intervention. The majority of the single-component exercise interventions ($n = 21$) were (supervised) in the hospital [21, 23, 24, 28, 33, 35, 41, 43, 45, 51, 54, 60, 61, 68, 72, 79, 82, 83, 85, 87], two studies were performed at home or in the community setting [67, 78], and eight exercise interventions were conducted both in the hospital and at home [22, 25, 26, 29, 36, 42, 58, 94]. The exercise interventions were delivered preoperatively [23, 35, 36, 42, 43], postoperatively [21, 22, 24–26, 29, 58, 72, 78, 82, 85], or both pre- and postoperatively [28, 33, 41, 45], during [74] or after radiotherapy [82, 83], during [51, 54, 60, 61, 67, 74, 79] or after [72, 82, 83] chemotherapy or during chemoradiotherapy [79], and during targeted therapy [68, 74]. Molassiotis et al. [94] recruited LC patients who were not currently receiving chemotherapy and/or radiotherapy. Tan et al. [87] did not report about the treatment and the timing of the intervention. Detailed information about the intervention characteristics and effects of the interventions is shown in Table 2 and Figure 2 (i.e., only studies with significant effects on more than one symptom) and Supplementary Files 3 and 4 (i.e., all included studies).

Fourteen articles reported statistically significant changes in one symptom (mostly PF) within the SC [21–23, 26, 29, 33, 35, 36, 60, 67, 72, 82, 85, 87]. Six articles showed statistically significant benefits on two symptoms within the SC (PF and dyspnea [45, 51, 60, 78], PF and RF [42], and dyspnea and fatigue [94]). In all six studies, the exercise interventions consisted of breathing exercises (e.g., inspiratory muscle training (IMT) and breathing techniques). In addition, four studies consisted of endurance and strength training [42, 51, 60, 78] of which one study investigated a high-intensity interval training (HIIT) tailored to the individual [78].

3.3. Diet Interventions. Six articles included a diet intervention consisting of nutritional counseling [96, 97] or oral supplements [55, 62, 65, 88]. The interventions were performed during treatment: chemotherapy [55, 62, 65, 96, 97], radiotherapy [97], immunotherapy [96], targeted therapy [96], or combined chemoradiotherapy [88, 96, 97] and chemoimmunotherapy [96]. In the study by Gioxari et al. [96], the nutritional intervention was also given to patients undergoing surgery. In addition to nutritional support during treatment, the study by Kiss et al. [97] provided nutritional guidance prior and after chemoradiotherapy. The duration of the interventions ranged from five weeks [88] to 12 weeks [96, 97]. Detailed information about the intervention characteristics and effects of the interventions is shown in Table 2 and Figure 2 (i.e., only studies with significant effects on more than one symptom) and Supplementary Files 3 and 4 (i.e., all included studies).

Of the six included studies, two articles reported statistically significant changes in one of the symptoms, fatigue [62], and physical functioning [88], within the SC, and two studies reported significant improvements in three symptoms within the SC [55, 65]: i.e., fatigue, dyspnea, and RF [65]/PF [55]. Characteristics of the studies are shown in Table 1. The study consisted of the intake of botanicals such as fermented red ginseng extract [55] during chemotherapy. Detailed information about the intervention is shown in Table 2. A similar study in terms of characteristics did not find statistically significant effects in one of our outcomes of interest [65]. Two studies focusing on oral supplements (both n-3 fatty acids supplements) showed statistically significant changes in one symptom (i.e., PF or fatigue) [62, 88], while the two studies focusing on nutritional counseling did not find statistically significant effects. Detailed information about the interventions is shown in Table 2.

3.4. Psychoeducational Interventions. Twenty-two of 89 included studies investigated the effects of a psychoeducational intervention. The psychoeducational interventions consisted either of treatment preparation [98], support, or assistance [20, 31, 39, 46, 47, 49, 53, 59, 63, 66, 69, 70, 81, 84, 92, 98–103]. Interventions ranged from motivational interviewing, self-efficacy enhancing interventions, acceptance and commitment therapy, and wellness education, to supportive peer group interventions. The interventions were

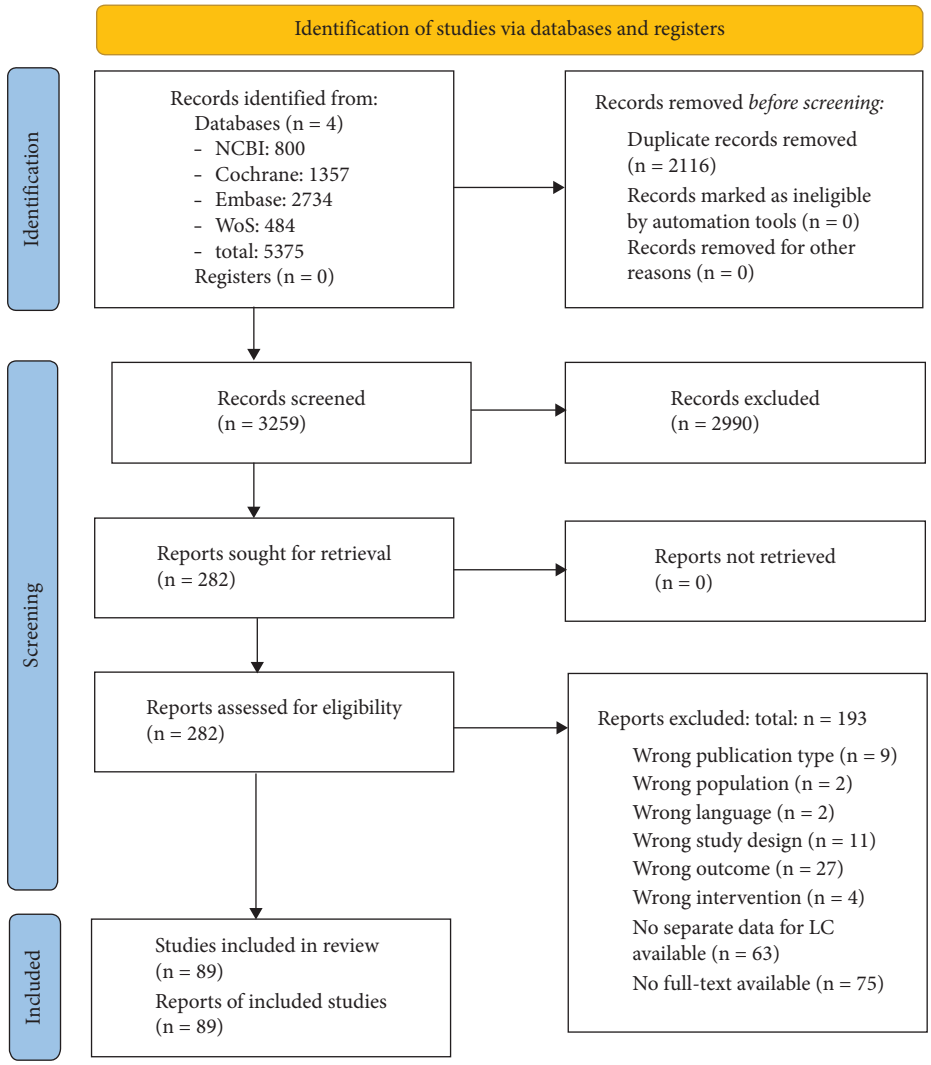

Figure 1: PRISMA flowchart.

delivered postoperatively [20, 31, 39, 81, 100, 101], during [20, 47, 49, 53, 59, 63, 66, 84, 92, 103] or postchemotherapy [53, 81, 100, 101], during [20, 46, 84, 103] or post-radiotherapy [81, 100, 101], or after combined chemo-radiotherapy [81, 101], during hormone therapy [20], targeted therapy [69, 70, 92, 103], or immunotherapy [103]. Porter et al. delivered a psychoeducational intervention at any point in the illness trajectory by patients undergoing surgery, chemotherapy, or radiotherapy. Krug et al. [99] and Li et al. [80] did not report about a specific treatment [80, 99] while the authors of [102] did not report about the timing of the intervention. Duration of the psychoeducational interventions ranged from 4 sessions of 30 minutes [103] to 12 months [100]. Detailed information about the intervention characteristics and effects of the interventions is shown in Table 2 and Figure 2 (i.e., only studies with significant effects on more than one symptom) and Supplementary Files 3 and 4 (i.e., all included studies).

Of the 22 included studies, five articles reported statistically significant changes in one of the symptoms within the SC [20, 31, 59, 63, 66]. Two studies reported statistically significant changes in more than one symptom, i.e., dyspnea and fatigue [39, 46]. One intervention consisted of a 40 min educational package on symptom management and coaching in progressive muscle relaxation (PMR) delivered by nurses one week prior to the beginning of the course of radiotherapy (RT) and repeated three weeks after commencing RT. Patients were encouraged to practice PMR daily for 12 weeks [46]. The other intervention was a 90 minute supportive peer group psychotherapy once a week for eight weeks [39].

3.5. Multicomponent Intervention. 19 studies investigated the effects of interventions combining one or more of the previous intervention types (i.e., exercise, diet and/or psychoeducational interventions, and acupressure). 13 studies combined exercise with psychoeducation [30, 38, 40, 44, 50, 58, 71, 75–77, 86, 104, 105]. One study combined exercise with a diet intervention [27]. Three studies combined exercise with an acupressure intervention and psychoeducation [91, 95, 106], and one study combined exercise,

Table 1: Study characteristics (significant effects on more than one symptom).

Study author, year, country	*N* total (start)	Population				Intervention type	Outcome(s)	Outcome measurement instrument (patient (PR)/researcher reported (RR))	Time-points measured
		Cancer stage	Treatment	Age (mean year)	Sex (% male)				
Ahmedzai et al. 2004, UK [93]	12	Stage I (9) Stage II (2) Stage III (1)	NR	68	58.33	Other	Distance walked	6MWT while breathing test gas mixtures (RR, Y)	Three times between VAS and Borg scale measurement with a minimum 15-min rest in between
							General extent of their dyspnea at rest and on exertion	Visual Analogue Scale (PR, Y) The modified Borg scale (RR, Y)	Before 6MWT, immediately after 6MWT
Chan et al. 2011, UK and Hong Kong [46]	140	Stage III or IV	Palliative radiotherapy	NR	83	Psychoeducational intervention	Intensity of breathlessness Intensity of fatigue	Visual Analogue Scale (VAS) (PR, Y) The revised Piper Fatigue Scale (PR, Y)	Baseline (T0), at week 3 (T1), at week 6 (T2), and at week 12 (T3)
Cheng 2022, China [27]	58	NR	Lobectomy	63.6	48.28	Multicomponent intervention: Exercise intervention + diet	Exercise ability Dyspnea	6MWT (RR, Y) Self-feeling score (PR, N)	Before and after treatment
Doğan and Taşcı, 2020, Turkey [48]	60	Stage II (2) Stage III (20) Stage IV (38)	Chemotherapy	61.05	88.1	Acupressure intervention	Walking distance Dyspnea	6MWT (RR, Y) Borg scale (PR, Y)	Baseline, postintervention
Edvardsen et al. 2014, Norway [78]	61	Stage I (33) Stage II (19) Stage III (10) Stage IV (1)	Mixed: Surgery additional chemotherapy after surgery: $n = 18$ Additional radiotherapy after surgery: $n = 7$	65.15	45.5	Exercise intervention	Concentric leg strength Maximum hand strength Physical functioning Dyspnea	The sum of the maximum weight that could be lifted once using a horizontal hip and knee extension movement (RR, NR) Grip strength dynamometer (RR, Y) Chair stand test (RR, Y), maximum stair steps for 15 s (RR, Y), a modified one-foot static balance test on soft ground for a maximum of 60 s (RR, Y), and SF-36 (PR, Y) EORTC QLQ-C30 (PR, Y)	Before surgery (T0), 4–6 weeks after surgery (T1), and immediately after 20-week intervention (T2)

Table 1: Continued.

Study author, year, country	*N* total (start)	Population				Intervention type	Outcome(s)	Outcome measurement instrument (patient (PR)/researcher reported (RR))	Time-points measured
		Cancer stage	Treatment	Age (mean year)	Sex (% male)				
Henke et al. 2014, Norway and Germany [51]	29	Stage IIIa or IIIb or IV	Palliative chemotherapy	NR	NR	Exercise intervention	Functional capacity	6MWT (RR, Y) Staircase walking (amount of steps) (RR, Y)	Baseline (T0) and after chemotherapy (T1)
							Muscle strength (max. amount of rep.)	Biceps curl (RR, NR) Triceps extension (RR, NR) Bridging (RR, NR) Abdominal exercise (RR, NR)	
							Physical function Role functioning Fatigue	EORTC QLQ-C30 (PR, Y)	
							Dyspnea	EORTC QLQ-C30 (PR, Y) EORTC QLQ-LC-13 (PR, Y)	
							Patient's independence in activities of daily living	Barthel index	
Hoffman et al. 2017, US [30]	73	Stage I (62%) Stage II (21%) Stage III (11%) Stage IV (3%) Indeterminate (3%)	Surgery	66.5	44.5	Multicomponent intervention: Exercise intervention + Psychoeducational intervention	Cancer-related fatigue (CRF)	The 9-item Brief fatigue inventory (BFI) (PR, NR)	Presurgery and postsurgery (week 1, week 2, week 3, week 4, week 5, and week 6)
							Functional status or fatigability	6MWT (RR, Y)	
							Functional performance (physical health component)	The modified Borg scale (PR, Y)	Presurgery and postsurgery (week 3 and week 6)
Jiang et al. 2017, China and Korea [55]	60	Stage III (2) Stage IV (18)	Chemotherapy	58.62	70	Diet intervention	Fatigue Shortness of breath Functional status	Fatigue symptom inventory (FSI) (PR, Y) CM symptoms questionnaire (PR, Y) FACT-L scale (PR, Y)	Pre- and posttreatment

Table 1: Continued.

Study author, year, country	*N* total (start)	Population				Intervention type	Outcome(s)	Outcome measurement instrument (patient (PR)/researcher reported (RR))	Time-points measured
		Cancer stage	Treatment	Age (mean year)	Sex (% male)				
Molassiotis et al, 2014, Hong Kong, UK, Cyprus [94]	47	Stage I: $n = 3$ Stage II: $n = 8$ Stage III: $n = 14$ Stage IV: $n = 13$ Unknown: $n = 8$	Mixed: Chemotherapy and/or radiotherapy and/or surgery	69.5	80.4	Exercise intervention	Dyspnea Worst breathlessness Average breathlessness Fatigue	mBorg scale (PR, Y) The chronic respiratory disease questionnaire-short form (CRDQ) (PR, Y) Numerical rating scale (PR, Y) The chronic respiratory disease questionnaire-short form (CRDQ) (PR, Y)	Baseline (T0), week 4 (T1), week 8 (T2), week 12 (T3)
Peng et al. 2019, China [39]	160	Stage III/IV	Surgery (GKS)	60.4	53.15	Psychoeducational intervention	Physical well-being (QoL) Functional well-being (Qol)	FACT-L (RR, Y)	Baseline, posttest, and four-month follow-up
Quist et al. 2018, Denmark [40]	235	Stage IA (51) Stage IB (70) Stage IIA (24) Stage IIB (28) Stage IIIA (35) Stage IIIB (3)	Surgery	65.5	45	Multicomponent intervention: Exercise intervention + psychoeducational intervention	Role functioning Physical functioning Fatigue Dyspnea Exercise performance (6MWD)	EORTC QLQ-C30 (PR, Y) 6MWT (RR, Y)	Baseline, after 14 weeks, 26 weeks, and 52 weeks

Table 1: Continued.

Study author, year, country	*N* total (start)	Population				Intervention type	Outcome(s)	Outcome measurement instrument (patient (PR)/researcher reported (RR))	Time-points measured
		Cancer stage	Treatment	Age (mean year)	Sex (% male)				
Rutkowska et al. 2019, Poland and VS [60]	40	Stage IIIB: 24 Stage IV: 6	Chemotherapy	60.23	NR	Exercise intervention	Functional wellbeing Role physical Physical functioning	FACT-L (PR, Y) SF-36 (PR, Y)	Baseline (pre) and day 42 (post)
Sebio García et al. 2017, Spain [42]	40	Stage I	Lung resection surgery	70.2	10	Exercise intervention	Exercise capacity Functional capacity (6MWD in m) Upper and lower body strength Physical functioning Role physical	Constant-load cycle endurance test (CCET) (RR, Y) 6MWT (RR, Y) Arm curl test (RR, Y) 30's chair-to-stand test (RR, NR) SF-36v2 (PR, Y)	Baseline (preintervention), postsurgery, and 3 months Baseline and postintervention
Sunahara et al. 2023, Japan [86]	46	Primary LC: $n = 31$ Lung metastasis: $n = 15$	Surgery: $n = 23$ Surgery and chemo: $n = 23$	71	60.9	Multicomponent (PE + exercise)	Physical function Role function Dyspnea Fatigue	Physical component summary, accelerometer (Y) Role/social component summary Cancer dyspnea scale Cancer fatigue scale	Baseline and 2 months postoperative
Tang et al. 2014, Taiwan [64]	57	Stage I (4) Stage II (2) Stage III (13) Stage IV (38)	Chemotherapy	58.27	59.3	Acupressure intervention	Fatigue (total score) Fatigue in daily living activities Physical functioning	The Chinese version of the Tang Fatigue Rating Scale (PR, Y)	Before initial chemotherapy (T0), on day 1 of third chemotherapy (T1), and on day 1 of sixth chemotherapy (T2)
Tian et al. 2010, China [65]	70	Stage IIIb: $n = 21$ Stage IV: $n = 39$	Chemotherapy	NR	50	Diet intervention	Fatigue Dyspnea Physical functioning Role functioning	EORTC QLQ-C30 (PR, Y)	Before and after receiving the treatment

Table 1: Continued.

Study author, year, country	*N* total (start)	Population				Intervention type	Outcome(s)	Outcome measurement instrument (patient (PR)/researcher reported (RR))	Time-points measured
		Cancer stage	Treatment	Age (mean year)	Sex (% male)				
Wang et al. 2020, China [45]	65	Carcinoma in situ (6) Stage I (48) Stage II (3) Stage III (8)	Surgery	57 (median)	33.9	Exercise intervention	Dyspnea 6MWD	The modified Medical Research Council (mMRC) (RR, Y) 30-m corridor for 6 minutes according to the American Thoracic Society Guidelines (RR, NR)	On the day of admission (T0), before surgery (T1), the first day after operation (T2), and discharge from the hospital (T3)
Yorke et al., 2022, UK [95]	263	Mesothelioma: $n = 32$ Primary LC: $n = 230$ Secondary LC: $n = 1$	Palliative: $n = 159$ Radical: $n = 104$	69	49.8	Multicomponent intervention	Dyspnea Fatigue	Dyspnea-12 (D-12) (Y) The functional assessment of chronic illness-fatigue (NR)	Baseline, 4 weeks, and 12 weeks

Table 2: Intervention characteristics (sign. effects on more than one symptom).

Study, author, year, country	Control group		Intervention group						
	N_C	Content control group	N_I	Content of intervention	Timing	Duration	Frequency	Duration of intervention	Setting
Exercise interventions									
Edvardsen et al. 2014, Norway [78]	31	Usual care	30	(a) High-intensity endurance training (HIIT): walking on a treadmill (b) Strength training: the leg press, leg extension, back extension, seat row, bicep curls, and chest-and-shoulder press (c) Inspiratory muscle training (IMT)	Posttreatment	60 min	(a) 3x/week (b) 3x/week (c) Daily	20 weeks	Fitness centre
Henke et al. 2014, Norway and Germany [51]	11	Usual care	18	Additional to usual care (a) Endurance training: walking and stair walking exercise (b) Strength training: a bridging exercise, biceps curl, triceps extension (c) Breathing techniques	During treatment	(a) 6 min. walking, 2 min. stairs (b) — (c) —	(a) 5x/week (b) Every other day of the week (c) 5x/week	Start: first day of chemo End: after completing the 3rd cycle of chemo	Hospital
Molassiotis et al, 2014, Hong Kong, UK, Cyprus [94]	23	Usual care	24	Inspiratory muscle training	NR	30 min. per day	5 IMT sessions weekly	12 weeks	Hospital + home
Rutkowska et al. 2019, Poland and VS [60]	10	Usual care	20	Exercise training program: (a) Individualized, fitness and respiratory exercises (b) Training on a cycle ergometer or treadmill (c) Resistance exercise (d) Nordic walking (e) Relaxation training	During treatment	20–45 min	5 sessions per week, for 4 weeks (on days 7–20 and days 28–41): (a) 30 min of fitness and respiratory exercises, 30 min of respiratory exercises (b) 20–30 min training on a cycle ergometer or treadmill (c) NR (d) 45 min Nordic walking NR	4 weeks	Hospital
Sebio García et al. 2017, Spain [42]	12	Usual care	10	Rehabilitation programme: (a) Moderate endurance training: cycle ergometer (b) Strength training: elastic bands, body-weight exercises (c) Breathing exercises	Pretreatment	60 min. (a) 30 min (b) NR (c) —	(a) 3-5x/week (b) 3-5x/week (c) 2x/day	NR	(a) Hospital (b) Home

Table 2: Continued.

Study, author, year, country	Control group		Intervention group						
	N_C	Content control group	N_I	Content of intervention	Timing	Duration	Frequency	Duration of intervention	Setting
Wang et al. 2020, China [45]	34	Usual pre- and postsurgery care	31	Breathing exercises program: (a) Abdominal breathing training (b) Pursed-lips breathing (c) Incentive spirometry exercises (d) Blow balloon training	Pre and posttreatment	From admission to 1 day before surgery: 15–20 min 1 day after surgery: 5–10 min Day 2 after surgery until discharge: 15–20 min	2x/day	—	Hospital
Acupressure interventions									
Doğan and Taşcı, 2020, Turkey [48]	31	Usual care	29	56 sessions of acupressure Acupoints: LU-1, LU-10, P-6	Posttreatment	18 min	2x/day	4 weeks	Home
Tang et al. 2014, Taiwan [64]	16	Sham acupressure		Acupressure with essential oils Acupoints: L14, ST36, SP6 Acupressure only Acupoints: L14, ST36, SP6	During treatment	6 min	Daily	5 months	Home
Diet interventions									
Jiang et al. 2017, China and Korea [55]	26	Chemotherapy alone	34	300 mg of fermented red ginseng (FRG) extract additional chemotherapy	During treatment	—	Daily	60 days	Home
Tian et al. 2010, China [65]	20	Chemotherapy (treated with vinorelbine plus cisplatin (NP) or gemcitabine plus cisplatin (GP)	20	Feiji recipe (group A)	During treatment	—	One treatment contained 250 ml of herbal preparation, each subject received two treatments a day	2 months	Home
Psychoeducational interventions									
Chan et al. 2011, UK and Hong Kong [46]	70	Usual care	70	Additional to usual care (a) Educational package (b) Progressive muscle relaxation (PMR) (c) Telephone reminder to enhance participation in the week 3 sessions	During	(a) 40 min (b) NR (c) NR	(a) 2 sessions: one week prior to the beginning of the course of RT, and reinforced 3 weeks after commencing RT (b) Daily (c) At the end of the second week	12 weeks of PMR	Hospital

Table 2: Continued.

Study, author, year, country	Control group		Intervention group						
	N_C	Content control group	N_I	Content of intervention	Timing	Duration	Frequency	Duration of intervention	Setting
Peng et al. 2019, China [39]	78	Usual care	82	Supportive group psychotherapy: each session is based around 8 themes (exploration of life stories, implications of living with cancer, stress coping, mindfulness and feeling anxious, relationships and support, self-identity, hope, and moving forward), within each session opportunity for individual expression, group discussion, teaching, and problem-solving	Posttreatment	90 min	1x/week	8 weeks	Hospital
Multicomponent interventions									
Cheng 2022, China [27]	29	Routine nursing	29	Lung rehabilitation therapy additional to routine nursing: (a) Exercise training: lower and upper limb muscle training, the whole physical exercise (b) Respiratory muscle training (c) Nutritional therapy	Posttreatment	—	(a) 3-5x/week (b) — (c) —	12 weeks	Hospital

Table 2: Continued.

Study, author, year, country	Control group		Intervention group						
	N_C	Content control group	N_I	Content of intervention	Timing	Duration	Frequency	Duration of intervention	Setting
Hoffman et al. 2017, US [30]	36	Usual care	37	(a) Initial home visit (connecting the Nintendo Wii fit plus, teaching the exercise intervention, and reinforcing the CRF self-management education and exercise safety (b) Phone visit (to answer any questions and concerns regarding the intervention) (c) Follow-up home visit (with additional visits scheduled on request of the participant): teaching self-efficacy CRF self-management educations (d) Diary (to record exercise activity each week) (e) Exercise program (warm-up walking and balance exercises; with the goal of walking with the Wii of 30 minutes per day during week 6) (f) Exercise program safety checklist (to review ensuring safety prior to the start of exercise)	Posttreatment	—	(a) At start (b) Within 24 hours after initial home visit (c) At start of week 2, the average number of home visits = 2.8 (d) Daily, each week (e) Duration of warm-up walking built up from 5 minutes per day for 5 days during week 1 to 5 minutes per day each week. 5 days per week for 6 weeks balance exercises (f) Provided prior to the start of exercise		Home
Quist et al. 2018, Denmark [40]	119	Late initiated postoperative rehabilitation (14 weeks after surgery (LRG))	116	Early initiated postoperative rehabilitation (14 days after surgery (ERG)) (a) Group-based exercise sessions (the exercise consisted of an individually prepared supervised strength exercise and a group-based cardiovascular exercise) (b) individual counseling sessions (c) and group-based lessons in health-promoting behavior d. If the participants had special needs in terms of smoking cessation, nutritional counseling, or patient education, this was offered too	Posttreatment	(a) 60 min (b) — (c) —	(a) 2x/week (b) 3 sessions (c) 3 lessons	12 weeks	Hospital

Table 2: Continued.

Study, author, year, country	Control group		Intervention group						
	N_C	Content control group	N_I	Content of intervention	Timing	Duration	Frequency	Duration of intervention	Setting
Sunahara et al. 2023, Japan [86]	18	Postoperative rehabilitation program	16	Postoperative rehabilitation program and received physical activity instruction preoperatively and at discharge Instructions twice on promoting physical activity during the hospitalization period (preoperatively and at discharge) in addition to the postoperative exercise program	Pre- and posttreatment	20 min	Instructions: twice: (a) Postoperative exercise program: once a day for 20 min. per session, 5 times a week	—	Hospital

Table 2: Continued.

Study, author, year, country	Control group		Intervention group						
	N_C	Content control group	N_I	Content of intervention	Timing	Duration	Frequency	Duration of intervention	Setting
Yorke et al., 2022, UK [95]	131	Usual care	132	(a) Controlled breathing techniques: consisting of diaphragmatic breathing exercises or pursed lip breathing, practised twice a day or used as needed beyond that for episodes of intense breathlessness and/or anxiety (b) Cough suppression techniques include education (capacity for voluntary cough easing), identifying warning signs for cough and replacing with sips of water, modified swallow technique, huff cough technique, or relaxed throat breathing (c) Acupressure: a small number of acupressure points were taught: L7, L9 (for cough and dyspnea, located on the wrist areas), LI4 (for energy, located in hand), CV21, CV22 (for cough and dyspnea, located in sternum), and ST36 (for energy, located in the knee). Patients could select any of these points in any combination to apply pressure for 1 min at least twice a day for symptom relief (d) Exercise: individually tailored exercise plan, for example, walking incrementally increasing distances in their local environment, and incorporating breathing techniques as required	Posttreatment	(a) — (b) — (c) 1 min (d) —	(b) twice a day or used as needed (c) — (d) at least twice a day (e) individually	—	Hospital
Other interventions									
Ahmedzai et al. 2004, UK [93]	12 (crossover)	(a) Oxygen-enriched air (72% N_2, 28% O_2) (b) Medical air (78.9% N_2, 21.1% O_2)	12 (crossover)	Heliox 28 gas mixture (72% He, 28% O_2)	Pretreatment	5 min	—	—	Hospital

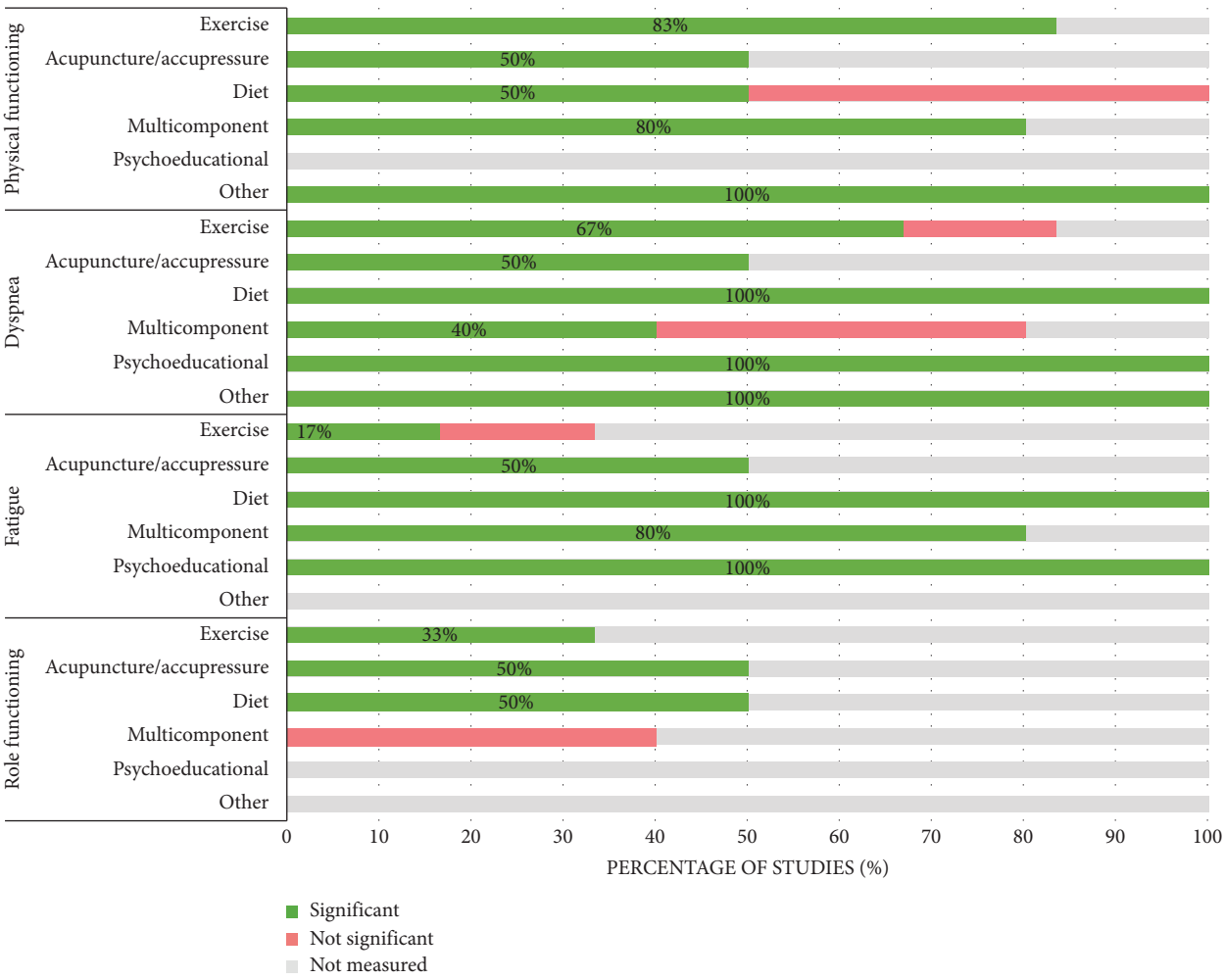

Figure 2: Percentage of studies with significant improvement of more than one symptom per intervention type*. *The total amount of studies with a significant improvement in more than one symptom is 18 including 6 exercises, 2 acupuncture/acupressure, 2 diet, 5 multicomponent, 2 psychoeducational, and 1 other intervention type study.

psychoeducation, and a diet intervention [37]. The interventions were carried out pre- [37, 38] and postoperatively [27, 30, 40, 44, 86], during [50, 71, 76] and after chemotherapy [58, 71, 75–77, 89], after both chemo- and radiotherapy [58, 77, 89], during [71] and after both chemo- and immunotherapy [71], during [76] or after both chemo- and targeted therapy [76], after radiotherapy [58, 75, 77, 89] and after both radiotherapy and targeted therapy [77], during [71] and after targeted therapy [71, 76, 77], and during [71] and after immunotherapy [71]. Four articles did not report about a specific treatment [104]. Johnson et al. [105], Yorke et al. [91], Yorke et al. [95], and Lau et al. [106] did not report about the treatment and the timing of the intervention. The duration of the multicomponent interventions ranged from two weeks [37] to six months [77]. Detailed information about the intervention characteristics and effects of the interventions is shown in Table 2 and Figure 2 (i.e., only studies with significant effects on more than one symptom) and Supplementary Files 3 and 4 (i.e., all included studies).

Of the 19 included studies, eleven articles reported statistically significant changes in one symptom within the SC [27, 37, 44, 58, 71, 75–77, 86, 91, 104]. Five studies reported statistically significant changes in two symptoms within the SC: PF and fatigue [30, 40, 86], dyspnea and fatigue [95], and PF and dyspnea [27]. Interestingly, all three multicomponent interventions consisted of an exercise intervention. The studies combined exercise with psychoeducation [30], exercise with nutritional guidance [27], exercise with both psychoeducation and acupressure [95], and exercise with both psychoeducation and nutritional guidance [40].

3.6. Acupuncture/Acupressure Intervention. Six studies investigated the effects of acupressure ($n = 4$) or acupuncture ($n = 2$). Acupressure uses firm pressure from hands/wrists/elbows, and acupuncture uses hair-thin needles. The acupuncture/acupressure interventions were performed by trained healthcare providers [19, 52, 73], the patient

[48, 56, 64], or their caregiver [48, 56]. The acupuncture/acupressure interventions were conducted during [48, 52, 56, 64, 73] or after [19, 48] chemotherapy or during radiotherapy [73]. Strong et al. [19] did not report about the treatment and the timing of the intervention. The duration of the intervention was three days [19], four weeks [48, 52, 73], nine weeks [56], or five months [64]. Detailed information about the intervention characteristics and effects of the interventions is shown in Table 2 and Figure 2 (i.e., only studies with significant effects on more than one symptom) and Supplementary Files 3 and 4 (i.e., all included studies).

Of the six included studies, two articles showed statistically significant benefits on two symptoms within the SC: PF and dyspnea [48] and role functioning and fatigue [64]. In both studies, the patients self-administered acupressure at home during chemotherapy treatment. Additionally, one of the studies offered the possibility of acupressure being performed by a caregiver [48]. The acupressure lasted for four weeks [48] or five months [64] and varied between one session of six min. per day [64] to two sessions of 18 min. per day [48].

Interestingly, the other four studies conducting a similar acupuncture/acupressure intervention also found statistically significant benefits but only on one of the symptoms within the SC (fatigue or dyspnea). However, all four studies only measured one symptom that is part of the SC so significant improvements on other symptoms within the SC may be missed.

3.7. Other Intervention. Five articles included an intervention type that could not be classified into one of the above categories (heliox 28 gas, CPAP, neuromuscular electrical stimulation ($n = 2$), and additional comfort nursing). Detailed information about the intervention characteristics and effects of the interventions is shown in Table 2 and Figure 2 (i.e., only studies with significant effects on more than one symptom) and Supplementary Files 3 and 4 (i.e., all included studies).

Of the five included studies, two articles reported statistically significant changes in one of the symptoms within the SC [32, 90]. Only one study reported significant changes in two symptoms within the SC, more specifically in PF and dyspnea [93]. The study assessed whether breathing heliox 28 via a facemask (72% He/28% O_2) for five min at rest and while performing the 6-min walk test could reduce dyspnea and improve the exercise capability compared with oxygen-enriched air (72% N_2/28% O_2) or medical air (78.9% N_2/21.1% O_2).

3.8. Risk of Bias. A summary of the risk of bias assessment of the randomized controlled trails is presented in Supplementary File 4. Overall, if we look at the RCTs having significant effects on at least two symptoms within the SC ($n = 18$), eleven RCTs were considered to have a high risk of bias [27, 40, 42, 45, 46, 48, 51, 60, 86, 95, 94] and seven studies were judged to have some concerns [30, 39, 55, 64, 65, 78, 93].

4. Discussion

This review is the first to provide an overview of the literature regarding nonpharmacological interventions in LC patients which have a positive effect on multiple symptoms within the following SC: dyspnea, fatigue, physical, and role functioning. Eighteen interventions were identified with effects on multiple symptoms within the SC. Intervention types were exercise interventions ($n = 6$), diet interventions ($n = 2$), psychoeducational interventions ($n = 2$), a combination of exercise with diet and/or psychoeducation ($n = 5$), acupuncture/acupressure ($n = 2$), and breathing heliox 28 ($n = 1$). Across studies, the most evidence within the SC was found for PF [27, 30, 40, 42, 45, 48, 51, 55, 60, 78, 93] and dyspnea [27, 39, 45, 46, 48, 51, 55, 58, 60, 65, 78, 93–94].

The majority of the evidence was found for the exercise interventions, both in single component and multicomponent interventions including exercise. Three out of six single-component studies [45, 60, 78] and one multicomponent intervention [27] reported a positive effect on dyspnea and PF. Two multicomponent interventions and every included exercise-only study in this review contained breathing exercises, which can explain the positive impact on dyspnea [104, 107]. Furthermore, exercise provides muscle building, improved cardiovascular function, and increased physical capacity which consequently leads to an improved PF. In turn, an increased cardiovascular function and endurance also lead to an increased oxygenation which facilitates breathing with, therefore, a decrease in dyspnea [108]. There were fewer studies reporting an effect on fatigue among the studies that had an impact on multiple symptoms, which could be explained by the fact that fatigue was not always measured. However, in general literature, exercise interventions have a positive effect on fatigue [109–112]. Evidence for role functioning on the other hand is scarce as this outcome is relatively unassessed in exercise studies.

This review showed the most evidence for supervised exercise interventions in the hospital setting. There is a need for more research concerning exercise in different settings such as the community or home setting. LC patients are a vulnerable patient population, who are not very physically active. A home-based exercise program focused on walking to reduce sedentary behavior can be a low-threshold alternative, but more research is needed to study these effects.

The second most investigated interventions in this review were psychoeducational interventions. Two psychoeducation-only studies [39, 46] and two multicomponent interventions consisting of psychoeducation [30, 40] reported effects on more than one symptom. Fatigue was improved in all four studies. Dyspnea was improved in both psychoeducational-only interventions, and PF was improved in both multicomponent interventions. These results are in line with current literature as significant outcomes for psychoeducational interventions are primarily reported for fatigue [13, 113, 114]. Psychoeducational interventions mainly focus on education, coping, improving self-care skills, and motivation and confidence to implement self-care [13]. Studies addressing fatigue in this review contained such aspects. The multicomponent interventions consisting

of psychoeducation also included exercise intervention, potentially explaining the improvement in PF as well. Fatigue along with PF was most frequently assessed, whereas dyspnea and RF were barely measured.

Regarding dietary interventions, only two studies improved multiple symptoms, one using ginseng [55], the other using a feiji recipe [65], and one multicomponent intervention including nutritional therapy [27]. Fatigue and dyspnea were both improved due to the diet-only intervention, and dyspnea and PF improved due to the multicomponent intervention. Ginseng and feiji are not frequently documented, but some studies show that ginseng has a positive effect on fatigue [115, 116] and feiji inhibits tumor progression and resolves phlegm, which improves breathing [117]. An improvement in fatigue often improves dyspnea [118], RF, and PF [119]. This could explain why PF and dyspnea improved with ginseng and the multicomponent intervention, and role functioning and dyspnea with the feiji recipe.

It is important to note that only half of the included articles measured all four symptoms. Therefore, it is likely that many effects have been missed due to not being measured. PF was frequently assessed [55, 62, 88, 96] and improved in each of these studies. Supplements, particularly protein and fatty acid supplements, were shown to have benefits on PF, as well as on RF and fatigue in studies included in our review [62, 88] and literature [120, 121].

According to the literature, one of the most common indications to apply acupuncture is fatigue, while PF or RF is barely reported [122–125]. Similarly, the articles in this review evaluated fatigue most frequently with consistent beneficial results. Concerning dyspnea, however, contradictory results were found. A systematic review [126], for instance, showed that in seven out of twelve studies, a significant improvement occurred after acupuncture, whereas, in others, there was no significant improvement [127, 128]. One multicomponent intervention [95] consisted of acupressure, for which an improvement was seen in both fatigue and dyspnea, thus confirming results found in the literature.

Regarding other interventions, only one article in this review affected more than one symptom, i.e., dyspnea and PF [93]. This intervention included the administration of a heliox 28 gas mixture. Currently, few studies are available on the treatment of LC symptoms with heliox 28 gas. However, one study cites the same respiratory physiology, and the way helium and oxygen can interact [129].

This review is the first to provide a summary of evidence regarding nonpharmaceutical interventions on the SC, containing PF, dyspnea, fatigue, and RF. In addition, this innovative review created an opportunity to encourage further evidence and research on SCs and nonpharmacological interventions that are relevant to LC patients.

4.1. Study Limitations. However, it is important to acknowledge certain limitations in this review. There is a high variability in the characteristics of participants (age, stage and type of lung cancer, and treatment) and outcome measurement. For example, the diversity of outcome measures used to assess fatigue limits the comparability of the findings [130]. Also, some studies contained small sample sizes, with a minimum of eleven participants. Further, a lot of the studies did not measure all symptoms. It is unknown whether the interventions had no effect on these symptoms, or effects were missed as they were not measured. Only 12 out of 89 studies measured all symptoms of SC [28, 29, 40, 49, 51, 65, 68, 71, 72, 76, 88, 100]. It is important to point out that we have only looked at four specific outcomes (i.e., fatigue, dyspnea, physical, and role functioning). It is possible that interventions included in this review were underpowered to find a statistically significant effect on the specific outcomes of our interest but did find an effect on other outcomes measured in that particular study. Another limitation is that only randomized controlled studies were included in the search strategy. Although RCTs are considered the most reliable form of scientific evidence in efficacy studies, it is possible that other important evidence was missed as nonpharmaceutical interventions are not always evaluated with an RCT design. Further, three of the reviewed articles were rather old, with the oldest being published in 1982, 1996, and 1999 [75, 81, 104]. Also, the risk of bias in the included studies should be considered as a limitation as most studies have some concerns or high risk of bias. Risk of bias, small sample sizes, old publications, and not measuring every symptom of the SC can contribute to a lower generalizability. Another limitation of this study is that we did not conduct a meta-analysis to assess the effectiveness of each component within the included interventions. Given the focus on nonpharmacological interventions, it would have been relevant also to include CINAHL (which reflects articles published in nursing journals, mainly) among the databases consulted. However, we included four databases which might lower the risk of missing eligible studies [131]. Lastly, a few methods could have been undertaken to increase the representability of the current literature such as including non-English language articles (with the use of artificial intelligence), checking the reference lists of the included articles, and searching other sources such as grey literature or literature reviews on similar topics [132].

4.2. Clinical Implications. Based on the available evidence, nonpharmacological can be effective to treat multiple symptoms within SCs. In particular, exercise interventions demonstrate promising results. A feasible approach would be to start with exercise interventions and then extend to diet and psychoeducation based on individual patient needs. Further research should examine the impact on all symptoms, short term, and long term. Although positive findings might be found on short-term outcomes, more research is needed to evaluate the sustainability of both intervention adherence (e.g., engaging in sufficient exercise) and intervention effects on the patients' health and well-being in the long term. Although role functioning is part of patients' QoL, evidence for effects on role functioning is scarce. It should be considered important to assess the intervention's

clinical significance. Additionally, potential patient burden in multicomponent interventions might be important. Further qualitative research is recommended for analyzing patient burden and patients' perceptions regarding nonpharmacological interventions since they are key stakeholders. Another focus for future research is to investigate the underlying mechanisms that explain the impact of exercise, diet, and psychoeducational interventions on more than one symptom within the SC.

5. Conclusion

This review aimed to summarize the evidence regarding the effectiveness of nonpharmacological interventions on SCs. Overall, most evidence was found for exercise interventions, followed by multicomponent, psychoeducational, diet, acupuncture, and other interventions. Among these, interventions that addressed multiple symptoms had most frequently a positive impact on dyspnea, followed by PF and fatigue. The least evidence was found regarding RF. Nonpharmacological interventions appear to have the potential to treat multiple symptoms within the SC; however, further research is recommended to identify optimal interventions, including dose-response relationship, and report more symptoms.

Data Availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Supplementary file 1: search strategy for all databases. Supplementary file 2: study characteristics. Supplementary file 3: intervention characteristics of all included studies. Supplementary file 4: effect of the interventions and risk of bias of all included studies. Supplementary file 5: PRISMA 2020 checklist. Supplementary file 6: PRISMA 2020 abstract checklist. (*Supplementary Materials*)

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