Title

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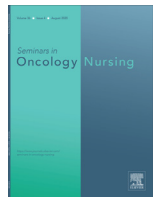# Systematic Review of the Literature on Multiple Co-occurring Symptoms in Patients Receiving Treatment for Gynecologic Cancers

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ABSTRACT

Objective: Patients with gynecologic cancers experience a very high symptom burden that has a negative impact on their quality of life. This systematic review aims to identify the common co-occurring symptoms, the prevalence of common symptoms, common instruments used to measure symptoms, associated risk factors, and the symptom burden in patients with gynecologic cancers.
Data Sources: A search of four databases (ie, PubMed, Embase, Web of Science, and CINAHL) was done from January 1, 2012, through September 5, 2022. A qualitative synthesis of the extant literature was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA 2020).
Conclusion: A total of 118 studies met the prespecified inclusion criteria. Ninety-six symptoms were assessed across these studies. The top six symptoms and their grand mean prevalence rates were lack of energy (64.4%), fatigue (62.1%), abdominal pain (53.3%), depression (52.6%), concentration dysfunction (52.0%), and drowsiness (51.9%). Numerous methodologic challenges were evident across studies. Future research needs to develop a disease-specific symptom assessment measure, evaluate for risk factors associated with a higher symptom burden, and determine the impact of multiple symptoms on patient outcomes.
Implication for Nursing Practice: The results are relevant for oncology clinicians to assess patients with gynecologic cancers for the presence of common symptoms and risk factors for higher symptom burden in the patients and to offer effective management interventions.

Introduction

More than 1.3 million new cases of gynecologic cancer and 671,875 deaths occurred worldwide in 2020.[1] In the United States in 2023, it is estimated that 114,810 patients will be diagnosed with gynecologic cancer and 34,020 will die of the disease.[2] As the incidence and mortality rates for these cancers continue to increase globally,[1,3] albeit limited research suggests that these patients experience a very high symptom burden. In fact, in our previous study,[4] patients with gynecologic cancers reported an average of 14 co-occurring symptoms. These unrelieved symptoms have a negative impact on women's functional status and quality of life (QOL).[5-7]

Given the deleterious effects of these symptoms, detailed information on their occurrence, severity, and distress is needed to guide the development of effective symptom management interventions for these patients.

Symptom Burden in Patients With Gynecologic Cancers

The symptom burden of patients with gynecologic cancers is partly attributable to treatment-related effects. For example, women experience changes in body image and sexual function, hot flashes, and hair loss following surgery and/or chemotherapy.[8] In addition, gastrointestinal symptoms (eg, nausea, vomiting, abdominal bloating, constipation) are common in these patients.[8,9] The severity of pain, fatigue, sleep disturbance, and peripheral neuropathy tends to increase during and after chemotherapy.[8,10-12] Taken together, these findings suggest that the symptom burden of patients with gynecologic cancers is higher during active treatment.[10]

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Previous Reviews of Symptoms in Patients With Gynecologic Cancers

A systematic review of the literature is one way to develop a more comprehensive picture of the symptom burden of patients with gynecologic cancers.[13,14] Three reviews were identified that broadly evaluated symptoms and QOL outcomes associated with treatment for gynecologic cancers.[15-17] While these reviews did not evaluate a comprehensive list of symptoms; or reported on different dimensions of the symptom experience (i.e., occurrence, severity, distress) and associated risk factors, they provided a foundation and some guidance for the structure of the current systematic review.

In a systematic review that synthesized the evidence from 11 qualitative studies on supportive care needs of women with gynecologic cancers,[16] five themes were identified: psychological support, information support, social support, disease-specific symptom management, and forms of care (ie, continuity of care and holistic care). Relevant to the current systematic review, the negative psychological consequences of having gynecologic cancers were identified. The most common consequences—isolation, fear, anxiety, and shame—were intertwined and persistent. In terms of disease-specific symptom management, the most common areas that warranted support included loss of fertility, premature menopause, pelvic floor dysfunction, and sexual difficulties. While this review is extremely informative, the occurrence rates for and impact of these symptoms in patients with gynecologic cancers need to be synthesized in a systematic fashion.

In an integrative review that focused on an overview of the current literature and research on remote monitoring of symptoms in patients following gynecologic and urologic surgery,[15] five studies of patients with gynecologic cancers were included. Four of the five studies used web-based tracking or mobile applications. The most common measure used was the Patient Reported Outcomes (PRO) version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). While specific information was not provided on all of the symptoms that were evaluated across the five studies, nausea and fatigue were listed as common symptoms in this review. Again, while the authors concluded that remote monitoring of symptoms was feasible, detailed information on the symptom experience of this vulnerable group of patients is warranted.

In a scoping review that aimed to synthesize evidence on the efficacy of exercise for a variety of physical and psychosocial outcomes in women during and after gynecologic cancer treatment,[17] 11 studies were included. Relevant to the current review, the outcomes that were assessed included sleep, fatigue, mental health, sexual function, stress, and QOL. Because the number of studies that examined associations between these outcomes and exercise were limited, the authors noted that findings related to mental well-being were inconsistent. In addition, no definitive conclusions could be made about the other outcomes.

Given the limited findings on symptoms from these three reviews,[15-17] and albeit limited information on the negative impact of symptoms,[5-7] a need exists to systematically assess multiple symptoms and risk factors for an increased symptom burden in patients with gynecologic cancers. Therefore, the overall purpose of this systematic review was to identify common co-occurring symptoms in patients with gynecologic cancers receiving chemotherapy. Specifically, this review addressed the following questions: (1) What are the common co-occurring symptoms in patients with gynecologic cancers? (2) What are the prevalence rates for common symptoms in patients with gynecologic cancers? (3) What are the common risk factors for multiple co-occurring symptoms in patients with gynecologic cancers? (4) What are the instruments used to measure multiple co-occurring symptoms in patients with gynecologic cancers? (5) What are the most common dimensions of the symptom experience (ie, occurrence, severity, distress) that are used to assess multiple co-occurring symptoms in patients with gynecologic cancers? (6) What

are the most common outcomes that are evaluated in studies that assess multiple co-occurring symptoms in patients with gynecologic cancers?

Methods

Search Strategy

This review was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA 2020)[14] and registered in Prospero (CRD42022355554). Studies that were published between January 1, 2012, and September 5, 2022, were retrieved from the Web of Science, Embase, PubMed, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search strategy for each database is provided in Table 1.

Eligibility Criteria

Inclusion criteria: Studies were included if they met the following eligibility criteria: (1) included only adults who were 18 years or older; (2) included only patients diagnosed with gynecologic cancers of any stage (ie, vulva, vaginal, cervix, uterine corpus, endometrial, or ovarian); (3) included patients who received chemotherapy with or without another form of cancer treatment; (4) used cross-sectional, longitudinal, or randomized clinical trial (RCT) designs; (5) used valid and reliable measures to assess the characteristics of symptoms in patients with gynecologic cancers; (6) were published in English; and (7) were published between January 1, 2012, and September 5, 2022. The January 2012 date was chosen because poly(ADP)-ribose polymerase (PARP) inhibitors were approved by the US Food and Drug Administration in that year and would provide information on symptoms from studies with more recent chemotherapy protocols for maintenance therapy or the management of recurrent disease.
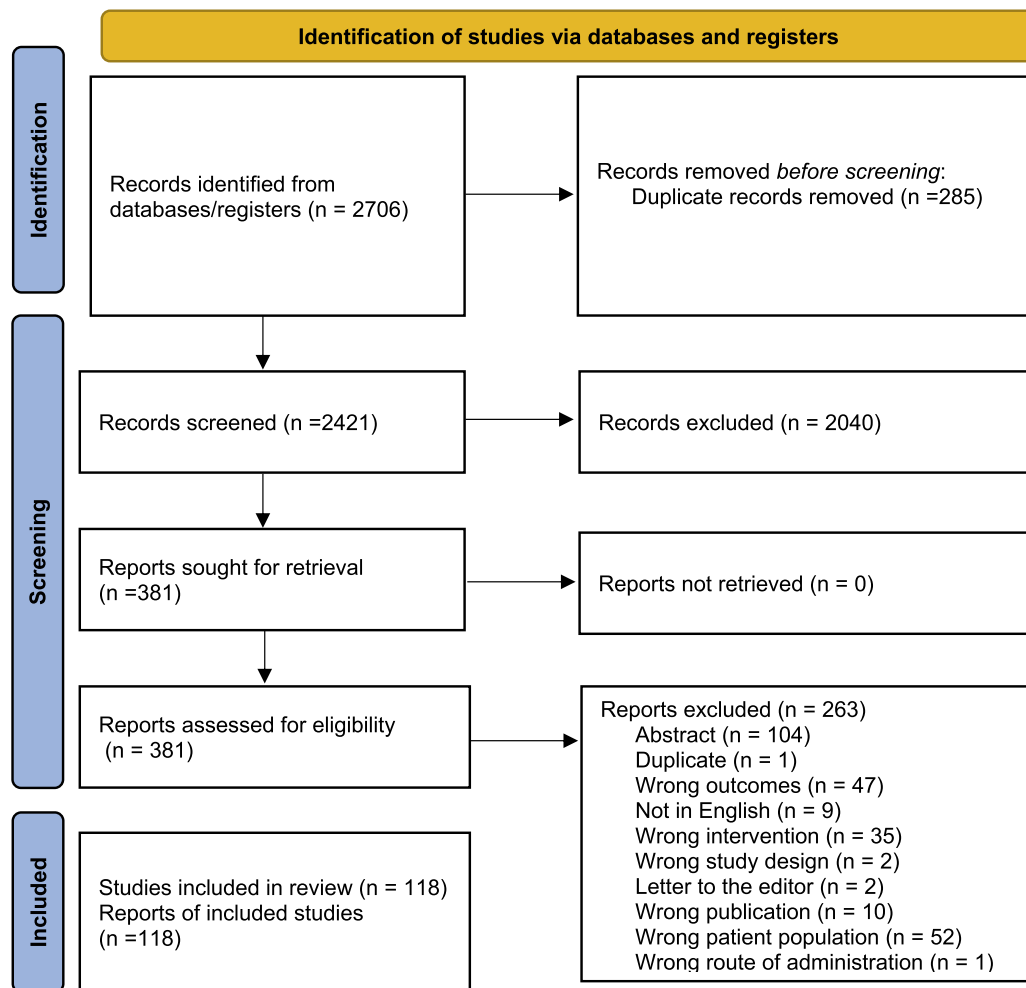
Exclusion criteria: Studies were excluded if they (1) included patients who received palliative chemotherapy; (2) measured symptoms after completion of treatment; (3) included patients diagnosed with cancers other than gynecologic cancers; and (4) were systematic reviews, meta-analyses, conference abstracts, case reports, or qualitative studies.

Information Sources and Search Strategies

In collaboration with a medical librarian, literature search strategies were developed using medical subject heading (MeSH) terms

TABLE 1
Summary of Search Strategy.

Databases	Search terms
PubMed	(symptom*) AND ("gynecological cancer*" OR "gynecological tumor*" OR "gynecological neoplasm*" OR "vaginal cancer" OR "vagina cancer" OR "vulva cancer" OR "cervical cancer" OR "uterine cancer" OR "endometrial cancer" OR "ovarian cancer" AND chemotherapy Filters: in the last 10 years
CINAHL	(symptom*) AND ("gynecological cancer*" OR "gynecological tumor*" OR "gynecological neoplasm*" OR "vaginal cancer" OR "vagina cancer" OR "vulva cancer" OR "cervical cancer" OR "uterine cancer" OR "endometrial cancer" OR "ovarian cancer") AND chemotherapy (Last 10 years)
Web of Science	Results for (symptom*) AND ("gynecological cancer*" OR "gynecological tumor*" OR "gynecological neoplasm*" OR "vaginal cancer" OR "vagina cancer" OR "vulva cancer" OR "cervical cancer" OR "uterine cancer" OR "endometrial cancer" OR "ovarian cancer") AND chemotherapy (All Fields) *Timespan: 2012-01-01 to 2022-09-05 (Publication Date)*
Embase	('symptom'/exp OR symptom) AND ('female genital tract cancer'/exp OR 'female genital tract cancer') AND 'chemotherapy' AND [2012-2022]/py 2022:py AND [06-09-2022]/sd NOT [19-05-2023]/sd

Identification of studies via databases and registers

Identification	
Records identified from databases/registers (n = 2706)	Records removed *before screening*: Duplicate records removed (n =285)

Screening	
Records screened (n =2421)	Records excluded (n = 2040)
Reports sought for retrieval (n =381)	Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 381)	Reports excluded (n = 263) Abstract (n = 104) Duplicate (n = 1) Wrong outcomes (n = 47) Not in English (n = 9) Wrong intervention (n = 35) Wrong study design (n = 2) Letter to the editor (n = 2) Wrong publication (n = 10) Wrong patient population (n = 52) Wrong route of administration (n = 1)

Included
Studies included in review (n = 118) Reports of included studies (n =118)

FIG 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram to determine the final selection of studies that evaluated multiple co-occurring symptoms in patients with gynecologic cancers.[14]

and various text words or phrases related to symptoms in patients with gynecologic cancers (eg, symptoms, co-occurring symptoms, gynecologic cancers) that were specific for each database. The search was conducted on September 5, 2022.

Data Management

Studies identified were uploaded into Endnote reference software and duplicates were removed. All retrieved studies were imported into Covidence (Veritas Health Innovation, Melbourne, Australia), a web-based systematic review program. The researchers used Covidence to screen the titles, abstracts, and full texts of the imported studies. In addition, Covidence created the PRISMA flow diagram (Fig 1).

Selection Process

Using the Covidence software package, two independent reviewers (DAA and CM) screened the titles and abstracts created by the search based on the prespecified inclusion and exclusion criteria. Then, two reviewers (DAA and CM) reviewed the full texts of articles to clarify the inclusion of studies that could not be determined through only a review of the abstract. Full-text articles that met the inclusion criteria were retrieved. Interrater agreement was 0.84 for the title and abstract screening and 0.53 for the full-text review. The two reviewers (DAA and CM) resolved disagreements through discussion with a third independent reviewer (JJN). In addition, two reviewers (DAA and CM) recorded the reasons for excluding articles (see Fig 1).

Main Outcomes

The primary outcomes of this systematic review included a determination of the prevalence rates for common symptoms, identification of risk factors for multiple co-occurring symptoms, and a determination of the most common dimensions of the symptom experience that were evaluated (eg, occurrence, severity) in patients with gynecologic cancers. In addition, the most common instruments used to measure multiple co-occurring symptoms and the most common PROs in patients with gynecologic cancers were evaluated.

Risk of Bias in Individual Studies

The methodologic quality of the included studies was evaluated using the National Heart, Lung, and Blood Institute's (NHLBI) National Institute of Health Quality Assessment Tool for Observational and Cross-sectional studies (see Supplemental Table S1).[18] Questions on this tool were designed to enable researchers to critically appraise the internal validity of various types of research studies. Each question was answered with "yes," "no," "cannot determine or not reported," or "not applicable" choices. Items that received "no" or indeterminable responses were considered study weaknesses that could introduce bias. As recommended by the NHLBI guidelines, this potential risk of bias must be further evaluated by a reviewer and be factored into the final rating of "good," "fair," or "poor." Two reviewers (DAA and CM) independently assessed the quality of each study and combined their results in a shared Excel spreadsheet. All

studies that met the inclusion criteria were included in this review regardless of the methodologic quality assessment rating.

Data Extraction and Synthesis

Because of the descriptive nature and heterogeneity of the studies, a meta-analysis could not be performed. Therefore, a qualitative synthesis of the quantitative studies is reported for this systematic review. The data from each study were extracted based on prespecified review criteria. Our prespecified review criteria included author (s), year published, study aims, study design, sample size, patient characteristics (eg, age, race/ethnicity, employment status, inpatient/outpatient status), cancer diagnosis (vulva, vagina, cervix, uterine corpus, endometrial, ovaries), cancer treatment(s), the timing of symptoms assessment(s), study methods (eg, symptoms, symptom measure(s)), symptom dimensions (eg, occurrence, severity, distress), common risk factors, study outcomes (eg, QOL, functional status), and strength and limitations.

The data were organized using three tables (ie, one for cross-sectional studies [Supplemental Table S2], one for longitudinal studies [Supplemental Table S3], and one for the enrollment data from RCTs [Supplemental Table S4]). Two reviewers (DAA and CM) tested the data extraction tables with three studies in each category and revised the tables to optimize data extraction. These tables were used to synthesize the findings from this review.

Results

Study Selection

A total of 2706 articles were uploaded into Covidence (Fig 1). Following the removal of duplicates, 2421 articles remained. Next, the title and abstract of each study were reviewed against our inclusion and exclusion criteria, and 2040 studies were excluded. Two reviewers (DAA and CM) reviewed the full text of the remaining 381 articles against the inclusion and exclusion criteria. Following these steps, a total of 118 articles were retained and included in this systematic review (ie, 33 cross-sectional studies [28%], 32 longitudinal studies [27%], and 53 RCTs [45%]).

Methodologic Quality of Studies

Nineteen (58%) cross-sectional, 30 (94%) longitudinal, and 52 (98%) RCT studies received a "good" rating, and 13 (39%) cross-sectional, 2 (6%) longitudinal, and 1 (2%) RCT studies received a "fair" rating. Of note, only 1 of the cross-sectional studies received a "poor" rating. Across the 17 studies that received a "fair" or "poor" rating, the most common sources of bias were (1) participation rate of eligible persons was <50%; (2) loss to follow up after enrollment was >20% (in RCTs and longitudinal studies); and (3) key potential confounding variables were not measured and/or not adjusted for in the statistical analysis (Supplemental Table S1).

Study Characteristics

Of the 118 studies included in this review, 24 were multinational studies,[19-42] 22 were conducted in the United States,[4,8,43-62] 16 in China,[10,63-77] 6 in Turkey,[78-83] and 4 each in Australia,[84-87] India,[88-91] Austria,[92-95] and Korea.[11,96-98] Three studies each were conducted in Indonesia,[99-101] Poland,[102-104] Denmark,[105-107] Thailand,[108-110] Taiwan,[111-113] and Italy.[114-116] Of the remaining studies, two each were conducted in the United Kingdom,[117,118] Canada,[119,120] Brazil,[121,122] Israel,[123,124] and Norway,[125,126] and single studies were conducted in the Netherlands,[6] Zimbabwe,[127] South Korea,[128] Kazakhstan,[129] Germany,[130] and Japan.[131]

The total sample size across the studies in this review was 31,960 patients. Sample sizes ranged from 10[114] to 2268.[21] Of the 118 studies, 105 reported the mean age of the patients. Across these studies, the weighted grand mean age was 56.17 years. The majority of the patients were outpatients with recurrent disease. Most patients had an International Federation of Gynecology and Obstetrics (FIGO) stage of III to IV. Cancer types varied across studies and included: ovarian (48%), cervical (23%), multiple types of gynecologic cancer (22%), endometrial (6%), and vulvar (1%). All patients received chemotherapy alone or with surgery and/or radiotherapy.

Common Symptoms

Across 105 studies, a total of 96 symptoms were evaluated in patients with gynecologic cancers receiving chemotherapy. Across these studies, the top 20 symptoms evaluated were fatigue, pain, appetite loss, sleep disturbance, dyspnea, constipation, diarrhea, nausea/vomiting, financial difficulties, change of body image, peripheral neuropathy, depression, menopausal symptoms, sexual function, anxiety, chemotherapy-related side effects, abdominal pain, lymphedema, sexual worry, and attitude toward disease and treatment (Table 2). The remaining 13 studies reported composite scores across the symptom measures or described symptom clusters.

Prevalence of Common Symptoms

Of these 105 studies, 45 reported on the prevalence of the symptoms that were evaluated. The weighted grand mean prevalence rates for the 96 symptoms are listed in Table 2. The prevalence rates for the symptoms that were reported in seven or more studies were lack of energy (64.4%), fatigue (62.1%), abdominal pain (53.3%), depression (52.6%), concentration dysfunction (52.0%), drowsiness (51.9%), paresthesia (50.5%), anxiety (50.3%), pain (49.1%), sleep disturbance (44.5%), feeling bloated (43.0%), dyspnea (42.6%), nausea and vomiting (40.7%), hair loss (40.3%), changes in taste (35.2%), appetite loss (35.2%), constipation (34.7%), diarrhea (25.8%), and sore mouth (23%).

Common Dimensions of the Symptoms Experience

Of 118 studies, 105 reported on one or more dimensions of the symptom experience. Symptom severity was the most common dimension (ie, 86 of 105 studies [82%]), followed by occurrence in 40 studies (38%) and distress in 7 studies (7%). Two of 105 studies (1.9%) reported on three dimensions (ie, occurrence, severity, and distress), 21 (20%) reported occurrence and severity, 3 (2.9%) reported severity and distress, 2 (1.9%) reported occurrence and distress, 60 (57.1%) reported only severity, and 17 (16.2%) reported only occurrence. No study was identified that evaluated only symptom distress.

Common Instruments Used to Evaluate Multiple Symptoms

Of 44 instruments that were used to evaluate symptoms, 17 of them evaluated 3 to 47 symptoms on the same measure (Table 3). The most common instruments that were used to measure multiple symptoms on the same measure are the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) (n = 59), EORTC-QLQ Ovarian Cancer 28 (EORTC-QLQ-OV28) (n = 28), EORTC-QLQ Cervical Cancer 24 (EORTC-QLQ-CX24) (n = 16), Memorial Symptom Assessment Scale (MSAS) (n = 7), MD Anderson Symptom Inventory (MDASI) (n = 7), Edmonton Symptom Assessment System (ESAS) (n = 6), and Measure of Ovarian Symptoms and Treatment concerns (MOST) (n = 4) (Table 4).

TABLE 2
Common Symptoms and Prevalence Rates in Patients With Gynecologic Cancers Receiving Chemotherapy.

	Common symptoms			Prevalence rates of common symptoms	
Rank	Symptom	# of studies that measured the symptoms	%	# of studies that reported prevalence rate	Grand mean prevalence (%)
1	Fatigue	74	62.7	21	62.1
2	Pain	64	54.2	19	49.1
3	Appetite loss	58	49.2	17	35.2
4	Sleep disturbance	57	48.3	21	44.5
5	Dyspnea	54	45.8	15	42.6
6	Constipation	52	44.1	12	34.7
7	Diarrhea	51	43.2	9	25.8
8	Nausea/vomiting	51	43.2	19	40.7
9	Financial difficulty	36	30.5	3	37.7
10	Change of body image	32	27.1	6	52.5
11	Peripheral neuropathy	31	26.3	3	73.9
12	Depression	30	25.4	13	52.6
13	Menopausal symptoms	29	24.6	1	8
14	Sexual function	28	23.7	4	30.7
15	Anxiety	24	20.3	12	50.3
16	Chemotherapy side effects	16	13.6	0	0
17	Abdominal pain	15	12.7	9	53.3
18	Lymphedema	14	11.9	4	19.9
19	Sexual worry	14	11.9	5	25.9
20	Attitude towards disease and treatment	14	11.9	1	95.0
21	Sexual activity	13	11.1	4	27.8
22	Changes in taste	13	11.1	9	35.2
23	Hair loss	13	11.1	7	40.3
24	Drowsiness	13	11.1	7	51.9
25	Low sleep quality	13	11.1	3	34.9
26	Concentration dysfunction	12	10.2	10	52.0
27	Feeling bloated	12	10.2	8	43.0
28	GI symptoms	11	9.3	0	0
29	Lack of energy	11	9.3	9	64.4
30	Numbness	11	9.3	6	43.0
31	Sexual enjoyment	11	9.3	2	76.0
32	Sore mouth	10	8.5	7	23.0
33	Urine frequency	10	8.5	6	16.9
34	Feeling sad	9	7.6	6	61.0
35	Burning urination	9	7.6	3	14.4
36	Urinary problems	9	7.6	6	29.2
37	Itching	9	7.6	4	28.6
38	Legs/feet swollen	8	6.8	6	27.7
39	Weight loss	7	5.9	4	25.6
40	Leakage of urine	7	5.9	4	23.5
41	Paresthesia	7	5.9	7	50.5
42	Changes in fingers/nails	6	5.1	5	33.0
43	Irritation	6	5.1	4	54.0
44	Dysphagia	6	5.1	5	16.6
45	Sweat	6	5.1	5	40.2
46	Indigestion	5	5.1	5	44.3
47	Dizziness	5	4.2	5	29.2
48	Dry mouth	5	4.2	5	37.9
49	Worry	5	4.2	4	67.2
50	Vagina discharge/odor	5	4.2	2	27.7
51	Hot flashes	5	4.2	4	64.2
52	Cough	5	4.2	5	30.5
53	Heartburns	4	3.4	2	30.9
54	Mood swings	4	3.4	2	47.3
55	Weight gain	4	3.4	3	26.0
56	Backache	4	3.4	3	34.6
57	Fecal incontinence	4	3.4	2	8.3
58	Painful sexual intercourse	4	3.4	0	0
59	Good appetite	4	3.4	1	47.4
60	Loss of sensation	4	3.4	4	38.3
61	Skin changes	4	3.4	4	13.9
62	Loss of power	3	2.5	3	35.9
63	Painful defecation	3	2.5	3	26.6
64	Interest in sexual intercourse	3	2.5	0	0
65	Vagina shortness	3	2.5	0	0
66	Vagina bleeding	3	2.5	2	28.0
67	Incomplete emptying of urine	3	2.5	3	14.8
68	Bodily pains	3	2.5	3	47.6
69	Distress	3	2.5	2	69.4
70	Being sensitive	3	2.5	3	74.4
71	Headache	2	1.7	2	6.0

(continued)

TABLE 2 (Continued)

	Common symptoms			Prevalence rates of common symptoms	
Rank	Symptom	# of studies that measured the symptoms	%	# of studies that reported prevalence rate	Grand mean prevalence (%)
72	Feeling swollen	2	1.7	2	47.2
73	Speak difficulty	2	1.7	2	37.3
74	Pelvic pain	2	1.7	2	17.0
75	Urge urinary incontinence	2	1.7	1	17.6
76	Feel ill	2	1.7	0	0
77	Vagina dryness	2	1.7	2	68.4
78	No interest in sex	2	1.7	1	50
79	Can eat food I like	2	1.7	0	0
80	Tiredness	2	1.7	0	0
81	Anorexia	2	1.7	1	6.8
82	Fever	2	1.7	2	49.3
83	Stress urinary incontinence	2	1.7	2	17.5
84	Incomplete emptying of stool	2	1.7	2	12.4
85	Orgasmic disorder	2	1.7	2	23.6
86	Blurred vision	1	0.8	1	4.1
87	Feeling less feminine	1	0.8	1	18.8
88	Dyspareunia	1	0.8	1	35.7
89	Vagina swollen	1	0.8	0	0
90	Spent time in bed	1	0.8	0	0
91	Fertility concerns	1	0.8	0	0
92	Like body appearance	1	0.8	0	0
93	Psychosis	1	0.8	0	0
94	Paranoid	1	0.8	0	0
95	Fear	1	0.8	0	0
96	Hostility	1	0.8	0	0

Risk Factors for a Higher Symptom Burden

Of 118 studies, 50 of them identified one or more risk factors associated with a higher symptom burden.

Studies That Evaluated Demographic and/or Clinical Risk Factors

Of 50 studies, 32% identified age, 8% identified educational level, 10% identified employment status, and 2% identified marital status as demographic characteristics associated with higher symptom burden in patients with gynecologic cancers. In addition, 52% of the 50 studies identified cancer treatments, 32% identified comorbidities, 18% identified stage of cancer, and 20% identified functional status as clinical characteristics associated with a higher symptom burden in these patients. The next sections describe the specific associations.

Specific Characteristics Associated With Symptom Occurrence

Older age,[43,76,94] being unemployed,[63] having a lower educational level,[64,125] having advanced stage disease,[64] being on active treatment,[19,61,67,75,94,96,130] and receipt of a higher number of chemotherapy cycles[63,96] were associated with higher symptom occurrence rates. Specifically, receipt of a higher number of chemotherapy cycles was associated with increased rates of paresthesia, fatigue, and pain,[96] as well as anxiety and depression.[63] Of note, an earlier stage of cancer was associated with higher rates of menopausal symptoms,[115] and an increased number of chemotherapy cycles was associated with urinary symptoms.[61,94] Having a higher body mass index (BMI)[5,22] and being a smoker and/or using alcohol[94] were associated with higher rates of peripheral neuropathy and bladder incontinence, respectively.

Specific Characteristics Associated With Symptom Severity

Younger age,[8,22,87,103,105,125] being unemployed,[22,112] and having a higher educational level [22,43] were associated with higher symptom severity scores. Of note, lower educational status was associated with higher anxiety, depression, and nervousness scores.[64,125] In addition,

a history of advanced disease,[64,105,109,119] being on active treatment,[19,52,56,60,76,90,96,125,126,129] receipt of a higher number of chemotherapy cycles,[63,96] and having a lower functional status[22,40,112,125] were associated with more severe symptoms. In addition, the presence of depression and anxiety,[128] a higher body mass index (BMI),[5,8,83] and lower income[22,64,76,111] were associated with worse symptom severity scores.

Specific Characteristics Associated With Symptom Distress

Older age,[75,119] a history of advanced disease,[64,91,105,109,111,119] and receiving chemoradiation[88,90,111] were associated with higher symptom distress ratings. In addition, a high number of comorbidities and higher BMI were associated with higher symptom distress scores.[7,85] Of note, no study included in this review identified race and/or ethnicity as a risk factor for a higher symptom burden.

Common Outcomes Assessed Across Studies

Of the 64 studies that examined the association between symptoms and a variety of PROs, 3 evaluated interferences with daily life activities, 9 evaluated functional ability, and 59 evaluated various aspects of QOL. The most common instruments used to assess PROs are listed in Table 5.

Strengths and Limitations of the Included Studies

Of the 118 studies, 115 used valid and reliable instruments to evaluate symptom occurrence, severity, and/or distress. In addition, while 37% of the studies had sample sizes that ranged from 200 to 2268, 63% had smaller sample sizes (ie, 10 to 200). Finally, 20% of the studies recruited patients from multiple clinical settings.

In terms of limitations, 3 studies used investigator-developed measures to evaluate symptoms and 13 did not report individual symptom scores. Other limitations included that 109 studies did not report the patients' menopausal status, 72 studies did not report functional status, 84 studies did not provide information on comorbid

TABLE 3

Multiple Co-Occurring Symptoms in Patients With Gynecologic Cancers Using Instruments That Assessed Three or More Symptoms

Symptom	Instrument																
	QLQ-C30	FLIC	SRQ	MSAS	ESAS	MDASI	PRO-CTCAE	MOST	SPHERE	FACT-CX	FACT-V	SCL-90	PFDI-20	QLQ-CX24	QLQ-OV28	QLQ-EN	CMUOV-QOL
Fatigue	X	X	X	X	X	X		X	X	X							
Pain	X	X	X	X	X	X			X								
Appetite loss	X		X	X	X	X			X								
Sleep disturbance	X		X			X			X								
Dyspnea	X		X		X	X			X								
Constipation	X		X	X		X			X				X				
Diarrhea	X		X	X		X		X	X								
Nausea/vomiting	X	X	X	X	X	X		X	X								
Financial difficulty	X																
Change of body image				X		X								X	X		
Peripheral neuropathy														X	X		
Depression	X				X		X							X			
Menopausal symptoms			X											X	X		
Sexual function			X	X		X								X	X		
Anxiety				X	X		X							X			
Chemotherapy side effects								X	X						X		
Abdominal pain				X		X		X	X					X	X		X
Lymphedema														X			
Sexual worry			X	X										X			
Attitude towards disease											X				X		
Sexual activity				X										X			
Changes in taste	X			X		X									X	X	
Hair loss	X		X	X		X	X	X							X	X	
Drowsiness			X	X	X	X											
Low sleep quality					X												
Concentration dysfunction	X		X	X		X	X	X									
Feeling bloated				X		X	X	X							X		
GI symptoms				X											X	X	
Lack of energy				X		X		X			X			X			
Numbness				X	X	X	X	X								X	
Sexual enjoyment														X			
Sore mouth	X			X	X	X	X	X									
Urine frequency	X			X		X							X	X	X		
Feeling sad				X		X	X										
Burning urination				X							X			X			X
Urinary problems			X	X		X								X		X	
Itching	X			X							X				X		
Legs/feet swollen				X		X		X						X			X
Weight loss			X	X		X									X		
Leakage of urine	X							X						X			X
Changes in fingers/nails	X			X	X			X									
Irritation				X		X								X			
Dysphagia				X			X	X									
Sweat				X											X		X
Paresthesia			X	X	E	X											
Dizziness			X	X													
Dry mouth				X		X											
Worry				X		X											
Vagina discharge/odor										X				X			
Painful sexual intercourse							X			X				X			X
Good appetite				X						X	X						
Distress				X													

TABLE 3 (*Continued*)

Symptom	Instrument																
	QLQ-C30	FLIC	SRQ	MSAS	ESAS	MDASI	PRO-CTCAE	MOST	SPHERE	FACT-CX	FACT-V	SCL-90	PFDI-20	QLQ-CX24	QLQ-OV28	QLQ-EN	CMUOV-QOL
Interest in sex										X					X		
Vagina shortness										X	X						x
Vagina bleeding										X				X			
Incomplete urine emptying													X	X			
Bodily pains				X		X										X	
Vagina discharge/odor										X				X			
Hot flashes				X										X	X		X
Heartburns	X														X		
Mood swings			X						X								
Weight gain			X	X		X											
Cough				X		X											
Loss of sensation	X			X													
Headache	X		X														
Being sensitive				X		X						X					
Indigestion				X		X		X									
Pelvic pain																X	X
Urge urinary incontinence													X	X			
Feel ill				X										X			
Vagina dryness															X		X
No interest in sex							X										
Can eat food I like															X		
Tiredness					X									X			
Fever				X		X											
Feeling less feminine															X		
Blurred vision	X																
Loss of power	X																
Vagina swollen																	X
Incomplete emptying of stool													X	X			
Painful defecation													X				
Spent time in bed										X							
Fertility concerns										X							
Like body appearance										X							
Psychosis												X					
Paranoid												X					
Fear												X					
Hostility												X					
Stress urinary incontinence														X			
TOTAL	23	3	21	47	14	32	10	17	12	12	5	5	7	28	21	7	11

Abbreviations: CMUOV-QOL, Chiang Mai University Ovarian Cancer Quality of Life; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-CX24, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervix 24; EORTC-QLQ-EN, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial cancer; EORTC-QLQ-OV28, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian cancer 28; ESAS, Edmonton Symptom Assessment System; FACT-CX, Functional Assessment of Cancer Therapy-Cervix; FACT-V, Functional Assessment of Cancer Therapy-Vulva; FLIC, Functional Living Index-Cancer; MDASI, M. D. Anderson Symptom Inventory; MOST, Measure of Ovarian Symptoms and Treatment concerns; MSAS, Memorial Symptom Assessment Scale; PFDI-20, Pelvic Floor Distress Inventory-Short Form; PRO-CTCAE, Patient Reported Outcomes-Common Terminology for Criteria Adverse Events; SPHERE, Somatic and Psychological Health Report; SCL-90, Symptom Check List 90; SRQ, Symptom Representation Questionnaire.

TABLE 4
Number of Studies That Used the 17 Instruments That Assessed Three or More Symptoms in Patients With Gynecologic Cancers.

Author (Year)	QLQ-C30	FLIC	SRQ	MSAS	ESAS	MDASI	PRO-CTCAE	MOST	SPHERE	FACT-CX	FACT-V	SCL-90	PFDI-20	QLQ-CX24	QLQ-OV28	QLQ-EN	CMUOV-QOL
Afiyanti et al (2019)	X													X			
Afiyanti et al (2020)	X																
Akkuzu et al (2012)	X																
Akkuzu et al (2014)		X															
Bjelic-Radisic et al (2012)	X													X			
de Arruda et al (2019)	X																
Donovan et al (2016)			X														
Friedlander et al (2014)	X														X		
Hwang et al (2016)				X		X											
Kim et al (2018)				X													
Li et al (2013)	X													X			
Mikkelsen et al (2017)	X													X			
Nazik et al (2012)					X												
Perkowska et al, (2019)	X														X		
Pozzar et al (2021)			X														
Robinson et al (2012)	X																
Różycka et al (2021)	X														X		
Sailors et al (2013)						X											
Sawant et al (2012)	X													X			
Sivapornpan et al (2020)	X																
Stavraka et al (2012)	X														X		
Techata et al (2022)	X																X
Wang et al (2017)						X											
Wang S et al (2021)													X				
Webber et al (2019)									X								
Wu et al (2017)	X																
Aishanjiang et al (2021)	X																
Brotto et al (2016)	X														X		
Brundage et al (2016)	X														X		
Chase et al (2015)												X					
de Arruda et al (2020)	X													X			
De-Boer et al (2016)	X													X	X		
Donovan, et al (2022)			X														
Greimel et al (2013)	X																
Kim et al (2022)	X					X									X		
Koole et al (2021)	X													X			
Krasner et al (2012)	X														X		
Lanceley et al (2017)	X														X		
Li et al (2020)													X				
Lindemann et al (2017)	X														X		
Madariaga et al (2022)							X										
Oaknin et al (2022)	X																
Paşalak et al (2022)	X				X												
Piccirillo et al (2018)	X														X		
Shalom-Sharabi et al (2017)	X				X												
Shanmugam et al (2019)	X													X			
Sharma et al (2021)	X														X		
Stockler et al (2014)	X														X		
Taylor et al (2015)						X											
Tsao et al (2019)						X											
Wenzel et al (2015)												X					
Zhou et al (2020)	X																

TABLE 4 (*Continued*)

Author (Year)	QLQ-C30	FLIC	SRQ	MSAS	ESAS	MDASI	PRO-CTCAE	MOST	SPHERE	FACT-CX	FACT-V	SCL-90	PFDI-20	QLQ-CX24	QLQ-OV28	QLQ-EN	CMUOV-QOL
Alimena et al (2022)	X																
Beesley et al (2022)								X									
Ben-Arye et al (2015)					X												
Campbell et al (2022a)	X							X							X		
Chase et al (2022)	X														X		
Conway et al (2020)					X												
Dahiya et al (2016)	X														X		
Dan et al (2022)						X									X		
Domenici et al (2016)															X		
Dybeck et al (2022)	X																
Ferrandina et al (2014)	X													X			
Fokdal et al (2018)	X													X			
Forsse et al (2022)	X															X	
Haryani et al (2022)				X													
Huang et al (2016)				X													
King et al (2018)	X							X							X		
Kirchheiner et al 2015)	X													X			
Kirchheiner et al (2016)	X													X			
Lee et al (2022)	X							X							X		
Likhacheva et al (2013)					X												
Liu et al (2019)	X													X			
Meraner et al (2012)	X														X		
Mizrahi et al (2015)									X								
Mustea et al (2013)	X																
Pak et al (2021)	X																
Pellegrino et al (2016)											X						
Pozzar et al (2022)				X													
Richter et al (2012)	X														X		
Roncolato et al (2017)	X														X		
Roncolato et al (2018)	X														X		
Roncolato et al (2020)	X														X		
Seppenwoolde et al (2021)	X													X			
Seppenwoolde et al (2021)	X														X		
Vistad et al (2018)				X													
Vittrup et al (2021)	X													X			
Webster et al (2018)							X										
Wen et al (2017)	X														X		
TOTAL	59	1	2	7	6	7	2	4	2	2	1	1	1	16	28	1	1

Abbreviations: CMUOV-QOL, Chiang Mai University Ovarian Cancer Quality of Life; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-CX24, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervix 24; EORTC-QLQ-EN, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Endometrial cancer; EORTC-QLQ-OV28, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian cancer 28; ESAS, Edmonton Symptom Assessment System; FACT-CX, Functional Assessment of Cancer Therapy-Cervix; FACT-V, Functional Assessment of Cancer Therapy-Vulva; FLIC, Functional Living Index-Cancer; MDASI, MD Anderson Symptom Inventory; MOST, Measure of Ovarian Symptoms and Treatment concerns; MSAS, Memorial Symptom Assessment Scale; PFDI-20, Pelvic Floor Distress Inventory-Short Form; PRO-CTCAE, Patient Reported Outcomes-Common Terminology for Criteria Adverse Events; SPHERE, Somatic and Psychological Health Report; SCL-90, Symptom Check List 90; SRQ, Symptom Representation Questionnaire.

TABLE 5

Most Common Instruments Used to Assess Patient-Reported Outcomes in Patients With Gynecologic Cancers.

Author (Year)	QLQ-C30	FACT-G	FACT-O	FACT-B	EQ-5D	MGQOL	MOS-SF	HSQ	GFI	CD-RISC	GSS	LI	KI	IPAQ-SF	FSFI	HHS	Daily rating	MYCAW
Afiyanti et al (2019)	X																	
Afiyanti et al (2020)	X																	
Akkuzu et al (2012)	X																	
Bjelic-Radisic et al (2012)	X																	
Cheong et al (2019)												X						
de Arruda et al (2019)	X								X									
Hwang et al (2016)			X															
Kim et al (2018)		X																
Li et al (2013)	X																	
Mikkelsen et al (2017	X										X							
Nho et al (2017)		X																
Pang et al (2022)										X								
Perkowska et al (2019)	X																	
Różycka et al (2021)	X																	
Sailors et al (2013)						X						X						
Sawant et al (2012)	X																	
Techata et al (2022)	X																	
Wang et al (2017)			X									X						
Wang S et al (2021)					X													
Webber et al (2019)		X																
Wu et al (2017)	X																	
Brotto et al (2016)	X																	
Brundage, et al (2016)	X																	
de Arruda et al (2020)	X																	
De-Boer et al (2016)	X																	
Donovan, et al (2022)		X																
Greimel et al (2013)	X																	
Kim et al (2022)	X																	
Koole et al (2021)	X																	
Krasner et al (2012)	X				X													
Li et al (2020)							X											
Lindemann et al (2017)	X																	
Paşalak et al (2022)	X																	
Piccirillo et al (2018)	X																	
Shalom et al (2017)	X																	X
Shanmugam et al (2019)	X																	
Sharma et al (2021)	X																	
Spencer et al (2020)								X										
Stockler et al (2014)	X																	
Teskereci et al (2022)																X		
Wang et al (2022)				X														
Zhou et al (2020)	X																	
Alimena et al (2022)	X											X						
Beesley et al (2020)		X																
Ben-Arye et al (2015)																		X
Campbell et al (2022b)																	X	
Dahiya et al (2016)	X																	
Domenici et al (2016)	X																	
Ferracini et al (2021)			X															
Forsse et al (2022)	X																	
Kirchheiner et al 2015	X																	
Kirchheiner et al (2016)	X																	

TABLE 5 (Continued)

Author (Year)	Instrument																	
	QLQ-C30	FACT-G	FACT-O	FACT-B	EQ-5D	MGQOL	MOS-SF	HSQ	GFI	CD-RISC	GSS	LI	KI	IPAQ-SF	FSFI	HHS	Daily rating	MYCAW
Liu et al (2019)	X																	
Meraner et al (2012)	X																	
Mizrahi et al (2015)			X				X											
Mustea et al (2013)	X																	
Omichi et al (2017)		X																
Oswald et al (2022)														X				
Pak et al (2021)	X														X			
Richter et al (2012)	X																	
Roncolato et al (2018)	X																	
Ross et al (2020)		X																
Shao et al (2017)	X	X																
Sjoquist et al (2013)	X																	
Wen et al (2017)	X																	
TOTAL	42	5	4	1	2	1	2	1	1	1	3	1	1	1	1	1	1	2

Abbreviations: CD-RISC, Connor-Davidson Resilience Scale, EQ-5D, European Quality of Life -5 Dimensions, FACT-B, Functional Assessment of Cancer Therapy -Breast cancer, FACT-G, FACT-General, FACT-O, FACT-Ovarian cancer, FSFI, Female Sexual Function Index, GFI, Groningen Frailty Indicator, GSS, Generalized Self-Efficacy Scale, HHS, High Hope Scale, HSQ, Humor Styles Questionnaire, IPAQ-SF, International Physical Activity Questionnaire-Short Form, KI, Katz Index, LI, Life Interference, MGQOL, Measure of Global Quality of Life questionnaire, MOS-SF, Medical Outcome Survey -Short Form, MYCAW, Measure Yourself Concerns and Wellbeing questionnaire, QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

conditions, and 77 studies did not report the patients' employment status.

Discussion

This systematic review is the first comprehensive evaluation of research on co-occurring symptoms in patients with gynecologic cancers. Guided by six questions, the goals of this review were to provide a detailed picture of the most common symptoms reported by these patients and to identify gaps in knowledge that could be used to guide future research. While the goals of this review were to evaluate common co-occurring symptoms and associated risk factors and PROs in patients with gynecologic cancer, the included studies did not provide sufficient evidence to achieve these objectives. Therefore, findings are reported on common symptoms in these patients and on a limited number of risk factors and PROs. This discussion focuses on the major findings and limitations associated with the extant literature and provides recommendations for future research on symptoms in patients with gynecologic cancers.

Study Characteristics

The majority of the studies were conducted in Asia, North America, Europe, or multiple locations. While this distribution of locations is extensive, limited information is available on the symptom burden of patients with gynecologic cancers from Africa, South America, and Australia. Given the increasing worldwide prevalence of gynecologic cancers[1,3] as well as disparities in the stages of disease at the time of diagnosis,[132-134] additional research is warranted across geographic regions to obtain a more comprehensive and culturally appropriate picture of the symptom burden of these patients.

Consistent with previous reviews,[15,17] across the studies in this review, the grand mean age of the women was 56.17 years. While exact ranges do not exist, women between the ages of 45 and 60 are in a menopausal transition period.[135,136] During this transition, women experience a variety of symptoms (eg, sleep disturbances, hot flashes, sexual worries, mood swings) that are common to women undergoing treatment for gynecologic cancers.[19,61,71,75,82,87,95,114,115] One of the limitations of the studies included in this review is that only 7.6% of them obtained information on patients' menopausal status at enrollment. In addition, none of the studies evaluated for differences in symptom burden based on patients' menopausal status. Future studies need to assess patients' menopausal status, determine the effects of cancer treatment on menopausal status, and assess for differences in symptom burden based on patients' pretreatment menopausal status.

Consistent with the current provision of cancer care,[137] 92% of the included studies were conducted in the outpatient setting. In addition, consistent with international prevalence rates,[1,2] ovarian (48%) and cervical (23%) cancers were the most common cancers evaluated across the 118 studies. In 22% of the studies, the samples consisted of patients with heterogeneous types of gynecologic cancer. None of the studies evaluated for differences in symptom burden between or among patients with different types of gynecologic cancer.

Timing of the symptom assessments is important because it provides information on the occurrence and severity of symptoms across the continuum of cancer treatment. Across the studies in this review, 47.5% provided specifics on the relationship between the symptom assessment(s) and the administration of chemotherapy. The majority of the studies (62.7%) enrolled patients prior to the initiation of chemotherapy.

Common Symptoms and Prevalence Rates

Across the 118 studies, while a total of 96 symptoms were evaluated, only 41 were assessed in 7 or more studies (Table 2). The

symptoms that occurred with grand mean prevalence rates of 50% or greater in 7 or more studies included lack of energy, fatigue, abdominal pain, depression, anxiety, concentration dysfunction, drowsiness, and paresthesia. The grand mean prevalence for fatigue of 62.1% is slightly higher than the rates of 45% to 53% reported by patients with other types of cancer.[138] While within the range of 47% to 61% reported by patients with gastrointestinal cancer,[139] the relatively high prevalence rate for abdominal pain (53.3%) can be partially explained by the proximity of the female reproductive organs to the gastrointestinal tract, the occurrence of abdominal ascites,[140] and/or the adverse effects from the chemotherapy.[141]

In terms of psychological symptoms, the prevalence rate for depression (52.6%) was somewhat higher than the rates of 17% to 45% reported in a systematic review.[142] In contrast, the prevalence rate of 50.3% for anxiety is significantly higher than the 16.6% to 41.9% reported in previous reviews.[143-145] These findings suggest that a large number of patients with gynecologic cancer require evaluation of psychological distress.

The remaining three highly prevalent symptoms were concentration dysfunction (52.0%), drowsiness (51.9%), and paresthesia (50.5%). Given that chemotherapy-induced cognitive impairment occurs in up to 50% of patients receiving chemotherapy,[146-148] our findings are congruent with the rates reported in patients with heterogenous types of cancer.

While less well studied, drowsiness may be associated with the administration of antiemetics[149,150] and/or sleep disturbance following the administration of chemotherapy.[151] While the prevalence rates for chemotherapy-induced peripheral neuropathy range from 30% to 60%,[152] the prevalence of paresthesia across the various studies in this review is at the higher end of this range. This finding is most likely attributable to the platinum and taxane regimens used to treat various types of gynecologic cancers.[153]

It should be noted that the prevalence rates of some of the symptoms listed in Table 2 need to be interpreted with caution because they were assessed in only a limited number of studies. Additional research is warranted that uses a comprehensive list of the common and gynecologic cancer−specific symptoms to determine the prevalence rates for these symptoms.

Common Dimensions of the Symptoms Experience

While an assessment of multiple dimensions of the symptom experience (ie, occurrence, severity, frequency, and distress) is recommended,[154-156] only 28 studies (24%) assessed two or more dimensions of the symptom experience. Most of the studies (82%) assessed symptom severity, 38% assessed occurrence, and 6% assessed distress. These findings are most likely attributable to the fact that most of the instruments evaluated a single dimension of the symptom experience.

Common Instruments Used to Evaluate Multiple Symptoms

A large amount of variability existed in the instruments that were used to assess symptoms in the studies included in this review. While the majority of the instruments have well established validity and reliability, the choice of one or more instruments was made primarily based on the purpose of the study and/or the type(s) of gynecologic cancer that were being evaluated.

Across 89 studies, 17 instruments were used that assessed between 3 and 47 symptoms (Table 3). As shown in Table 4, the EORTC-QLQ-C30, which was used in 66.3% of the studies, was the most common instrument. While the EORTC-QLQ-C30 is a simple and widely used measure of symptoms and QOL in oncology patients, it evaluates only 10 symptoms. As noted in Table 4, in order to assess symptoms specific to patients with ovarian and cervical cancers, the EORTC-QLQ -OV28 (ie, used in 31.5%) and EORTC-QLQ-CX24 (ie, used

in 18.0%), respectively, were added to the study measures. One limitation of all three measures is the lack of assessment of symptom distress.

Seven studies used either the MDASI (7.9%) or the MSAS (7.9%) and six studies used the ESAS (6.7%). However, the MDASI (13 symptoms), MSAS (32 symptoms), and ESAS (9 symptoms) differ in the number of symptoms assessed. In addition, only the MDASI and the MSAS evaluate two or more dimensions of the symptom experience. However, the MSAS is the only measure that allows for an evaluation of occurrence, frequency, severity, and distress.[157]

As shown in Table 3, an equally important consideration in the determination of the most common, severe, and distressing symptoms in patients with gynecologic cancers is the lack of uniformity in the number of symptoms assessed on various instruments; the lack of consistency in the specific words used for a symptom (eg, fatigue versus lack of energy); numerous modifications to existing instruments; and the lack of both common and disease-specific symptoms on a single instrument. For example, in one study that used the 22-item Functional Living Index Cancer,[158] only three symptoms were assessed. In other studies,[4,8,128] the 32-item MSAS[159] was modified to include between 38 and 47 symptoms. It should be noted that four studies in this review[71-73,87] assessed only a single symptom (eg, depression, anxiety).

Risk Factors for a Higher Symptom Burden

Only a limited number of risk factors associated with a higher symptom burden were evaluated in a relatively small number of studies. The most common risk factors were age, employment status, comorbidity burden, stage of disease, and treatment status. Consistent with the extant literature, in the 16 studies that evaluated for associations between age and symptom burden in patients with gynecologic cancer, findings were inconsistent. For example, as noted in previous reports of cancer patients,[160,161] older age was associated with increased symptom occurrence and distress.[43,75,76,94,119] In contrast, and consistent with other studies of oncology patients,[162-164] in six of the studies in this review,[8,22,87,103,105,125] younger age was associated with higher symptom severity scores. Reasons for these inconsistent findings may be related to differences in patients' cancer diagnoses, the instruments used to assess the symptoms, and/or the timing of the assessments.[162] In addition, older patients may experience a response shift in their evaluation of symptoms as part of the aging process.[165]

Consistent with previous studies,[166,167] in six (12%) of the studies in this review,[22,63,64,76,111,112] being unemployed and/or having a lower household income was associated with higher symptom occurrence and severity. Reasons for these associations may include inadequate resources to manage symptoms as well as living in environments with increased levels of stress.[168]

As noted in one review,[169] a higher comorbidity burden is associated with more severe symptoms. In the four studies in this review that assessed specific comorbidities (ie, depression, anxiety, obesity),[5,8,83,128] each of these conditions was associated with higher symptom severity. Treatments for various comorbidities and common biological mechanisms (eg, inflammation)[170] may explain this positive association. It should be noted that none of the studies in this review evaluated for associations between symptom burden and comorbidities using a valid and reliable measure (eg, Self-Administered Comorbidity Question,[171] Charlson Comorbidity Index[172]).

Being on active treatment was the most common risk factor that was evaluated for its association with a higher symptom burden in 15 studies.[19,52,56,60,61,67,75,76,90,94,96,125,126,129,130] Consistent with previous reviews of oncology patients,[161,173] this risk factor was associated with higher symptom occurrence and severity. In addition, as noted previously,[174] in three studies,[88,90,111] the receipt of radiation with chemotherapy was a risk factor for increased symptom distress.

TABLE 6
Recommendations for Future Research On Symptoms In Patients With Gynecologic Cancers.

Topic	Recommendations
Symptom burden	• Conduct research on symptom burden in patients with gynecologic cancers across additional geographic regions, particularly in Africa, South America, and Australia • Evaluate for differences in symptom burden between or among patients with different types of gynecologic cancers • Evaluate for differences in symptom burden associated with various types of cancer treatments and across the continuum of cancer care
Symptom prevalence	• Determine prevalence rates for the most common symptoms associated with cancer and its treatments (eg, depression, pain, sleep disturbance) • Determine the prevalence rates for specific symptoms associated with each type of gynecologic cancer • Evaluate how the prevalence of the most common cancer-related symptoms and gynecologic cancer-specific symptoms change over time • Compare the prevalence rates for symptoms across different types of gynecologic cancer across the continuum of cancer care • Determine the mean number of co-occurring symptoms in patients with various types of gynecologic cancer across the continuum of cancer care
Symptom dimensions	• Assess for differences in symptom severity and distress for the most common symptoms associated with cancer and its treatments • Determine the severity and distress ratings for specific symptoms associated with each type of gynecologic cancer • Evaluate how the severity and distress of the most common cancer-related symptoms and gynecologic cancer-specific symptoms change over time • Compare the severity and distress ratings for symptoms across different types of gynecologic cancer across the continuum of cancer care
Symptom measures	• Develop a single instrument to assess multiple co-occurring symptoms (ie, an instrument that includes common symptoms associated with cancer and its treatments and gynecologic cancer-specific symptoms, as well as multiple dimensions of the symptom experience) • Evaluate an electronic version of the measure listed above that can collect symptom data over the continuum of cancer care • Determine clinically meaningful cutpoints for multiple co-occurring symptoms in patients with various types of gynecologic cancers
Risk factors associated with a higher symptom burden	• Develop a comprehensive list of demographic, clinical, and behavioral risk factors • Examine the relationships between demographic, clinical, and behavioral risk factors and symptom burden • Determine if different risk factors are associated with a higher symptom burden in patients with different types of gynecologic cancers • Determine if different risk factors are associated with a higher symptom burden across the continuum of cancer care
Impact of symptoms on patient reported outcomes	• Determine the most valid and reliable patient-reported outcomes to use to assess the impact of symptom • Assess the impact of changes in patient's symptom burden on patient-reported outcomes across the continuum of cancer care

In terms of stage of disease, consistent with a previous review of colon cancer patients,[161] across six studies in this review,[64,91,105,109,111,119] patients with an advanced stage of gynecologic cancer reported higher ratings of symptom occurrence, severity, and/or distress. Given that the FIGO staging system is used across all types of gynecologic cancers,[175-177] of the 81 studies that reported stage of disease, 85% evaluated patients with stages III to IV. Given this limitation, comparisons need to be done of patients' symptom burden within and across different types of gynecologic cancers and stages of the disease.

In four studies included in this review,[22,40,112,125] and consistent with previous reports of patients receiving chemotherapy,[178,179] a lower functional status was associated with higher symptom severity. However, only 38% of the included studies assessed the functional status of the patients at enrollment. In the seven studies that used the KPS scale, the grand mean score was 74.4.[4,8,10,59,68,86,125] In the 32 studies that used the ECOG scale, the grand mean prevalence score of ≤2 was 90.7%. In the four studies that used the WHO functional status scale,[6,25,26,41] the grand mean prevalence rate for a score of ≤2 was 87.7%. Given the importance of functional status to oncology patients[180] and its association with a higher symptom burden, a significant limitation across the 118 studies is that only 8.5% evaluated for this association.

Given the paucity of studies and the limited number of risk factors evaluated, this review identified a significant gap in knowledge regarding risk factors associated with a higher symptom burden. In addition, none of these studies examined relationships between a comprehensive list of demographic and clinical risk factors and various dimensions of the symptom experience of patients with gynecologic cancers.

Common Outcomes Across the Studies

Across the 118 studies, only three outcomes (ie, daily life interference, functional status, QOL) were evaluated in 64 studies. As noted in Table 5, of the 59 studies that evaluated QOL, the most common measures used were EORT-QLQ-C30 (n = 42), Functional Assessment of Cancer Therapy-General (n = 5), and Functional Assessment of Cancer Therapy-Ovarian Cancer (n = 4). Equally important, only one study[96] conducted a correlational analysis between symptoms and functional status. In this study,[96] higher severity scores for paresthesia, fatigue, and pain were associated with lower levels of functional independence. Finally, consistent with previous reviews of patients receiving chemotherapy[181] or chemoradiation,[182] in a single study,[11] a higher symptom burden was associated with poorer QOL. Given the paucity of research on associations between symptom burden and

QOL outcomes in patients with gynecologic cancers, additional research is warranted on this important topic.

Summary of the Limitations of the Studies Included in This Review

Of 118 studies, only 38% reported symptom prevalence rates. In addition, in 13 studies, composite rather than individual symptom scores were reported so occurrence rates for these studies could not be included in the grand mean calculations. Given the unidimensional nature of the instruments, 76% of the studies assessed only a single dimension of the symptom experience. Equally important, 52.5% of the studies did not provide the exact timing of the symptom assessments.

Given the heterogeneity in the number of symptom assessment instruments, the number of symptoms on each instrument, and the lack of consistency in symptom terminology across instruments, true prevalence rates for common cancer symptoms (eg, depression, pain) and gynecologic cancer−specific symptoms cannot be determined. Equally important, given the limited number of studies that evaluated associations between a limited number of risk factors and symptom burden, knowledge to guide clinicians in the identification of high-risk patients is extremely limited. Finally, the lack of evaluation of the relationships between symptom burden and PROs represents a large gap in the extant literature.

Limitations of This Systematic Review

Several limitations warrant consideration. First, this review may have potential publication bias because the gray literature was excluded. However, the gray literature may have methodologic drawbacks and lack peer review. Second, this review was limited to articles written in English. And third, its findings may not generalize to palliative care patients.

Conclusion

Despite these limitations, this review identified significant methodologic challenges in the field, as well as gaps in knowledge that can be used to guide future research on co-occurring symptoms and their impact on patients with gynecologic cancers (Table 6). In terms of methodologic challenges, in order to determine the most prevalent, severe, and distressing symptoms in patients with gynecologic cancer, a comprehensive symptom inventory needs to be developed that includes common symptoms associated with cancer and its treatments, as well as specific symptoms for each type of gynecologic cancer. This instrument should allow for the assessment of various dimensions of the symptom experience. Ideally, this instrument could be administered on an adaptive online platform to facilitate data collection and decrease symptom burden. In addition, a comprehensive list of risk factors needs to be developed that can be used to identify patients who are at the highest risk for multiple co-occurring symptoms associated with gynecologic cancer.

In terms of research, several areas for consideration are summarized in Table 6. Based on the significant gaps in knowledge identified in this review, it is not possible to determine the salient risk factors associated with multiple co-occurring symptoms in patients with gynecologic cancer. For example, none of the studies in this review totaled the number of symptoms experienced by these patients and examine associations with either salient risk factors or PROs. Given that a huge disparity exists in the funding of studies of patients with gynecologic cancers compared to other types of cancer,[183] the findings from this review and related recommendations can be used to guide future research on multiple co-occurring symptoms in patients with gynecologic cancers, their associated risk factors, and their impact on PROs. Once this information is obtained additional research is warranted on underlying mechanisms and targeted interventions to decrease symptom burden in this highly vulnerable group of patients.

Authorship Contributions

David Ayangba Asakitogum was responsible for conceptualization, data curation, analysis of data, writing original draft of the manuscript, review and editing of the manuscript, visualization, and final approval of the manuscript. Jerry John Nutor was responsible for conceptualization, review and editing of the manuscript, and final approval of the manuscript. Rachel Pozzar was responsible for conceptualization, editing of the manuscript, and final approval of the manuscript. Marilyn Hammer was responsible for conceptualization, editing of the manuscript, and final approval of the manuscript. Christine Miaskowski was responsible for conceptualization, data curation, formal analysis, review and editing of the manuscript, visualization, supervision, and final approval of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.soncn.2023.151572.

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