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REVIEW

Associations of frailty with symptoms, and HRQOL in older cancer survivors after cancer treatments: a systematic review and meta-analyses

Claire J. Han[1,2] · Ashley E. Rosko[3] · Daniel J. Spakowicz[4] · Marilyn J. Hammer[5] · Diane Von Ah[1,2]

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Abstract

Purpose Frailty in older adult cancer survivors after cancer treatments is associated with various health outcomes. However, there is less agreement on how frailty affects symptoms and health-related quality of life (HRQOL). This systematic review and meta-analysis aimed to evaluate the current literature on frailty, symptoms, and HRQOL, as well as the associations of frailty with these factors in older adult cancer survivors with chemotherapy.

Methods A review was conducted on peer-reviewed publications from 2008 to 2023, using seven electronic databases. Meta-analyses were performed using random effects models to determine pooled effect estimates for frailty prevalence, symptom severity, and HRQOL scores.

Results A total of 26 studies involving older cancer survivors were included in the analysis. Most of these studies were conducted in Western countries and focused on White survivors, particularly those with breast cancer. The mean pooled prevalence of frailty was 43.5%. Among frail survivors, the most common symptoms reported after cancer treatments were pain (36.4%), neuropathy (34.1%), and fatigue (21.3%). Frailty was associated with higher pooled mean symptom severity ($B = 1.23$, $p = 0.046$) and lower functional HRQOL ($B = -0.31$, $p = 0.051$, with marginal significance) after cancer treatments.

Conclusion Frail older cancer survivors are at high risk of adverse symptoms and poor HRQOL after cancer treatment. Further research on screening for frailty is needed to prevent older adults from developing worse symptoms burden and maintain HRQOL. It is also essential to understand the mechanisms of the associations between frailty, symptoms and HRQOL in this population.

Keywords Frailty · Geriatric oncology · Symptoms · Quality of life · Older adults

✉ Claire J. Han
Han.1985@osu.edu

Ashley E. Rosko
ashley.rosko@osumc.edu

Daniel J. Spakowicz
Daniel.Spakowicz@osumc.edu

Marilyn J. Hammer
marilynj_hammer@dfci.harvard.edu

Diane Von Ah
vonah.1@osu.edu

[1] Center for Healthy Aging, Self-Management and Complex Care, College of Nursing Columbus, The Ohio State University, Office 377, Newton Hall, 1585 Neil Avenue, Columbus, OH 43210, USA

[2] Cancer Survivorship and Control Survivorship, Ohio State University-James: Cancer Treatment and Research Center, Columbus, OH, USA

[3] Division of Hematology, The Ohio State University-James: Cancer Treatment and Research Center, Columbus, OH, USA

[4] Division of Medical Oncology, Pelotonia Institute for Immuno-Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

[5] Dana-Farber Cancer Institute, and Member of the Faculty, Medical Oncology Harvard Medical School, Boston, MA, USA

Plain English Summary

Older adult cancer survivors often suffer from negative symptoms such as pain, neuropathy, fatigue, and an impaired health-related quality of life (HRQOL) post-treatment. However, it is still not fully understood if a frailer state is related to these experiences and HRQOL. Our review of 26 pertinent articles revealed a negative impact of frailty on these factors in older cancer survivors after cancer treatments. Further research is required for effective frailty screening and management in older adults to improve symptom control and HRQOL

Introduction

The global population of people aged 80 years or older is expected to triple by 2050, from 143 million in 2019 to 426 million by 2050, due to population aging and growth [1]. Cancer disproportionately affects older people, with an estimated more than 33% of cancer diagnoses in those over 70 by 2050 [2]. Further, an estimated 6.9 million new cancer cases (21.5% of global cases) are expected to be diagnosed in adults aged 80 or older worldwide [3]. The most commonly diagnosed cancer types among adults aged 80 years or older include lung, gastrointestinal (GI) (colorectal cancer, predominately), female breast, and prostate cancers, accounting for 52.4% of all new cancer cases in this age group [3].

Cancer management is complex for aging adults due to underlying heterogeneity in health. Challenges may include multiple comorbidities, polypharmacy, frailty, and limited life expectancy [4]. Frailty specifically is highly prevalent in aging populations and is defined as a "biologic syndrome of decreased reserve and resistance to stressors, resulting from a decline across multiple physiological systems, leading to vulnerability to adverse outcomes" [5]. Frailty, however, is not synonymous with disability. Instead, frailty is defined as a decline in one of three dimensions: physical (i.e., increased vulnerability to physical health conditions, psychologic (i.e., age-related psychological changes involved in the frail brain and mental health problems and interactions with cognitive functions), and social (i.e., decline in social functions, and networks) dimensions [5]. Of note, emerging evidence supports that frailty predicts survival and treatment-related toxicity in older cancer survivors [5, 6]. Specifically, symptom toxicity after cancer treatments is an integral aspect of cancer treatment-related toxicity and HRQOL among cancer survivors [7–9].

A growing number of older cancer survivors are also burdened with long-term physical and psychological symptoms that often last several years after a cancer diagnosis or treatment [10, 11]. These symptoms may cause cancer treatments to be delayed or stopped altogether, especially in older patients who may have a lower tolerance for side effects [12, 13]. These complex symptom burdens resulted in poor HRQOL and hampered optimal treatment options in older cancer survivors [9, 12, 13].

Older cancer patients constitute a significant group of the patient population in oncology and require special consideration of symptom assessment and management and QOL care [14]. Given the lack of optimal cancer treatment guidelines specific to older adults, older cancer survivors are often excluded from clinical trials, which results in a major gap in knowledge as it applies to treatment stratification, treatment dosage, anticipated toxicities, and symptom burden [15, 16]. Despite this, symptom toxicity and HRQOL have been under-investigated in older cancer survivors [9, 12–14]. Several reviews [2, 17, 18] reported the association of frailty with mortality rates and cancer treatment toxicities (e.g., longer hospital stays, hematologic complications, surgical complications, emergency department visits, adverse symptom events assessed by clinicians) in older cancer survivors. However, patient-reported individual cancer symptom toxicity and HRQOL after cancer treatments were not examined in detail in older cancer patients, according to frailty status [2, 17]. Given the lack of guidelines to decide optimal treatment modalities in frail older cancer survivors, a comprehensive understanding of cancer symptom burden and HRQOL in frail older cancer survivors is necessary [19].

Therefore, we conducted a systematic review and meta-analyses to investigate frailty, patient-reported symptoms, and HRQOL and examined the associations of frailty with symptom toxicity and HRQOL after cancer treatments in older cancer survivors. Understanding the symptom experiences (e.g., occurrence, prevalence, severity) and HRQOL after cancer treatments in frail older cancer survivors is important. We anticipate that this information will aid in identifying older adults who are at higher risk of worse symptom toxicity and poorer HRQOL after cancer treatments and the development of targeted approaches for interventions for older cancer survivors with frailty.

Conceptual framework

The conceptual framework for this review is based on an Integral Conceptual Model of Frailty (See Fig. 1 [20]). Figure 1 displays this framework which depicts various factors (e.g., life course determinants) and diseases (e.g., cancer and cancer treatment) that may impact frailty and its sub-dimensions (i.e., physical, psychological, and social frailty). The three sub-dimensions can be characterized by a decline in various factors. A decline in nutrition, mobility, physical activity, strength, endurance, balance, and sensory function

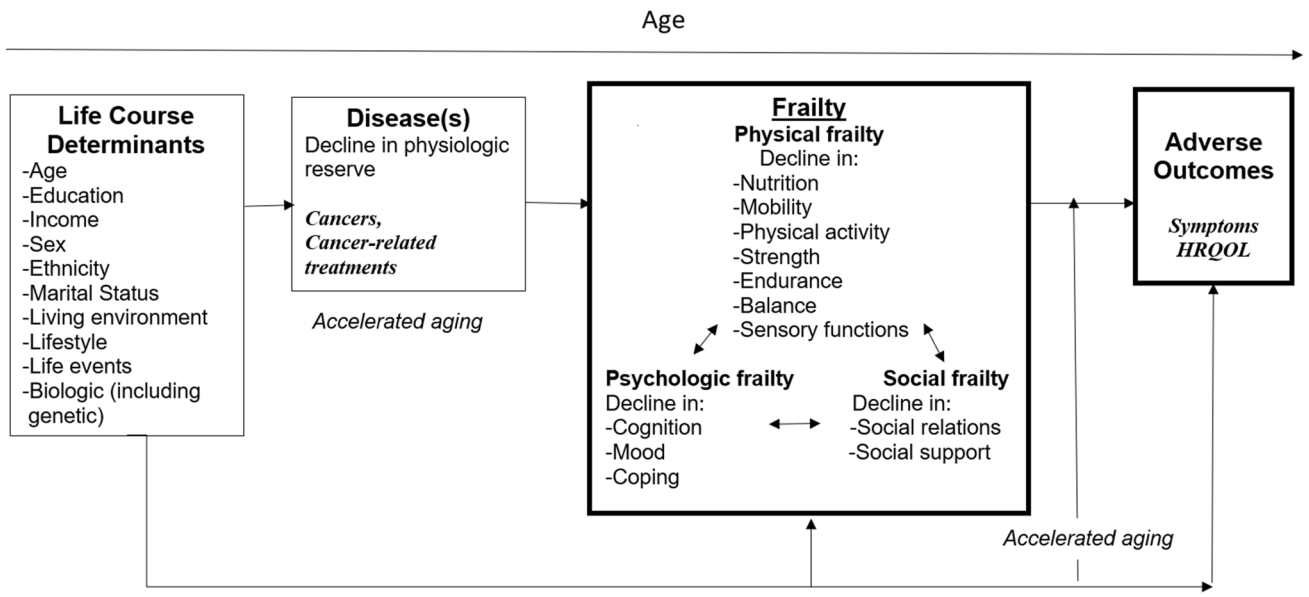

Fig. 1 Conceptual framework. Integral conceptual model of frailty conceptual framework. Note. This conceptual framework guides the current systematic review. We focus on the core of the model including "disease = cancer per se, cancer treatments", "frailty—physical, psychological, and social", and "adverse outcomes of the frailty—symptoms toxicities and HRQOL after cancer treatments." *Reproduced from Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Towards an integral conceptual model of frailty. J Nutr Health Aging. 2010;14(3):175–181. 20

impacts the physical dimension of frailty. A decline in cognition, mood, and coping impacts the psychological dimension of frailty. A decline in social relations and social support impacts the social dimension of frailty. While these three dimensions are separate, it is important to note that they are interconnected, and often a decline in one dimension can have effects on the other two. Declines in any one of the three dimensions of frailty; however, ultimately result in adverse events (i.e., symptoms, and HRQOL). Our review analyzed and synthesized the data by mapping symptom experiences and HRQOL in older cancer survivors to elements of the Integral Conceptual Model of Frailty. In this review and meta-analyses, we focused on the associations of frailty with symptom experience and HRQOL.

Methods

Search strategies and data sources

This review and meta-analyses followed the guideline provided by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) report [21]. A literature search was conducted using seven electronic databases: Scopus, CINAHL, Medline via PubMed, Web of Science, EMBASE, Cochrane Library (Review and CENTRAL), and PsycINFO. Phrase truncation was used to pick up on all forms of the selected words. A research librarian was consulted to assist with identifying and refining research terms. Using MeSH terms and manual searches, the keywords examined were: "quality of life" OR "health-related quality of life"; AND "cancer" OR "carcinoma" OR "malignant" OR "neoplasm"; AND "frailty" OR "frail*" OR "frail elderly"; AND "older" or "old"; AND "cancer care, oncology, treatment, management, breast, prostate, colorectal, cervical, thyroid, brain, lung, lymphoma, stomach, liver; GI"; AND "patients" OR "survivors"; "symptom*" OR "toxicity" OR "bowel," OR "GI," OR "psychological distress," OR "fatigue," OR "pain," OR "peripheral," OR "sleep"; AND "chemotherapy* OR "surgery" OR "radiation" OR "hormone therapy" or "immune checkpoint inhibitor.*".

Inclusion and exclusion criteria

Studies were included if they met the following criteria: published over the last 15 years between March 2008 and Feb 2023; reported frailty related to physical, psychological, and social dimensions, symptoms, and HRQOL using quantitative measures with validated instruments; available in English; only studies with a mean age of over 60 years old; studies with patients receiving any cancer treatments; symptoms or HRQOL assessed after cancer treatments (including the recovery phase, or long-term follow-up). Studies were excluded if they: presented only qualitative results; were abstract only; and were review papers or editorials, theory-based works, meta-syntheses, or case studies. Additional

relevant research was identified by reviewing the reference lists of the publications obtained from the initial search. The process of selecting studies followed the PRISMA flow chart (Fig. 2) [21].

Study selections and screening/data extraction, and data synthesis

The articles gathered from eligible studies were evaluated independently by the first author (CH) and a graduate research assistant (JH). Articles to include were agreed upon by CH and JH. Discrepancies were resolved through discussion. Then, a database of extracted data was developed using Microsoft Excel with the following headings: authors and publication year, country of origin, samples and settings, cancer characteristics, timepoints to assess primary outcomes, measures, main findings of frailty, symptoms, and HRQOL, and risk factors relevant to severe symptoms and poor HRQOL. CH extracted the data, which was then verified for accuracy by JH.

Methodological quality appraisal

To evaluate the strength of conclusions drawn from the evidence, we identified quality appraisal tools to assess the risk of bias, as applicable. Both CH and JH assessed the

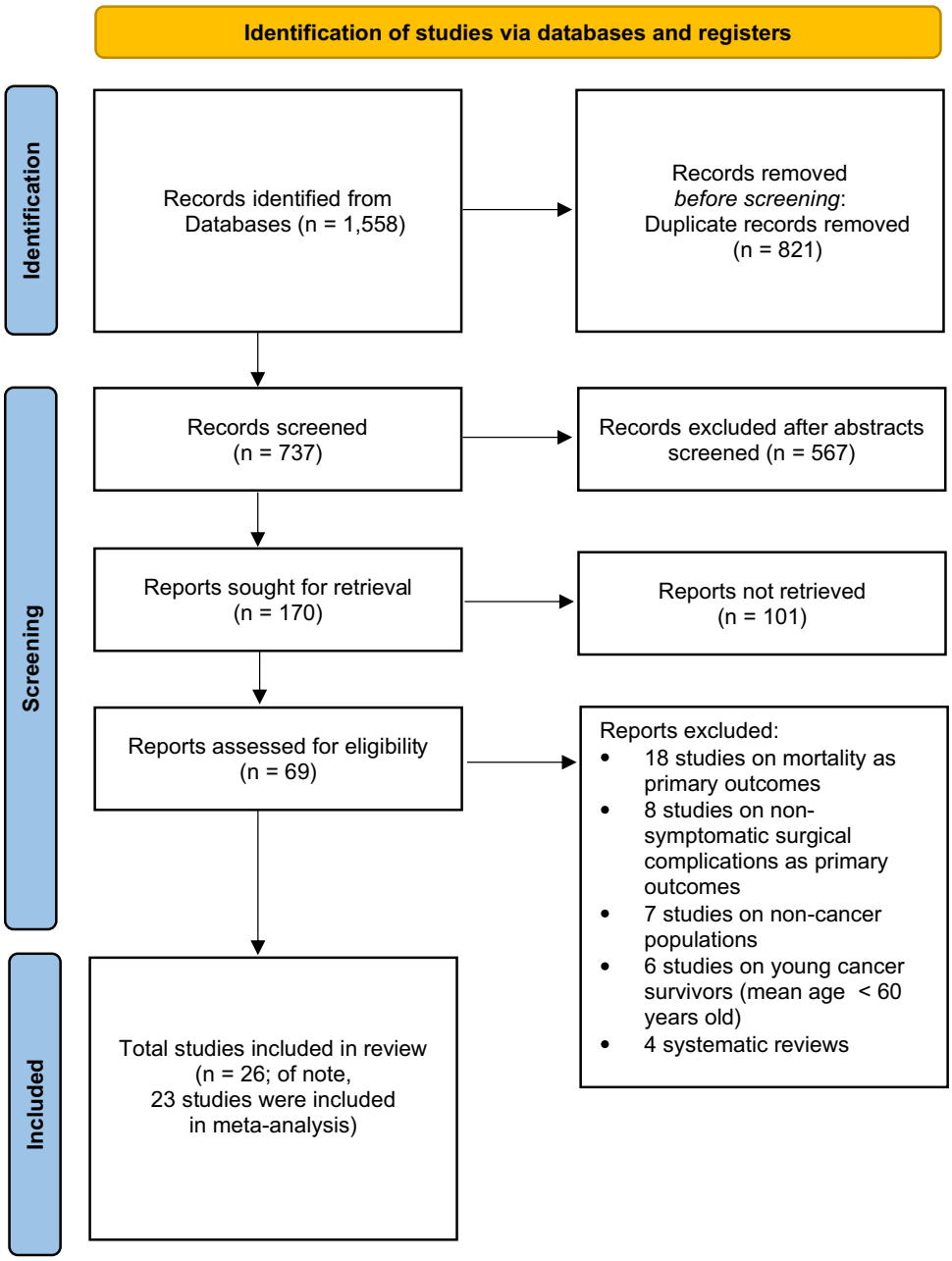

Fig. 2 The PRISMA 2020 Flow diagram

methodological quality of each article independently using the 2022 Critical Appraisal Skills Program (CASP) checklists for quantitative cohort studies and randomized control trials [22]. These checklists consist of 12 questions that evaluate research rigor and the possibility of investigator bias, responding with "Yes," "Can't tell," or "No," to each question [23]. We used a common convention used in critical appraisal of research studies to evaluate an article as "high" quality if it met at least 80% of the checklist criteria (i.e., at least 10 of the 12 questions in each study), "medium" quality if it met more than 50% but less than 80% of the criteria, and "low" quality if it met 50% or less of the criteria [23].

Meta-analytical and statistical methods

Pooled mean estimates of frailty, symptoms, and HRQOL

To increase the statistical power of the findings, data from multiple studies were combined for the meta-analyses. Weighted means and standard errors were used to calculate the pooled mean estimates of frailty prevalence, symptom prevalence, and severity; and HRQOL scores, along with 95% Confidence Intervals (CIs). Only studies that reported numerical ratings of prevalence or severity on a 0–100 scale were included. The pooled estimates were analyzed only if it was present in at least three studies per variable (i.e., frailty, symptoms, HRQOL) [24, 25]. Forest plots were used to display the pooled mean estimates of these variables with 95% CIs.

Publication bias

We assessed funnel plots, Begg's test, and Egger's test for evidence of asymmetry, with $p < 0.05$ considered significant publication bias [26]. The heterogeneity between studies was analyzed using Q statistics and I^2 statistics (I^2 value of < 25.0%: no heterogeneity, > 75%: high or extreme heterogeneity) [27]. A p value of less than 0.10 was considered statistically significant for Q statistics. Random effects models were chosen if data had high heterogeneity, while fixed-effects models were chosen for others.

Meta-regression

A meta-regression was performed to examine the relationships of pooled estimates of frailty prevalence (predictor of interest) with pooled estimates of symptoms (prevalence/severity) and HRQOL scores (outcomes). Country, publication year, study design, sex, sample size, mean age, and cancer types were included as covariates. Unadjusted and adjusted regression models were conducted on frailty. For meta-regression, a two-sided p value of less than 0.05 was considered statistically significant. Meta-analyses, including statistical analyses and forest plots, were performed using MedCalc software version 20.218.

Results

Search results and methodological quality evaluation

The search strategies yielded 737 published articles after excluding duplicates. A review of titles and abstracts reduced the number of relevant studies to 69, and a total of 26 [8, 28–52] were identified for final analysis following the assessment of the full-text articles. Three studies [41, 42, 51] among the 26 selected studies were excluded from the meta-analyses due to the absence of analytic data on frailty (Supplementary Tables 1 and 2). A consort diagram of the literature search is shown in Fig. 2. Results from evaluating each of the 26 quantitative studies using CASP tools are reported in Supplementary Table 3 (the inter-rater agreement between the two authors = 97.4%). No studies were excluded due to low quality.

Study characteristics

Overall study characteristics are shown in Table 1. Ten [8, 29, 33–36, 38, 39, 46, 52] out of the 26 studies had cross-sectional designs, while 16 had longitudinal, prospective designs. Only one study used a mixed-method approach in lung cancer survivors [33]. Three studies included interventions (two randomized control trials—i.e., geriatric assessment-based cancer treatment decision on lung cancer [30] and mixed types of cancer survivors [45]; one feasibility lifestyle intervention for frail patients [51]). In ten cross-sectional studies, symptoms or HRQOL were frequently measured 3 months after cancer treatments [8, 28–30]. The longitudinal studies measured symptoms or HRQOL before and after cancer treatments with various time points ranging from 4 weeks [47] to 7 years [43]. The majority of the studies were conducted in the United States ($n = 9$ [29, 35, 38, 41–46, 52]) or Europe ($n = 10$ [28, 30–32, 34, 36, 40, 49–51]), while 4 studies were conducted in Asian countries ($n = 4$ [8, 33, 37, 39]). Among the 9,606 samples across the 26 studies, the majority of participants were White (92.1%) and female (52.5%). The mean age of participants across studies was 73 years old (range: 59 [51] to 81 [46]). The majority of studies ($n = 10$ [29–31, 35, 36, 40, 45, 46, 49, 50]) were conducted on cancer patients with a mean age range of 75–80 years old. Ten studies[8, 35, 38–40, 45, 46, 48, 49, 51] were conducted for cancer survivors with mixed cancer types, followed by breast ($n = 6$ [29, 36, 42–44, 52]), GI [31, 34, 50], lung [28, 30, 33] ($n = 3$, respectively), head and neck ($n = 2$ [32, 47]), acute myeloid leukemia

Table 1 Characteristics of studies in older adult cancer survivors ($N=26$)

Authors (year)/country	Cancer type/frailty (%)	Samples (*N*)/Sex/Race	Symptoms and/or HRQOL
Cross-sectional cohort studies ($n=10$)			
Clough-Gorr et al. [29]/USA	Breast /43% frail	660/F (100%)/White (94%)	Depression, Anxiety/No
Duan et al. [33]/China	Lung/23.2% frail	302/F(33%)/Asian(100%)	Fatigue, Anxiety, Sleep/No
Gharagozlian et al. [34]/Norway	Stomach/5% frail	21/F (48%)/White (90%)	Gastrointestinal Symptoms/HRQOL (Yes)
Gilmore et al. [35]/USA	Mixed /31% frail	541/F (48.9%)/White(89.3%)	Depression, Anxiety/No
Hamaker et al. [36]/Dutch	Breast/56% frail	78/F (100%)/Not reported	CTCAE grade 3–5 toxicity/HRQOL(Yes)
Hurria et al. [38]/USA	Mixed/43% frail	500/F (56%)/White 85%	CTCAE grade 3–5 toxicity/No
Kim et al. [39]/S Korea	Mixed/42% frail	65/F (25%)/Asian (100%)	HRQOL (Yes)
Pandya et al. [46]/USA	Mixed/71% frail	359/F (45.4%)/white (74.4%)	Pain, distress, cognition, sleep, fatigue, dyspnea, anorexia, depression, dry mouth/No
Su et al. [8]/China	Mixed /55.9% frail	229/F (20.5%)/Asian (100%)	Depression, anxiety/HRQOL(Yes)
Williams et al. [52]/USA	Breast/18% frail	63/F (100%)/White (91%)	Fatigue, pain, anxiety, depression, sleep/ HRQOL (Yes)
Longitudinal studies ($n=16$)			
Biesma et al. [28]/Europe	Lung/45% frail	181/F (23%)/White (100%)	CTCAE grade 3–5 toxicity/HRQOL (Yes)
Corre et al. [30]/Europe	Lung/10% frail	494/F (26%)/ White (100%)	Depression, anxiety, CTCAE grade 3–5 toxicity/HRQOL (Yes)
Cummings et al. [31]/Europe	Colorectal/45% frail	501/F (39.9%)/White (100%)	Pain, anxiety, depression/HRQOL(Yes)
de Vries et al. [32] /Netherlands	Head and Neck/32% frail	288/F (31.2%)/White (100%)	Fatigue, pain, dyspnea, sleep, appetite loss, vomiting, constipation diarrhea/ HRQOL (Yes)
Hamaya et al. [37]/Japan	Prostate/90.3% frail	409/F (0%)/Asian (100%)	Fatigue, pain, dyspnea, sleep, appetite loss, vomiting, constipation diarrhea/ HRQOL (Yes)
Kirkhus et al. [40]/Norway	Mixed/49% frail	288/F (44%)/Not reported	Fatigue, pain, dyspnea, sleep, appetite loss, vomiting, constipation diarrhea/ HRQOL (Yes)
Klepin et al. [41]/USA*	Acute myeloid leukemia/No data	49/F (44%)/white (95.9%)	Depression, distress/HRQOL (Yes)
Magnuson et al. [42]/USA*	Breast/No data	376/F (100%)/white (92.1%)	Cognition (subjective/objective)/No
Mandelblatt et al. [43]/USA	Breast/5.1% frail	353/F (100%)/White (80%)	Anxiety, fatigue, depression, sleep/ HRQOL (Yes)
Mandelblatt et al. [44]/USA	Breast/76.2% frail	1280/F (100%)/white (88.1%)	Subjective cognitive impairment/HRQOL (Yes)
Mohile et al. [45]/USA	Mixed/57.5% frail	718/F (43.3%)/white (87.5%)	CTCAE grade 3–5 toxicity/No
Pottel et al. [47]/Belgium	Head and Neck/59.1% frail	100/F (14%)/not reported	Appetite loss, nausea, vomiting, pain, fatigue, cognitive impairment/HRQOL (Yes)
Puts et al. [48]/Canada	Mixed/87% frail	112/F (69.6%)/white (84.9)	Fatigue, nausea, diarrhea, anorexia/ HRQOL (Yes)
Quinten et al. [49]/Belgian	Mixed/77.5% frail	1424/F (44.4%)/whites (100%)	HRQOL (Yes)
Rønning et al. [50]/Norway	Colorectal/41% frail	180 /F (53%)/whites (100%)	Fatigue, pain, dyspnea, sleep, appetite loss, vomiting, constipation diarrhea/ HRQOL (Yes)
Shehu et al. [51]/German*	Mixed/No data	35/F (58%)/Not reported	Depression, fatigue, pain, dyspnea, sleep, appetite loss, vomiting, constipation, diarrhea/HRQOL (Yes)

CTCAE common terminology criteria for adverse events, *F* female, *HRQOL* health-related quality of life

*Three studies were excluded for meta-analyses due to no available prevalence of frailty data

($n=1$[41]), and prostate ($n=1$[37]) cancers. Mean percentages for each cancer stage were 23.9% (stage I), 23.1% (stage II), 18.4% (stage III), and 34.6% (stage IV) across all 26 studies. Older cancer survivors underwent multiple cancer treatments, including surgery, chemotherapy, and/or radiation in most of the studies ($n=18$) [8, 29, 31–35, 37, 39, 40, 43, 44, 46–49, 51, 52], while single treatments were reported in the other 8 studies [28, 30, 36, 38, 41, 42, 45, 50].

Frailty, symptoms, and HRQOL

Frailty was measured mostly at the initial phase of cancer treatments across the 26 studies. As shown in Supplementary Tables 1 and 2, the Comprehensive Geriatric Assessment (CGA) was the most frequently used tool to assess frailty ($n=9$) [28–30, 36, 38–40, 45, 47], followed by Geriatric-8 (G8, $n=2$) [37, 47], Groningen Frailty Indicator (GFI, $n=2$) [32, 36], and Frailty Phenotype Scale ($n=2$) [33, 42]. Each frailty instrument has its own evaluation criteria to decide frail status. For example, the CGA is a multidimensional diagnostic process that assesses the medical, psychosocial, and functional capabilities of older adults. The CGA applies the standard deficit-accumulation approach to calculate the frailty index (FI). The CGA-FI can range from 0 to 1, with higher values indicating a greater degree of frailty. The following categories of frailty are used in clinical practice and research: robust (less than 0.15), pre-frailty (0.15 to less than 0.25), mild frailty (0.25 to less than 0.35), moderate frailty (0.35 to less than 0.45), severe frailty (0.45 to less than 0.55), and advanced frailty (0.55 or higher) [28]. The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) is a tool to quantify cancer patients' general well-being and functional status. The ECOC-PS was assessed in 7 studies [28, 39–41, 48–50]. Thirteen studies examined both symptoms and HRQOL after cancer treatments, while nine studies examined only symptoms [29, 33, 35, 38, 41, 42, 45, 46, 48], and one study examined only HRQOL [49].

Symptoms were most frequently measured using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) ($n=5$) [28, 30, 36, 38, 45] and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) symptom scales ($n=9$) [28, 32, 37, 39, 40, 43, 47, 50, 51]. Depression, anxiety, and cognition were often included as part of the CGA in 16 studies [8, 29–33, 35, 37, 40, 41, 43, 44, 46, 50–52]. Seven studies examined psychological symptoms (i.e., depression, anxiety, sleep disturbance) with additional validated tools including: Hospital Anxiety and Depression Scale (HADS [33]), Pittsburgh Sleep Quality Index (PSQI [33]), General Anxiety Disorder (GAD [35]), Geriatric Depression Scale (GDS [35]), Clinical Symptom Inventory [46], Patient-Reported Outcomes Measurement Information System (PROMIS [52]), EuroQol-Dimensional (EQ-D5 [8, 29, 31]), Patient Health Questionnaire (PHQ-9 [51]). Cognition was assessed separately, not as part of the frailty assessment in 3 studies [41, 42, 44]. For example, Magnuson et al. [42] used multiple cognitive tests, including the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) and CANTAB. Only one study [34] used GI Symptom Rating Scale (GSRC) to assess comprehensive GI symptoms (e.g., heartburn, nausea, vomiting, loss of appetite, abdominal pain, bloating, belching, flatulence, diarrhea, constipation, fecal leakage, urgent bowel movement, and indigestion) in stomach cancer survivors.

The EORTC QLQ-C30 was the most frequently used tool to assess HRQOL in older adult cancer survivors across the 26 studies. Six studies [37, 39, 40, 43, 46, 50] compared symptoms and HRQOL between frail and non-frail groups in older cancer survivors. The frail group reported a higher symptom burden (e.g., high prevalence and severity of fatigue, depression, anxiety, sleep disturbance, GI symptoms, pain, and cognitive impairment) and poor HRQOL after cancer treatments compared to the non-frail group [37, 39, 40, 43, 46, 50]. De Vries et al.[32] presented the correlations with beta-coefficients between frailty (predictor of interest) and symptoms and HRQOL (outcomes), and frailty positively predicted severe symptoms and poor HRQOL after cancer treatments. Five studies [33, 34, 39, 47, 48] reported that grip strength and malnutrition were the most significant factors contributing to the frailty status affecting symptoms and HRQOL after cancer treatments.

Meta-analyses

Publication bias and test of heterogeneity

Among the 26 studies in this review, only 23 studies were included in meta-analyses (three studies [41, 42, 51] did not report frailty prevalence data were excluded). Publication bias was tested based on the 'frailty' data affecting symptoms and HRQOL. There was no publication bias in the 23 selected studies, with p values from the Kendall's and Egger's tests of p ranging from 0.129 to 0.785 (Table 1, Fig. 3). Overall heterogeneities in frailty, symptom subgroups, and HRQOL subitems were high, with $I^2>75\%$, thus we mostly used random-effects models for our results (Tables 2 and 3).

Pooled estimates of frailty, symptoms, and HRQOL

As shown in Table 3, a total of 23 studies were included in the pooled analysis of the prevalence of frailty-affecting symptoms and HRQOL. The pooled mean prevalence of frailty was 43.5% (95% CI 30.1–57.8) among 9146 older cancer survivors (Fig. 4). We also analyzed the pooled prevalence of moderate-to-severe symptoms after

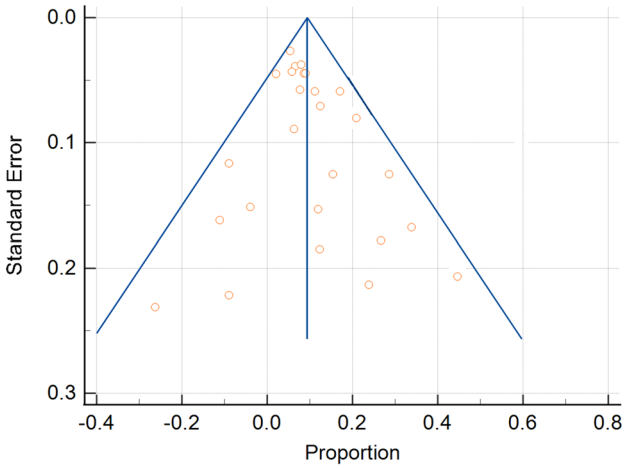

Fig. 3 Funnel plot for assessing publication bias on frailty prevalence (studies $n=23$). Funnel plot with pseudo 95% confidence limits

cancer treatments (Fig. 5). Given the limited symptoms and HRQOL data availability due to inconsistent units of measures, we included only seven studies [8, 28, 30, 31, 38, 46, 49] that presented available symptom data (i.e., the prevalence of moderate-to-severe symptoms) for the meta-analyses. Six symptoms after cancer treatment (i.e., appetite loss, nausea, dyspnea, fatigue, neuropathy, and pain) were included in the analysis (Table 4, Fig. 5) [8, 28, 30, 31, 38, 46, 49]. Among these symptoms, the pooled mean prevalence was highest for pain (36.4, 95% CI 17.7, 57.6), followed by neuropathy (34.1%), and fatigue (21.3%). In the pooled mean estimates of symptom severity and HRQOL scores, only five studies [37, 39, 40, 46, 50] provided symptoms or HRQOL scores with a 0–100 scale after cancer treatments and were included in the analysis (Table 4, Fig. 6). The frail group reported lower global and functional HRQOL (pooled standard mean differences − 7.4 and − 14.9, respectively), and higher severity of symptom scores (14.4) compared to the non-frail group.

Meta-regression

We conducted a meta-regression to examine the associations of frailty with symptoms and HRQOL after cancer treatments (Table 5). The associations of frailty with symptoms and HRQOL are shown in Table 5. Being frail was associated with worse symptom ($B=0.65$, $p=0.011$), poor global ($B=-0.04$, $p=0.046$), and functional ($B=-0.36$, $p=0.035$) HRQOL in the unadjusted model. In the adjusted model, being frail was of marginal significance ($B=-0.31$, $p=0.051$). In both the unadjusted and adjusted models, frailty had the greatest association with the symptom severity ($\beta=0.88$, $p=0.011$, unadjusted model; $\beta=2.92$, $p=0.046$, adjusted model).

Discussion

To our knowledge, this review is the first to summarize the findings from studies that examined the associations of frailty with patient-reported individual symptoms and HRQOL after cancer treatments in older adult cancer survivors. Given the previous findings on the relationships between frailty and cancer-specific mortality, chemotoxicity, and hospital admission rates in older cancer survivors [3, 20], our study significantly contributes to the existing literature by broadening the understanding of how frailty affects patient-reported individual symptoms and HRQOL across many studies. By exploring these connections, we provide deeper insights that may ultimately improve patient care and treatment outcomes in older cancer survivors.

Symptom and HRQOL assessment

The instruments across the studies in this review to assess symptoms and HRQOL were inconsistent, including time points, dimensions, and types of symptoms. Despite the number of valid and reliable instruments that are available to assess multiple co-occurring symptoms in oncology patients [53], multiple co-occurring symptoms specific to certain cancer types (e.g., common GI symptoms such as abdominal pain and bloating in GI cancers, genitourinary

Table 2 Tests of publication bias (based on the prevalence of frailty at baseline)

Meta-analyses: prevalence of frailty (# of studies)	Begg's test		Egger's test	
	Kendall's *T*	*p*	SE	*p*
Pooled prevalence of frailty combined cross-sectional cohort studies and longitudinal study designs ($n=23$)	0.50	0.312	1.32	0.231
Pooled prevalence of frailty (cross-sectional cohort studies, $n=10$)	0.35	0.621	1.28	0.477
Pooled prevalence of frailty (longitudinal studies, $n=13$)	0.22	0.785	2.45	0.129

SE standard error

$p<0.05$ considered to show significant publication bias

Table 3 Heterogeneity test for the meta-analyses: pooled prevalence of frailty at baseline

Study characteristics	Sub-variables	Studies *n*	Prevalence of frailty[a] % (95% CI)	Test for heterogeneity between studies[b]		
				$Q_{df\text{Between}}$	I^2 (%)$_{\text{Between}}$	p_{Between}
Total (articles with available frailty data)		23	43.5 (30.1, 57.8)	1324.4_{22}	98.34	< 0.001
Country	United States ($n=8$)/Canada ($n=1$)	9	44.4 (32.6, 60.2)	154.21_{8}	87.93	0.032
	Europe	10	44.5 (42.2, 57.5)	125.32_{9}	94.52	0.082
	Asia	4	43.2 (57.2, 70.2)	163.88_{3}	82.34	0.003
Publication year	2008–2012	5	41.0 (33, 65.2)	168.31_{4}	97.53	0.032
	2013–2017	5	44.2 (28.1, 53.4)	152.43_{4}	97.52	0.048
	2018–2023	13	42.6 (35, 77.5)	177.23_{12}	96.23	0.032
Study design	Cross-sectional	10	39.2 (29.3, 49.5)	340.85_{9}	96.35	0.013
	Longitudinal	13	47.1 (35.3, 57.5)	321.75_{12}	98.09	0.035
Female prevalence	< 50.0%	14	41.3 (35.2, 55.7)	15.32_{13}	21.23	0.410
	≥ 50.0%	9	44.4 (25.8, 56.2)	18.52_{8}	29.41	0.543
Sample size	$n<100$	4	30.3 (10.1, 56.0	153.32_{3}	78.72	< 0.001
	$100 \le n < 500$	13	52.5 (23.2, 90.3)	188.52_{12}	76.41	< 0.001
	$n \ge 500$	6	53.8 (50.2, 55.4)	145.23_{5}	84.32	< 0.001
Mean age (year)	60 ≤ & < 70	5	38.5 (34.2, 42.3)	132.32_{4}	88.31	0.009
	70 ≤ & < 75	8	45.5 (35.3, 53.8)	145.44_{7}	85.62	0.031
	75 ≤	10	42.1 (37.1, 53.5)	55.74_{9}	88.75	0.055
Cancer types[c]	Mixed types	9	42.2 (38.2, 49.3)	321.32_{8}	98.52	0.032
	Breast	5	39.7 (30.1, 48.5)	39.32_{4}	58.53	0.055
	GI (CRC $n=2$; Stomach $n=1$)	3	44.3 (35.3, 49.8)	98.49_{2}	92.33	0.038
	Lung	3	36.1 (31.5, 39.9)	98.99_{2}	91.48	0.002
	Head and neck	2	45.6 (37.5, 53.9)	101.52_{1}	95.67	0.043

CI confidence interval, *CRC* colorectal cancer, *df* degree of freedom, *GI* gastrointestinal

[a]Weighted effect size and standard error were applied, resulting in pooled prevalence and 95% confidence intervals (CIs)

[b]p value < 0.10 considered significant for heterogeneity tests

[c]Hamaya et al. [38] in prostate cancer study was excluded as Hamaya et al. [38] was the only article conducted for prostate cancer survivors. Three articles [ref #, [42, 43, 52]] were excluded as no available frailty data for meta-analyses

symptoms in prostate cancer) were not consistently measured. Across the 23 studies included in the meta-analyses, limited symptoms (i.e., appetite loss, dyspnea, fatigue, neuropathy, and pain) measured with the EORTC-QLQ-C30 in 5 studies [37, 39, 40, 46, 50] were only available for the meta-analyses. Multiple symptom toxicities after cancer treatments were measured in 5 studies [28, 30, 36, 38, 45], but these symptoms were assessed by the clinician, not by the patient-reported outcomes (PRO). Thus, further research is warranted to examine self-reported symptoms in frail older adult cancer survivors to better capture their symptom experiences [54]. Cancer survivors experience distinct symptom profiles or HRQOL phenotypes [55, 56]. For example, in a study of 1500 breast cancer survivors after cancer treatments, using a latent class profile analysis, four distinct symptom subgroups for the symptom cluster of pain, fatigue, sleep disturbance, and depression were identified (normal, high pain, high depression, all high) [56]. In a study of 1396 individuals with lung cancer who completed cancer treatments, four distinct classes of symptoms and HRQOL were identified: poor HRQOL, pain dominant impairment, mobility/usual activities impairment, and good HRQOL groups [55]. These findings highlight the need for individualized symptom assessment for some cancer types as well as the interindividual variability in HRQOL.

Associations of frailty with symptoms and HRQOL

Our findings demonstrated that compared to non-frail cancer survivors, frail cancer survivors had worse symptoms and lower HRQOL after cancer treatments. These associations can be explained by many subcomponents of different frailty scales (e.g., nutritional status, function, cognition, and

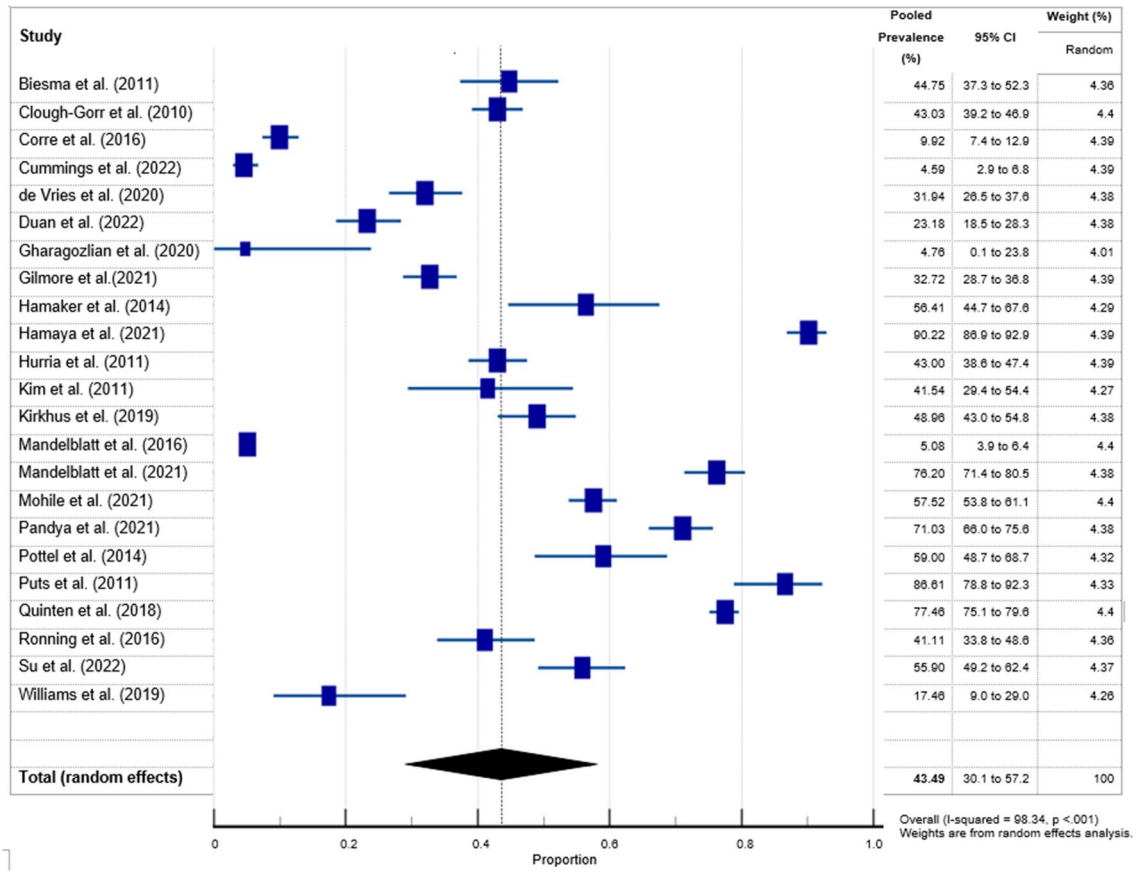

Fig. 4 Forest plots showing pooled prevalence of frailty in the overall sample (studies $n = 23$)

social support). Notably, malnutrition and sarcopenia measured by hand grip strengths, body mass index (BMI), and weight change were frequently measured as part of frailty assessments; and these factors were associated with symptoms and HRQOL [34, 39, 49]. This has also been observed previously in community-dwelling older adults [57–59]: Malnutrition and sarcopenia were associated with constipation [57], poor appetite [58], depression and anxiety, and cognition decline [59].

In light of our findings, it is plausible that nutritional frailty may contribute to an increased risk for a worse symptom burden and poorer HRQOL in older cancer survivors. This connection emphasizes dietary factors when addressing overall health and well-being in this population. Furthermore, social frailty may have been a strong risk factor for symptoms and poor HRQOL in cancer survivors. Social frailty in older adult cancer survivors has been associated with long-term depressive symptoms after cancer treatments [60]. However, studies assessing how these subcomponents of frailty might contribute to symptoms or HRQOL are scant. Therefore, future research that examines subcomponents of frailty associated with a higher symptom burden is warranted.

Pain was the most associated symptoms with frailty, followed by neuropathy and fatigue in our meta-analyses. Furthermore, we identified clinically meaningful differences in the EORTC QLQ C-30 measures (functional HRQOL standard mean difference 14.9 points, and symptom scores mean difference 14.4 points [61]), indicating a moderate difference in symptoms and HRQOL between frail and non-frail groups (Table 4, Fig. 6). Frailty may be linked to pain, neuropathy, and fatigue in cancer patients through potential biological mechanisms, specifically chronic systemic inflammation. Frailty in cancer patients was associated with increased pro-inflammation, which resulted in altered pain sensitivity, neuropathy, and fatigue [62]. Frail older adults might have increased systemic inflammation, worsening the vulnerability to chemotherapy-related symptom side effects. Future

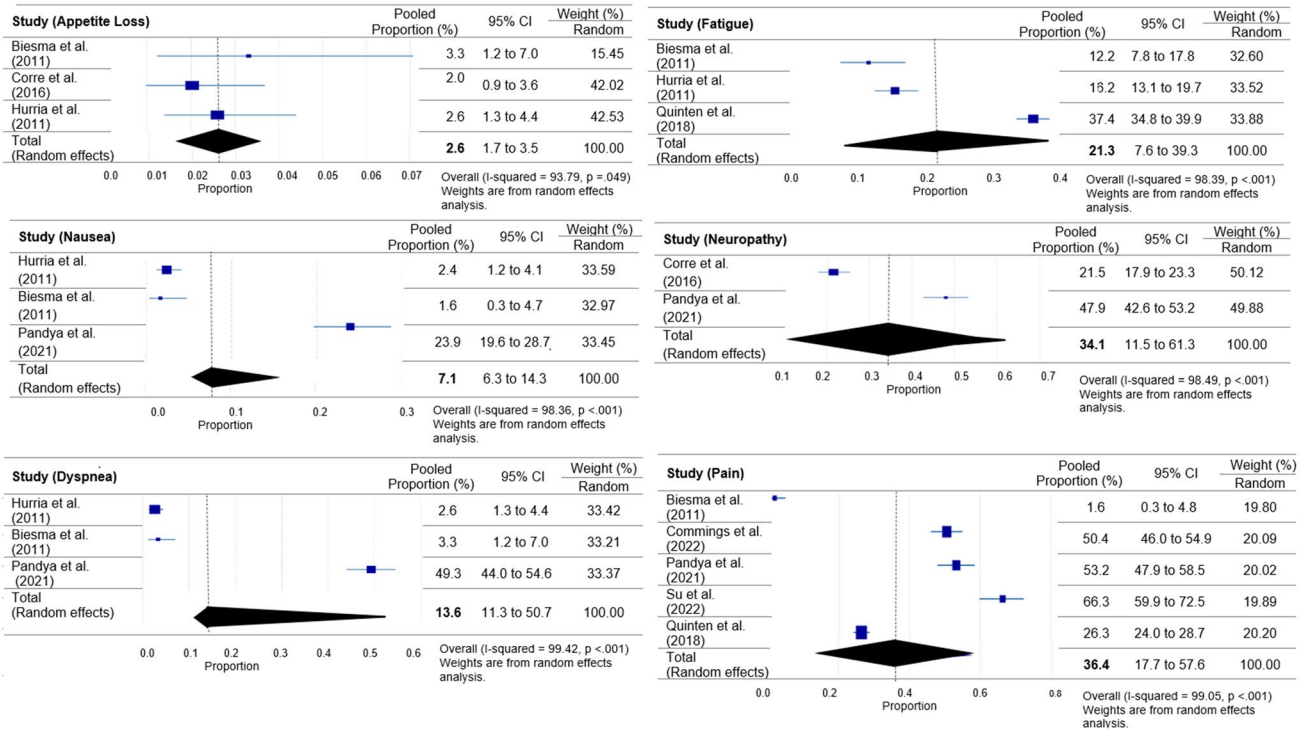

Fig. 5 Forest plots showing pooled prevalence of moderate-to-severe symptoms

biological mechanisms and intervention studies of predominant symptoms associated with frailty are warranted with validated, comprehensive symptom assessment instruments (e, g., EORTC QLQ C-30, Memorial Symptom Assessment Scale [MSAS], PROMIS).

Psychological distress (e.g., depression, and anxiety) are common symptoms in cancer survivors [53]. The majority of the studies included in our review ($n = 7$) assessed psychological distress as part of the frailty assessment. Frailty was associated with psychological distress and sleep in older adults with chronic diseases, including cancer [63, 64], via bidirectional relationships or unidirectional relationships (frailty as a predictor [64] or an outcome [35]). Frail older adult cancer survivors are more likely to have physical and social frailty such as functional limitation, greater comorbidities, and social isolation, which can lead to depression, anxiety, or insomnia [35, 64]. Vice versa, older adult cancer survivors with psychological distress tend to have poor physical activity and poor self-management. This can worsen their overall frailty [35, 64]. Although there is some overlap between frailty and psychological distress, it is important to identify which component of frailty (e.g., nutritional status, active daily living functionality, or sarcopenic status) is the primary driver of a particular symptom [65]. Therefore, the distinction of measuring mental health and frailty will allow for a more comprehensive understanding of their interactions and offer valuable insights into targeted intervention for older cancer survivors at high risk of psychological distress.

Limitations

Our findings are limited by the number of published studies that directly examined the relationships between frailty, symptoms, and HRQOL. The high heterogeneity across the selected studies (e.g., the lack of unified assessment measures of symptoms and HRQOL) prevented further use of advanced review methods such as meta-analysis. In addition, the measures of frailty (e.g., physical, psychological, and social) were inconsistent across the selected studies. Therefore, this study may not be able to completely capture which components of frailty are associated with symptoms and HRQOL. Inconsistent time points to measure frailty, symptoms, and HRQOL after cancer treatments also limited the potential causal relationships of frailty with symptoms and HRQOL. Despite the meta-analysis can be conducted if a variable is present in at least three studies per variable, the number of studies included in our meta-regression of frailty with symptoms and HRQOL

Table 4 Publication bias and heterogeneity tests for the meta-analyses: pooled mean estimates of symptoms and HRQOL after cancer treatments

Study Sub-variables[a]	Studies *n*	Pooled values (95% CI)[b]	Publication bias				Test for heterogeneity between studies		
			Begg's test		Egger's test				
			Kendall's *T*	p^c	*SE*	p^c	$Q_{df\text{Between}}$	I^2 (%)$_{\text{Between}}$	$p^c{}_{\text{Between}}$
Pooled mean prevalence of moderate-to-severe symptoms in frail group (%, 95% CI)									
Appetite loss	3	2.6 (1.7, 3.5)	0.33	0.605	2.3	0.393	111.79_2	93.79	0.049
Nausea	3	7.1 (6.3, 14.3)	0.33	0.602	5.6	0.978	121.73_2	98.36	< 0.001
Dyspnea	3	13.6 (11.3,50.7)	0.33	0.601	2.2	0.975	347.64_2	99.42	< 0.001
Fatigue	3	21.3 (7.6, 39.3)	0.33	0.601	5.4	0.274	124.01_2	98.39	< 0.001
Neuropathy	2	34.1 (11.5, 61.3)	0.99	0.317	6.5	0.311	66.4_1	98.49	< 0.001
Pain	5	36.4 (17.7, 57.6)	0.12	0.999	5.3	0.726	420.07_4	99.05	< 0.001
Pooled mean scores of symptoms and HRQOL in frail group (0–100 points, 95% CI)									
Symptom severity	5	56.6 (29.5, 83.6)	0.33	0.444	2.3	0.567	221.88_4	98.62	< 0.001
Global HRQOL	5	57.2 (45.5, 69.0)	0.42	0.623	4.2	0.623	213.04_4	87.05	< 0.001
Functional HRQOL	4	74.6 (60.9, 88.4)	0.33	0.523	4.3	0.952	121.53_3	97.43	< 0.001
Pooled standard mean differences of EORTC QLQ-C30 symptoms and HRQOL: frail group versus non-frail group (95% CI)[d]									
Symptom severity	5	14.4 (− 2.6 to 31.4) SE (11.3)	− 0.20	0.624	6.3	0.677	345.67_4	98.84	< 0.001
Global HRQOL	5	− 7.4 (− 26.6 to 12.6), SE (9.7)	0.20	0.624	1.4	0.789	34.67_4	88.46	< 0.001
Functional HRQOL	4	− 14.9 (− 27.1 to − 2.8), SE (9.9)	0.99	0.999	3.6	0.612	35.75_3	91.61	< 0.001

CI confidence interval, *EORTC-QLQ C30* European Organization for Research and Treatment of Cancer Quality of Life questionnaire-C30, *df* degree of freedom, *HRQOL* health-related quality of life, *SE* standard error

[a]Symptoms or HRQOL data were only included if present in at least three studies per data. Symptoms and HRQOL data based on 0–100 scale. Higher scores indicate worse symptoms and better HRQOL

[b]Weighted effect size and standard error were applied, resulting in pooled estimates and 95% Confidence Intervals (CIs)

[c]$p < 0.05$ considered significant publication bias; $p < 0.10$ considered significant for heterogeneity tests

[d]For the EORTC QLQ-C30 questionnaire, a crude Minimally important clinical differences (MICD) (≤ 5 and < 10 points = a small difference, ≤ 10 and < 20 points = a moderate difference; ≥ 20 = a large difference)

is limited, thus, our findings should be interpreted with caution [66]. Finally, different confounding variables not addressed in this review (e.g., socioeconomic status, marital status, and race) may influence the analysis results. In particular, the majority of patients identified in this study were identified as White, which may result in a lack of representation of minority groups and therefore potentially limiting the generalizability of this study.

The longitudinal patterns of symptoms and HRQOL changes over time are unknown in frail older adult survivors. There is a need for more rigorous study designs, such as longitudinal study designs with validated instruments and randomized control trials, to examine the efficacy of an intervention to improve frailty for cancer survivors at high risk of symptoms and poor HRQOL. Future studies should include a generalized guideline that consistently measures specific factors of frailty in older adults to better understand which dimension of frailty most likely contributes to symptoms and HRQOL.

Conclusions

Compared to other studies currently in the literature, this systematic review and meta-analysis focused on frailty on symptoms and HRQOL in older cancer populations not generally studied. This study demonstrated that frailty may be a risk factor for two primary components of cancer survivorship care: worse symptom experiences and poorer HRQOL in older adult cancer survivors. Early identification and management of frailty may prevent and alleviate adverse symptom toxicities and HRQOL impairment. Given the inter-individual variability in symptoms and HRQOL, a person-centered approach to symptom and HRQOL assessment and management in each cancer type is warranted to develop targeted and effective survivorship care for these patients.

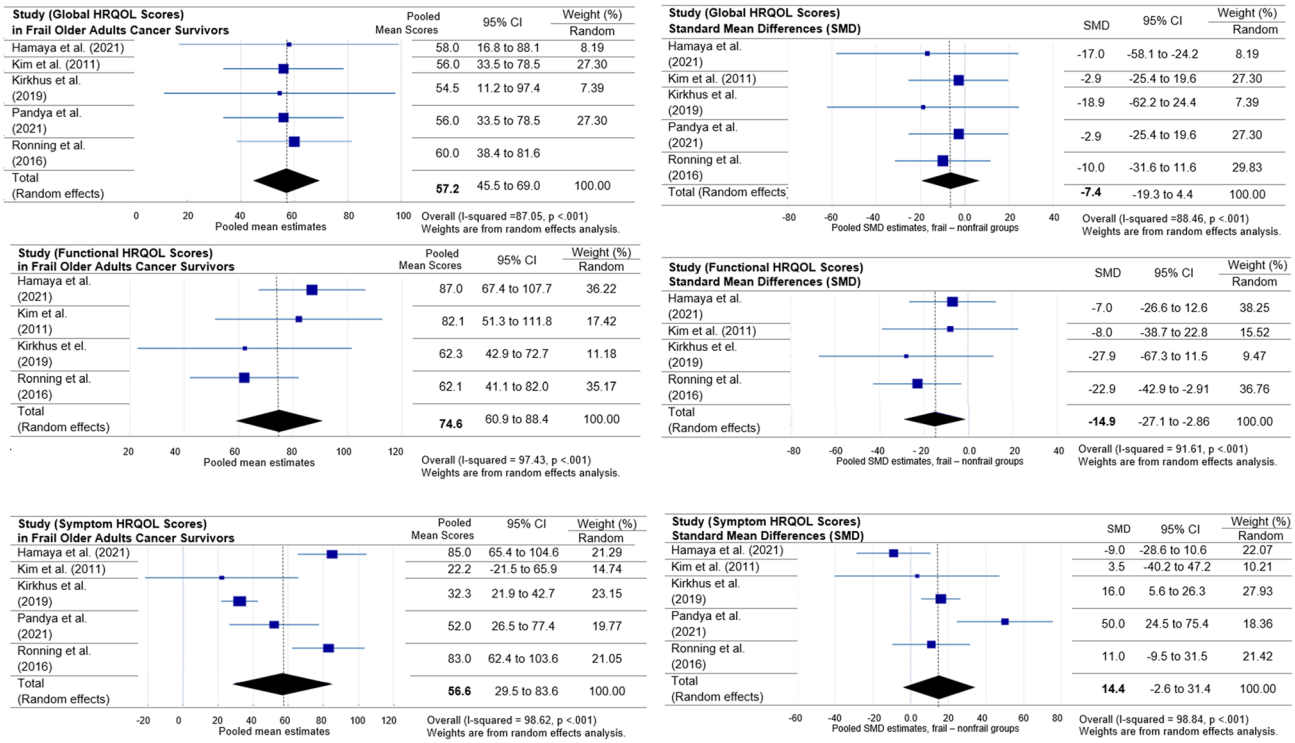

Fig. 6 Forest plots showing pooled mean estimates of symptom and HRQOL scores (left part), and pooled standard mean differences between frail and non-frail older cancer survivor groups (right part)

Table 5 Meta-regression analyses: associations of frailty with symptoms and HRQOL

Frailty at baseline (Predictor of interest)	Studies *n*	Unadjusted				Adjusted[c]			
		Unstandardized *B*[d]	SE	Standardized *β*	*p*[b]	Unstandardized *B*[d]	SE	Standardized β	p[b]
Pooled mean scores of EORTC QLQ-C30 Symptoms and HRQOL after cancer treatments (Outcomes)[a]									
Symptom severity	5	0.65	0.67	0.88	0.011	1.23	0.11	2.92	.046
Global HRQOL	5	− 0.04	0.57	− 0.24	0.046	− 0.05	0.54	− 0.34	.895
Functional HRQOL	4	− 0.36	0.30	− 0.65	0.035	− 0.31	0.10	− 0.67	.051

EORTC-QLQ C30 European Organization for Research and Treatment of Cancer Quality of Life questionnaire-C30, *HRQOL* health-related quality of life, *SE* standard error

[a]Pooled mean scores of EORTC QLQ-C30 Symptom and HRQOL data were used for the regression as outcome variables. Data based on 0–100 scale. Higher scores indicate worse symptoms, and better HRQOL

[b]*p* value of <0.05 was considered statistically significant. Significant findings ($p<0.05$) were highlighted in bold

[c]Adjusted regression models included country, publication year, study design, female sex, sample size, mean age group, and cancer types

[d]Unstandardized Beta Coefficient interpreted as change in symptom or HRQOL scores for 1-unit change in frailty prevalence

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Author contributions All authors contributed to the study conception and design. Material preparation was performed by CH and reviewed by all authors. CH (first author) primarily contributed study design, conducted primary database search, study selection and screening. CH wrote the first draft of the manuscript, and all authors commented on previous versions. AR, DS, MH, and DVA have substantial contributions to the acquisition, analysis, and interpretation of the data and writing of the paper. All authors read and approved the final manuscript. All authors have reviewed, discussed, and agreed to their individual contributions ahead of this time.

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Data Availability The data that support the findings of this study are available from the corresponding author, CH, upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All other authors declare no conflicts of interest.

Ethical approval/consent to participate This is a review study. There are no human participants' data being directly studied for the purpose of the review, therefore, ethics approval and consent to participate are not applicable. The Ohio State University Human Subject Department Research Ethics Committee has confirmed that no ethical approval is required.

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