

An Integrative Review of Sex Differences in Quality of Life and Symptoms Among Survivors of Hematologic Malignancies

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OBJECTIVES: To conduct an integrative review of studies to identify disparities in quality of life (QOL), symptoms, and symptom burden between men and women diagnosed with hematologic malignancies.

SAMPLE & SETTING: 11 studies comprising 13,546 participants aged 18 years or older were included in the analysis. Studies were original peer-reviewed research published in English between January 2005 and December 2020.

METHODS & VARIABLES: A literature search was performed using keywords associated with health-related QOL, hematologic malignancy, and sex/gender differences. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed to identify relevant studies. Data were extracted for sex differences in QOL, symptoms, and symptom burden. All studies were appraised for quality and level of evidence.

RESULTS: Women have worse physical health and function, more pain, and higher symptom burden compared with men.

IMPLICATIONS FOR NURSING: Healthcare providers need to understand the impact of sex-based differences on QOL, symptoms, and symptom burden to provide optimal, personalized care.

KEYWORDS quality of life; health-related quality of life; gender; cancer; hematologic malignancy

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An estimated 1.96 million Americans will be newly diagnosed with cancer in 2023 (Siegel et al., 2023). According to the American Cancer Society, 184,720 individuals in the United States will be diagnosed with hematologic malignancies such as leukemia, lymphoma, or myeloma in 2023 (Siegel et al., 2023). A cancer diagnosis is frequently associated with multiple symptoms that vary depending on cancer type and stage of disease. In addition, radiation therapy, chemotherapy, and surgery trigger an array of side effects that may affect the quality of life (QOL) of patients with cancer. There are sex-based differences in the bioavailability, enzyme expression, and chemical mechanisms of drug therapy for oncologic diseases (Schmetzer & Flörcken, 2012). Several studies in hematology-oncology report varying differences in side effects and survival rates between sexes, validating the need for a better understanding of how QOL differs between men and women diagnosed with hematologic malignancies (Klimm et al., 2005; Molica, 2006; Pfreundschuh et al., 2014).

In a large study of 10,700 symptom assessments focused on performance status trajectories and symptom scores in patients with cancer during the final six months of life, four symptoms (drowsiness, tiredness, well-being, and lack of appetite) were reported as moderate to severe (Seow et al., 2011). Fifty percent of the participants in this study were female. Researchers used multivariate analysis to assess the likelihood that participants would report a moderate to severe symptom score. Female participants were significantly more likely to report moderate to severe symptoms of nausea, anxiety, drowsiness, poor well-being, lack of appetite, and tiredness (Seow et al., 2011). This study established the importance of and need for additional research to increase the understanding of sex-based disparities in QOL, symptoms,

and symptom burden for individuals diagnosed with a hematologic malignancy.

The primary aim of this article is to provide a comprehensive review of studies published in peer-reviewed journals that investigate how QOL, symptoms, and symptom burden differ between women and men diagnosed with hematologic malignancies. The research questions posed are as follows:

- How do symptoms of men and women diagnosed with a hematologic malignancy differ?
- Does symptom burden differ between men and women diagnosed with a hematologic malignancy?
- Based on the symptoms that are experienced, does QOL differ between men and women diagnosed with a hematologic malignancy?

Methods

Electronic Database Searches

Electronic database searches were performed in November 2020 with the support of a medical

librarian specializing in consumer health information. Citations from search results were downloaded into Covidence and subsequently imported into the reference manager software EndNote X9.

Studies published from January 2005 to December 2020 were included in the search using PubMed®, CINAHL®, and PsycINFO®. A span of 15 years was necessary to form a foundation for the research questions because of limited relevant publications. The authors used Medical Subject Headings (MeSH) terms and keywords related to sex-based QOL differences in patients with hematologic malignancies. Combination terms of QOL, health-related QOL (HRQOL), neoplasm, hematologic malignancy, and sex/gender differences were used. Additional publications were included after reviewing the reference lists of eligible articles. All abstracts and publications were reviewed by two investigators. When investigators disagreed on the inclusion of articles, they discussed the articles until they came to a resolution.

Studies in this integrative review met the following inclusion criteria: (a) being randomized controlled trials or qualitative studies focused on sex-based differences in QOL, symptoms, or symptom burden between men and women with a hematologic malignancy; (b) containing a study sample aged 18 years or older; (c) being original research published in English; (d) being published between January 2005 and December 2020; and (e) being published in peer-reviewed journals. Exclusion criteria for studies were as follows: (a) being abstracts or results of dissertations; (b) not reporting separate outcomes for QOL in men and women; (c) being published before January 1, 2005; or (d) focusing on a pediatric population. For this review, the terms “sex” and “gender” were used interchangeably, although the authors acknowledge sex as a biologic variable and gender as a set of socially allocated roles and expectations associated with being designated either male or female.

Search Outcomes

A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram was used to screen and remove manuscripts (see Figure 1). Overall, 511 records were initially screened from database searches, and 2 were identified from reference lists of eligible studies. After removing 54 duplicates, 459 studies were screened against the titles and abstracts, with 358 studies excluded. The full texts of the remaining 101 studies were screened for eligibility. Ninety studies were excluded for the following reasons: (a) 44 did not include patients with hematologic cancers, (b) 43

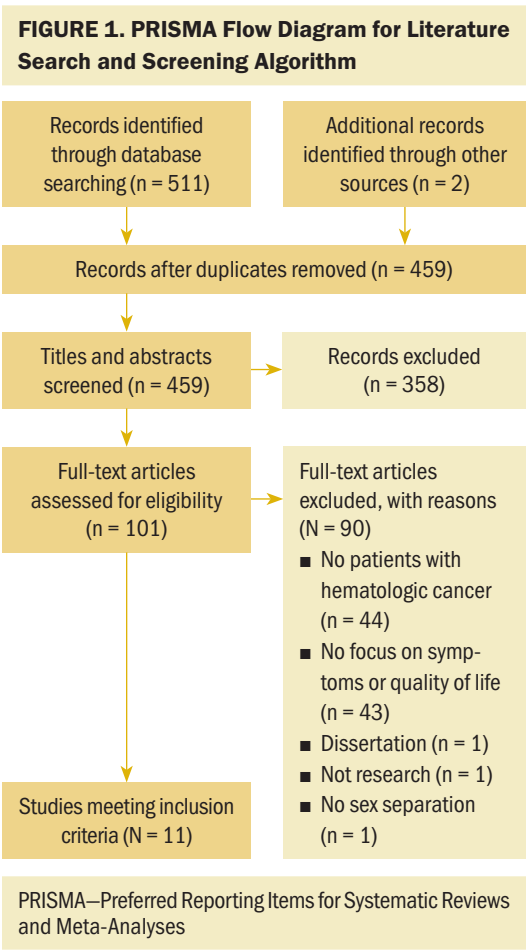


TABLE 1. Summary of Study Results

Study (Country)	Sample	Design and QOL Instruments	Quality Appraisal	Results
Arden-Close et al., 2011 (United Kingdom)	■ 115 HL and NHL survivors ■ 57 males, 58 females	■ Prospective, cohort, correlational ■ QOL-Cancer Survivor ■ SF-12v2®	Cohort 8/12	No gender differences in number of patient-reported late effects or perceived vulnerability were found; males who reported worse late effects from treatment indicated worse psychological HRQOL ($p < 0.001$).
Geyer et al., 2017 (International)	■ 2,006 survivors with MPNs ■ 917 males, 1,089 females	■ International, prospective ■ BFI ■ MPN Symptom Assessment Form	Cohort 10/12	Females had more severe and more frequent symptoms based on total scores for abdominal symptoms (pain/discomfort) ($p \leq 0.001$) and microvascular symptoms (headache, fatigue, insomnia, concentration problems, dizziness) ($p < 0.01$).
Heutte et al., 2009 (Europe)	■ 935 HL survivors ■ 468 males, 467 females	■ Prospective, longitudinal ■ EORTC QLQ-C30 ■ Multidimensional Fatigue Inventory	Cohort 11/12	Physical and sexual functioning scores were higher for males at all time points. Gender influenced almost all scores ($p = 0.0088$), including emotional and sexual functioning, global QOL, and fatigue. Females had lower HRQOL and higher symptom scores.
Immanuel et al., 2019 (United Kingdom)	■ 131 survivors of B-cell malignancies □ Leukemia ($n = 14$) □ Lymphoma ($n = 102$) □ Multiple myeloma ($n = 14$) □ Unknown ($n = 1$) ■ 78 males, 53 females	■ Cross-sectional ■ EORTC QLQ-C30 ■ EQ-5D	Cohort 10/12	There were equal reports for males and females in mobility, self-care, anxiety, and depression. There were statistically significant differences ($p = 0.015$) in the proportion of females (49.1%) who reported no pain versus males (70.1%). Males reported better physical functioning ($p = 0.041$), less loss of sleep ($p = 0.001$), and fewer symptoms of pain ($p < 0.001$).
Kreissl et al., 2020 (Germany)	■ 4,215 survivors of HL assessed at a range of time points (at diagnosis to 5 years after diagnosis) ■ 2,325 males, 1,890 females	■ Prospective, longitudinal ■ EORTC QLQ-C30	Cohort 12/12	Females reported higher symptom scores, lower QOL, and lower functioning scores; however, differences were evident at baseline.
Leak et al., 2013 (United States)	■ 741 NHL survivors ■ 377 males, 364 females ■ 86% Caucasian	■ Retrospective, correlational ■ FACT-Leukemia	Cohort 10/12	QOL scores were higher for females overall but did not differ as much in older female patients.

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TABLE 1. Summary of Study Results (Continued)

Study (Country)	Sample	Design and QOL Instruments	Quality Appraisal	Results
Morishita et al., 2013 (Japan)	■ 100 patients with hematologic cancers □ Acute myeloid leukemia (n = 55) □ NHL (n = 29) □ MDSs (n = 12) □ Severe aplastic anemia (n = 2) □ Chronic myeloid leukemia (n = 1) □ CLL (n = 1) ■ 66 males, 34 females	■ Prospective, observational ■ Exercise (6-minute walk test, hand grip strength test, and knee extensor strength test) ■ HADS ■ Piper Fatigue Scale ■ SF-36®	Cohort 11/12	Female patients scored lower on physical function and general health ($p < 0.01$). Fatigue and psychological status did not differ between genders.
Pashos et al., 2013 (United States)	■ 1,140 patients with CLL ■ 710 males, 430 females	■ Prospective, longitudinal, observational ■ BFI ■ EQ-5D ■ FACT-Leukemia	Cohort 12/12	Females reported worse global fatigue ($p < 0.0001$), severity of fatigue ($p < 0.0001$), pain/discomfort ($p = 0.0077$), and anxiety/depression ($p = 0.012$). Females reported better social/family scores ($p = 0.0238$). The mean FACT-General total scores were similar between genders.
Sarker et al., 2017 (United Kingdom and United States)	■ 993 NHL survivors □ 326 in the United Kingdom (176 males, 150 females) □ 667 in the United States (331 males, 336 females)	■ Prospective, observational ■ Chalder Fatigue Scale ■ HADS ■ Impact of Cancer, version 2.0 ■ SF-36	Cohort 10/12	Females experience greater effects of cancer-associated symptoms ($p < 0.001$).
Shanafelt et al., 2007 (International)	■ 1,482 CLL survivors ■ 846 males, 636 females	■ Prospective, observational ■ BFI ■ FACT-General	Cohort 12/12	In a multivariate analysis, female gender was associated with lower emotional QOL and more fatigue.
Stauder et al., 2018 (Europe and Israel)	■ 1,690 patients with MDSs sourced from the European LeukemiaNet Registry	■ Prospective, longitudinal ■ EQ-5D	Cohort 10/12	Anxiety and depression were higher in female patients ($p < 0.001$) and restrictions in all parameters of EQ-5D ($p < 0.05$). Mobility restrictions were most pronounced in male survivors ($p < 0.01$).
BFI—Brief Fatigue Inventory; CLL—chronic lymphocytic leukemia; EORTC QLQ-C30—European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire—Core 30; EQ-5D—EuroQol 5-Dimension; FACT—Functional Assessment of Cancer Therapy; HADS—Hospital Anxiety and Depression Scale; HL—Hodgkin lymphoma; HRQOL—health-related quality of life; MDS—myelodysplastic syndrome; MPN—myeloproliferative neoplasm; NHL—non-Hodgkin lymphoma; QOL—quality of life				

lacked focus on symptoms or QOL, (c) 1 was part of a dissertation, (d) 1 was not a study, and (e) 1 did not separate data by sex. This resulted in 11 studies.

Data Extraction, Level of Evidence, and Quality Appraisal

Data related to study authors and setting, sample, study design, measurement instruments, quality appraisal, and results were extracted (see Table 1). Results related to QOL, symptoms, and symptom burden were synthesized, and levels of evidence were assessed (see Table 2). Level of evidence was defined as strong if two or more high-quality studies provided consistent findings, moderate if only one high-quality study provided findings, inconclusive if there were inconsistent findings regardless of the study quality, and no evidence if no associations were found.

All studies were reviewed using the Critical Appraisal Skills Programme (2022) checklists according to study design to assess methodologic quality, presence of bias, degree of uncertainty in the results, and relevance of the findings. The first and second authors independently used these checklists to record whether each item had been reported adequately. Based on appraisals, studies were then reported using the Cohort Study Checklist, and the number of criteria that each study met was determined (Critical Skills Appraisal Programme, 2022). A consensus was reached by the authors on whether to include each study.

Data Analysis

Because of the heterogeneity of study design, research questions, and QOL instruments used in the studies in this review, a narrative synthesis approach was adopted. This approach involves grouping results to examine similarities and differences and synthesizing them into a coherent narrative. This allowed related information to be collected and organized in relation to sex-related differences in QOL, symptoms, and symptom burden. Meaningful conclusions were drawn using ideas webbing (Clinkenbeard, 1991) and concept mapping (Mulrow et al., 1997) techniques.

Results

Study Characteristics

Among the 11 studies, 9 were prospective (Arden-Close et al., 2011; Geyer et al., 2017; Heutte et al., 2009; Kreissl et al., 2020; Morishita et al., 2013; Pashos et al., 2013; Sarker et al., 2017; Shanafelt et al., 2007; Stauder et al., 2018), and 4 of these 9 were longitudinal

(Heutte et al., 2009; Kreissl et al., 2020; Pashos et al., 2013; Stauder et al., 2018). Only one cross-sectional study (Immanuel et al., 2019) and one retrospective study (Leak et al., 2013) were included.

Measurement Instruments

Measurement of QOL and symptoms varied within each study. Three studies used the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 (EORTC QLQ-C30) instrument (Heutte et al., 2009; Immanuel et al., 2019; Kreissl et al., 2020). The EuroQol 5-Dimension (EQ-5D), a generic instrument to measure QOL, was used in three of the studies (Immanuel et al., 2019; Pashos et al., 2013; Stauder et al., 2018). The Functional Assessment of Cancer Therapy (FACT)–General (FACT-G) and the leukemia-specific FACT–Leukemia (FACT-Leu) were used in three studies to measure QOL (Leak et al., 2013; Pashos et al., 2013; Shanafelt et al., 2007). Geyer et al. (2017) developed their own instrument for a study evaluating common symptoms associated with myeloproliferative neoplasms (MPNs), the MPN Symptom Assessment Form (MPN-SAF). The SF-36® and the 12-item version of this survey, the 12-item SF-12v2®, were used in three studies (Arden-Close et al., 2011; Morishita et al., 2013; Sarker et al., 2017) to measure functional health and well-being. One study used the QOL–Cancer Survivor instrument to measure HRQOL (Arden-Close et al., 2011).

Several instruments were used to measure fatigue. The Brief Fatigue Inventory (BFI) was the most frequently used instrument (Geyer et al., 2017; Pashos et al., 2013; Shanafelt et al., 2007). Other fatigue scales used were the Piper Fatigue Scale (Morishita et al., 2013), the Multidimensional Fatigue Inventory (MFI) (Heutte et al., 2009), and the Chalder Fatigue Scale (Sarker et al., 2017). See Table 3 for a full comparison of instruments used to measure QOL, symptoms, and symptom burden.

Participant Characteristics

From the 11 studies, there were 13,546 participants, consisting of 6,158 women and 7,388 men. Several different hematologic malignancies were investigated, with Hodgkin lymphoma and non-Hodgkin lymphoma reported in nine studies (Arden-Close et al., 2011; Heutte et al., 2009; Immanuel et al., 2019; Kreissl et al., 2020; Leak et al., 2013; Morishita et al., 2013; Pashos et al., 2013; Sarker et al., 2017; Shanafelt et al., 2007). One study concentrated on MPNs (Geyer et al., 2017), and one study included only

TABLE 2. Levels of Evidence for Sex-Based Differences in QOL, Symptoms, and Symptom Burden

Symptom	Reference	Instrument	Results	Level of Evidence
Fatigue	Geyer et al., 2017	BFI	Female survivors of MPNs had worse fatigue, fatigue severity, and interference with daily activities. Participants were tested at unknown time points in treatment.	Inconclusive
Fatigue	Heutte et al., 2009	MFI	Sex is not a significant predictor of fatigue following treatment for HL among survivors.	Inconclusive
Fatigue	Morishita et al., 2013	Piper Fatigue Scale; SF-36®	There was similar fatigue between men and women before and after allogeneic hematopoietic stem cell transplantation.	Inconclusive
Fatigue	Pashos et al., 2013	BFI	Women with CLL had worse fatigue and severity of fatigue at baseline and 2 months following treatment.	Inconclusive
Fatigue	Shanafelt et al., 2007	BFI	Female survivors of CLL had more fatigue than men in a multi-variate analysis.	Inconclusive
Overall QOL score	Geyer et al., 2017	MPN-SAF	There were similar overall QOL scores between men and women with MPNs.	Inconclusive
Overall QOL score	Heutte et al., 2009	EORTC QLQ-C30	Female survivors of HL reported lower QOL scores.	Inconclusive
Overall QOL score	Kreissl et al., 2020	EORTC QLQ-C30	There were similar overall QOL scores between male and female survivors of HL.	Inconclusive
Overall QOL score	Leak et al., 2013	FACT-Leukemia	QOL scores were higher for female NHL survivors, but they did not differ as much for older female survivors.	Inconclusive
Overall QOL score	Pashos et al., 2013	EQ-5D; FACT-Leukemia	Total QOL scores on the EQ-5D were similar between genders, but FACT-Leukemia scores were better for men than women.	Inconclusive
Pain	Geyer et al., 2017	MPN-SAF	A greater proportion of women with MPNs reported problems with pain than men. Women reported higher scores for abdominal pain.	Strong
Pain	Immanuel et al., 2019	EORTC QLQ-C30	Male survivors of B-cell malignancies reported fewer symptoms of pain.	Strong
Pain	Pashos et al., 2013	EQ-5D	Women with CLL reported more pain/discomfort.	Strong
Physical function	Heutte et al., 2009	EORTC QLQ-C30; MFI	Female survivors of HL experienced worse physical function and overall health.	Strong
Physical function	Immanuel et al., 2019	EORTC QLQ-C30; EQ-5D	Female survivors of B-cell malignancies had worse physical functioning.	Strong
Physical function	Kreissl et al., 2020	EORTC QLQ-C30	Female survivors of HL had lower functioning scores.	Strong
Physical function	Morishita et al., 2013	SF-36	Women with hematologic malignancies had lower physical functioning.	Strong
Physical function	Stauder et al., 2018	EQ-5D	Women with MDSs experienced restrictions in all elements tested by the EQ-5D.	Strong

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TABLE 2. Levels of Evidence for Sex-Based Differences in QOL, Symptoms, and Symptom Burden (Continued)

Symptom	Reference	Instrument	Results	Level of Evidence
Psychological effects	Arden-Close et al., 2011	QOL-Cancer Survivor	Male survivors of HL and NHL with late treatment effects had worse psychological QOL.	Inconclusive
Psychological effects	Pashos et al., 2013	EQ-5D	Women with CLL had worse anxiety and depression.	Inconclusive
Psychological effects	Stauder et al., 2018	EQ-5D	Anxiety and depression were higher in women with MDSs.	Inconclusive
Symptom burden	Geyer et al., 2017	MPN-SAF	There was a higher symptom burden for female survivors of MPNs.	Strong
Symptom burden	Heutte et al., 2009	EORTC QLQ-C30	Female survivors of HL reported higher symptom scores.	Strong
Symptom burden	Kreissl et al., 2020	EORTC QLQ-C30	Female survivors of HL reported higher symptom scores.	Strong
Symptom burden	Pashos et al., 2013	EQ-5D	Women with CLL experienced increased pain, fatigue, anxiety, depression, and difficulty doing normal activities.	Strong

BFI—Brief Fatigue Inventory; CLL—chronic lymphocytic leukemia; EORTC QLQ-C30—European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire—Core 30; EQ-5D—EuroQol 5-Dimension; FACT—Functional Assessment of Cancer Therapy; HL—Hodgkin lymphoma; MDS—myelodysplastic syndrome; MFI—Multidimensional Fatigue Inventory; MPN—myeloproliferative neoplasm; MPN-SAF—Myeloproliferative Neoplasm Symptom Assessment Form; NHL—non-Hodgkin lymphoma; QOL—quality of life

patients diagnosed with myelodysplastic syndromes (MDSs) (Stauder et al., 2018). Acute leukemias were not well represented, with data from only 69 patients included. This review identifies vital knowledge gaps around sex differences in QOL, symptoms, and symptom burden experienced by patients with acute or chronic leukemia.

QOL, Symptom, and Symptom Burden Differences

QOL: Differences in QOL between men and women among survivors of hematologic malignancies were inconclusive (Geyer et al., 2017; Heutte et al., 2009; Kreissl et al., 2020; Leak et al., 2013; Pashos et al., 2013). Three studies (Geyer et al., 2017; Kreissl et al., 2020; Pashos et al., 2013) showed similar overall QOL scores between sexes. In contrast, Heutte et al. (2009) reported that among survivors of Hodgkin lymphoma, women had lower QOL scores than men on the EORTC QLQ-C30 following treatment. Leak et al. (2013) reported that women scored higher than men on the FACT-Leu for overall QOL. These measurements were taken after the completion of treatment in survivors of non-Hodgkin lymphoma.

Fatigue: Staging and treatment are different for patients with diagnoses of hematologic malignancies

than for patients with solid tumors. However, both groups experience fatigue as a common troubling symptom that interferes with QOL (Hofer et al., 2018). Five studies identified sex-based differences in fatigue, with conflicting results (Geyer et al., 2017; Heutte et al., 2009; Morishita et al., 2013; Pashos et al., 2013; Shanafelt et al., 2007). Pashos et al. (2013) noted that fatigue was worse, more severe, and more hindering to activities among women. This study was focused on patients with chronic lymphocytic leukemia (CLL) initiating treatment. It comprised 1,140 patients, with females representing 38% ($n = 430$) of the sample. Fatigue was measured using the BFI. Shanafelt et al. (2007) found similar results in patients with CLL using multivariate analysis that controlled for different cancer stages, with women reporting more fatigue than men. Overall, 40% had been treated with chemotherapy or monoclonal antibody-based therapy, and 9% were receiving active treatment (Shanafelt et al., 2007). Research on patients with MPNs found fatigue as measured by the BFI to have greater severity, higher frequency, and more interference with activities among women (Geyer et al., 2017). A study by Morishita et al. (2013) found similar fatigue scores on the Piper Fatigue Scale

TABLE 3. QOL, Symptom, and Symptom Burden Assessment Instruments

Name	Number of Items, Format, and Scoring	Subscales Measured	Reliability and Validity	Time to Administer and Recall Period
Brief Fatigue Inventory	■ 9-item, 11-point Likert-type scale measuring fatigue level and interference with daily life with responses to statements ranging from 0 (no fatigue) to 10 (as bad as you can imagine) ■ Suggested cut points for fatigue levels are 1–3 (mild), 3–7 (moderate), and 8–10 (severe).	■ Not applicable	■ Internal consistency = 0.96 ■ Test-retest not reported in original study ■ Validity: criterion related, concurrent, construct, divergent	■ Recall period: current and past 24 hours ■ Time to administer: 3–5 minutes
Chalder Fatigue Scale	■ 11-item, 5-point Likert-type scale measuring fatigue with responses to questions ranging from 1 (none of the time) to 5 (all the time) ■ Higher scores indicate greater fatigue.	■ Mental fatigue ■ Physical fatigue	■ Cronbach's alpha: 0.86–0.92 ■ Relative operating characteristic of 0.845 ■ Validity: known group	■ Recall period: past month ■ Time to administer: less than 5 minutes
European Organisation for Research and Treatment of Cancer QOL Questionnaire—Core 30	■ 30-item, 4-point Likert-type scale measuring QOL with responses to questions ranging from 1 (not at all) to 4 (very much) ■ Higher scores indicate worse QOL. ■ The final 2 questions use a 7-point Likert-type scale with responses ranging from 1 (very poor) to 7 (excellent).	■ Cognitive functioning ■ Emotional functioning ■ Physical functioning ■ Role functioning ■ Social functioning	■ Cronbach's alpha greater than or equal to 0.7 ■ Test-retest not reported in original study ■ Validity: criterion related, concurrent, predictive, construct, convergent, divergent, known group	■ Recall period: past week ■ Time to administer: 11 minutes
EuroQol 5-Dimension	■ 5-item, 3-point Likert-type scale measuring QOL with responses to statements ranging from 1 (no problem) to 3 (incapacity) ■ Higher scores indicate worse QOL. ■ The final item uses a visual analog scale with scores ranging from 0 (the worst health you can imagine) to 100 (the best health you can imagine).	■ Anxiety/depression ■ Mobility ■ Pain/discomfort ■ Self-care ■ Usual activities	■ Cronbach's alpha = 0.85 ■ ICCs: 0.78 and 0.73 ■ Validity: criterion related, construct, predictive, convergent, divergent, known group	■ Recall period: current ■ Time to administer: 3–5 minutes
FACT—General	■ 27-item, 5-point Likert-type scale measuring well-being with responses to statements ranging from 0 (not at all) to 4 (very much) ■ Reverse scored for some items	■ Emotional well-being ■ Functional well-being ■ Physical well-being ■ Social well-being	■ Internal consistency: 0.69–0.82 ■ Test-retest: 0.82–0.92 ■ Validity: criterion related, concurrent, construct, convergent, divergent, known group	■ Recall period: past 7 days ■ Time to administer: 5–10 minutes

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TABLE 3. QOL, Symptom, and Symptom Burden Assessment Instruments (Continued)

Name	Number of Items, Format, and Scoring	Subscales Measured	Reliability and Validity	Time to Administer and Recall Period
FACT-Leukemia	■ 44-item, 5-point Likert-type scale measuring well-being with responses to statements ranging from 0 (not at all) to 4 (very much) ■ Reverse scored for some items	■ Emotional well-being ■ Functional well-being ■ Leukemia ■ Physical well-being ■ Social well-being	■ Internal consistency: 0.75–0.96 ■ ICC = 0.86	■ Recall period: past 7 days ■ Time to administer: 10–15 minutes
Hospital Anxiety and Depression Scale	■ 14-item, 4-point Likert-type scale measuring anxiety and depression with responses to statements ranging from 0 (not at all) to 3 (all the time) ■ Reverse scored for some items ■ A total score of 0–7 indicates healthy, 8–10 indicates borderline, and 11–21 indicates unhealthy.	■ Anxiety ■ Depression	■ Cronbach's alpha: 0.77 for anxiety and 0.79 for depression ■ Validity: criterion related, construct, known groups	■ Recall period: past week ■ Time to administer: 2–5 minutes
Impact of Cancer, version 2	■ 37-item, 5-point Likert-type scale measuring impact of cancer with responses to statements ranging from 1 (strongly disagree) to 5 (strongly agree) ■ Higher scores indicate greater impact of cancer.	■ Positive impact of cancer ■ Negative impact of cancer	■ Cronbach's alpha: 0.76–0.89 ■ Validity: concurrent, construct	■ Recall period: current ■ Time to administer: 10–15 minutes
MPN Symptom Assessment Form	■ 18-item, 11-point Likert-type scale measuring the effects of symptoms of MPNs with responses to statements ranging from 0 (absent) to 10 (worst imaginable) ■ 0–100 scaled score, with higher numbers for total symptom scores indicating higher symptom burden	■ Abdominal pain ■ Bone pain ■ Concentration difficulties ■ Early satiety ■ Fatigue ■ Inactivity ■ Night sweats ■ Pruritus ■ Weight loss	■ Cronbach's alpha = 0.83 ■ ICC > 0.7	■ Recall period: current ■ Time to administer: about 5 minutes
Multidimensional Fatigue Inventory	■ 20-item, 5-point Likert-type scale measuring fatigue with responses to statements ranging from 1 (yes, that is true) to 5 (no, that is not true) ■ Higher scores indicate more fatigue. A score range from 0–19 indicates no fatigue, 20–39 indicates low to medium fatigue, and 40–100 indicates high fatigue. ■ A change of greater than 10 points is clinically significant.	■ Mental fatigue ■ Reduced activity ■ Reduced motivation	■ Good internal consistency except for activity and motivation subscales ■ Validity: content, construct, between and within groups, convergent with a visual analog scale	■ Recall period: lately ■ Time to administer: 5–10 minutes
Piper Fatigue Scale	■ 22-item, 10-point Likert-type scale measuring fatigue with responses to questions ranging from 1 (none or no distress) to 10 (a great deal) ■ The total score is the mean of the 22 individual item responses. A score of 1–3 indicates mild fatigue, 4–6 indicates moderate fatigue, and 7–10 indicates severe fatigue.	■ Affect ■ Behavior ■ Cognition/mood ■ Sensory	■ Cronbach's alpha: 0.69–0.95 ■ ICC for test-retest: 0.98 ■ Internal consistency ■ Content validity	■ Recall period: current or today ■ Time to administer: 5–10 minutes

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TABLE 3. QOL, Symptom, and Symptom Burden Assessment Instruments (Continued)

Name	Number of Items, Format, and Scoring	Subscales Measured	Reliability and Validity	Time to Administer and Recall Period
QOL-Cancer Survivor	■ 41-item, 11-point scale measuring QOL with responses to statements ranging from 0 (worst) to 10 (best) ■ Reverse scored for some items	■ Physical well-being ■ Psychological well-being ■ Social well-being ■ Spiritual well-being (subcomponents: fears and distress)	■ Cronbach's alpha between items and subscales: 0.81–0.9 ■ Test-retest = 0.89 ■ Validity: criterion related, known experts, construct with known groups ■ Construct with 17 variables accounting for 91% of variance in QOL ■ Correlation with FACT-General of 0.78	■ Recall period: current ■ Time to administer: 10 minutes
SF-36®	■ 36-item scale measuring overall health and functional status scored in 2 steps ■ In the first step, each item is scored from 0 (lowest) to 100 (best). In the second step, the average scores of items within each subscale are taken to find the 8 subscale scores.	■ Vitality ■ Physical functioning ■ Body pain ■ General health perceptions ■ Physical role functioning ■ Emotional role functioning ■ Social role functioning ■ Mental health	■ Cronbach's alpha = 0.85 ■ Reliability = 0.75 (for all dimensions except social functioning) ■ Social functioning reliability = 0.73	■ Recall period: 4 weeks, 1 week, and 24 hours ■ Time to administer: 5–10 minutes
SF-12v2®	■ 12-item scale measuring overall health and functional status with 8 subscale scores weighted and summarized into physical and mental component summaries	■ Vitality ■ Physical functioning ■ Body pain ■ General health perceptions ■ Physical role function ■ Emotional role function ■ Social role function ■ Mental health	■ Test-retest: 0.86–0.89 ■ Validity: criterion related, concurrent, construct, convergent, divergent, known group	■ Recall period: typical day and past 4 weeks ■ Time to administer: 5–10 minutes

FACT—Functional Assessment of Cancer Therapy; ICC—interclass correlation coefficient; MPN—myeloproliferative neoplasm; QOL—quality of life

between men and women before and after allogeneic hematopoietic stem cell transplantation. In a separate study, Heutte et al. (2009) found fatigue among survivors of Hodgkin lymphoma as measured by the

MFI not to be predicted by sex. In terms of fatigue, the results are inconclusive for sex differences, with three studies suggesting that fatigue is increased in women compared with men. Two studies of patients

with CLL found that women reported more fatigue. The other study results may have been confounded by disease and setting, showing similar fatigue scores for men and women.

Physical functioning: Patients with hematologic malignancies often experience symptoms that affect physical functioning. In this review, physical functioning was measured using the EORTC QLQ-C30, EQ-5D, MFI, and SF-36 (Heutte et al., 2009; Immanuel et al., 2019; Kreissl et al., 2020; Morishita et al., 2013; Stauder et al., 2018). Women reported reduced physical functioning than men in five studies (Heutte et al., 2009; Immanuel et al., 2019; Kreissl et al., 2020; Morishita et al., 2013; Stauder et al., 2018). The results from these studies were consistent, providing strong evidence that women have reduced physical functioning associated with a hematologic malignancy diagnosis compared with men. Immanuel et al. (2019) found that physical functioning among survivors of hematologic malignancies was reduced in women compared with men. Morishita et al. (2013) found that in the early phase following hematopoietic stem cell transplantation, scores for HRQOL and physical functioning as measured by knee extensor strength, hand grip strength, and the six-minute walk test, were significantly lower for women than for men ($p < 0.01$). Heutte et al. (2009) conducted research focused on 935 survivors of Hodgkin lymphoma with more than 2,516 assessments performed during the study, which found that female survivors had lower physical functioning scores than male survivors at all time points. Kreissl et al. (2020) also examined the physical symptoms throughout the cancer trajectory in survivors of Hodgkin lymphoma from the time of diagnosis to five years into survivorship. They found that women reported lower functional scores than men on the EORTC QLQ-C30. Stauder et al. (2018) reported that being female with low- to intermediate-1-risk MDS was significantly associated with decreased scores on the EQ-5D index ($p < 0.001$). In all studies for this review, women reported reduced physical functioning in comparison to men.

Psychological effects: The review of differences between men and women in psychological effects among patients with hematologic malignancies was inconclusive, with three studies (Arden-Close et al., 2011; Pashos et al., 2013; Stauder et al., 2018) reporting sex-based differences. In a prospective, observational study, Pashos et al. (2013) compared 710 males with 430 females diagnosed with CLL. Women (35.3%) reported greater anxiety/depression than men (27.8%) on the EQ-5D ($p = 0.012$). The patients were

KNOWLEDGE TRANSLATION

- Improved awareness and understanding of sex differences in quality of life, symptoms, and symptom burden may improve care.
 - A tailored approach with awareness of sex-based differences may enhance delivery of care.
 - Ongoing research is needed to identify and confirm sex-based differences in symptoms or other health-related outcomes associated with specific types of hematologic malignancy.
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measured at baseline and within two months of starting treatment for CLL. On average, women ($\bar{X} = 71$ years, $SD = 11$ years) were older than men ($\bar{X} = 68$ years, $SD = 11$ years), and it is unclear whether this discrepancy in age influenced the results (Pashos et al., 2013). In another study, Arden-Close et al. (2011) evaluated the HRQOL of 115 survivors of lymphoma aged 18–45 years for whom it had been more than five years since their last treatment. Men who experienced more late effects from their treatment reported worse psychological HRQOL as measured by the QOL-Cancer Survivor instrument ($r = 0.5$, $p < 0.001$). Analysis of variance indicated that although women reported being able to discuss topics of concern, men related that they wanted to review more topics than had been discussed ($p = 0.01$). These two studies showed varying sex-based differences in anxiety and depression; however, they were also conducted at different time points in the disease trajectory, which may have influenced the results. Stauder et al. (2018) measured anxiety and depression of individuals recently diagnosed with lower-risk MDS using the EQ-5D. They reported that women experienced increased problems with anxiety and depression ($p < 0.001$) (Stauder et al., 2018). The studies by Pashos et al. (2013) and Stauder et al. (2018) indicated that anxiety and depression were reported more frequently among women when they were initially diagnosed with their hematologic malignancies or at the beginning of treatment. In the study by Arden-Close et al. (2011), which evaluated patients more than five years into survivorship, men reported worse psychological HRQOL. It is unclear why these results differ. However, time of measurement in relation to diagnosis and treatment is an important variable to consider for psychological differences reported.

Pain: The results from three studies (Geyer et al., 2017; Immanuel et al., 2019; Pashos et al., 2013) indicate that women diagnosed with hematologic malignancies experience more pain than men with a

similar diagnosis. In a study of 2,006 patients diagnosed with MPNs, Geyer et al. (2017) reported that women had particularly high scores for abdominal-related symptoms ($p \leq 0.001$). Of the 2,006 participants, 1,089 were female, lending credibility to their findings that abdominal pain is a greater problem for women diagnosed with MPNs. In a study by Immanuel et al. (2019) of 131 participants with a median age of 66 years, men reported fewer symptoms of pain on the EORTC QLQ-C30 and the EQ-5D instruments. Most participants in this study had lymphoma (Immanuel et al., 2019). Similarly, a study by Pashos et al. (2013) found that, of 1,140 patients (710 males and 430 females), more women (45.2%) than men (35.8%) reported problems with pain or discomfort as measured by EQ-5D domain-specific data ($p = 0.0077$). Additional research is warranted to improve understanding of the trajectory of pain experienced among patients diagnosed with a hematologic malignancy.

Symptom burden: Symptom burden often results when multiple symptoms occur together, which may cause distress that impairs functioning; this is common among patients with cancer (Cleeland, 2007). In addition to symptom burden, hematologic malignancies may also cause symptom clusters. A symptom cluster is defined as a stable group of concurrent symptoms that are related to one another and distinct from other symptom clusters (Kim et al., 2005). Based on this integrative review, women have a greater symptom burden than men (Geyer et al., 2017; Heutte et al., 2009; Kreissl et al., 2020; Pashos et al., 2013). Among patients with MPNs, Geyer et al. (2017) noted that the microvascular symptom cluster dominated the symptom burden experienced by women. Symptoms in this cluster were headache, fatigue, insomnia, concentration difficulties, and dizziness. Pashos et al. (2013) described a higher symptom burden for female patients diagnosed with CLL. These symptoms were pain ($p = 0.0077$), fatigue ($p < 0.0001$), anxiety/depression ($p = 0.012$), and difficulty doing normal activities ($p = 0.0015$). Both studies enrolled more than 1,000 patients, and each studied only one type of hematologic malignancy—either MPNs (Geyer et al., 2017) or CLL (Pashos et al., 2013). Studies by Heutte et al. (2009) and Kreissl et al. (2020) focused on survivors of Hodgkin lymphoma. Both studies found that women experienced a greater symptom burden than men. Studies focused on only one type of hematologic malignancy may be key to understanding differences in symptom burden between men and women, because hematologic malignancies are heterogeneous. Additional evidence is needed to further explore

symptom burden and symptom clusters among the various hematologic malignancies.

Discussion

Clinical and Research Implications Affecting QOL

Although there are many different hematologic malignancies that affect men and women almost equally, an integrative review of the literature around sex-based differences in QOL, symptoms, and symptom burden experienced by patients and survivors has not been previously published. As a result, these differences have not been recognized or treated effectively. This review integrates the results of several studies to identify the evidence from research of how symptoms, symptom burden, and overall QOL differ between men and women. This knowledge may enable healthcare providers to focus on the relevant needs identified in this integrative review. Current studies indicate that women experience hematologic malignancies differently than men and have increased physical symptoms and limitations, including increased pain and symptom burden, when diagnosed and during treatment. Areas of conflicting data about sex-based differences in the experience of hematologic malignancies include overall QOL, fatigue, and psychological effects, with some studies describing similar experiences between sexes. The data are primarily limited to patients with CLL and lymphoma. More studies are needed to identify or confirm disparities in patients with other hematologic malignancies, such as acute myeloid leukemia, chronic myeloid leukemia, and MDS.

Limitations

This integrative review has several limitations. There were several different instruments used to measure QOL and symptoms in survivors of various hematologic malignancies. This limits comparison between the studies. Other limitations included the number of hematologic malignancies studied and the potential confounding variables of cancer stage and type of treatment. Some of the studies controlled for other confounding variables. However, there was not consistency from one study to another, which limits the generalizability of the results.

Implications for Nursing

Lower physical functioning in women compared with men has been reported in an evaluation of more than 5,000 cancer survivors (Oertelt-Prigione et al., 2021). These survivors were diagnosed with colorectal, hematologic (e.g., CLL, non-Hodgkin lymphoma,

Hodgkin lymphoma, multiple myeloma), basal cell/squamous cell, and thyroid cancers. These findings are similar to those of the current integrative review. With this knowledge, nurses are better prepared to assess and support female patients and survivors. Practice improvements could include enhanced baseline assessments of physical status and customized plans of care developed to assist with identified weaknesses, such as physical therapy consultations. Women may need more conditioning exercises during and following transplantation to maintain physical function and continue independently performing activities of daily living. Other additions to the nursing plan of care may include an expanded pain assessment with the goal of identifying sex-specific interventions to better manage pain.

Conclusions

Despite the limitations, consistent findings were identified for sex-based differences in specific symptoms of hematologic malignancies. Women diagnosed with hematologic malignancies experience a greater physical effect from their cancer and treatment, experience more pain, and carry a greater symptom burden. Improved understanding of sex-based differences in symptoms and treatment side effects in patients with hematologic malignancies may lead to better patient outcomes, and tailored support for individual, sex-specific needs can improve QOL, improve symptom management, and decrease symptom burden.

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