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<Original Article>

Quality of Life and Related Factors in Patients with Metastatic Breast Cancer Undergoing Cancer Pharmacotherapy: Systematic Review and Meta-analysis

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Key words: Metastatic breast cancer, Quality of Life, Cancer Pharmacotherapy, Meta-analysis, Systematic review

ABSTRACT

Purpose: To determine the Quality of Life (QoL) and related factors of patient with metastatic breast cancer (MBC) undergoing cancer pharmacotherapy. **Methods:** Pub Med, CINAHL, Web of Science, PsycINFO, and Scopus were searched for studies published in English between January 2011 and March 2022. Data on QoL scores and related factors of patients with MBC were extracted. For QoL scores, a meta-analysis was conducted for each QoL scale. **Results:** Twenty-one studies were included in this systematic review. The meta-analysis showed that the mean of the Functional Assessment of Cancer Therapy-Breast score for 828 participants was 86.98 (95% CI [76.12, 97.84]). The global QoL score on the European Organization for Research and Treatment of Cancer QLQ-C30 for 621 patients was 56.70 (95% CI [52.33, 61.06]). Chemotherapy, pain, fatigue, disease progression, anxiety, and depression were regarded as factors associated with QoL of patients with MBC. **Conclusion:** Factors associated with decreased QoL in patients with MBC undergoing cancer pharmacotherapy included chemotherapy, physical symptoms, disease progression, anxiety, and depression. Further exploration of QoL and related factors in patients with MBC is warranted.

INTRODUCTION

Breast cancer has the highest incidence and mortality rate among all diagnosed cancer cases in many countries [1]. Overall, 20 – 50% of patients with early breast cancer eventually develop metastatic diseases, such as bone and lung metastases [2]. The 5-year relative survival rate for metastatic breast cancer (MBC) has improved from 18% to 36% [3], yet the median overall survival remains 3 years [2] and its cure remains elusive. Therefore, the goal of MBC treatment is to prolong life, while maintaining good Quality of Life (QoL) through cancer pharmacotherapy.

Patients diagnosed with MBC present higher levels of anxiety and depression than those diagnosed with early-stage breast cancer [4]. Anxiety, depression, and other psychosocial problems contribute to a decline in the QoL of patients with MBC [5]. Furthermore, the medical condition and cancer pharmacotherapy place immense physical burden on patients with MBC [6], including fatigue, pain, sleep disturbances [7], changes in body weight and appetite, and hair loss [8]. The

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physical symptoms lead to a decline in the QoL of patients with MBC [9, 10] and lower their QoL compared with those with early-stage 0breast cancer [11].

The advances in cancer pharmacotherapy over the past decade have been remarkable, with the advent of molecular targeted therapies and immune checkpoint inhibitors along with chemotherapy [12]; they are expected to improve survival for patients with MBC [2]. Since the side effects of these drugs often differ from those of chemotherapy [12] and the QoL of patients with MBC may be altered, clarifying the QoL of patients with MBC and its associated factors is crucial.

Systematic reviews have been published on the QoL of survivors of breast cancer [13, 14] and on that of patients with MBC who participated in clinical trials [12]. However, a recent systematic review on the QoL and factors related to patients with MBC undergoing cancer pharmacotherapy is lacking. Since cancer pharmacotherapy is the mainstay of treatment for patients with MBC, clarifying the QoL of patients with MBC receiving cancer pharmacotherapy and its associated factors is critical. These findings may contribute to the research field by improving or maintaining the QoL of patients with MBC who are undergoing cancer pharmacotherapy for a long duration. Therefore, this study aimed to investigate the QoL and related factors in patients with MBC who are undergoing cancer pharmacotherapy.

METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement guidelines [15].

Search strategy

A literature search was conducted using Pub Med, CINAHL, Web of Science, PsycINFO, and Scopus in April 2022. The following keywords were used for the systematic literature search: "Breast Cancer 'Title'," "Recurrence OR Metastatic OR Advance*," and "Quality of Life." According to Cardoso [2], over the past decade, the quality of clinical research on breast cancer has improved; the search period was limited to studies published in English between January 2011 and March 2022.

Inclusion and exclusion criteria

The inclusion criteria were patients diagnosed with recurrent, advanced, and MBC and recipients of cancer pharmacotherapy. The primary endpoints were QoL and related factors. The exclusion criteria were studies on patients with Stage I–III breast cancer; studies with no variable of the QoL; and studies, clinical trials, interventional studies, and systematic reviews on patients with breast cancer undergoing surgery or radiation therapy. Moreover, studies that involved qualitative analysis were not included in this review.

Data selection process

Figure 1 shows that the literature search review yielded 7,928 studies. Duplicates were excluded. The selected studies were further scrutinized based on the inclusion and exclusion criteria. Thereafter, titles and abstracts were screened. The remaining studies were read in their entirety to determine whether they met the selection criteria.

Quality assessment

The selected studies were evaluated based on the Joanna Briggs Institute's critical appraisal tools. "Yes" was indicated for assessment items that were clear, "No" for items that were not clear, "Unclear" for items that were unclear, and "Not applicable" for items that were inapplicable. One point was assigned to items that were clear. With reference to a previous study [16], studies with a total score of 4 or more points were selected.

Methods of analysis

To organize the study findings, information such as author names, year of publication, country, study population, QoL scale, QoL scores, and QoL-related factors were extracted. A meta-analysis was carried out for a pooled estimate of patients' QoL. Given the undeniable variability across studies, including differences in participants and protocols, heterogeneity was considered and a meta-analysis was conducted using a random effects model (Der Simonian-Laired method). The analysis was performed using STATA 17 (TX, USA).

Ethical considerations

This study was not reviewed by the Ethics Review Committee of Osaka University of Medical and Pharmaceutical Sciences because it did not involve human participants. Studies published in available information and was approved by the Ethical Review Committee. Ethical issues related to publication and publicity, such as copyright and plagiarism, were accounted for.

RESULTS

Study selection

The literature search yielded 7,928 studies, and duplicates were excluded (**Figure 1**). The studies were further scrutinized based on the selection and exclusion criteria and 960 studies were screened. Thereafter, the titles and abstracts were scrutinized, which lead to the exclusion of 888 studies. The remaining 72 studies were read in their entirety, and 23 studies met the selection criteria. Two studies were further excluded because their total assessment scores were below 4 points. Finally, 21 studies were included in this systematic review.

Study overview

The overview of the study is presented in **Table 1**. Ten studies used the Functional Assessment of Cancer Thera-

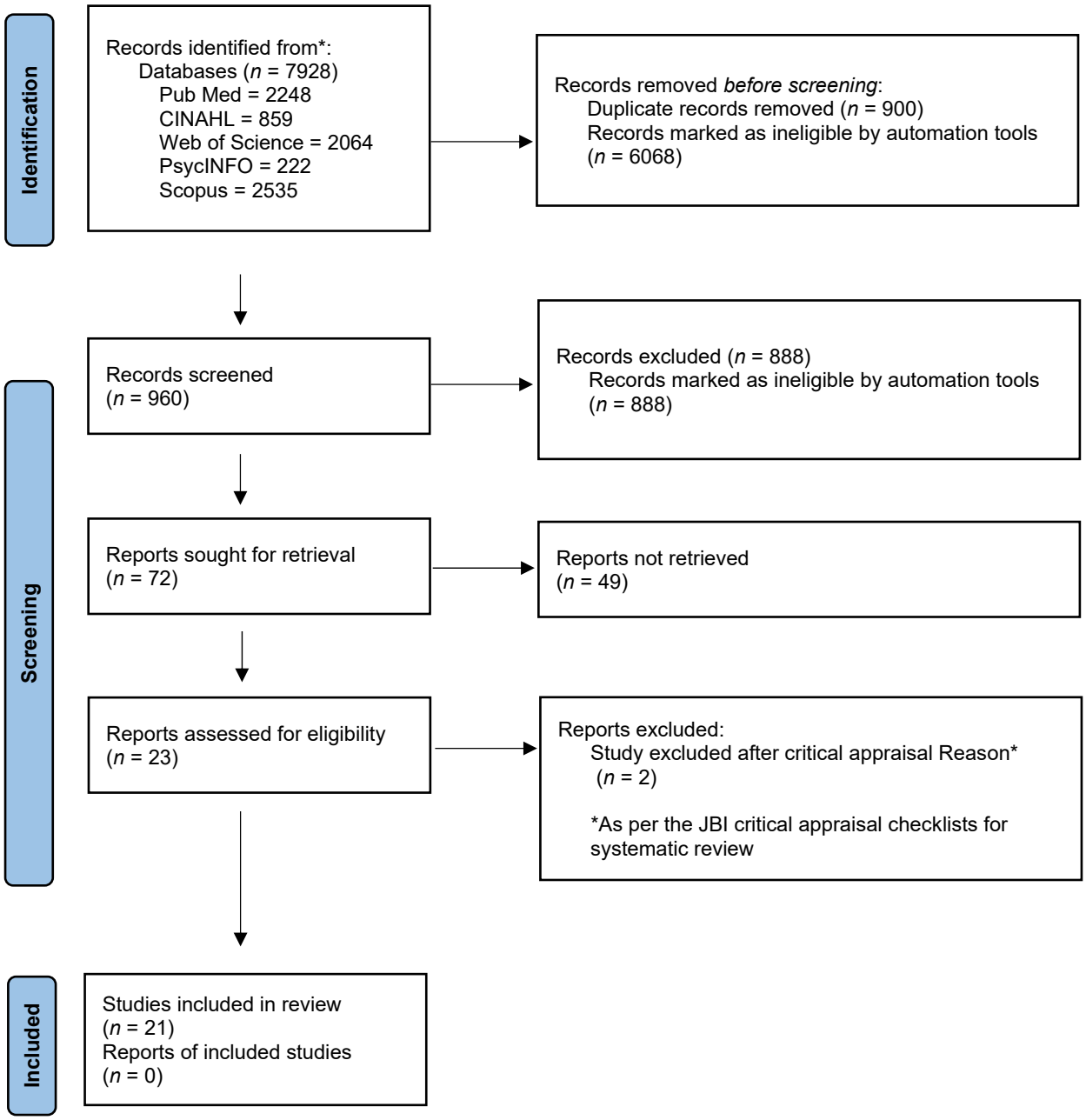


Fig. 1 Flowchart of the study selection.

py-Breast (FACT-B) as a measure of QoL [17–26]. The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) was used in eight studies [27–34]. The European QoL 5 dimensions (EQ-5D) was used in five studies [26, 29, 34–36]. The Medical outcomes study 36-Item Short-Form Health Survey (SF-36) was used in two studies [28, 37].

Characteristics of the study population

The number of participants in the studies ranged from 18–739 people. The participants' age ranged from 25–93 years. The time between the diagnosis of MBC and participants' responses to the survey ranged from less than one week to more than 15 years. Metastatic sites included bones, lungs, liver, and brain, with cancer spreading to multiple sites from a single site. Treatment types included endocrine therapy, chemotherapy, and molecular targeted therapy.

Table 1 Characteristics of included trials (*n* = 21)

First author, year,country	Questionnaire	Participants	Age years mean ± SD or range	Sites of Metastasis *n* (%)	Treatment *n* (%)	Time since diagnosis with MBC mean ± SD or range
Ecclestone[17], 2016,Canada	FACT-B	Total = 174	32 - 93	Bone meta = 43 Visceral disease = 131	Bone meta / Visceral disease RT = 38 (88.37) / 113 (86.26) Chemo = 28 (66.67) / 115 (87.79) ET = 39 (90.70) / 99 (75.57)	Bone meta / Visceral disease 0–1 year = 14(35.90) / 35(27.13) > 1 to 4 years = 16(41.03) / 60(46.51) > 4 years = 9(23.08) / 34(26.36)
Gupta[18],201 4,USA and UK	FACT-B FACT-G	Total = 360	58.3 ± 6.3	-	ET = 169(46.9) Chemo = 191(53.1)	4.51 ± 5.02 yrars Median 3.00(2.0 - 5.0) yrars
Meisel[19],201 2,USA	FACT-B	Total = 28 (Responder = 18)	34.5 - 63.5 (34.5 - 63.5)	Bone meta = 4(14.3) Bone + Visceral = 18(64.3) Visceral disease = 6(21.4)	ET = 10 (35.7) Chemo = 16 (57.1) None = 2 (7.1)	Women who had been living with metastatic breast cancer for 5 years or more and who were receiving care
Park[20],2012, Korea	FACT-B	Total = 55 (Responder = 52)	48.34 ± 8.28	Bone and soft tissue = 18 (51.4) Visceral = 13 (37.1) Visceral + bone and soft tissue = 4 (11.4)	-	20.26 ± 22.19 months
Reed[21],2012, UK	FACT-B	Total = 235 (Hospital = 110, Wesite = 125)	Hospital = 25 - 84 Wesite = unknown	Bone only = 75 (31.9) Other = 159 (67.7) Unknown = 1 (0.4)	-	median two years (range one week to 15 years)
Shaikh[22],202 2,Kenya	FACT-B	Total = 114	51.4 ± 12.7	-	-	-
Sheean[23],201 5,USA	FACT-B	Total = 25	58.8 ± 12.8	Bone = 14 (56) Liver = 4 (16) Lung = 13 (52) Brain = 6 (24) Other = 6 (24)	ET = 11 Chemo = 12	36.9 ± 29.3 months
Shin[24],2016, USA	FACT-B FACT-B TOI	Total = 140	- ET = 66.0 ± 11.3 Chemo = 58.6 ± 11.8	-	ET = 40 Chemo = 100	ET = 52.9 (0 – 353.9) months Chemo = 58.5 (0 – 274.9) months
Wood[25],201 7,USA,Europe	FACT-B	Total = 739 StageIII = 128 (17.3) StageIV = 611 (82.7)	65.2 ± 10.6	Bone only = 174 (28.5) Visceral only = 254 (41.6) Bone and visceral = 119 (19.5) Other = 141 (19.1)	Chemo = 305(41.3) ET = 293(36.9) Other = 141(19.1)	-
Yang[26],2020 ,China	FACT-B EQ-5D-5L	Total = 446 P state = 125 R state = 20 S state = 258 M state = 43	52.03 (± 8.97) P state = 51.37 ± 8.62 R state = 49.9 ± 7.08 S state = 52.65 ± 8.75 M state = 51.23 ± 11.6	-	RT = 60.76 % Chemo = 91.70 % Targeted therapy = 9.64 % ET = 68.83 %	-
Costa[27],2017 ,Brazil	EORTC QLQ-C30	Total = 400 without meta = 118 loco-regional meta = 160 distant meta = 122	-	-	Late post-surgery = 4 % Chemo = 70 % RT = 4 % ET = 25.3 % Bisphosphonates = 19.8 %	-
Kokkonen[28], 2017,Finland	SF-36 EORTC QLQ-C30	Total = 211 (Responder = 128)	60 (34 – 84)	Skeleton = 95 (74.2) Liver = 60 (46.9) Lungs = 32(25.0) Brain = 11(8.6) Other organs = 48(37.5)	Chemo = 122(95)	The time from the primary diagnosis to that of the metastases was median to 3 years (0 – 12 years).
Lambert[29],20 18,Canada	EORTC QLQ-C30 QLQ-BR23 EQ-5D-5L	Total = 202 First-line-pf = 67 First-line-pd = 17 2nd line-pf = 88 2nd-line-pd=29	- First-line-pf = 66 ± 10 First-line-pd = 60 ± 10 ≧ 2nd-line-pf = 64 ± 10 ≧ 2nd-line-pd = 64 ± 9	Bone was the most frequent site of metastasis	Most patients in first line were treated with hormonal therapy only, and most patients in ≥2nd line were receiving Chemo only.	First-line-pf = 1.6 ± 2.1 Fiest-line-pd = 1.3 ± 1.1 ≧ 2nd -line-pf = 4.4 ± 3.2 ≧ 2nd-line-pd = 4.6 ± 3.8
Lima[30],2020, Brazil	EORTC QLQ-C30	Total = 199 stage II = 23 stage III = 31 stage IV = 145	-	-	-	-
McClelland[31] ,2015,USA	EORTC QLQ-C30 EORTC QLQ-BR23	Total = 113	58 ± 11.61 (30 - 84)	Bone meta = 67 % Bone+Visceral = 38 % Visceral disease = 64 %	Chemo = 94 (83)	36.11 ± 39.56 months
Muller[32],201 8,Germany	EORTC QLQ-C30 EORTC QLQ-BR23	Total = 1744 (Responder = 329) Patients without progression = 266 Patients with progression = 63	 Patients without progression = 59.8 ± 12.3 Patients with progression = 59.0 ± 10.6	-	not progression/progression ET = 25.5 % / 19.0 % Chemo=28.1%/47.6% Everolimus and ET = 2.7% / 9.5% Other = 12.2 % / 9.5 % Unknown = 31.6 % / 14.3 %	-
Soylu[33],2016 ,Turkey	EORTC QLQ-C30	Total = 69 (Responder = 55)	50 ± 9.96	-	-	-
Wallwiener[34] ,2016,Germany	EORTC QLQ-C30 EORTC QLQ-BR23 EQ-5D-5L	Total = 96 metastatic = 65 (68) adjuvant = 31(32)	56.68 ± 12.38	Osseous = 49 (75) Pulmonary = 26 (40) Hepatic = 17 (26) Cerebral = 3 (5)	-	-
Claessens[35],2 020,Dutch	EQ-5D-3L	Total = 92	< 65 = 60 (65) ≧ 65 = 32 (35)	Bone only = 11 (12) Soft tissue without visceral or CNS involvement = 17 (18) Visceral without CNS involvement = 60 (65) CNS = 4 (4)	None = 6 (7) ET (with or without targeted therapy) = 47 (51) Chemo (with or without targeted therapy) = 34 (37) Targeted therapy alone = 5 (5)	De novo metastatic disease = 14 (15) < 24 months = 10 (11) ≧24 months = 68 (74)
Zigman[36],20 20,Croatia	EQ-5D	Total = 135 (Responder = 114) healthy highrisk = 33 localized stage = 49 advanced stage = 32	-	-	-	-
Seah[37],2014, USA	SF-36	Total = 57 (Responder = 52) (Women = 50,Men = 2)	Median, at metastatic diagnosis 51.6 (22.4 - 80.8)	Brain = 3 (6) Liver = 24 (46) Lung = 13 (25) Bone = 30 (58) LN = 20 (38) Others = 12 (23)	Chemo = 20 (39) ET = 23 (44) Anti-HER2 = 2 (4) Chemo+anti-HER2 = 3 (6) ET+Anti-HER2 = 4 (8)	Median 5.5 (0.9 - 12.4) months

ET = Endocrine therapy
Chemo = Chemo therapy
Anti-HER2 = Anti-HER2 therapy
RT = Radiation therapy
P state = without cancer recurrence and metastasis
R state = with cancer recurrencewithin a year
S state = with primary and recurrent breast cancer for the second year and above
M state = metastatic cancer
pf = progression-free
pd = progressive disease

The QoL of Patient with MBC

Meta-analysis of the FACT-B scores

The FACT-B scores are presented in **Table 2**. Total FACT-B score ranged from 0–148, with higher scores indicating better QoL. The mean total FACT-B scores in the included literature [18–21, 24, 26] ranged from 61.66–111.6. The meta-analysis showed that the mean FACT-B score for 828 participants was 86.98 (95% CI [76.12, 97.84]), with high heterogeneity (I^2 = 98.18%; p = 0.00). The results of the meta-analysis are presented in **Table 4**.

Table 2 The FACT -B scores and factors related to the QOL (n = 10)

First author	Participants	FACT -B						
		Total score	Physical well -being	Social well -being	Emotional well -being	Functional well -being	Breast cancer subscale	Factor related to the QOL
		Ave ± SD or Median	Ave ± SD or Median	Ave ± SD or Median	Ave ± SD or Median	Ave ± SD or Median	Ave ± SD or Median	
Ecclestone[17]	Bone meta = 43	106	22	25	17	18	27	Brain metastases was significantly associated with higher physical well -being scores (p = 0.034).
		(61.4 - 140.0)	(5.0 - 28.0)	(7.0 - 28.0)	(2.0 - 24.0)	(0.0 - 28.0)	(7.8 - 36.7)	
	Visceral meta = 131	107	22	24	17	19	26	Participation in clinical trials was significantly associated with QOL(p = 0.024).
		(38.8 - 143.3)	(1.0 - 28.0)	(5.0 - 28.0)	(3.0 - 24.0)	(0.0 - 28.0)	(6.0 - 40.0)	
								Time of diagnosis of metastasis (at or after initial diagnosis) was not significantly associated with QOL.
Gupta[18]	n = 360	74.10 ± 19.22	13.54 ± 6.14	18.68 ± 5.05	11.97 ± 4.95	12.20 ± 5.12	17.71 ± 5.94	ET users have higher health -related QOL (p < 0.05), higher satisfaction with treatment, and better feelings about side effects (p < 0.001) than chemo users.
Meisel[19]	n = 18	100.44 ± 19.30	21.72 ± 4.94	20.94 ± 4.57	11.33 ± 4.04	20.33 ± 6.07	26.11 ± 4.43	
Park[20]	n = 52	90.44 ± 20.33	19.90 ± 6.66	17.19 ± 6.27	16.62 ± 4.62	17.25 ± 5.63	20.12 ± 6.20	Higher level of education (> 13 years) was a significant predictor for better QOL among women with MBC (p = 0.023).
								Older age (≧50 years at recurrence) was associated with better QOL (p =0.054).
								Age at first visit, marital status, occupation, and economic status showed no significant differences.
								Clinical variables such as menstruation, time since first diagnosis, time since recurrence, PS, chemotherapy, and recurrence pattern showed no significant differences.
								Strong predictors of QOL were psychological needs(p = 0.008), physical and daily living needs(p = 0.022) and sexuality needs(p = 0.040).
Reed[21]	n = 235	89.0 ± 21.8	16.8 ± 7.4	20.1 ± 5.6	12.9 ± 5.3	17.3 ± 6.2	21.9 ± 7.5	Marital status, economic status, time since metastatic diagnosis, and site of metastasis were not associated.
								Older women have lower Psysical well -being (p = 0.04) and higher Socical well -being (p = 0.002) than younger women.
								Women with children have lower functional well -being and (p = 0.001) and Total Score (p = 0.03)
								Older women (p < 0.001) and women with bone metastases (p = 0.002) were significantly better in social well -being.
								Chemotherapy had a more negative impact on functional well -being than ET (P = 0.007).
								Maternal status, economic status, length of time since metastatic diagnosis, and site of metastasis were not relevant.
Shaikh[22]	n = 114	-	-	-	-	-	-	QoL was better scores with urban residence (p =0.002), internet access (p =0.010), and stable disease (p =0.042).
Sheean[23]	n = 25	-	21.8 ± 5.1	21.7 ± 6.5	18.6 ± 4.0	19.8 ± 5.0	25.9 ± 5.5	Physical well -being (p = 0.05) and emotional well -being(p < 0.01) were significantly lower for females with MBC when compared to women with all stages of breast cancer.
Shin[24]	ET = 40	111.6 ± 18.4	23.4 ± 4.4	21.7 ± 6.5	17.9 ± 3.6	21.1 ± 5.2	28.0 ± 5.9	Patients with MBC who are treated with chemotherapy experience worse FACT -B TOI than those treated with ET(p < 0.01） .
	Chemo = 100	104.9 ± 20.0	20.4 ± 5.5	22.4 ± 5.2	17.0 ± 4.6	19.2 ± 5.6	26.1 ± 6.1	In particular, patients who received chemotherapy had significantly lower physical well -being than those who received ET (20.4 vs. 23.4, p < 0.01).
								Higher scores on the FACT -B TOI were associated with lower depression (p < 0.01) and anxiety (p < 0.01)
Wood[25]	n = 739	85.9 ± 19.7	18.8 ± 5.5	17.4 ± 5.7	13.1 ± 4.5	12.7 ± 5.4	24.1 ± 5.6	ET users have higher FACT -B score than chemotherapy users(p < 0.00001)
	(StageII = 128, StageIV = 611)							Patients with both bone and visceral metastases was lowest mean (SD) scores(p < 0.0001) than patients with both bone only or visceral metastases only.
								Receipt of a greater number of prior lines of therapy was associated with poorer well being scores(p < 0.0001).
								Patients with higher treatment expectations, fewer side effects, and higher treatment satisfaction had significantly higher HRQOL(p < 0.0001).
Yang[26]	R state = 20	61.66 ± 16.86	-	-	-	-	-	Patients in the R and M states had lower scores for overall QOL(R, p < 0.01; M,p < 0.05)
	M state = 43	64.27 ± 14.84	-	-	-	-	-	

ET = Endocrine therapy

Chemo = Chemotherapy

R states = with cancer recurrence within a year

M states = metastatic cancer

Meta-analysis of EORTC QLQ-C30 scores

The EORTC QLQ-C30 scores are presented in **Table 3**. The EORTC QLQ-C30 consists of global QoL, five functional scales, three symptom scales, and several single items as-

Table 3 The EORTC QLQ-C30 scores and factor related to the QOL (n = 8)

First author	Participants	EORTC QLQ-C30						Factor related to the QOL
		Global QOL	Physical	Role	Emotional	Cognitive	Social	
		Ave ± SD or Median	Ave ± SD or Median	Ave ± SD or Median	Ave ± SD or Median	Ave ± SD or Median	Ave ± SD or Median	
Costa[27]	Distant meta =122	-	-	-	-	-	-	Pain had the worst scores for QOL with a functional scale (p < 0.009),a Symptom Scale (p < 0.001) and a Global Health Scale(p < 0.006).
	With pain = 105	48.6 ± 23.1	54.0 ± 27.4	27.1 ± 31.3	47.9 ± 27.7	70.5 ± 30.2	77.1 ± 29.6	
	Without pain = 17	67.6 ± 20.4	74.5 ± 23.9	53.9 ± 36.1	70.1 ± 29.0	79.4 ± 23.9	88.2 ± 20.2	
Kokkonen[28]	n =128	61.5 ± 20.38	64.9 ± 22.10	68.2 ± 26.45	79.3 ± 18.39	83.1 ± 20.05	78.2 ± 23.71	QOL scores were generally lower in MBC patients compared to healthy controls
								Depression, pain, and advanced age are contributors to lower
Lambert[29]	n = 202	-	-	-	-	-	-	QOL was lower for patients in progressive disease than for patients in progression-free regardless of line-of-treatment group.
	First-line-pf = 67	-	77.1 ± 18.8	76.4 ± 28.4	77.7 ± 19.3	80.8 ± 21.6	80.8 ± 25.3	
	First-line-pd = 17	-	71.4 ± 20.9	65.7 ± 41.4	63.6 ± 23.6	80.4 ± 22.2	73.5 ± 29.5	
	≥2nd line-pf =88	-	75.0 ± 20.9	75.4 ± 27.9	78.8 ± 20.5	80.3 ± 21.1	79.9 ± 24.1	Fatigue was the symptom scale with the most negative impact on quality of life in MBC patients
	≥2nd-line-pd =29	-	68.9 ± 24.5	56.3 ± 33.5	72.1 ± 26.5	78.2 ± 19.0	66.7 ± 27.5	
Lima[30]	Stage IV = 145	29.7	21.4	8.6	34.3	56.7	44.6	Advanced disease negatively impacted health-related QoL.
McClelland[31]	n = 113	-	-	-	-	-	-	Age groups (30 - 49, 5 0- 65, 6 6- 85) were not associated with global QoL.
								Women 36 months after diagnosis with MBC reported a significant increase in global QoL (p = 0.005)
								Pain(p =.01) and fatigue (p < .001) was associated with decreased global QoL.
								Greater fatigue (p < .001) was decreased physical function.
								Both fatigue (p = .02) and body image (p = .001) were significant predictors of emotional function.
Muller[32]	without progression = 266	56.8 ± 20.0	69.4 ± 21.9	57.2 ± 31.2	58.0 ± 26.1	74.9 ± 25.1	61.0 ± 31.9	Progression status negatively impacts HRQOL(p = 0.04).
	with progression = 63	52.2 ± 21.7	69.1 ± 22.3	56.4 ± 28.8	55.2 ± 23.2	75.8 ± 25.5	60.8 ± 26.4	
Soylu[33]	n = 55	-	-	-	-	-	-	There was a statistically positive rela tionship between optimism, hope, and QoL (p < 0.05).
								Comparison of QoL subscales between patients who misunderstood and did not misunderstand the purpose of treatment showed no significant difference (p > 0.05)
Wallwiener[34]	Pooled score = 74	58.2 ± 21.0	72.9 ± 22.1	59.4 ± 32.5	63.6 ± 24.7	75.4 ± 26.2	61.4 ± 32.4	MBC patients have significantly poorer HRQOL than the general population(p < 0.0001)
	Meta = 42	57.4 ± 22.0	71.3 ± 23.1	62.6 ± 33.2	65.5 ± 25.2	71.7 ± 36.7	60.4 ± 30.5	
	Adjuvant = 32	59.0 ± 20.0	74.8 ± 21.0	55.6 ± 31.7	61.4 ± 24.4	78.4 ± 25.7	62.6 ± 35.0	

Table 4 Meta-analysis of the FACT-B scores

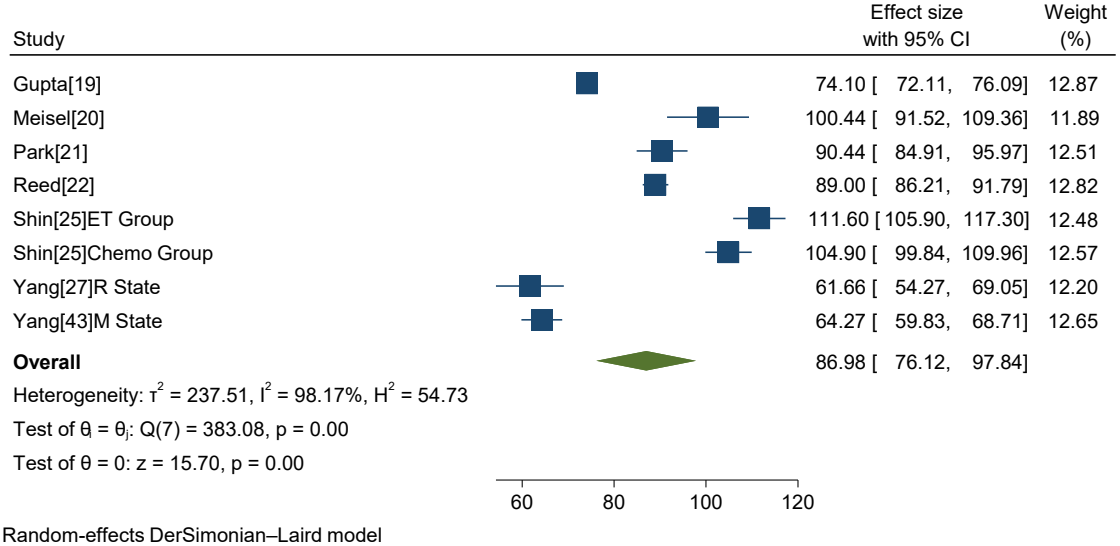
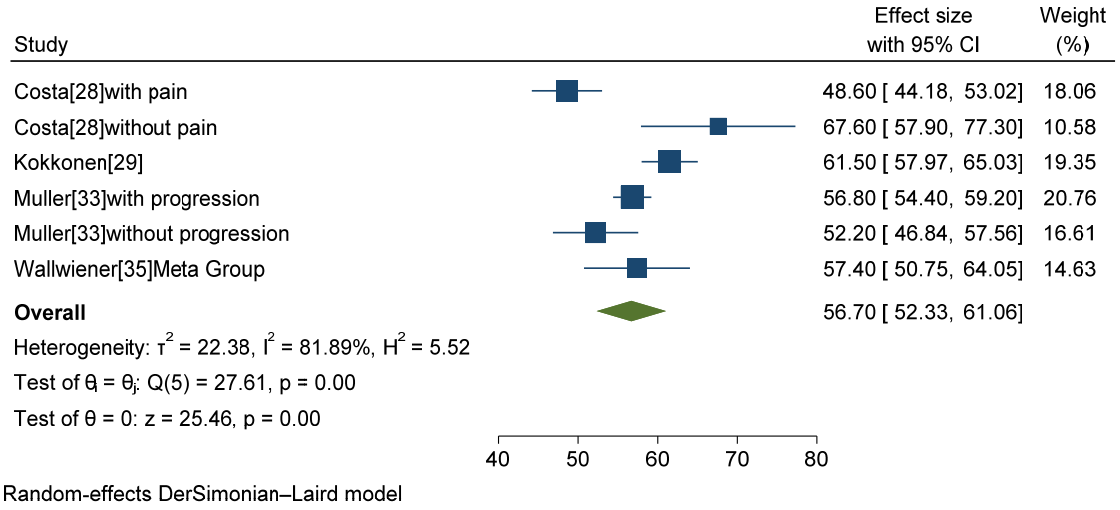


Table 5 Meta-analysis of EORTC QLQ-C30 scores



sessing additional symptoms commonly reported by cancer patients and the perceived financial impact of the disease. The QoL scores ranged from 0–100, with higher scores indicating better QoL on the global QoL and functional scales and lower scores indicating better QoL on the symptom scales. The mean global QoL score on the EORTC QLQ-C30 in the included literature [27, 28, 32, 34] ranged from 48.6–67.6. The meta-analysis showed that the mean global QoL score for 621 participants was 56.70 (95% CI [52.33, 61.06]), with high heterogeneity (I^2 = 81.89%; p = 0.00). The results of the meta-analysis are presented in **Table 5**.

Factors related to the QoL in patients with MBC (**Table 2, 3**)

Individual factors

Five studies [20, 21, 28, 31, 35] reported the association between age and QoL. Patients under 50 years of age at the time of MBC diagnosis had significantly lower FACT-B scores than those older than 50 years [20]. A significant difference in EQ-5D scores between patients under 65 years of age and those aged 65 or above was reported; moreover, the QoL of these patients was reported to decrease with old age [28, 35]. Two studies reported no association between age and QoL scores [21.31]. Two studies [20, 37] investigated the association between education and QoL. Patients with higher educational levels scored higher on the FACT-B [20] and SF-36 [37] than those with lower educational levels. Four studies [20–22, 37] investigated the association between marital status and QoL. One study established an association between marital status and QoL [22], whereas the other three reported no association [20, 21, 37]. Three studies [20, 21, 37] investigated the association between economic status and QoL. One study established an association between economic status and QoL [37], whereas the other two reported no such association [20, 21]. Patients without children [21], urban dwellers, and internet users [22] were reported to have significantly higher QoL scores as measured by the FACT-B.

Clinical factors

Seven studies [18, 20–22, 24, 25, 30] investigated the association between cancer treatment types and QoL. The patients undergoing chemotherapy had significantly lower QoL as measured by the FACT-B [18, 21, 22, 24, 25] than those undergoing endocrine therapy. Patients with comorbidities had significantly higher EQ-5D scores and lower QoL than those without [35]. One study established an association between menopausal status and QoL [22], whereas the other one reported no association [20]. Six studies [19–21, 31, 35, 37] investigated the association between the time since the MBC diagnosis and patients' QoL. Patients with less than 3 years since diagnosis had significantly lower EORTC QLQ-C30 scores than those with 3 years or more since diagnosis [30]. However, five studies [17, 20, 21, 35, 37] confirmed no association between time since MBC diagnosis and QoL. Six studies [17, 20, 21, 25, 31, 35] investigated the association between the location of metastases. Three studies [22, 35, 37] reported an association between the number of metastatic sites and QoL. These findings were not consistent across studies. Five studies [27–29, 35, 36] investigated the association between physical symptoms and QoL. Among the physical symptoms, pain [27, 28, 31, 36] and fatigue [29, 31] were identified as factors associated with a significant decrease in the QoL of patients with MBC. Cancer progression was also reported to have a significant negative impact on the QoL scores of patients with MBC [22, 29, 32].

Intrapersonal factors

Four studies [24, 28, 36, 37] investigated the association

between anxiety/depression and the QoL of patients with MBC. Anxiety and depression were identified as factors contributing to a significant reduction in the patients' QoL. Their unmet needs were significantly associated with lower FACT-B scores [20, 22]. Optimism has been reported to have a statistically positive relationship with FACT-B [33]. In addition, patients' EORTC QLQ-C30 scores were reported to decline significantly, as their body image decreased [33]. Perception of disease progression, perception of treatment intent, and expectations for the future were not found to be associated with EORTC QLQ-C30 scores [33].

DISCUSSION

QoL scores of patients with MBC

The results of the meta-analysis showed that the mean total FACT-B score for the patients with MBC was 86.98 and the mean QLQ-30 score was 56.70. Javan (2022) [14] reported a meta-analysis of survivors of breast cancer during and after treatment, with a FACT-B score of 84.39 and QLQ-30 score of 64.72. Hashemi (2020) [38] reported a meta-analysis of Eastern Mediterranean patients with early-stage and MBC, with a FACT-B score of 93.2 and a QLQ-30 score of 60.5. Since participants in these previous studies had mixed stages and treatment courses and the analyses were not adjusted for background factors, their comparisons with the results of this study must be made with caution. In future meta-analyses of QoL scores of breast cancer patients, considering the stage of disease and course of treatment is necessary.

Heterogeneity in the meta-analysis of patients' QoL was relatively high because patients undergoing chemotherapy and patients undergoing endocrine therapy were mixed in the assessment of QoL. As chemotherapy has a more negative impact on the QoL of patients than endocrine therapy [14], the treatment types should be considered when assessing or analyzing QoL.

QoL and individual factors in patients with MBC

There were conflicting results between studies regarding the relationship between QoL, age, and marital status of patients with MBC. Moreover, the patient's background, data collection methods, and sample size influenced the discrepancies in the results. Studies identifying an association between QoL and economic status of patients with MBC were conducted in the US, while the two studies identifying no association were conducted in the UK and Korea. The US lacks a public health insurance system with universal coverage [39], resulting in high medical expenses, which negative affects the QoL of patients with MBC. Conversely, the UK has a state-run National Health Service and Korea has a public medical insurance system [39], making it economical for individuals to pay for treatments. Therefore, no association was found between the QoL of patients with MBC and their economic status.

Higher educational levels, absence of children, urban residence, and access to the Internet is shown to be associated with a higher QoL in patients with MBC. However, the number of these studies is small, and the evidence is inadequate to regard them as factors associated with the QoL of patients with MBC. In the future, researchers should consider the background of the participants, the sample size, and the country's healthcare system while investigating the QoL and individual factors of patients with MBC.

QoL and clinical factors in patients with MBC

Regarding QoL of patients with MBC and treatment types, five of seven studies reported that chemotherapy had a more negative impact on the QoL of patients than endocrine therapy. Approximately 20–40% of patients undergo chemotherapy as first-line treatment [40] and experience side effects such as hair loss, nausea, and fatigue [41]. Since chemotherapy for these patients is long-term, the side effects overlap and symptoms accumulate [42]. Patients undergoing endocrine therapy were reported to be less troubled by side effects compared with the those undergoing chemotherapy [43]. Hence, chemotherapy has a stronger negative impact on the QoL of patients than endocrine therapy, and it can be regarded as a factor contributing to the decline of the QoL of patients with MBC.

In the association between QoL and physical symptoms in patients with MBC, pain and fatigue were associated with a decline in patients' QoL. The prevalence of pain in cancer patients ranges from about 20–50% in early-stage cancer patients, but as the cancer metastasizes, the prevalence of pain increases to 90% [44, 45]. Pain affects the levels of anxiety, depression, and social isolation [46], impairing functional capacity and limiting daily life [47]. Therefore, pain decreases the QoL of patients with MBC. Moreover, fatigue is caused by the progression of cancer and pharmacotherapy for cancer, which affects the functional capacity and the role functioning of patients [48]. Therefore, fatigue is related to the decline in the QOL of patients with MBC.

Furthermore, disease progression had a negative impact on the QoL of patients. Disease progression was associated with worsening general physical conditions, physical symptoms such as fatigue and sleep disturbances, and treatment side effects [49]. The progression of disease in patients with MBC is a complex interplay of various physical symptoms, side effects of treatment, and deterioration of general condition, all of which contribute to a decline in QoL and its related factors.

Therefore, for patients undergoing cancer pharmacotherapy, nurses need to conduct a detailed assessment of pain and fatigue, along with other physical symptoms, and focus on support and physical activity-based interventions aimed at symptom relief [50] to improve QoL.

QoL and intrapersonal factors in patients with MBC

Anxiety and depression were associated with QoL in patients with MBC. They are more aware of death than patients with early breast cancer [51], leading to a higher level of anxiety and depression that harms patients' mental health. Consequently, anxiety and depression contribute to the reduced QoL owing to their effect on decreased physical functioning [52]. Therefore, nurses should focus on psychological interventions to alleviate anxiety and depression in patients with MBC.

Only one study examined the association of the QoL of patients with MBC with optimism, unmet needs, and body image, thus providing insufficient evidence to assert that these intrapersonal factors are associated with the QoL of patients of MBC. In future research, these factors should be regarded as factors that may be associated with the QoL of patients with MBC.

Study limitations

Although a comprehensive literature search was conducted for this systematic review, it was limited to studies published in English. Therefore, it remains unclear whether the present study succeeded at comprehensively covering the literature on the QoL of patients with MBC. Moreover, discrepancies were found among the studies pertaining to factors associated with the QoL of the target population. This can be attributed to participants' backgrounds, treatment types, confounding factors, and use of varied QoL scales. It is careful conclusions need to be drawn regarding whether the factors identified are specific to patients with MBC. Therefore, further research is needed.

CONCLUSION

The meta-analysis showed that the mean of the FACT-B score for 828 participants was 86.98 (95% CI [76.12, 97.84]). The global QoL score on the EORTC QLQ-C30 for 621 patients was 56.70 (95% CI [52.33, 61.06]). The QoL of patients with MBC was found to be associated with treatment types, physical symptoms, disease progression, anxiety, and depression. With advancements in cancer pharmacotherapy, increased life expectancy may be possible for patients with MBC in the future. Nurses must not only support patients with early-stage breast cancer but also those with MBC to improve their QoL so that they can live independently as "cancer survivors." Therefore, we need to explore factors associated with the QoL of these patients and accumulate additional research to enhance support for improving their QoL.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin. CA*. 2021;71(3):209–49.
2. Cardoso F, Spence D, Mertz S, Corneliussen-James D, Sabelko K, Gralow J, Cardoso MJ, Peccatori F, Paonessa D, Benares A, Sakurai N, Beishon M, Barker SJ, Mayer M. Global analysis of advanced/metastatic breast cancer: decade report (2005-2015). *Breast*. 2018;39:131–8.
3. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the number of women living with metastatic breast cancer in the United States. *Cancer Epidemiol Biomarkers Prev*. 2017;26(6):809–15.
4. Tsaras K, Papathanasiou IV, Mitsi D, Veneti A, Kelesi M, Zyga S, Fradelos EC. Assessment of depression and anxiety in breast cancer patients: prevalence and associated factors. *Asian Pac J Cancer Prev*. 2018;19(6):1661–9.
5. Delgado-Sanz MC, García-Mendizábal MJ, Pollán M, Forjaz MJ, López-Abente G, Aragonés N, Pérez-Gómez B. Heath-related quality of life in Spanish breast cancer patients: a systematic review. *Health Qual Life Outcomes*. 2011;14;9:3.
6. Tometich DB, Mosher CE, Hirsh AT, Rand KL, Johns SA, Matthias MS, Outcalt SD, Schneider BP, Mina L, Storniolo AMV, Newton EV, Miller KD. Metastatic breast cancer patients' expectations and priorities for symptom improvement. *Support Care Cancer*. 2018;26(11):3781–8.
7. Niklasson A, Paty J, Rydén A. Talking about breast cancer: which symptoms and treatment side effects are important to patients with advanced disease? *Patient*. 2017;10(6):719–27.
8. Reed E, Corner J. Defining the illness trajectory of metastatic breast cancer. *BMJ Support Palliat Care*. 2015; 5(4):358–65.
9. Ganz PA, Stanton AL. Living with metastatic breast cancer. *Adv Clin Exp Med*. 2015;862:243–54.
10. Haddou RB, El RK, Ouasmani F, Nejjari,C, Bekkali R, Montazeri A., & Mesfioui A. Quality of life in Arab women with breast cancer; a review of the literature. *Health Qual Life Outcomes*. 2016;14:64. doi: 10.1186/s12955-016-0468-9
11. Gonzalez L, Bardach A, Palacios A, Peckaitis C, Ciapponi A, Pichón-Riviere A, Augustovski F. Health-related quality of life in patients with breast cancer in Latin America and the Caribbean: A systematic review and meta-analysis. *Oncologist*. 2021;26(5):e794–e806.
12. Ghislain I, Zikos E, Coens C, Quinten C, Balta V, Tryfonidis K, Piccart M, Zardavas D, Nagele E, Bjelic-Radisic V, Cardoso F, Sprangers MAG, Velikova G, Bottomley A. European Organization for Research and Treatment

of Cancer (EORTC). *Qual Life Group Breast Cancer Group*. EORTC Headquarters. Health-related quality of life in locally advanced and metastatic breast cancer: methodological and clinical issues in randomised controlled trials. *The Lancet Oncology*. 2016;17(7):294–304.
13. Chopra I, Kamal KM. A systematic review of quality of life instruments in long-term breast cancer survivors. *Health Qual Life Outcomes*. 2012;10(10):14.
14. Javan BA, Raoofi S, Rafiei S, Pashazadeh KF, Kazerooni M, Bagheribayati F, Masoumi M, Doustmehraban M, Sanaei M, Zarabi F, Raoofi N, Beiramy CZ, Ahmadi B, Seyghalani TF, Sadat HB, Asadollahi E, Mir M, Deylami S, Zareei M, Sanaei H, Ghashghaee A. Global quality of life in breast cancer: systematic review and meta-analysis. *BMJ Support Palliat Care*. 2022-003642.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *J Clin Epidemiol*. 2021;134:178–89.
16. Mares MA, McNally S, Fernandez RS. Effectiveness of nurse-led cardiac rehabilitation programs following coronary artery bypass graft surgery:a systematic review. *rep.. JBI Database System Rev Implement Rep*. 2018; 16(12):2304–29.
17. Ecclestone C, Chow R, Pulenzas N, Zhang L, Leahey A, Hamer J, DeAngelis C, Bedard G, McDonald R, Bhatia A, Ellis J, Rakovitch E, Vuong S, Chow E, Verma S. Quality of life and symptom burden in patients with metastatic breast cancer. *Support Care Cancer*. 2016;24(9):4035–43.
18. Gupta S, Zhang J, Jerusalem G. The association of chemotherapy versus hormonal therapy and health outcomes among patients with hormone receptor-positive, HER2-negative metastatic breast cancer: experience from the patient perspective. *Expert Rev Pharmacoecon Outcomes Res*. 2014;14(6):929–40.
19. Meisel JL, Domchek SM, Vonderheide RH, Giobbie-Hurder A, Lin NU, Winer EP, Partridge AH. Quality of life in long-term survivors of metastatic breast cancer. *Clin Breast Cancer*. 2012;12(2):119–26.
20. Park BW, Hwang SY. Unmet needs and their relationship with quality of life among women with recurrent breast cancer. *J Breast Cancer*. 2012;15(4):454–61.
21. Reed E, Simmonds P, Haviland J, Corner J. Quality of life and experience of care in women with metastatic breast cancer: a cross-sectional survey. *J Pain Symptom Manage*. 2012;43(4):747–58.
22. Shaikh AJ, Dhillion N, Shah J, Kathomi C, Kiragu A, Asirwa FC, Nyongesa C, Kasmani R, Abayo I, Kirathe G, Sayed S. Supporting Kenyan women with advanced breast cancer through a network and assessing their needs and quality of life. *Support Care Cancer*. 2022;30(2):1557–67.
23. Sheean P, Kabir C, Rao R, Hoskins K, Stolley M. Exploring diet, physical activity, and quality of life in females with metastatic breast cancer: A pilot study to support future intervention. *J Acad Nutr Diet*. 2015;115(10):1690–8.
24. Shin JA, El-Jawahri A, Parkes A, Schleicher SM, Knight HP, Temel JS. Quality of life, mood, and prognostic understanding in patients with metastatic breast cancer. *J Palliat Med*. 2016;19(8):863–9.
25. Wood R, Mitra D, de Courcy J, Iyer S. Patient-reported quality of life and treatment satisfaction in patients with HR+/HER2- advanced/metastatic breast cancer. *Clin Ther*. 2017;39(8):1719–28.
26. Yang Q, Yu X, Zhang W. Health variations among breast-cancer patients from different disease states: evidence from China. *BMC Health Serv Res*. 2020;20(1):1033.
27. Costa WA, Monteiro MN, Queiroz JF, Gonçalves AK. Pain and quality of life in breast cancer patients. *Clinics (Sao Paulo)*. 2017;72(12):758–63.
28. Kokkonen K, Saarto T, Mäkinen T, Pohjola L, Kautio H, Järvenpää S, Puustjärvi-Sunabacka K. The functional capacity and quality of life of women with advanced breast cancer. *Breast Cancer*. 2017;24(1):128–36.
29. Lambert OV, Gouault LA, Castonguay A, Zanotti G, Tran T, Mates M, Lemieux J, Chabot P, Prady C, Couture F, Lachaine J. Real-world patient and caregiver reported outcomes in advanced breast cancer. *Curr Oncol*. 2018; 5(4):e282–e290.
30. Lima EOL, Silva MMD. Quality of life of women with locally advanced or metastatic breast cancer. *Rev Gaúcha Enferm*. 2020;41:e20190292.
31. McClelland SI, Holland KJ, Griggs JJ. Quality of life and metastatic breast cancer: the role of body image, disease site, and time since diagnosis. *Qual Life Res*. 2015;24(12): 2939–43.
32. Müller V, Nabieva N, Häberle L, Taran FA, Hartkopf AD, Volz B, Overkamp F, Brandl AL, Kolberg HC, Hadji P, Tesch H, Ettl J, Lux MP, Lüftner D, Belleville E, Fasching PA, Janni W, Beckmann MW, Wimberger P, Hielscher C, Fehm TN, Brucker SY, Wallwiener D, Schneeweiss A, Wallwiener M. Impact of disease progression on health-related quality of life in patients with metastatic breast cancer in the PRAEGNANT breast cancer registry. *Breast*. 2018;37:154–60.
33. Soylu C, Babacan T, Sever AR, Altundag K. Patients' understanding of treatment goals and disease course and their relationship with optimism, hope, and quality of life: a preliminary study among advanced breast cancer outpatients before receiving palliative treatment. *Support Care Cancer*. 2016;24(8):3481–8.
34. Wallwiener M, Simoes E, Sokolov AN, Brucker SY, Fas-

ching PA, Graf J. Health-related quality of life in metastatic and adjuvant breast cancer patients. *Geburtshilfe Frauenheilkd*. 2016;76(10):1065–73.
35. Claessens AKM, Ramaekers BLT, Lobbezoo DJA, van Kampen RJW, de Boer M, van de Wouw AJ, Dercksen MW, Geurts SME, Joore MA, Tjan-Heijnen VCG. Quality of life in a real-world cohort of advanced breast cancer patients: a study of the SONABRE Registry. *Qual Life Res*. 2020;29(12):3363–74.
36. Žigman T, Lukša I, Mihaljević G, Žarković M, Kirac I, Vrdoljak DV, Šerman L. Defining health-related quality of life in localized and advanced stages of breast cancer - the first step towards hereditary cancer genetic counseling. *Acta Clin Croat*. 2020;59(2):209–15.
37. Seah DS, Lin NU, Curley C, Weiner EP, Partridge AH. Informational needs and the quality of life of patients in their first year after metastatic breast cancer diagnosis. *J Community Support Oncol*. 2014;12(10):347–54.
38. Hashemi SM, Rafiemanesh H, Aghamohammadi T, Badakhsh M, Amirshahi M, Sari M, Behnamfar N, Roudini K. Prevalence of anxiety among breast cancer patients: a systematic review and meta-analysis. *Breast Cancer*. 2020;27(2):166–78.
39. Health and Welfare Statistics Association Japan. *J Health Welf Stat*. 2016;63(8):41–4.
40. Bonotto M, Gerratana L, Di Maio M, De Angelis C, Cinausero M, Moroso S, Milano M, Stanzione B, Gargiulo P, Iacono D, Minisini AM, Mansutti M, Fasola G, De Placido S, Arpino G, Puglisi F. Chemotherapy versus endocrine therapy as first-line treatment in patients with luminal-like HER2-negative metastatic breast cancer: A propensity score analysis. *Breast*. 2017;31:114–20.
41. Partridge, A. H., Burstein, H. J., & Winder, E. P. Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer. *J Natl Cancer Inst Monogr*. 2001;30:135–42. doi: 10.1093/oxfordjournals.jncimonographs.a003451
42. Asaumi K, Murakami Y. Investigation on the performance and difficulties of outpatient nurses engaging in prognosis of patients with metastatic/recurrent breast cancer who have multiple symptoms and are undergoing outpatient pharmacotherapy. *J Jpn Soc Cancer Nurs*. 2021;35:1–9.
43. Vivar CG, Canga N, Canga AD, Arantzamendi M. The psychosocial impact of recurrence on cancer survivors and family members: a narrative review. *J Adv Nurs*. 2009;65(4):724–36.
44. Beaton R, Pagdin-Friesen W, Robertson C, Vigar C, Watson H, & Harris SR. Effects of exercise intervention on persons with metastatic cancer: A systematic review. *Physiother Can*. 2009;61:141–53. doi: 10.3138/physio.61.3.141
45. Liu Y, Zhang PY, Na J, Ma C, Huo WL, Han L, Yu Y, & Xi QS. (2013). Prevalence, intensity, and prognostic significance of common symptoms in terminally ill cancer patients. *J Palliat Med*. 2013;16(7):752–7. doi: 10.1089/jpm.2013.0028
46. Mehta A, Chan LS. Understanding of the concept of "Total Pain" A prerequisite for pain control. *J Hosp Palliat Nurs*. 2008;10(1):26–32.
47. Fontanella C, Fanotto V, Rihawi K, Aprile G, Puglisi F. Skeletal metastases from breast cancer: pathogenesis of bone tropism and treatment strategy. *Clin Exp Metastasis*. 2015;32(8):819–33.
48. Penttinen HM, Saarto T, Kellokumpu-Lehtinen P, Blomqvist C, Huovinen R, Kautiainen H, Järvenpää S, Nikander R, Idman I, Luoto R, Sievänen H, Utriainen M, Vehmanen L, Jääskeläinen AS, Elme A, Ruohola J, Luoma M, Hakamies-Blomqvist L. Quality of life and physical performance and activity of breast cancer patients after adjuvant treatments. *Psycho Oncol*. 2011;20(11):1211–20.
49. Walker MS, Hasan M, Yim YM, Yu E, Stepanski EJ, Schwartzberg LS. Retrospective study of the effect of disease progression on patient reported outcomes in HER-2 negative metastatic breast cancer patients. *Health Qual Life Outcomes*. 2011;9:46.
50. Mokhtari-Hessari PP, Montazeri A. Health-related quality of life in breast cancer patients: review of reviews from 2008 to 2018. *Health Qual Life Outcomes*. 2020;18(1):338.
51. Vilhauer RP. A qualitative study of the experiences of women with metastatic breast cancer. *Palliat Support Care*. 2008;6(3):249–58.
52. Inhestern L, Beierlein V, Bultmann JC, et al. Anxiety and depression in working-age cancer survivors:a register-based study. *BMC Cancer*. 2017;17(1):347.

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