



A Systematic Review of Health-Related Quality of Life in Women with HER2-Positive Metastatic Breast Cancer Treated with Trastuzumab

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Abstract

Background Many trials of human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer treatment with trastuzumab have provided evidence of improved clinical outcomes. This systematic review examined how a regimen that includes trastuzumab affects patients' health-related quality of life (HRQoL) during and after treatment.

Methods A systematic search for articles published up to February 2023 without restrictions of language or publication year was performed using the Pubmed, Embase, and Scopus databases. We included studies of women aged > 18 years with metastatic HER2-positive breast cancer treated with a trastuzumab-containing regimen. We assessed the quality of the studies using the Cochrane Risk of Bias (RoB) tool (2.0) for randomized controlled trials (RCTs) and the Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I) tool for cross-sectional studies. We used Microsoft Excel to extract and synthesize data, and documented the review procedure following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results In total, eight studies compared 1104 trastuzumab-treated patients and 1003 non-trastuzumab-treated patients. Most studies were RCTs ($n = 7$) and one was a prospective observational study. All the included studies used the EORTC-QLQ-C30, EORTC-QLQ-BR23, FACT-B, or FACT-G questionnaires. During treatment, patients taking regimens that included trastuzumab showed clinical improvement in HRQoL, social functioning, and role functioning. After the treatment, patients' HRQoL profiles in the trastuzumab and chemotherapy arms were similar. However, trastuzumab (versus chemotherapy) treatment led to clinically improved functional status, role and physical functioning, and fatigue. The quality assessment revealed some concerns in most RCTs, with the risk of bias being high in two studies, low in one study, and moderate in the cross-sectional study.

Conclusions Trastuzumab-containing regimens administered to HER2-positive breast cancer patients at the metastatic stage evidenced beneficial effects on total HRQoL during and after treatment. Upon therapy cessation, patients' HRQoL scores for both interventions improved. Nevertheless, HRQoL profiles of patients treated with trastuzumab were more favorable, particularly for functional status, role functioning, physical well-being, and fatigue.

Clinical Trials Registration This review was registered in PROSPERO (registration number: CRD42021259826).

1 Introduction

Overexpression of human epidermal growth factor receptor 2 (HER2) is associated with an increased incidence of metastasis in approximately 20% of breast cancer survivors [1–3]. Patients with metastatic breast cancer and overexpression of HER2 typically have advanced disease with a poor prognosis as well as shorter overall survival and disease-free survival periods [2]. Trastuzumab, a HER2-targeted therapy,

has shown improved clinical outcomes and is recommended for patients with metastatic breast cancer with overexpression of HER2 [4]. Numerous trials have demonstrated the advantageous survival-related effects of trastuzumab, either when used alone or in conjunction with chemotherapy [5–8]. According to the findings of several studies, the addition of trastuzumab to a chemotherapy regimen significantly increases overall survival as well as progression-free survival compared with these survival outcomes associated with a chemotherapy regimen alone [9, 10].

The objective of metastatic breast cancer treatment is to extend survival and improve health-related quality of

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Key Points for Decision Makers

The addition of trastuzumab in human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer treatment regimens improved treatment outcomes and did not cause a deterioration in health-related quality of life (HRQoL).

While being treated with trastuzumab-containing regimens, HER2-positive breast cancer patients showed more favorable HRQoL profiles than those treated solely with chemotherapy.

Although metastatic breast cancer patients undergo prolonged treatment, incorporating trastuzumab into their treatment reportedly has a positive impact on their complete HRQoL profile, including their physical functioning, fatigue, emotional and role functioning, pain, insomnia, and financial constraints.

life (HRQoL) [11, 12]. In particular, treatment is aimed at supporting patients in overcoming challenging obstacles throughout their illness, including severe medical conditions, emotional suffering, and decreased everyday functioning [13, 14]. The physical and psychological impacts of breast cancer can be captured using HRQoL measurements. They reflect an increasingly widely acknowledged crucial endpoint of cancer therapy [15, 16], offering essential details on treatment effects from patients' perspectives [17]. Therefore, assessing the HRQoL of breast cancer patients to contextualize the results of treatment is important [18, 19]. Notably, HRQoL measurements should include both disease symptoms and the potential adverse effects of treatments [20].

This systematic review was aimed at summarizing findings on how trastuzumab affects the HRQoL of patients with HER2-positive metastatic breast cancer. Although previous studies have explored the overall HRQoL of women with metastatic stage breast cancer [21–23], none have specifically investigated the influence of trastuzumab on HRQoL. Therefore, this review examined how a regimen that includes trastuzumab affects a patient's HRQoL both during and after treatment.

2 Materials and Methods

2.1 Protocol and Registration

The protocol for this systematic review, which follows the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) guidelines [24], was recorded in PROSPERO (registration number: CRD42021259826).

2.2 Systematic Literature Search and Study Selection

We performed a systematic search of the literature published up to February 2023 across three databases (Pubmed, Embase, and Scopus); the search terms were based on three key thematic focus areas, i.e. breast cancer, trastuzumab, and HRQoL. The search terms are presented in the Online Resource (Table A). We manually searched the included articles' reference lists to identify any other potentially relevant articles for inclusion in the review.

This review included articles published in any language and in any year. All of the selected articles focused on women with HER2-positive metastatic breast cancer, with the intervention groups comprising regimens with and without trastuzumab. Review articles, articles that had not been peer reviewed, and posters and abstracts for which full-text articles were not available were excluded from the review. We included women aged ≥ 18 years, with no age limit, as breast cancer mostly affects adults and its incidence increases with age [25].

Applying the study's inclusion criteria, two reviewers (SMK and FDAS) independently screened the titles and abstracts of papers to select those for inclusion in the full-text review. The full text of the articles was reviewed to select studies for inclusion in the final analysis. Disagreements arising during the review process were discussed and resolved by the reviewers. Data extraction was conducted using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), and the review procedure was documented as a PRISMA flow diagram, which helped to clarify reasons for excluding studies.

The data in all the studies were extracted by SMK and subsequently verified by FDAS. The data items comprised the author(s), year of publication, study methods, patients' ages, instrument type, participant criteria, interventions, HRQoL outcomes, and conclusions.

2.3 Health-Related Quality of Life (HRQoL) Assessment

Changes in the significance of the minimal important difference (MID) reported in the included studies were used to summarize the HRQoL measures. The MID scores in the Functional Assessment of Cancer Therapy—Breast (FACT-B) were 7–8, whereas those for the Functional Assessment of Cancer Therapy—General (FACT-G) and Trial Outcome Index (TOI) were 5–6 points [26]. For the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), differences of ≥ 10

points were deemed clinically significant for all domains [27].

2.4 Quality Assessment

Quality assessments of randomized controlled trials (RCTs) were conducted using the Cochrane Risk of Bias (RoB) tool 2.0 [28], and the cross-sectional study was evaluated using the Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I) tool [29]. The evaluation was independently performed by two authors (SMK and FDAS).

3 Results

3.1 Study Selection

The database search yielded 5752 articles, which were subsequently reduced to 257 records after eliminating duplicates and screening titles and abstracts. Following the application of eligibility criteria, this number was further reduced to 89 full-text articles, which were subsequently assessed. Ultimately, only eight records matched the

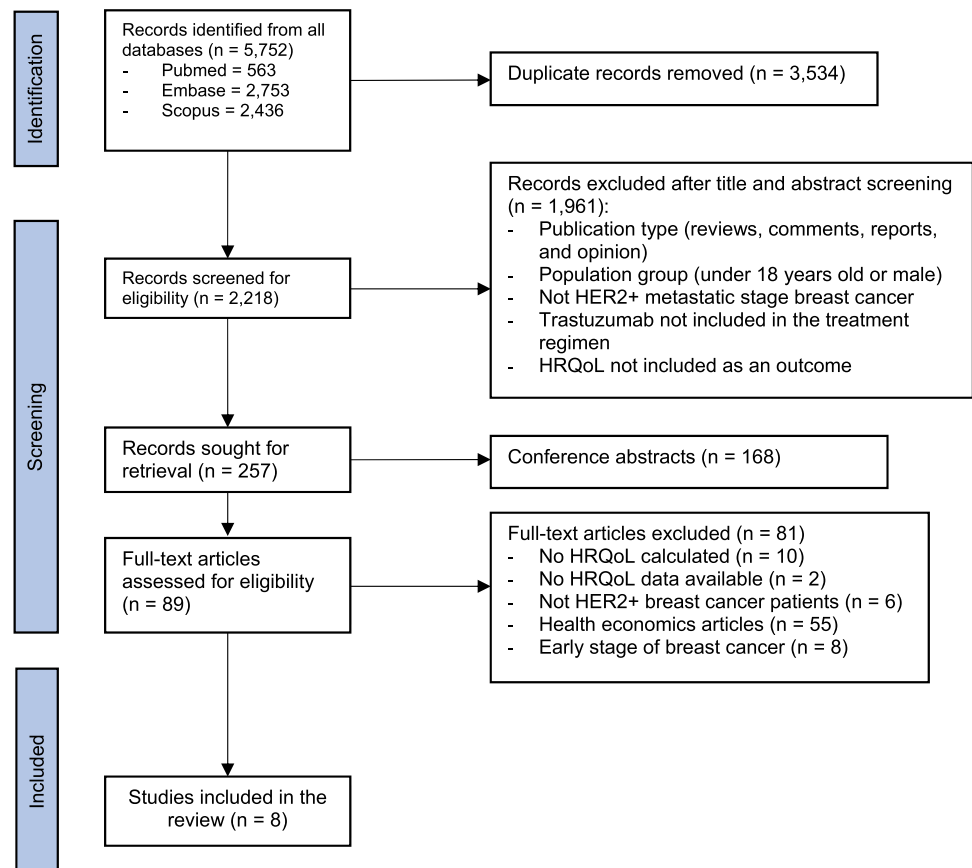
inclusion characteristics and were included in this review. The selection process is outlined in detail in Fig. 1.

3.2 Characteristics of the Included Studies

The majority of the studies included recruited patients aged >18 years [30–36], with one study limiting participants to those aged 18–80 years [37]. Five studies [30, 33–35, 37] focused on patients who had received hormonal treatment but not chemotherapy [30, 32], and one study [31] included patients who had received anthracycline, taxane, and trastuzumab in the neoadjuvant and adjuvant settings. Another study [32] included postmenopausal women who had undergone hormonal and trastuzumab treatments. Some studies [32, 34–36] only recruited patients with adequate organ function and excluded those with untreated or symptomatic bone and brain metastasis [33, 35, 36]. In addition, five studies [30, 32, 34, 35, 37] recruited participants with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, while two studies [33, 36] only enrolled patients with a Karnofsky Index value $\geq 60\%$. Table 1 presents the characteristics of the included studies.

Of the eight studies, seven were RCTs [30–36] and one was a prospective observational study [37]. The duration of all the studies ranged between 8 and 52 months. The median

Fig. 1 PRISMA flow diagram for the study. *HER2* human epidermal growth factor receptor 2, *HRQoL* health-related quality of life, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses



treatment durations for the treatment arms in the RCTs were 48 weeks [36], 54 months [32], 32 weeks [33], 56 weeks [36], and 18 weeks [34]. The median follow-up times were 35 months [30] and 14 months [35]. In addition, one study was conducted over a 1-year period [37].

The interventions were as follows: five studies [30, 33, 35–37] assessed trastuzumab combined with chemotherapy versus chemotherapy alone, and the remaining studies examined the effects of trastuzumab combined with targeted therapy [31], hormone therapy [32], and eribulin mesylate [34]. Specifically, patients in three studies [33, 36, 37] were administered anthracycline plus cyclophosphamide combined with trastuzumab, while trastuzumab emtansine (T-DM1) and docetaxel, considered a comparator group, were evaluated in two other studies [30, 35]. In one study [31], a combination of trastuzumab and lapatinib versus lapatinib monotherapy was administered until either disease progression or withdrawal due to the occurrence of toxicity. In another study, trastuzumab and lapatinib were administered after treatment with aromatase inhibitors [32]. A combination of trastuzumab with eribulin mesylate was assessed in one study [34].

The EORTC-QLQ-C30 questionnaire was administered in three studies [33, 36, 37] and the FACT-B questionnaire was administered in four studies [30–32, 35]. In one trial [31], the FACT-B questionnaire was used along with the FACT-G questionnaire and the TOI. The EORTC-QLQ-C30 and QLQ-BR23 questionnaires were implemented together in one study [34], and the FACT-B and FACT-G questionnaires were administered together in another study [32]. Most studies [31, 33–36] showed a response rate for questionnaire completion that exceeded 50% (Table 1); however, in one study [32], the response rate was 24%, while two studies did not report the response rate.

3.3 HRQoL Evaluation

3.3.1 HRQoL During Treatment

In all studies that reported HRQoL during patients' treatment [30–34, 36], on the whole the HRQoL scores significantly favored patients treated with trastuzumab combined with chemotherapy compared with other intervention groups. A significant difference was observed between the assessments performed at baseline and those performed in Week 12 [31], using the FACT-B questionnaire. Patients in a trastuzumab-treated group showed a clinically significant improvement in their HRQoL, which corresponded to stabilization regarding the progression of the disease [31]. In other domains, such as physical, functional, and social well-being, the HRQoL profile was slightly lower than at baseline but the difference was not significant [31, 32]. However, patients treated solely with trastuzumab maintained

the baseline HRQoL for a shorter period than patients in the T-DM1 treatment group [30].

One study [34] that used the EORTC-QLQ-C30 questionnaire showed a clinically non-significant decrease in the total HRQoL score from baseline [33, 36], and an improvement compared with chemotherapy, T-DM1, and eribulin mesylate. A worsening score relative to the baseline was obtained for role, physical, and social functioning [33], whereas two studies [34, 36] reported improvements for fatigue, emotional functioning, pain, insomnia, and financial hardships. Furthermore, one study reported an improvement in social and role functioning in Week 12 [33]. The results of the HRQoL measurements are presented in Table 2, and the HRQoL scores for the included studies are shown in the Online Resource (Table B).

3.3.2 HRQoL After Treatment

In general, the post-treatment HRQoL profile increased in four studies [31–33, 36], and the mean change improved in all the intervention groups. Two studies using the FACT-B instrument showed that while the post-treatment HRQoL profiles for the trastuzumab and non-trastuzumab arms were similar, the total HRQoL scores, as well as the scores for all domains, were still more favorable in patients who received trastuzumab combined with chemotherapy than those who received chemotherapy alone [31, 35]. A similar profile was obtained using the EORTC-QLQ-C30 instrument—the overall HRQoL score and scores for all domains improved [33, 34, 36, 37]. Notably, the proportion of patients with improved HRQoL scores was considerably higher among women treated with trastuzumab plus chemotherapy than among those who only received chemotherapy [33, 34, 36]. In addition, more patients in a trastuzumab arm experienced an improvement relative to the baseline in terms of global health, physical functioning, fatigue, role functioning, emotional functioning, pain, insomnia, and financial difficulties compared with those in a non-trastuzumab arm [34]. The fatigue domain showed significant improvement in trastuzumab-treated patients [33, 36]. Notably, following the cessation of chemotherapy, patients treated with trastuzumab and chemotherapy who continued to receive trastuzumab beyond Week 20 up to the onset of disease progression showed a trend of overall improvement in quality of life, role functioning, and social functioning, and there was a clinically significant improvement in fatigue [33].

3.4 Quality Assessment

The quality assessment showed that for most of the RCTs [31, 32, 35, 36], the risk of bias was a concern to varying degrees. Two studies [33, 36] were found to have a high risk of bias (Fig. 2 and Online Resource Table C).

Table 1 Characteristics of the included studies

No.	Author, year, country	Study design	Study period	Age range (years)	Type of instrument	Mode of data collection	Treatment duration/follow-up	Participants (response rate, %)	Participant criteria	Trastuzumab regimen and sample size	Non-trastuzumab regimen and sample size
1	Perez et al. [30], 2017, 38 countries	Randomized controlled trial	July 2010–May 2012	≥ 18	FACT-B	Not reported	Median follow-up: 35 months	Not reported	Patients who had not received chemotherapy; prior hormonal therapy was permitted for advanced breast cancer Patients with an ECOG PS of 0	Trastuzumab 8 mg/kg IV loading dose, 6 mg/kg IV for subsequent cycles plus docetaxel 75 mg/m ² or 100 mg/m ² IV every 3 weeks, or paclitaxel 80 mg/m ² IV weekly (n = 365)	T-DM1 3.6 mg/kg IV every 3 weeks with placebo (n = 367); T-DM1 3.6 mg/kg IV every 3 weeks with pertuzumab 840 mg IV loading dose, 420 mg IV every 3 weeks for subsequent cycles (n = 363)
2	Syrios et al. [37], 2018, Greece	Prospective observational study	December 2015–May 2016	18–80	EORTC-QLQ-C30	Self-reported	Not reported	Not reported	Patients who had received chemotherapy and concomitant treatment with pertuzumab were included Patients with an ECOG PS of 0 or 1	Subcutaneous trastuzumab 600 mg every 3 weeks, chemotherapy, endocrine therapy (n = 36)	Chemotherapy without trastuzumab (n = 27)
3	Wu et al. [31], 2011, USA	Randomized controlled trial	January–June 2007	≥ 18	FACT-B, FACT-G, TOI	Self-reported	Treatment duration = 48 weeks	296 (66–96%)	Patients who had received adequate treatment with anthracyclines, taxanes, and trastuzumab	Lapatinib 1000 mg per oral dose; trastuzumab 4 mg/kg IV followed by 2 mg/kg IV weekly; baseline n = 137, follow-up n = 29	Lapatinib 1500 mg daily per oral; baseline n = 137, follow-up n = 29
4	Johnston et al. [32], 2021, 29 countries	Randomized controlled trial	2019	≥ 18	FACT-B, FACT-G	Self-reported	Treatment duration = 53.6 months	355 (24%)	Postmenopausal women Prior treatment with endocrine therapy Patients with ECOG PS of 0 or 1 Patients with sufficient renal, bone, and liver function	Aromatase inhibitor; trastuzumab 8 mg/kg followed by 6 mg/kg IV every 3 weeks; baseline n = 117, follow-up n = 101 Trastuzumab 8 mg/kg, followed by 6 mg/kg IV every 3 weeks, lapatinib 1000 mg oral daily, aromatase inhibitor; baseline n = 120, follow-up n = 105	Lapatinib 1000 mg oral daily, aromatase inhibitor; baseline n = 118, follow-up n = 104

Table 1 (continued)

No.	Author, year, country	Study design	Study period (years)	Age range (years)	Type of instrument	Mode of data collection	Treatment duration/follow-up	Participants (response rate, %)	Participant criteria	Trastuzumab regimen and sample size	Non-trastuzumab regimen and sample size
5	Rugo et al. [33], 2010, USA	Randomized controlled trial	Not reported	≥ 18	EORTC-QLQ-C30	Self-reported	Treatment duration = 32 weeks	469 (85%)	Women had not previously undergone chemotherapy regimens Patients with bone metastases, untreated or unstable brain metastasis that had not been treated, and a Karnofsky performance status of <60% were excluded	Anthracycline (either doxorubicin 60 mg/m ² or epirubicin 75 mg/m ²) plus cyclophosphamide: 600 mg/m ² , trastuzumab 4 mg/kg IV Anthracycline (either doxorubicin: 60 mg/m ² or epirubicin 75 mg/m ²) with cyclophosphamide: 600 mg/m ²	T-DMI 3.6 mg/kg IV every 3 weeks (n = 67)
6	Schwartzberg et al. [34], 2019, USA	Randomized controlled trial	Not reported	≥ 18	EORTC-QLQ-C30-BR23	Self-reported	Treatment duration = at cycle 2, 4, 6	108 (80%)	No prior chemotherapy treatment ECOG PS of 0–2 ≥ 12 months since treatment with neo- or adjuvant chemotherapy Patients had adequate renal, bone, and liver function	Trastuzumab 8 mg/kg, eribulin mesylate 1.4 mg/m ² (n = 52)	Eribulin mesylate 1.4 mg/m ² (n = 32)
7	Hurvitz et al. [35], 2013, USA	Randomized controlled trial	Not reported	≥ 18	FACT-B	Self-reported	Median follow-up = 14 months	137 (90%)	No prior chemotherapy or trastuzumab ECOG PS of 0 or 1 Patients had sufficient renal, bone, and liver function Patients with bone metastases, untreated or unstable brain metastasis that had not been curatively treated, and/or those with peripheral neuropathy were excluded	Trastuzumab 8 mg/kg followed by 6 mg/kg IV every 3 weeks, docetaxel 100 mg/m ² or 75 mg/m ² (n = 69)	T-DMI 3.6 mg/kg IV every 3 weeks (n = 67)

Table 1 (continued)

No.	Author, year, country	Study design	Study period	Age range (years)	Type of instrument	Mode of data collection	Treatment duration/follow-up	Participants (response rate, %)	Participant criteria	Trastuzumab regimen and sample size	Non-trastuzumab regimen and sample size
8	Osoba et al. [36], 2002, Canada	Randomized controlled trial	Not reported	≥ 18	EORTC-QLQ-C30	Self-reported	Treatment duration = 56 weeks	469 (92%)	Patients who had not received chemotherapy Patients with adequate organ function Karnofsky performance status > 60% Patients who did not have clinically unstable or untreated brain metastasis	Trastuzumab 4 mg/kg IV followed by 2 mg/kg every week, doxorubicin 60 mg/m ² or epirubicin 75 mg/m ² , cyclophosphamide 600 mg/m ² Paclitaxel 75 mg/m ² IV (n = 78)	Doxorubicin 60 mg/m ² or epirubicin 75 mg/m ² , cyclophosphamide 600 mg/m ² (n = 114)

ECOG PS Eastern Cooperative Oncology Group performance status, EORTC-QLQ-C30 European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EORTC-QLQ-BR23 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Breast 23, FACT-B Functional Assessment of Cancer Therapy—Breast, FACT-G Functional Assessment of Cancer Therapy—General, IV intravenous, T-DMI trastuzumab emtansine, TOI Trial Outcome Index

One study was deemed to be of high quality [30]. Three studies [32, 33, 36] had some issues relating to the randomization process domain (D1) because of insufficient reporting of the strategy applied to allocate interventions to participants. There were some issues in the domain of deviation from the intended intervention (D2) in three trials [33, 35, 36] because of the lack of reporting adherence by trial subjects regarding their assigned intervention. In addition, some concerns were raised about the selection of the reported result in three studies [31, 34, 36].

The risk of bias in the observational study assessed using the ROBINS-I tool is shown in Online Resource Table D. This study was deemed to have a moderate risk of bias and adequate reporting quality. All confounding variables in the study [37] were evaluated and controlled, and critical domains were appropriately monitored and measured for both reliability and validity. Nevertheless, there may have been issues relating to selection bias, lack of information on adjustment techniques, an inadequate explanation of the sample size calculation, and insufficient reporting on missing data.

4 Discussion

This systematic review highlighted the effect of trastuzumab, administered as a targeted therapy, on HRQoL of HER2-positive metastatic breast cancer patients. All studies included in the review showed that treatment with trastuzumab had a more beneficial effect on HRQoL than treatment without trastuzumab. Patients undergoing a treatment regimen that included trastuzumab generally had better HRQoL profiles than those on a regimen that excluded trastuzumab. After the therapy was stopped, the HRQoL scores of the trastuzumab and non-trastuzumab groups were comparable. However, a more favorable profile was observed for the domains of functional status, role functioning, physical functioning, and fatigue in patients on a regimen containing trastuzumab.

Both groups of patients (with and without inclusion of trastuzumab in their treatment) generally experienced a decline in their HRQoL scores between the commencement and midpoint of their treatment. However, those in the trastuzumab arm evidenced better HRQoL than those in the chemotherapy arm up to follow-up. Two studies [31, 32] that used the FACT-B questionnaire also reported a favorable HQoL profile. They indicated an improved pattern of HRQoL and physical, social, and functional well-being during treatment with trastuzumab. Measurements obtained using the EORTC-QLQ-C30 instrument were similar, indicating that the deterioration in patients' HRQoL in the trastuzumab group was less than that of patients in the non-trastuzumab group, which was also the

Table 2 HRQoL scores during and after treatment

No	Author, year, country	Quality-of-life instrument(s)	HRQoL during treatment	HRQoL after withdrawal	Comments
1	Perez et al. [30], 2017, 38 countries	FACT-B	The median times to significant declines from baseline were 3.6 months and 7.7 months for the trastuzumab and T-DMI arms, respectively	Not reported	Trastuzumab-treated patients experienced a shorter time to a meaningful decrease, indicating they had better baseline HRQoL for a shorter period than T-DMI-treated patients
2	Syrios et al. [37], 2018, Greece	EORTC-QLQ-C30	Not reported	Not reported	<p>Patients in the trastuzumab intervention had a better HRQoL than those in the non-trastuzumab intervention</p> <ul style="list-style-type: none"> • Patients in the trastuzumab arms experienced less diarrhea, nausea, vomiting, and cognitive and therapy adverse effects
3	Wu et al. [31], 2011, USA	FACT-B, FACT-G, TOI	The scores for physical, functional, and social well-being for both treatment arms were lower than baseline. At Week 12, the HRQoL score was significantly favorable in the trastuzumab arm compared with the non-trastuzumab arm. A slight decrease in HRQoL was seen in both groups during the first 6 months of treatment	The comparable profile between arms	<p>The average quality-of-life changes obtained with the FACT-B, FACT-G, and TOI instruments did not differ significantly between the two arms. After 24 weeks, the HRQoL score was slightly higher in the trastuzumab arm.</p> <p>Lapatinib and trastuzumab were associated with slightly more favorable HRQoL outcomes than lapatinib monotherapy; the results were not significant for all instrument types; more patients in the trastuzumab arms withdrew from the study between the 12th and 16th weeks of observation compared with those in the non-trastuzumab arm.</p>
4	Johnston et al. [32], 2021, 29 countries	FACT-B, FACT-G	For all instruments, the mean difference between arms was not significant	For all instruments, the mean difference between arms was not significant	HRQoL profiles between arms were comparable
5	Rugo et al. [33], 2010, USA	EORTC-QLQ-C30	Patients in both groups experienced worsening HRQoL scores and fatigue, as well as declining role, physical, and social functioning	<p>Non-significant improvements in HRQoL, social functioning, and role functioning were evident in the trastuzumab arm.</p> <p>The fatigue domain improved significantly in the trastuzumab arm.</p>	<p>Improvements in mean changes from the baseline did not differ significantly for the general health and functional scales.</p> <p>The fatigue domain showed more clinical improvement in the trastuzumab plus chemotherapy arm.</p> <p>More patients experienced a clinically significant improvement in QoL, function, and fatigue in the trastuzumab plus chemotherapy arm.</p>

Table 2 (continued)

No	Author, year, country	Quality-of-life instrument(s)	HRQoL during treatment	HRQoL after withdrawal	Comments
6	Schwartzberg et al. [34], 2019, USA	EORTC-QLQ-C30-BR23	Patients in the trastuzumab arm achieved better scores relative to baseline for HRQoL; physical, role, and emotional functioning; pain; insomnia; and financial difficulties than patients in the non-trastuzumab arm, but all these scores subsequently declined (at cycle 6). Patients in the trastuzumab intervention demonstrated more improvement in systemic therapy adverse effects	Not reported	HRQoL profiles of groups were comparable A large number of respondents in the trastuzumab arm had a more favorable score for global health, physical functioning, fatigue, role functioning, emotional functioning, pain, insomnia, and financial constraints compared with those in the non-trastuzumab arm
7	Hurvitz et al. [35], 2013, USA	FACT-B	Not reported	Not reported	The mean difference from baseline in the T-DMI arm was more favorable than in the trastuzumab arm, but not significant over time
8	Osoba et al. [36], 2002, Canada	EORTC-QLQ-C30	At Week 8, the HRQoL scores decreased relative to baseline, and scores for the fatigue domain increased non-significantly for both groups.	Non-significant improvements were observed in HRQoL and role and social functioning in the trastuzumab arms at 32 weeks The trastuzumab arm showed significant improvement for the fatigue domain	The fatigue domain showed significant improvement in the trastuzumab and chemotherapy arms The number of patients experiencing significant beneficial effects relating to their HRQoL profiles was considerably greater among participants who received trastuzumab combined with chemotherapy compared with those who were treated solely with chemotherapy

EORTC-QLQ-C30 European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, *EORTC-QLQ-BR23* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast 23, *FACT-B* Functional Assessment of Cancer Therapy—Breast, *FACT-G* Functional Assessment of Cancer Therapy—General, *HRQoL* health-related quality of life, *T-DMI* trastuzumab entansine, *TOI* Trial Outcome Index

case for the specific domains of fatigue, physical functioning, role functioning, and social functioning [33, 36]. In addition, one of the studies demonstrated an improvement in physical functioning, pain, insomnia, and financial constraints of the trastuzumab group relative to baseline [34].

The less favorable mean change from the baseline HRQoL in the chemotherapy group was probably due to the unfavorable adverse effects of chemotherapy. Patients treated with chemotherapy were associated with poorer HRQoL [38]. In addition, patients who had a worse prognosis or who were receiving chemotherapy were more likely to experience pain, fatigue, and other negative experiences [22, 39]. Trastuzumab presented a more favorable profile of adverse effect symptoms, with a lower prevalence of gastrointestinal problems, nausea, vomiting, and skin rash [40].

After treatment, and following the initial decline at baseline, all the intervention groups showed an improvement in HRQoL for all domains. There was no meaningful difference in HRQoL scores between the two intervention arms, although the HRQoL profile was slightly higher for

trastuzumab-treated patients, more of whom had a better total HRQoL score than those in the chemotherapy group. At the same time, some domains, measured using both the FACT-B and EORTC-QLQ-C30 questionnaires, demonstrated a significant improvement. These domains included functional status, role functioning, physical functioning, and fatigue [33, 34, 36]. In addition, diarrhea and cognitive adverse effects were experienced less by patients undergoing trastuzumab treatment.

The findings of the current review suggest that the addition of trastuzumab to the breast cancer treatment regimen results in faster recovery from fatigue. Breast cancer patients frequently experience fatigue both during and after treatment. Thus, fatigue has significant consequences for patients' overall quality of life [41, 42]. Moreover, one study [43] suggested that fatigue is a crucial predictor of survival.

It is necessary to consider the impact of a novel medicine introduced within a treatment regimen on a patient's quality of life when assessing its benefits [27, 44]. Ideally, the new drug should enhance treatment effectiveness without negatively affecting the HRQoL. The findings of this systematic review suggest that incorporating trastuzumab into the treatment regimen will improve treatment outcomes without causing a decline in HRQoL. Enhanced HRQoL is likely

Fig. 2 Quality assessment using the Cochrane Risk of Bias (RoB) tool, version 2.0 [28]

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Wu et al, 2011						
Johnston et al, 2021						
Rugo et al, 2010						
Hurvitz et al, 2013						
Schwartzberg et al, 2019						
Osoba et al, 2002						
Perez et al, 2017						

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
 High
 Some concerns
 Low

associated with a decrease in tumor size [36]. Research has shown that a significant number of patients who receive trastuzumab along with chemotherapy experience a decrease in tumor size, resulting in a prolonged duration of disease control and survival compared with individuals who receive only chemotherapy [9].

Treatment duration is not only limited to the adjuvant phase but it also extends to the stage of disease progression in metastatic patients, who are expected to undergo a more prolonged treatment course, which can increase their susceptibility to adverse effects. Patients with late-stage disease most frequently reported a higher burden of symptoms, including pain and fatigue [21]. Those at the metastatic stage of the disease had significantly lower scores on the functional scale than those without metastasis [23]. One study found that HRQoL of metastatic breast cancer patients treated with chemotherapy, who were assessed using the FACT-B questionnaire, had lower scores (103.64 ± 22.57) compared with those at an early stage of the disease (115.84 ± 20.91) [22]. However, the addition of trastuzumab to the treatment induced a beneficial effect on patients' HRQoL profiles; their physical, emotional, and role functioning; fatigue; pain; insomnia; and financial constraints [33, 34, 36]. Additionally, when incorporated into a breast cancer treatment regimen, trastuzumab reportedly reduces disease progression, improves the objective response rate, and extends the survival time [9, 45, 46]. Patients with metastasis on a regimen that included trastuzumab tolerated it well and had a significantly longer progression-free survival than those treated with chemotherapy alone [47].

This study had several strengths. It is the first systematic review of studies on HRQoL of patients during and after receiving trastuzumab for HER2-positive metastatic breast cancer treatment, which highlights the total HRQoL score as well as scores for specific domains. Its findings have significant clinical and economic implications. An understanding of how various treatments impact HRQoL has important clinical implications for customizing therapies to optimize patient well-being alongside disease management, thereby fostering more patient-centered care. Additionally, the identification of specific areas of marked decline in patients' HRQoL enables targeted allocation of psychosocial support resources and coping strategies during and after treatment. From an economic standpoint, integrating HRQoL evaluations into economic analyses aids in comprehensive evaluations of treatment cost effectiveness, potentially favoring therapies offering better HRQoL outcomes relative to costs. Ultimately, comprehensive assessments of HRQoL in breast cancer patients can potentially enhance clinical decision making, optimize resource allocation, and improve patients' well-being, while also considering the economic implications of various treatment strategies. Our search strategy

for identifying articles did not have any language or time limitations, thereby ensuring that all relevant publications were covered. However, we acknowledge the limitations of this review. The targeted studies entailed different treatment regimens, which may have led to discrepancies in the results for HRQoL profiles. Moreover, the instruments utilized in these studies varied. It is also important to note that because this review did not elaborate on the factors influencing HRQoL scores, its findings are only based on each study's HRQoL values.

In future studies aimed at assessing the HRQoL outcomes for breast cancer patients, several critical considerations should guide the research approach. Comparative analyses covering diverse treatment modalities would offer nuanced perspectives on the differential impacts of various treatments on HRQoL outcomes. Additionally, it is essential to encompass diverse patient demographics and breast cancer stages to ensure comprehensive representation. Moreover, evaluations of psychosocial factors and their impacts on HRQoL outcomes, for example, within supportive care programs, conducted alongside interventions can provide valuable insights. Incorporating multiple HRQoL measurement tools and emphasizing the importance of patient-reported outcomes within clinical trials would provide a holistic perspective. The validation of instruments for diverse populations is critical to ensure accuracy and applicability. Future studies that incorporate these elements would provide a more holistic understanding of HRQoL among breast cancer patients, fostering tailored interventions and improved patient-centered care approaches.

5 Conclusions

Treatment regimens for HER2-positive, metastatic breast cancer patients that include trastuzumab showed beneficial effects both during and after treatment. Upon cessation of therapy, HRQoL scores of patients undergoing both regimens (with and without trastuzumab) improved; however, patients treated with trastuzumab had more favorable HRQoL profiles, particularly in the domains of functional status, role functioning, physical well-being, and fatigue. These findings suggest that while overall HRQoL improved after the completion of treatment, trastuzumab conferred additional benefits for patients during and after their therapy.

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Declarations

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Availability of data and material All data generated and/or analyzed for this review are included in this published article.

Conflict of interest Sudewi Mukaromah Khoirunnisa, Fithria Dyah Ayu Suryanegara, Lisa Aniek de Jong, Didik Setiawan, and Maarten Jacobus Postma declare they have no competing interests in relation to this work.

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