

Burden of Illness of HER2+ Metastatic Breast Cancer (mBC) Patients: A Systematic Literature Review (SLR)

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Background

- HER2+ tumors make up approximately 20% of metastatic breast cancers (mBCs) (1).
- There is no cure for HER2+ mBC and even though the HER2+ subtype has the most favorable survival rates, fewer than 45% of patients are alive after 5 years (2,3).
- The objective of this SLR was to assess recent evidence on the burden of illness in HER2+ mBC patients.

Methods

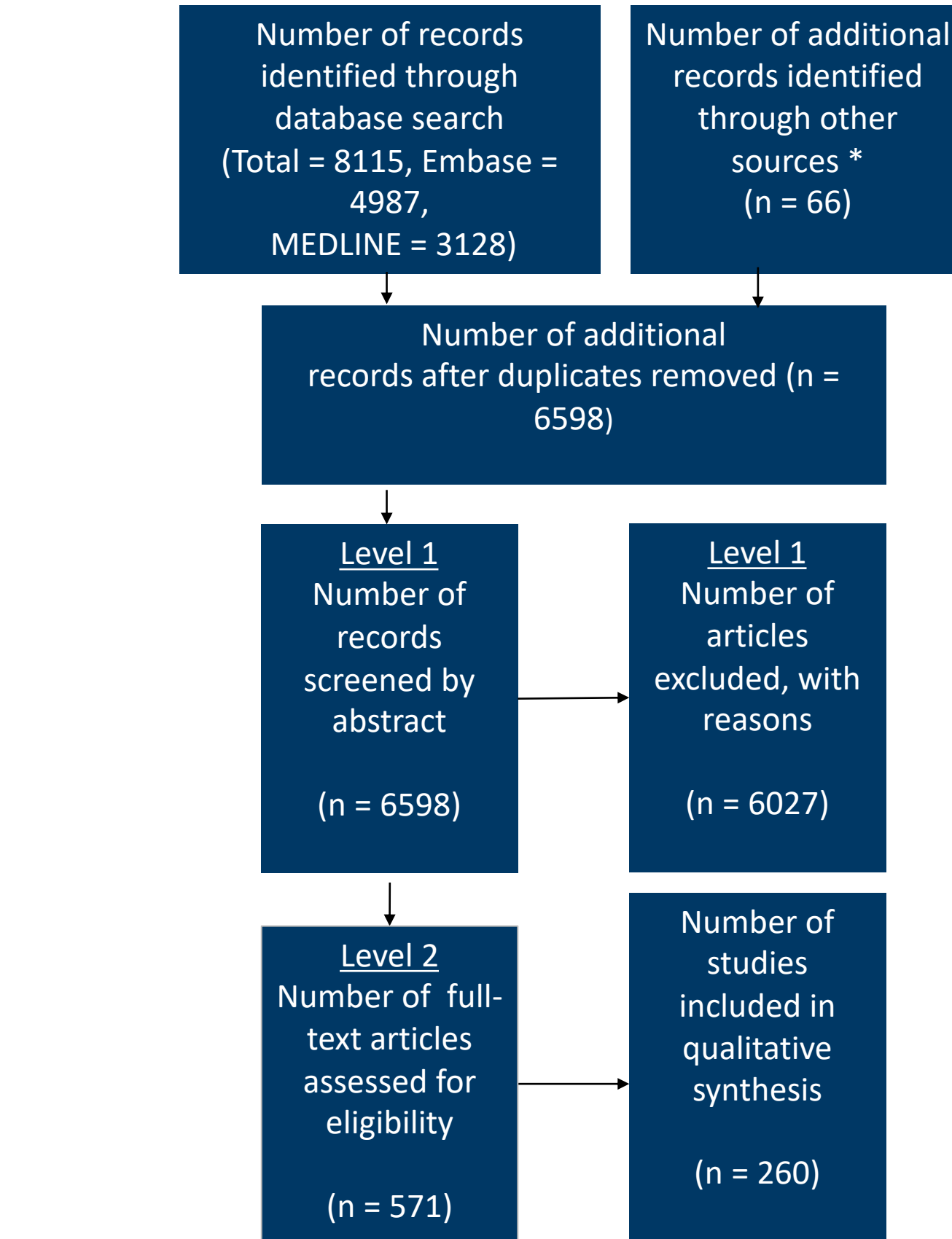
- A SLR was conducted in MEDLINE and EMBASE databases (2010-2020) and congress abstract repositories (2018-2020).
- Two reviewers independently screened titles and abstracts for eligibility.
- The search adhered to Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
- Inclusion and exclusion criteria are listed in **Table 1**.
- A total of 8,115 records were identified, of which 6,598 were retrieved upon deduplication.
- Finally, full-text review of 571 articles was carried out.

Table 1. Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population (P)	Adult (age ≥18 years) HER2-positive uBC and/or mBC patients (studies that contain a mixed population will be included regardless of the percentage of the study population)	Healthy volunteers, patients <18 years, diseases other than HER2+ uBC and / or mBC, patients with HER2- BC, non-invasive or Stage 0 breast cancer
Outcomes (O)	Data were reported on at least one of the following: <ul style="list-style-type: none">Disease overview and epidemiologyBOI on patients, caregivers, and societyClinical practice, clinical guidelines, HTA decisions, and pipeline products	<ul style="list-style-type: none">No data reported for any of the topics of interestData reported for just one treatment
Study design (S)	<ul style="list-style-type: none">Any study design that reported any of the outcomes of interest in the population of interest	<ul style="list-style-type: none">Articles without published resultsGuidelines superseded by a later guidelineComment, editorial, letter, news report, study in animals, case study, case series, clinical trial, preclinical study
Time limit	Published in or after 2010	Published earlier than 2010

Key: HER2, Human Epidermal Growth Factor Receptor 2; mBC, metastatic breast cancer; uBC, unresectable breast cancer

Figure 1. PRISMA flow diagram



* The most recent abstracts, posters, or podium presentations that may not yet be indexed in the medical literature databases, and searches were conducted of the websites of a selection of professional organizations to ensure that all relevant evidence was identified.

Results

- 260 studies met the inclusion criteria.
- Seven studies in **Table 2** compare HER2+ mBC patients to the general and/or breast cancer (BC) populations.
- Three studies focused on HER2+ patients, while other studies reported mixed population, specifying the proportion of HER2+ patients.
- Studies reported impaired health utility scores and moderate or worse health status.
 - This was assessed using a variety of tools, such as EQ-5D-5L, SF-36, EORTC QLQ-C30 and FACT-B (**Table 2**).

Table 2. Summary of health-related quality of life instruments and corresponding studies identified

Instrument	Study details	Main conclusion
Generic		
EQ-5D-5L	EQ-5D-5L: Verrill, 2017 (4), HER2+ eBC and mBC patients	Across all groups of patients (HER2+ eBC and mBC patients on treatment and eBC off treatment) higher work and activity impairments were associated with lower EQ-5D-5L health utility; $r=-.3950$; $p<0.001$, and $r=-0.6670$; $p<0.001$, respectively.
	EQ-5D-3L: Von Moos, 2018 (5), mixed population including HER2+ mBC patients	Patients with breast cancer and BMs have worse outcomes in terms of pain and QoL than those with breast cancer and non-BMs. Among patients with BMs, those treated with BTAs reported lower pain scores than those not treated with BTAs.
	EQ-5D: Cardoso, 2018 (6), literature review, mixed population including HER2+ mBC patients	Reported a numerical decrease in EQ-5D score over time, no statistical significance was estimated.
SF-36	EQ-5D: Mayer, 2015 (7), 100% HER2+ mBC patients	EQ-5D scores indicated less impairment among patients with more time since MBC diagnosis, as evidenced by higher overall utility scores for those diagnosed ≥72 months ago compared to those diagnosed 0–17 months ago (0.85 [±0.16] versus 0.77 [±0.19]).
	Seah, 2014 (8), 20% HER2+ mBC patients	There are clinically meaningful differences between patients with mBC and the US general population. Patients with mBC reported lower HRQoL across all subscales, most notably through reduced social functioning, and greater role limitations due to reduced physical and emotional functioning

Cancer-specific		
EORTC QLQ-C30	De Luca, 2019 (9), 35.6% HER2+ mBC patients	The HRQoL of mBC patients is clearly reduced compared to the general population in terms of function subscales, particularly in physical, role, and social functioning.
	Mierzynska, 2020 (10), 59.6% HER2+ mBC patients	These differences are even more prominent in terms of the symptoms, with mBC patients reporting higher scores across all subscales, especially for fatigue, pain, and dyspnea.
	Compared to General population based on Nolte et al. 2019 (11)	Emotional functioning in mBC patients was higher than reported in the European reference population.
Breast cancer-specific		
FACT-B	Hamer, 2016 (12), mixed population including HER2+ mBC patients	Patients with mBC had significantly lower scores in all five domains of the FACT-B as well as in the overall HRQoL score ($p<0.002$) compared to all other cancer stages
	Bajaj, 2017 (13), 100% HER2+ mBC patients	Women living with mBC ≥ 6 years had significantly greater emotional well-being (FACT-B EWB, $p<0.01$), lower distress (DT, $p<0.05$; RSCL Physical Symptom Distress, $p = 0.03$), and lower activity impairment due to breast cancer (WPAI-SHP, $p<0.01$) and therefore a better HRQoL score compared to more recently diagnosed patients, which indicates that women learn how to live and cope with their disease

Key: EORTC, European Organization for Research and Treatment of Cancer; EQ-5D, EuroQoL 5-Dimension; mBC, metastatic breast cancer; QLQ-BR23, Quality of Life Questionnaire Breast-23; QLQ-C30, Quality of Life Questionnaire-Core 30.

Table 3. European economic burden studies overview

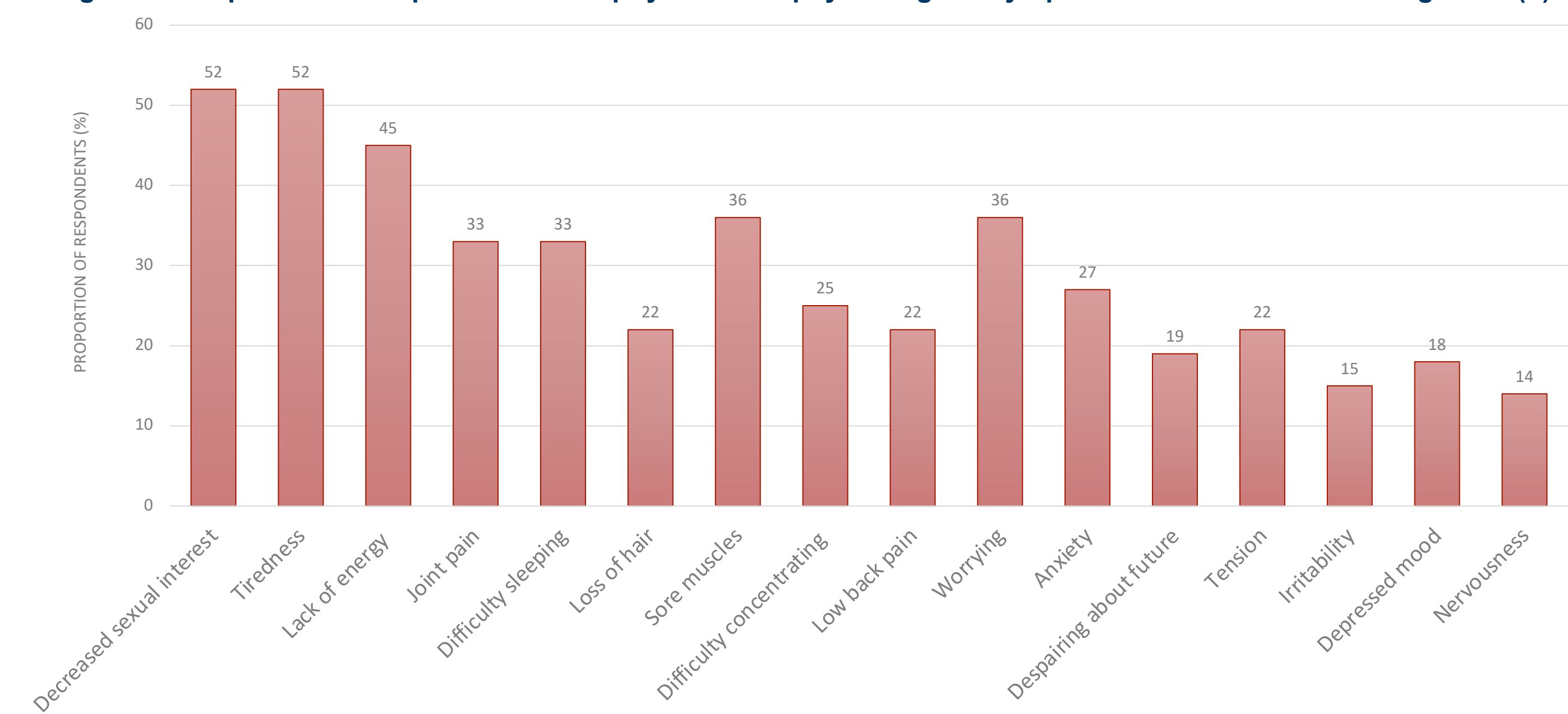
Citation	Study	Cost year	Direct and indirect costs
Spain			
The economic burden of mBC in Spain (14).	Incident cohort of patients with mBC (estimated n=2,923) Patient groups consisted of: HER2-negative/HR-positive: 1,575 HER2-positive/HR-positive: 1,575 HER2-positive/HR-negative: 324 Triple negative patients: 503	2016	Total costs for the overall population over 5 years, according to HER2 and HR status: <ul style="list-style-type: none">Total population: €469,492,731HER2-negative/HR-positive: €190,079,787HER2-positive/HR-positive: €151,045,260HER2-positive/HR-negative: €80,827,171Triple negative: €47,540,512 Costs per patient over 5 years, according to HER2 and HR status: <ul style="list-style-type: none">Total cost per patient: €160,642HER2-negative/HR-positive: €120,664HER2-positive/HR-positive: €290,346HER2-positive/HR-negative: €249,152Triple negative: €94,572
Cost and resource use analysis NHS and societal perspectives (15).	Unresectable/metastatic recurrences (MR) in patients with HER2-positive mBC, based on a hypothetical cohort of 100 patients with mBC recurrence	2016	<u>Costs of relapse per patient, according to line of therapy:</u> <ul style="list-style-type: none">First-line treatment (trastuzumab plus pertuzumab plus paclitaxel): Direct costs: €132,518; Indirect costs: €12,445; Total costs: €144,963Second-line treatment (T-DM1): Direct costs: €69,056; Indirect costs: €7,854; Total costs: €76,910Third-line treatment (lapatinib plus capecitabine): Direct costs: €25,595; Indirect costs: €6,200; Total costs: €31,795Fourth-line treatment (trastuzumab plus lapatinib): Direct costs: €22,094; Indirect costs: €4,915; Total costs: €27,009Fifth-line treatment (trastuzumab plus capecitabine): Direct costs: €21,095; Indirect costs: €5,529; Total costs: €26,624The total cost for the average patient during the course of their disease: €235,138 (Direct costs contributed 89% (of which 83% were systemic treatments, 14% other resources, 2% local treatments and 1% treatment of distant metastasis).

The Netherlands			
Time-dependent resource use and costs associated with different states of disease in patients diagnosed with HER2-positive mBC (16).	HER2-positive mBC patients (n=88)	2013	Direct costs per patient per month: <ul style="list-style-type: none">Stable disease: \$4,158Progressive disease: Month 1: \$5,576; Month 2: \$5,610; Month 3: \$3,607; Month 4: \$3,553; Month 5: \$3,281; Month 6: \$2,791; Month 7: \$3,210; Month 8: \$3,319Last months of life:<ul style="list-style-type: none">Third last month: \$3,398Second last month: \$3,534Last month: \$5,811
Real-world cost of HER2-positive mBC patients (17).	HER2-positive mBC patients (n=88)	2012	The total costs per patient for period from first diagnosis of HER2-positive mBC for 24 months or until the patient death: <ul style="list-style-type: none">The total costs of medical treatment and other resource use utilization: €48,301Overall costs driven by the use of pharmacotherapeutic treatment: 60.6% (€29,276), from which costs of trastuzumab 50%Total costs of other resource utilization: €19,025Resource utilization costs driven by healthcare professional visits €7,734, hospital stays €6,675 and imaging €2,369
Belgium			
Real-world cost of HER2-positive mBC patients (17).	HER2-positive mBC patients (n=44)	2012	The total costs per patient for period from first diagnosis of HER2-positive mBC for 24 months or until patient death: <ul style="list-style-type: none">The total costs of medical treatment and other resource use utilization: €37,431Overall costs driven by the use of pharmacotherapeutic treatment: 70% (€26,103), from which costs of trastuzumab 56%Total costs of other resource utilization: €11,240Resource utilization costs were driven by healthcare professional visits €4,068, hospital stays €1,953 and imaging €3,006

Key: HER2, Human epidermal growth factor receptor 2; HR, Hormone receptor; mBC, Metastatic breast cancer; MR, Metastatic recurrence; SD, Standard deviation; SLR, Systematic literature review.

- Due to the longer treatment duration and high treatment costs of anti-HER2 treatments, HER2+ mBC leads to greater costs than other types of mBC.
- In Europe, overall costs per patient of HER2+ mBC were €235,238-€269,749, of which €37,431-53,950 were annual treatment costs.
- Costs are primarily driven by treatment and hospitalization costs, and cumulatively increase by line of treatment (**Table 3**).
- The differences in HRQoL in mBC can be attributed to the presence of metastases at various sites in the body, which can greatly impact patient functioning.
 - In patients with HER2+ mBC specifically, up to 50% of patients will develop BM during the course of their disease (18).
 - Early development of BM will generally result in poorer survival outcomes and poorer HRQoL, because the presence of BMs often has acute and long-term neurocognitive consequences (19–21).
- In addition to lower health-related Quality of Life (HRQoL), the disease is associated with impairment of work and daily activity, negative body image perception, and mental disorders.
- All symptoms, comorbidities and treatment adverse events most frequently reported by HER2+ mBC patients are presented in **Figure 2** (7).

Figure 2. Proportion of respondents with physical and psychological symptoms with HER2+ mBC diagnosis (7)



Conclusions

- This SLR demonstrated that mBC has an impact on HRQoL in physical, mental, and social functioning, as well as on healthcare systems, with substantial direct and indirect costs and highest costs per patient for the HER2+ subtype. This highlights the need for more cost-effective treatment options.

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