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ORIGINAL RESEARCH

Economic evaluation of adjuvant trastuzumab therapy for HER2-positive early-stage breast cancer: systematic review and quality assessment

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ABSTRACT

Introduction: As the availability of new economic evaluations (EE) on adjuvant trastuzumab therapy for early-stage breast cancer (EBC) with HER2-positive since last search and other EEs missed warrant a more extensive review, this study aimed to systematically review EEs of adjuvant trastuzumab compared with chemotherapy alone for HER2-positive EBC.

Area covered: The search was performed in February 2019 using MEDLINE and Scopus. Reviewers independently selected studies based on eligibility criteria, extracted data, assessed quality of reporting, and appraised quality of data sources.

Expert opinion: 22 studies were included which were from high-income (HICs) and upper-middle income countries (UMICs). Incremental cost-effectiveness ratios (ICERs) from HICs were within their cost-effectiveness thresholds and ranged from 6,018 to 78,929 USD per quality-adjusted life year (QALY) gained. ICERs from UMICs mostly exceeded their thresholds ranging from 3,526 to 174,901 USD per QALY gained. Evidence shows cost-effectiveness of trastuzumab for HER2-positive EBC in HICs. There were no methodological variations. The extent and adequacy of reporting were high. The quality of data sources was moderate to high. The quality of future EEs can be improved by enhancing the reporting quality, by using context-based data and real-world efficacy data, which would impact cost-effectiveness.

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KEYWORDS
Adjuvant trastuzumab; systematic review; economic evaluation; HER2-positive; early breast cancer; cost-effectiveness

1. Introduction

Breast cancer continues to be the leading cancer among women with about 1.67 million cases and 521,907 deaths according to the 2012 GLOBOCAN cancer incidence, mortality, and prevalence report [1]. The World Health Organization (WHO) reported that, in 2008, almost 50% of cases and 58% of deaths due to breast cancer had occurred in less developed countries [2]. The report further noted a significant variation in survival rates, ranging from 80% or higher in North America, Sweden, and Japan, to around 60% in middle-income countries (MICs), and below 40% in low-income countries [3]. Limited access to detection and treatment facilities in less developed countries contributed to lower survival rates [4]. There is limited information on the economic impact of breast cancer, but it was estimated that its cost accounts to 10% to 20% of all cancer service costs, or about 0.15% of the Gross Domestic Product (GDP) of an average European nation [5].

While breast cancer is commonly viewed as a single disease, it is comprised of several histological subtypes that are classified according to biological marker expression, which are all different in presentation, response to therapy, and prognosis [6]. Among these subtypes are those detected with higher amount of 'human epidermal growth factor receptor 2' called HER2-positive breast cancer. HER2 is a tyrosine kinase receptor that facilitates signaling pathways of cell growth, division, motility, and repair [6]. HER2-positive breast cancer possesses more aggressive biological and clinical behavior, and has less favorable survival outcomes [7]. It is reported that such subtype is seen in 15% to 20% of all invasive breast cancers [8]. The differentiation of subtypes has changed the course of treatment and led to the emergence of new therapies for breast cancer such as trastuzumab, which is the first monoclonal antibody-based therapy developed to specifically target HER2. Its antitumor activity against HER2-overexpression works through the downmodulation of HER2 expression by binding to the juxtamembrane domain of the receptor. Based on its demonstrated relative efficacy and acceptable safety through key pivotal trials [9–16], trastuzumab in addition to standard chemotherapy is recommended both by US National Comprehensive Cancer Network (NCCN) Guideline 2017 [17] and 2015 European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment, and follow-up of primary breast cancer [18] for the

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Supplemental data for this article can be accessed here.

management of early-stage breast cancer (EBC) with HER2-positive in adjuvant settings.

Notwithstanding its years of efficacy to improve disease-free and overall survival of breast cancer patients, the use of adjuvant trastuzumab therapy incurs substantial economic impact. A price survey among different countries reported by the WHO in 2012 showed varied costs of trastuzumab produced by Roche, which is the patent holder, ranging from 3,035.95 USD per gram in Pakistan to 10,000 USD per gram in Brazil and Oman [19]. The report argued that trastuzumab had been costly even in India where price cuts were applied and lower priced versions were available. Adjuvant trastuzumab therapy also incurs additional cost of chemotherapy administration due to additional cycles of the regimen and due to monitoring and treating possible cardiotoxic effects associated with its use [9–16].

Because of existing resource constraints in many health systems, assessing the cost-effectiveness of trastuzumab became important for policy-makers to inform financing decisions. There have been several economic evaluations (EEs) on trastuzumab conducted across many countries. While there are two published systematic reviews of cost-effectiveness analysis studies of trastuzumab by Chan et al., 2009 [20] and Petrou 2019 [21], the availability of newly published EEs since last search of previous reviews and other EEs they missed, and the lack of more comprehensive appraisal and analysis using relevant assessment tools warrant the need for an updated and more extensive systematic review. The goals of this study were to conduct a systematic review of published EEs of adjuvant trastuzumab for HER2-positive EBC and to comprehensively describe and evaluate them based on their methodology, transparency, and adequacy of reporting, and quality of input data sources using the latest guidelines and tools. We further aimed to analyze and compare the evaluation results based on their country's income status, which may provide relevant guidance to other countries of comparable economic status.

2. Patients and methods

2.1. Data sources and searches

Economic evaluation studies of adjuvant trastuzumab therapy for HER2-positive EBC patients were identified through MEDLINE (via PubMed) and Scopus. We used search terms: ((her2 AND positive) AND early AND 'breast neoplasms') AND (trastuzumab AND 'chemotherapy, adjuvant') AND ('cost-benefit analysis' OR 'cost-utility analysis) in Medline, while ((her2 AND positive) AND early AND ('breast neoplasms' OR 'breast cancer') AND (trastuzumab AND ('adjuvant' OR 'post-operative') AND ('cost-benefit analysis' OR 'cost-utility analysis' OR 'cost-effectiveness analysis') for Scopus. Searches were run in February 2019. We did not limit the time period and language for the search.

2.2. Selection of studies

Two reviewers (AJG and MAG) independently assessed articles obtained from the databases. Studies were eligible and included if they were original EEs of any type that assessed cost-effectiveness, measured as incremental cost-effectiveness ratio (ICER), of one-year use of adjuvant trastuzumab therapy in addition to chemotherapy versus chemotherapy alone for EBC patients who are HER2-positive. Studies which assessed its cost-effectiveness with other anti-HER2 drugs or in neo-adjuvant settings were excluded. Full-text of eligible studies were obtained and reviewed independently. Any disagreements were resolved with the third reviewer (UC).

2.3. Data extraction and quality assessment

AJG and MAG independently extracted information on the research question, methods, and other general study characteristics using standard data extraction forms. The reviewers compared and validated data extraction tables for accuracy and completeness. The included studies were appraised in three domains: methodological variations, adequacy, and transparency of reporting and, quality of data input parameters. First, a standard extraction tool was used to provide a general overview of the study characteristics, in terms of study setting, first author affiliation, and funding source, and, to assess methodological variations by describing the types of EE, type of modeling used, incorporation of cardiotoxicity in the modeling as a significant side effect associated with the use of trastuzumab, study perspective, time horizon, cycle length, discounting, and uncertainty analysis. Second, the adequacy and transparency of reporting of the studies were evaluated using the 24-item Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [22]. Third, the quality of input data sources was rated using a ranking algorithm developed by Copper et al., 2005 [23] (see Supplementary Table 1), which reflected that the quality of sources for input parameters substantially affects the credibility of EEs as much as the rigor of methodology does. The sources of the following input parameters were evaluated: baseline clinical data, clinical effect size, costs, and utilities. Rank 1 was given for parameters which were derived from the most appropriate source, while rank 9 was given for parameters with unclearly stated sources. AJG and MAG independently appraised and extracted the studies using the above tools. Any discrepancy in the assessment was resolved with the third reviewer (UC).

2.4. Data synthesis and analysis

We compared value for money of trastuzumab for HER2-positive EBC across studies. As these EEs were undertaken in different time frames and settings, all ICERs were converted into a common currency – International dollars (I$) at 2017. Values were calculated using the national GDP deflator and implied purchasing power parity conversion rates from the International Monetary Fund (https://www.imf.org/external/datamapper/PPPEX@WEO/OEMDC/ADVEC/WEOWORLD) [24]. Necessary currency conversion rates and inflation adjustments applied using Consumer Price Indexes (CPIs) were derived from OECD website (https://data.oecd.org/conversion/exchange-rates.htm) [25] and World Bank website (https://data.worldbank.org/indicator/FP.CPI.TOTL) [26], respectively. The grouping of studies relative to the income status of country setting was referred from the World Bank classification based on Gross National Income (GNI) [27]. Studies which did

Table 1. General Study Information and Methodology of EEs on Adjuvant Trastuzumab regimen for HER2-positive EBC patients.

Study	Setting	Type of EE	Intervention	Comparator	Perspective	Time horizon
Neyt et al. [28]	Belgium	CEA	12 months of adjuvant trastuzumab plus CT	CT: Doxorubicin-cyclophosphamide-paclitaxel	Hospital	Not detailed
Dedes et al. [29]	Switzerland	CEA	12 months of adjuvant trastuzumab plus CT	CT: Anthracycline-based or Anthracycline-Taxane or Non- Anthracycline	Health care provider	15 years
Garrison et, al. [30]	US	CUA	12 months of adjuvant trastuzumab after CT	CT: Doxorubicin-cyclophosphamide-paclitaxel	Health care payer; Societal	20 years; Lifetime
Kurian et al. [31]	US	CUA	12 months of adjuvant trastuzumab after CT	CT 1: Doxorubicin-cyclophosphamide-paclitaxel CT 2: Carboplatin and docetaxel	Societal	Not detailed
Liberato et al. [32]	Italy	CUA	12 months of adjuvant trastuzumab after CT	CT: Doxorubicin-cyclophosphamide-paclitaxel	Health care system	15 years
Norum et al. [33]	Norway	CEA	FEC100 (fluorouracil, epirubicin, cyclophosphamide) regimen for six cycles on a 3-weekly basis followed by trastuzumab 3-weekly administration for 17 cycles	FEC100 regimen for six cycles on a 3-weekly basis	Not detailed	20 years
Neyt et al. [34]	Belgium	CEA	12 months of adjuvant trastuzumab plus CT	CT: Anthracycline-based or Anthracycline-Taxane or Non- Anthracycline	Health care payer	Lifetime
Shiroiwa et al. [35]	Japan	CEA	12 months of adjuvant trastuzumab plus CT	CT: Anthracycline-based or Anthracycline-Taxane or Non- Anthracycline	Health care payer	50 years
Chen et al. [44]	China	CUA	12 months of adjuvant trastuzumab after CT	CT: Anthracycline-Taxane	Health insurance system	Lifetime
Skedgel et al. [36]	Canada	CUA	12 months of adjuvant trastuzumab after CT	Regimen not detailed	Direct payer	25 years
Van Vlaenderen et al [37]	Belgium	CUA	Adjuvant trastuzumab plus CT	Regimen not detailed	Health care payer	Lifetime
Macedo et al. [38]	Portugal	CUA	12 months of adjuvant trastuzumab after CT	CT: Doxorubicin-cyclophosphamide-paclitaxel	Societal	45 years
Hall et al. [39]	UK	CUA	Trastuzumab administered every 3 weeks, sequentially after CT	CT: Anthracycline-based or Anthracycline-Taxane or Non- Anthracycline	Health care system	Lifetime
Hedden et al. [40]	Canada	CUA	12-month adjuvant trastuzumab plus CT	Regimen not detailed	Health care system	28 years
Buendia et al. [45]	Colombia	CUA	12 months of adjuvant trastuzumab after CT	CT: Doxorubicin-cyclophosphamide-paclitaxel	Health care payer	Lifetime
Aboutorabi et al. [46]	Iran	CUA	12 months of adjuvant trastuzumab after CT	CT: Doxorubicin-cyclophosphamide-docetaxel	Health care system	20 years
Pichon-Riviere et al. [47]	Argentina, Bolivia, Brazil, Colombia, Chile, Peru, Uruguay	CUA	12 months adjuvant trastuzumab plus CT	Regimen not detailed	Health care	Lifetime
Lang et al. [41]	Taiwan	CUA	12 months adjuvant trastuzumab plus CT	CT: combination of docetaxel or paclitaxel, doxorubicin and cyclophosphamide	National health insurance system	20 years
Leung et al. [42]	New Zealand	CUA	4-month CT regimen plus concurrent trastuzumab for a period of 12 months	CT: Taxane	Health care system	Lifetime
Seferina et al. [43]	Netherlands	CUA	12 months adjuvant trastuzumab plus CT	Regimen not detailed	Health care	Lifetime
Ansaripour et al. [48]	Iran	CUA	12 months adjuvant trastuzumab plus CT	Regimen not detailed	Healthcare system	Lifetime
Kongsakon et al. [49]	Thailand	CEA	12 months of adjuvant trastuzumab plus CT	CT: Taxane-only	Societal	Lifetime

not indicate the year of cost analysis were assumed to have the same base year as the year of publication.

3. Results

3.1. Review profile

The search yielded 562 records. After removing duplicates, 464 records were screened for relevance based on set criteria, which then resulted in 31 eligible studies. Of these articles, nine studies were excluded – four were inaccessible for full-text, three were experts' reviews, one was not the population of interest, and one was not the intervention of interest. There were three additional full-text papers identified through cited reference searching. Finally, we included 22 publications in this review. The flow diagram is shown in Figure 1.

3.2. General study information and methodological variations

We identified 22 EEs comparing adjuvant trastuzumab therapy with chemotherapy alone for HER2-positive EBC, published from year 2006 to 2018 (Table 1). As shown in Table 2, studies were mostly from high-income countries (HICs) [28–43], while some [44–49] were from upper-middle-income countries (UMICs). About half [15,28–37,44] were conducted and published as early as 2006 to 2009, which was within the early years of trastuzumab's market entry for HER2-positive early stage indication in 2006. More than half [28–40,44] have been published even before 2013 when the WHO reviewed its inclusion in the WHO Essential Medicines List [50]. In terms of methodology, majority of the studies [30–32,36–49] adopted cost-utility analysis, while some [28,29,33–35] used cost-effectiveness analysis. All except two studies [5,10] used decision analytic Markov modeling technique. Chemotherapy regimens were varied, but the most common was trastuzumab with anthracycline-taxane combination of standard chemotherapy [28,30–32,38,41,44–46]. More than half of the studies [30,32,33,37–46,48] incorporated cardiotoxicity effect of trastuzumab in the analysis. Health care payer or insurance perspective was the most commonly applied [28,35–37,39–41,44,45]. Half of the studies modeled for lifetime horizon [30,34,37,39,42–45,47–49], while others varied from 10 to 50 years. One-year cycle length was commonly applied [29,38,41–47]. As regards to discounting, both costs [29–38,41,42,44,46,49] and

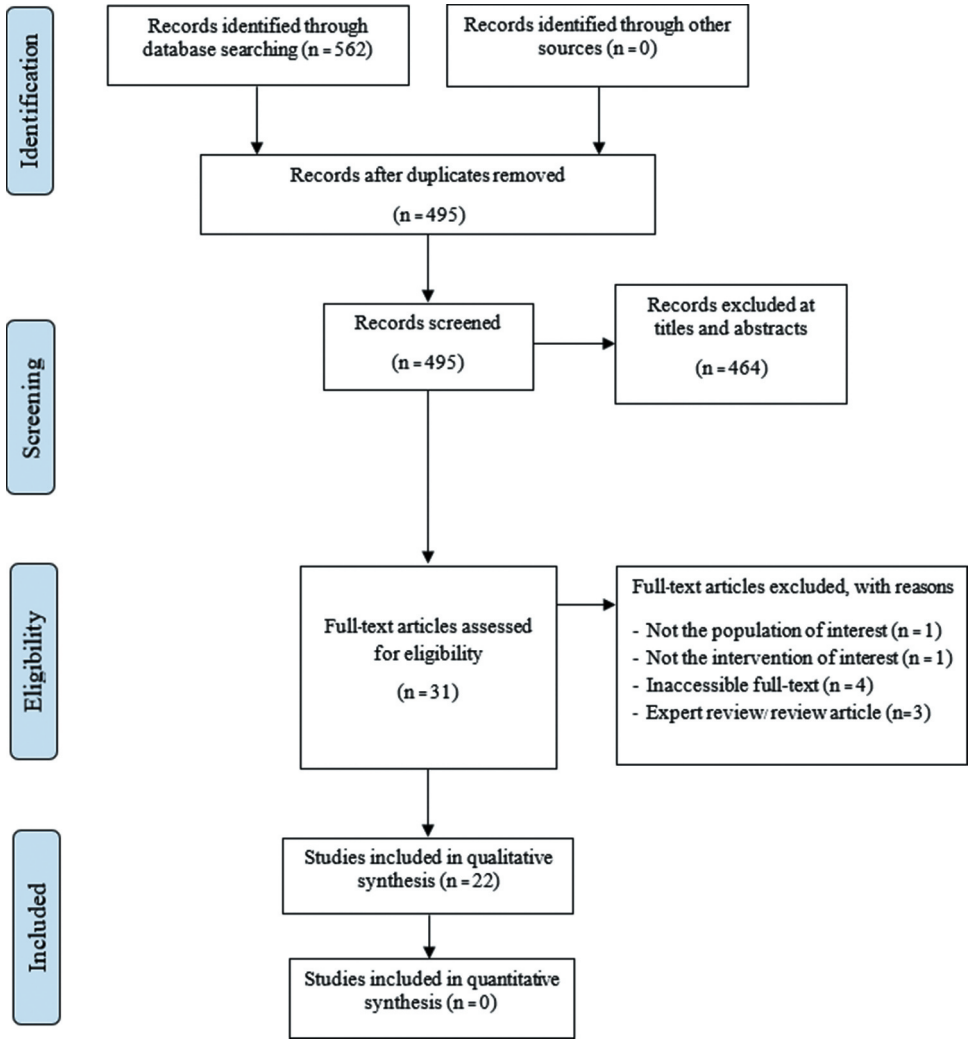

Figure 1. Study selection flow diagram of economic evaluations of adjuvant trastuzumab therapy for HER2-positive EBC patients.

Table 2. Summary of general study characteristics and different methodologies used in the included EEs (n = 22).

Study's Characteristics	Number of studies	%
Study setting		
High-Income Countries	16	72.7
Upper-Middle-Income Countries	6	27.3
First Author Affiliation		
Academe	17	77.3
Research agency/group	4	18.2
Hospital	1	4.5
Funding Source		
Research agencies/grants	5	22.7
Pharmaceutical industry	5	22.7
Academe	3	13.6
Declared no funding	3	13.6
Government	1	4.5
not reported	5	22.7
Type of Economic Evaluation		
Cost-utility analysis	17	77.3
Cost-effectiveness analysis	5	22.7
Type of Model		
Markov Model	20	90.9
Non-Markov Model	2	9.1
Intervention		
Trastuzumab + anthracycline-taxane chemotherapy	9	40.9
Trastuzumab + taxane chemotherapy	3	13.6
Trastuzumab + any chemotherapy	3	13.6
Regimen not detailed	7	31.8
Incorporation of cardiotoxicity in the modeling		
Yes	14	63.6
No	8	**36.4**
Study perspective		
Healthcare payer/insurance	9	40.9
Healthcare system	6	27.3
Societal and Healthcare payer	2	9.1
Societal	2	9.1
Health Care provider	1	4.5
Hospital	1	4.5
not reported	1	4.5
Time horizon		
10 years	1	4.5
15 years	2	9.1
20 years	2	9.1
25 years	1	4.5
28 years	1	4.5
45 years	1	4.5
50 years	1	4.5
Lifetime	11	50.0
Not reported	2	9.1
Cycle Length		
3 weeks	1	4.5
1 month	3	13.6
3 months	3	13.6
1 year	10	45.5
Not applicable	2	9.1
Not reported	3	13.6
Discounting for costs		
3%	15	68.2
3.5%	2	9.1
4%	1	4.5
5%	4	18.2
Discounting for outcomes		
0%	1	4.5
1.5%	3	13.6
3%	11	50.0
3.5%	2	9.1
5%	4	18.2
Not reported	1	4.5
Types of uncertainty analysis		
Univariate analysis alone	4	18.2
Probabilistic sensitivity analysis alone	2	9.1
Bivariate and Probabilistic sensitivity analysis	2	9.1
Univariate and Probabilistic sensitivity analysis	14	63.6

outcomes [30–33,35,36,38,46,49] were mostly discounted at 3.0%. Finally, most studies handled uncertainty by conducting both one-way and probabilistic sensitivity analyses [30,31,34–36,39–41,43–46,48,49].

3.3. Adequacy and transparency of reporting

The assessment of adequacy and transparency of reporting guided by the CHEERS checklist resulted in scores ranging from 61% by Neyt et al., 2006 [28] to 96% by Hall et al., 2011 [39] and Shiroiwa et al., 2008 [35]. The scores among HIC studies were from 61% [28] to 96% [35,39], while the scores among UMIC studies were from 83% [44,49] to 92% [45–47]. Less than half of the studies [29,30,32,35,39,42,45–48] attained high scores of 90% or higher. Of the 24 reporting domains in the checklist, only 10 items were reported by all studies. These were: abstract; background and rationale; target population and subgroups; setting and location; estimation of costs and resources; discount rates; analytical methods; incremental costs and outcomes; characterization of uncertainty; and, study findings. On the contrary, measurement, and valuation of preference-based outcomes, currency price date and conversion rate, assumptions, characterization of heterogeneity, and conflict of interest statements were noted to be the most commonly missing or unstated reporting items. Moreover, while input parameters were tabulated, not all parameter values and distributions were presented. In the discussion section, not all papers adequately explained their study limitations. The CHEERS scoring per reporting domain is shown in Table 3.

3.4. Quality assessment of input data sources

The baseline clinical data which transition probabilities were derived from were generally sourced from published reports of randomized clinical trials (RCTs), while two studies [42,43] used real-world country data. Correspondingly, the source of trastuzumab efficacy data was generally the same RCT source of the baseline clinical data. One study [32] referred to published meta-analysis results for the relative treatment effect. Majority of the studies [28,30,34,37–45,47–49] derived costing parameters from local data sources, while the remaining studies referred to published data sources from other jurisdictions [31,32,36,40,46] or were not clearly stated [33,35]. For studies which employed cost-utility analysis, the quality of utility parameter sources was varied. Some were referred from studies which employed direct utility assessment, while others were from studies with unstated method of elicitation from unclearly reported sources. The ranking was not much different between HIC and UMIC studies – a varied ranking quality across all parameter domains. The references and corresponding ranking of the parameters domains of each study are shown in Figure 2 (see Supplementary Table 2).

Table 3. Summary results of CHEERS scoring per reporting domain (n = 22).

Reporting Domain	Number of studies	%
Introduction		
Title	20	90.9
Abstract	22	100.0
Methods		
Background and Objectives	22	100.0
Target population and subgroups	22	100.0
Setting and location	22	100.0
Study perspective	21	95.5
Intervention	20	90.9
Comparator	20	90.9
Time Horizon	20	90.9
Discount Rate	22	100.0
Choice of Health Outcomes	21	95.5
Measurement of Effectiveness	18	81.8
Measurement and valuation of preference-based outcomes (n = 19)	4	21.1
Estimating costs and resources	22	100.0
Currency, price date and conversion	13	59.1
Choice of model	20	90.9
Assumptions	14	63.6
Analytical methods	22	100.0
Results		
Study parameters	18	81.8
Incremental costs and outcomes	22	100.0
Characterizing uncertainty	22	100.0
Characterizing heterogeneity	5	22.7
Discussion		
Study findings, limitations, generalizability, and current knowledge	22	100.0
Others		
Source of Funding	17	77.3
Conflicts of Interest	15	68.2

3.5. Cost-effectiveness analysis results

The results were measured in terms of cost per quality-adjusted life year (QALY) gained for cost-utility analyses, and were converted to international dollars per outcome for comparison (Table 4). The resulting ICERs from HICs ranged from 6,018 to 78,929 USD per QALY or 3,492 to 82,575 international dollars per QALY gained for cost-utility analyses. The values were within their corresponding country cost-effectiveness thresholds, except for Skedgel et al., 2009 [36] because of the absence of a cost-effectiveness threshold in the study's setting. Studies conducted by Liberato et al., 2007 (32) and Macedo et al., 2010 (39) also did not report their corresponding thresholds. Still, adjuvant trastuzumab was consistently concluded for its value for money among HER2-positive EBC in HICs.

Among UMICs, the ICER range was relatively wider at 3,526 to 174,901 USD per QALY or 1.76 to 74,905 international dollars per QALY. Notably, the ICERs of Kongsakon et al., 2018 [49] at 3,526 USD per QALY of Chen et al., 2009 [44] at 9,976 USD per QALY were significantly lower compared with the ICERs of all other UMIC studies. Correspondingly, all UMIC studies except Kongsakon et al, 2018 [49] and Chen et al., 2009 [44] concluded that adjuvant trastuzumab therapy was not cost-effective in their settings (Figure 3).

4. Discussion

In this review, we identified a sensible number of EEs (22 studies) on adjuvant trastuzumab therapy for HER2-positive EBC considering that it has only been approved in the market for such indication for the last decade. Since the last search in 2018 by Petrou's study, which identified 20 studies [21], 18 studies from our review were found to overlap with the previous review. There were many studies conducted from a healthcare payer perspective that covered only direct medical costs and guided policy decision-making on its coverage. Notably, the patients' out-of-pocket (OOP) expenses varied significantly among countries, such as Cambodia (74%), Indonesia (47%), China (32%), Japan (14%), and Thailand (12%) [51]. Thus, OOP expenses should also be considered since all healthcare costs may not be covered by the healthcare payers. According to our review, four economic evaluations [30,31,38,49] were performed based on a societal

Table 4. Summary of cost-effectiveness analysis results of EEs of adjuvant trastuzumab therapy for HER2-positive EBC.

Study	Country	Reported ICER at base year	Base year	ICER (USD 2017)	ICER I$ (PPP) 2017	CE Threshold (USD 2017)
HICs						
ICER and Threshold = Cost per QALY gained						
Garrison et, al. [30]	US	34,201 USD 27,637 USD	2007	40,420 32,663	40,420 44,743	81,949
Kurian et al. [31]	US	39,982 USD	2007	47,253	47,253	42,547–354,555
Liberato et al. [32]	Italy	18,970 USD	2007	21,790	29,849	Not reported
Skedgel et al. [36]	Canada	72,292 Canadian Dollars	2007	78,929	65,230	54,590–109,180
Van Vlaenderen et al [37]	Belgium	10,315 Euros	2005	15,956	19,458	61,874
Macedo et al. [38]	Portugal	7,790 Euros	2010	11,334	18,580	Not reported
Hall et al. [39]	UK	25,803 Pounds	2008	57,803	82,575	67,204
Hedden et al. [40]	Canada	13,095 USD	2012	15,355	12,690	58,630
Lang et al. [41]	Taiwan	51,863 USD	2016	51,863	3,492	67,355
Leung et al. [42]	New Zealand	56,050 New Zealand Dollars	2011	47,231	31,073	37,920–75,840
Seferina et al. [43]	The Netherlands	4,304 Euros	2012	6,018	7,523	111,859
UMICs						
ICER and Threshold = Cost per QALY gained						
Chen et al. [44]	China	8,046 USD	2009	9,976	3,218	Not reported
Buendia et al. [45]	Colombia	71,491 USD	2010	93,371	72	19,591
Aboutorabi et al. [46]	Iran	51,302 USD	2010	174,901	17	34,092
Pichon-Riviere et al. [47]	Argentina, Bolivia, Brazil, Colombia, Chile, Peru, Uruguay	42,104–110,283 USD	2012	63,036–153,554	80–74,905*	11,648–14,971
Ansaripour et al. [48]	Iran	16,695 Euros	2017	18,088	1.76	22,572
Kongsakon et al. [49]	Thailand	3,387 USD	2012	3,526	286	5,148

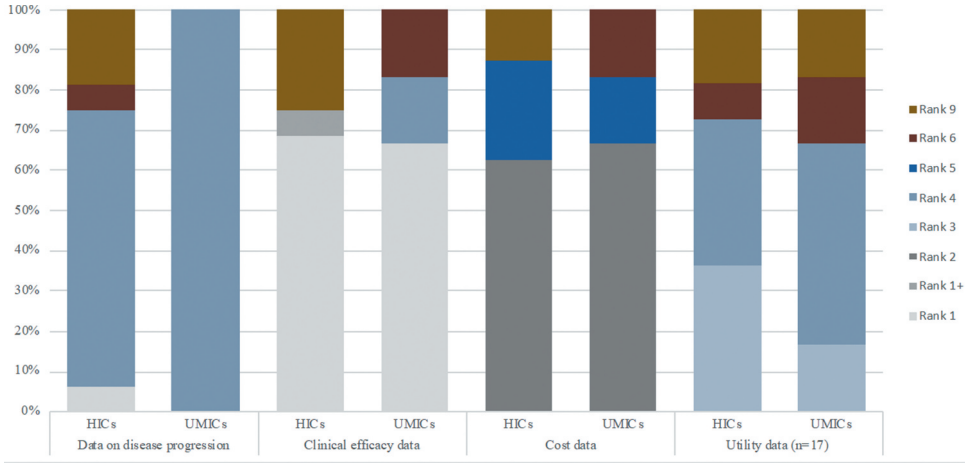

Figure 2. Quality assessment of evidence used in economic evaluations of trastuzumab. Y-axis represents percentage of economic evaluations having a rank based on the Quality Assessment of Sources of Input Data using tool from Cooper et al. X-axis accounts for the high-income countries (HICs) and upper-middle-income countries (UMICs) assessed based on different input parameters.

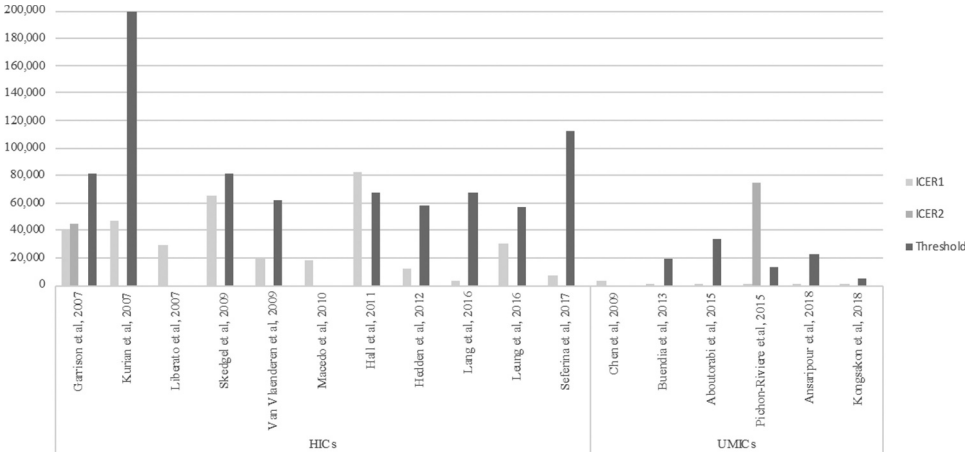

Figure 3. Incremental cost-effectiveness ratios (I$, 2017) of trastuzumab and corresponding thresholds reported from health economic evaluation. Y-axis represents the incremental cost-effectiveness ratios (ICERs) reported from different economic evaluations. X-axis accounts for EEs assessed from high-income countries (HICs) and upper-middle-income countries (UMICs).

perspective, which covered direct medical, non-medical, and indirect costs. However, none reported the patients' OOP expenses from direct medical costs. Furthermore, only two studies revealed that patients' OOP expenses from direct non-medical costs were transportation [30,48] and food [48] costs. About half of the studies were conducted during the first few years of its market introduction and were undertaken by HICs, which evidently have the larger fiscal space and higher capacity to afford such medication for national coverage. In contrary, the limited number of published EEs among MICs, which were mostly published recently, likely suggests the low priority among these countries to consider high-cost therapies even with proven relative treatment effect. This may also be attributed to the current technical and context-specific challenges that researchers working in lower-middle income countries (LMICs) face, such as limited expertise to conduct EEs or lack of reliable data.

Overall, the methodology of studies was appropriate and of good quality. This may due to the fact that they were undertaken by HICs where expertise on health economics is well-established, and with their first authors mostly affiliated with the academe where conduct of research is generally considered to be of high quality. Further, in the context of the evolution of health economics research, these studies were conducted in recent times where developments in EE methods have been importantly explored, and where guidelines for more robust and better quality evaluations are clearer.

As trastuzumab is relatively new in the market and in the clinical practice, it is evident that the studies identified applied modeling technique to evaluate the cost-effectiveness considering the paucity of longer follow-up data. As expected, the models were highly varied in terms of the number of health states but the key health states were comparable, with many of them incorporating cardiotoxicity as a significant side effect

of trastuzumab use. There were no detected major inconsistencies across their methods.

Although the range of scoring for the transparency of reporting was wide, most studies attained high scores since they were recently conducted when reporting tools have been released and recommended. Notably, the extent of reporting based on the CHEERS scoring guide was moderately higher in studies from UMICs (89%) compared with studies from HICs (85%). This may be explained by the fact that the most recent CHEERS checklist used in our review was only released in 2013, and most HIC studies were published prior to that year. Almost all UMIC studies, on the other hand, were published in 2013 and beyond.

As regards the appraisal of input data sources, the ranking scores were quite varied. Among all the parameter domains, only the data source/s clinical effect size attained mostly high ranking score across all studies and scored for the highest possible rank in that parameter domain. Each of the source parameter domains had a small number of studies (ranging from one to four studies) with the lowest ranking. It was evident though that there were more studies from HICs with lowest ranking (i.e., three studies in epidemiological data sources, four in clinical efficacy source, and two in cost data source) as compared with those studies from UMICs (i.e., one study in utility data source). This may be accounted for the fact that studies from UMICs were more recently published, hence had better quality of reporting. Although relatively transferable, the dependence of most studies on RCT data for clinical data may suggest the lack of established cancer registries even among HICs. The need for real-world data may be more imperative in developing countries where a possible significant difference in the observed efficacy under controlled conditions versus the actual effectiveness in the clinical practice cannot be ignored. We also noted that most RCT sources were of short follow-up period (i.e., three years) with about a decade of its entry in the market and the release of latest follow-up data on trastuzumab efficacy [9], utilizing longer follow-up clinical data is imperative, considering that duration of efficacy was cited by most studies to be an influential parameter in cost-effectiveness results. Moreover, the reliance of some studies on published costing data outside their jurisdiction for costing parameters, given its low transferability, may result in unreliable results. Furthermore, it is noted that there may be a difference in the costing data between the actual costs and the costs obtained from published studies since, in reality, approximately 14–17% of HER2- positive EBC patients are not provided with adjuvant trastuzumab [52], specifically for those with advanced age and who have co-morbidities, and about 15% discontinue the adjuvant treatment due to its cardiotoxicity [53]. Nonetheless, the overall input data sources of majority of the studies were of acceptable quality.

As with value for money, adjuvant trastuzumab for HER2-positive EBC was found to be cost-effective in HICs with ICERs ranging from 6,018 to 78,929 USD per QALY gained. Trastuzumab was found to be cost-effective in China [44] and in Thailand [49], contrary to the results of all other studies in UMICs where it was concluded as not cost-effective with ICERs at 18,088 to 174,901 USD per QALY. Several factors may have affected their significantly lower ICERs (i.e., 9,976 USD per QALY gained in China and 3,526 USD per QALY gained in Thailand) and favorable cost-effectiveness results. First, Chen et al., 2009 used a lower hazard ratio, thereby modeling for a more favorable trastuzumab efficacy. It also modeled for five-year efficacy duration with decreasing efficacy in a stepwise function for the trastuzumab cohort simulation, while other studies mostly applied a 5-year duration of efficacy only with zero applied for benefit onwards. On the other hand, Kongsakon et al., 2018 did not incorporate cardiac events in their analysis, resulting in an underestimated ICER.

The overall quality of future EEs on trastuzumab can be enhanced by improving the reporting quality through explicitly stating and discussing commonly missed reporting information that we have identified in this review – complete table of input parameters, their values, distribution, and sources; the underpinning model assumptions; the currency price date and conversion rate; comprehensive discussion section with limitations of the study; the funding source; and the conflict of interest statements. Future EEs on trastuzumab are further recommended to consider the use of local data parameters for a more contextualized and appropriate results that can guide decision-making. We also note the significance of using real-world clinical data of longer follow-up period that can better reflect the true effectiveness, and therefore cost-effectiveness of trastuzumab.

Our main findings are consistent with previously published reviews showing that majority of the studies showed favorable results mainly because majority were from HICs with higher willingness-to-pay or cost-effectiveness thresholds. Similarly, Chan et al., 2009 [20] rated a high rating for the quality of the studies based on a checklist; although our study applied CHEERS checklist which is a more comprehensive standard reporting list that what they used. The main limitation of our review is the non-inclusion of unpublished papers which may possibly capture EEs on adjuvant trastuzumab therapy among LMICs. Identifying and making them accessible to fellow LMICs, especially of those with lower capacity to conduct such evaluations, may guide them on their decision-making on trastuzumab coverage.

Nevertheless, it is noteworthy to highlight that six trastuzumab biosimilars have been recently approved by the European Union and are presently available in the market [54]. In effect, this has led to a significant price reduction by 20% to 30% [55]. Since trastuzumab is considered to be an effective drug used for the treatment of HER2-positive EBC and has already been included in the WHO Essential Medicines List since 2013 [50], the debate on its cost-effectiveness should be closed. Furthermore, the standard adjuvant treatment for HER2-positive EBC patients is currently transitioning after the approval of new drugs, such as pertuzumab, trastuzumab emtansine, and neratinib for oral use [56]. Consequently, future research on their cost-effectiveness as adjuvant therapy for HER2-positive EBC patients should be further investigated.

5. Conclusion

Our review, based on available EEs on adjuvant trastuzumab, suggests that the therapy, in comparison with chemotherapy alone, for HER2-positive EBC, may be cost-effective in HICs. We have yet to see more evidence on its value for money in developing countries, especially among LMICs where no economic evaluation currently exists. While

the quality of methods and the adequacy and transparency of reporting of EEs on trastuzumab were generally high, the quality of input data sources is challenged with the paucity of high-quality data. Future EEs on trastuzumab are recommended to consider reliable context-based data parameters, as well longer and real-world clinical data that can capture the true effectiveness of adjuvant trastuzumab therapy which significantly affects its value for money. Nevertheless, trastuzumab biosimilars are currently approved and available in the market with a reduced price by about 20% to 30% [55] and such information can absolutely change the results of our review.

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Authors' contribution

AJG and MAJG performed systematic reviews, quality assessment, and interpretation as well as drafted and revised the paper. AT and TR participated in the analysis and interpretation of data and the drafting of the paper. UC is involved in the conception and design, analysis, and interpretation of the data, the drafting of the paper, and revising it critically for intellectual content. All authors granted the final approval of the version to be published and agreed to be accountable for all aspects of the work.

Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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