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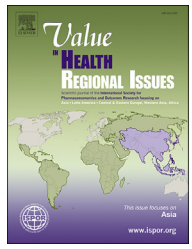

Systematic Review

Cost-Effectiveness of Adjuvant Trastuzumab Therapy for Early Breast Cancer in Asia: A Systematic Review

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ABSTRACT

Objectives: To systematically review and assess the quality of the economic evidence of adjuvant trastuzumab usage in early breast cancer in Asian countries. **Methods:** Literature search was performed using 6 electronic databases (PubMed, Scopus, Ovid MEDLINE, EconLit, National Health Service Economic Evaluation Database, and ISI Web of Knowledge). The final search was performed in October 2018. All potential economic studies were then checked for eligibility. The reporting and methodological qualities of each study were independently assessed by 2 authors of this review, using the Consolidated Health Economic Evaluation Reporting Standards, Drummond, and Philips checklists. To compare the different currencies used in these studies, all costs were converted into US dollars (2016). **Results:** A total of 6 studies were included; most of them were performed from the healthcare provider perspective. The incremental cost-effectiveness ratio for evaluation performed for a lifetime horizon were reported at $8573 and $20 816 per quality-adjusted life-year in 2 studies. The model outcome was generally sensitive to the changes in trastuzumab drug acquisition cost and discount rate, as well as its clinical effectiveness. For the quality assessment, all studies fulfilled more than 50% of the requirements in the Consolidated Health Economic Evaluation Reporting Standards, Drummond, and Philips checklists. **Conclusions:** Adjuvant trastuzumab therapy is considered a cost-effective option for early breast cancer in Asian countries including China, Iran, Japan, Singapore, and Taiwan. All studies were generally well conducted. Economic evaluations from the societal perspective, with inclusion of indirect and informal care costs, are warranted to facilitate informed decision making among policy makers.

Keywords: adjuvant, Asia, early breast cancer, HER2-positive, trastuzumab.

Introduction

Breast cancer is the most common type of cancer among women in the Asia-Pacific, accounting for 18% of all cancer diagnoses.[1] In fact, about 116 000 women (8 per 100 000 population) from this region were estimated to have died from breast cancer in 2012.[1] Despite a lower prevalence of breast cancer in Asian countries than in Western countries, their proportional contribution to global incidence rate has greatly increased alongside with their socioeconomic development.[2] The ever-rising incidence of breast cancer poses substantial financial burden to the healthcare systems worldwide.[3]

Human epidermal growth factor receptor (HER2)-positive is one of the genes that plays an important role in the development of breast cancer.[4] The introduction of anti-HER2 therapies, such as trastuzumab, was a significant step forward that resulted in improved overall survival (ie, 10 years) and quality of life among patients with early breast cancer.[5,6] Trastuzumab, a recombinant DNA-derived humanized monoclonal antibody, is used as an adjuvant treatment for patients in the early stage of breast cancer that overexpresses HER2.[7] According to the consensus statement from the Asian Oncology Summit, the treatment recommendations for managing HER2-positive breast cancer in Asia are consistent with the guidelines from Europe and the

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United States.[8] The optimum duration of trastuzumab is 1 year, whereas anthracycline-based regimens are preferred as adjuvant chemotherapy.[8] Tamoxifen is recommended for premenopausal women with endocrine-responsive HER2-positive breast cancer, whereas aromatase inhibitors are preferred for postmenopausal women.[8] Despite the recommendation of a 12-month adjuvant trastuzumab treatment for patients with HER2-positive breast cancer,[7,9] some middle-income countries in Asia did not provide a full 12-month treatment of trastuzumab to their patients with breast cancer because of financial consideration.[10,11]

Given that newer drug therapies (eg, trastuzumab) are often associated with higher acquisition costs, there is a need for assessing their health returns for expenditure. Economic evaluations would, therefore, be of great value to facilitate informed decision making with respect to the use of these agents in breast cancer, to maximize patient outcomes and minimize overall costs. Most of the economic studies that evaluated the adjuvant use of trastuzumab were performed in developed Western countries.[12–16] Cost-effectiveness data of adjuvant trastuzumab among patients with early breast cancer in Asian countries, however, remain scant. In addition, the previous systematic reviews did not perform quality assessment on the methodological aspects of the included economic evaluations.[3,17] Hence, the aim of this study was to systematically review and to assess the quality of the cost-effectiveness data of trastuzumab as an adjuvant treatment for patients with early breast cancer in Asia.

Methods

Search Strategy

A systematic search was developed (see Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.02.003) to identify economic evaluation of adjuvant trastuzumab for treating early breast cancer in the Asian setting. Literature search was performed using 6 electronic databases (ie, PubMed, Scopus, Ovid MEDLINE, EconLit, National Health Service Economic Evaluation Database, and ISI Web of Knowledge); the final search was carried out in October 2018. Free-text keywords and medical subject heading terms, combined with Boolean operators, were as follows: economic (cost, cost-analysis, health economics, economic evaluation, pharmacoeconomics, cost-effectiveness, cost-benefit, and cost-utility), breast cancer (breast tumor, breast carcinoma, breast neoplasm, and mammary), trastuzumab, and HER2/neu (ERBB2 receptor, epidermal growth factor receptor, herceptin, trastuzumab, and HER2). The PubMed search strategy served as a reference for the development of search strategies for the remaining databases. In addition, citations in each article were used to further identify relevant articles that were not captured by the electronic databases.

Study Selection

Economic evaluations (ie, cost-effectiveness analysis [CEA], cost-utility analysis [CUA], or cost-benefit analysis [CBA]) on adjuvant use of trastuzumab for patients with HER2-positive early breast cancer in Asian countries were included in this systematic review. The exclusion criteria were as follows: studies presented only as abstracts with no full reporting of economic findings, review articles, studies from non-Asian countries, or studies that included only costs of trastuzumab. All potential economic studies identified were checked for eligibility on the basis of the aforementioned inclusion criteria and were independently assessed by 2 authors of this review. Any discrepancies on the inclusion of a particular study were resolved through discussion and consensus.

Data Extraction

Data from the selected studies were extracted and synthesized using a tailored extraction data sheet in Microsoft Excel. The characteristics of each included economic study (ie, country, study year, year of costing, type of currency, type of economic evaluation, objective, study perspective, time horizon, comparators, cost components, outcome measure, sensitivity analysis, and economic findings) are summarized. To make a comparison between the different currencies used in different countries, the reported costs were converted into a common currency, using the same year as a reference.[18] For studies that did not state the year of costing,[19,20] the costs considered were 1 year before the publication year. All costs[10,19–23] were converted into US dollars (2016) using a web-based tool.[24] The tool adjusted the estimates for costs and price year according to specific target currency and year by taking into account the purchasing power parities between countries.[18]

Quality Assessment

Quality assessment was independently performed by 2 authors of this review. The reporting quality of the included economic studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards checklist[25]—a recommendation by the International Society for Pharmacoeconomics and Outcomes Research Task Force. It consists of 24 items, which are subdivided into 6 main categories: (1) title and abstract, (2) introduction, (3) methods, (4) results, (5) discussion, and (6) other. As for methodological quality, both the 10-item Drummond[26] and the 57-item Philips[27] checklists were used. They assessed the measures on the study design (eg, study objective, perspective, and alternative strategies), data collection (eg, data sources, currency, utility, and consequences), and result analysis (eg, sensitivity analysis, uncertainty, discounting, and treatment effect). The Philips checklist is recommended by both the Cochrane Collaboration and the National Institute for Health and Care Excellence[9] to assess modeling studies and it can be used in conjunction with other general checklists or guidelines on economic evaluation.[27]

Results

Of the 2899 articles identified using the search strategy (Fig. 1), 1050 were removed because of duplication, whereas another 994 studies were excluded on the basis of the titles and/or abstracts that were not relevant to the scope of this study. A total of 56 full-text articles were then retrieved and assessed for eligibility. Fifty articles were further excluded as per prespecified criteria. A total of 6 studies, published between 2007 and 2017, were included in this systematic review.[10,19–23]

Characteristics of the Included Studies

The characteristics of all the eligible studies and their main findings are presented in Table 1. Two studies were conducted in Iran, with 1 each from China, Japan, Taiwan, and Singapore. All included studies were CEAs,[10,19–22] except 1, which was a CBA.[23] All the economic analyses were performed from a healthcare provider perspective,[10,19–22] with only 1 from a societal perspective.[23] One study did not report the time horizon of analysis[23] and the shortest time horizon included was 20 years in 2 of the studies.[21,22] One study assessed a 50-year time horizon,[19] whereas the remaining 2 studies applied a lifetime horizon.[10,20]

All reported CEAs used Markov state transition models. Most of the models populated with the inputs such as rates of disease progression from the disease-free state to other health states such as local or metastatic recurrence and, lastly, death. Three

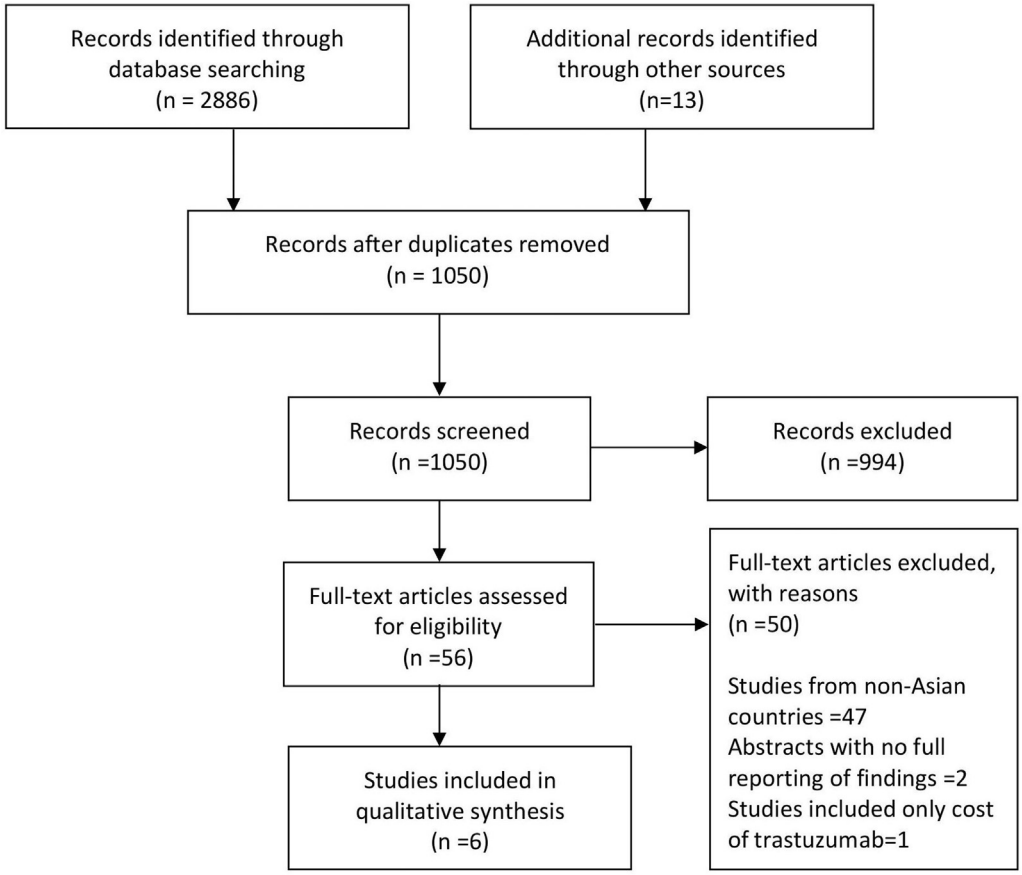

Fig. 1 – Flowchart of the study selection.

CEAs[19,20,22] used efficacy data from the HERA trial, and 2 studies[10,21] used data from the BCIRG 006 trial and the PHARE trial, respectively. Most of the studies used standard adjuvant treatment, which consisted of doxetacel, doxorubicin, or cyclophosphamide as a comparator. All studies[10,19–23] performed 1-way sensitivity analysis, and only 3[10,19,22] studies performed probabilistic sensitivity analysis. Parameters that affected the model outcome the most were trastuzumab drug acquisition cost, discount rate, and clinical effectiveness.

Most of the studies used 3 times the gross domestic product per capita as the incremental cost-effectiveness ratio (ICER) threshold, as proposed by the World Health Organization.[28] Only 1 study[19] adopted the ICER threshold from the National Institute for Health and Care Excellence guideline,[9] which ranged between £20 000 and £30 000 per quality-adjusted life-year (QALY) gained. The 2 studies[10,20] that examined the cost-effective use of adjuvant trastuzumab across lifetime horizon reported an ICER of $8573/QALY and $20 816/QALY (ie, >$50 000/QALY). When the analysis was run for a shorter time horizon (ie, 20 years), the ICER for adjuvant trastuzumab increased to more than $50 000/QALY.[21,22] In 1 study,[19] the ICER was affected by patient's body weight whereby the ICER value increased as the patient's body weight increased. All the studies[10,19–23] concluded that a 1-year treatment of adjuvant trastuzumab was cost-effective in treating early breast cancer in each respective country.

Quality Assessment

The checklist items used in this review for assessing the reporting quality of economic studies are presented in Table 2. All the studies[10,19–23] had a good reporting quality as per the Consolidated Health Economic Evaluation Reporting Standards checklist.[29] All the studies[10,19–23] reported their objectives, comparator(s), study parameters, measures of effectiveness, ICERs, and generalizability of study findings. Four of the studies described the currency conversion,[10,19,21,23] and only 2 studies reported on heterogeneity.[10,19]

As per the Drummond checklist[26] (Table 3), 5 of the studies had a well-defined question, comprehensive description of alternative(s), relevant cost and consequences, adjustment for present value, and sensitivity analysis performed to define the uncertainty.[10,19–22] Nevertheless, only half the studies described and justified the source of cost and consequences used in the model.[10,19,23] One of the studies did not involve any modeling method,[23] and therefore it was excluded from assessment using the Philips checklist. The Philips checklist[27] (Fig. 2) is divided into 3 main components consisting of structure, data, and consistency. Almost half the studies did not meet the requirement for questions that addressed primary decision maker,[19–21] justification of data,[19–22] and causal relationship used in the model.[19–22] Most studies did not justify the duration of the cycle length chosen. Furthermore, most of the studies did not evaluate the quality and relevance of the data used. The use of half-cycle correction was mentioned in only 1 study.[10] All the CEA studies[10,19–22] explored and fully justified structural assumptions that they used. Cost and utilities data were well described by most of the studies.[10,19–22] Nevertheless, only 1 type of uncertainty (ie, parameter uncertainty) was fully addressed in all the CEA studies,[10,19–22] using either deterministic sensitivity analysis[10,19–22] or probabilistic sensitivity analysis.[10,19,20,22] In terms of consistency, model validation was not carried out or perhaps not reported alongside with the model in all the CEA studies.[10,19–22]

Table 1 – Key features of the economic evaluation studies included in the review (n = 6).

Reference (country/ perspective/ type of analysis)	Mean age (weight)	Intervention (dose)	Comparator	Time horizon (discount rate)	ICER 2016 (cost/QALY)	Most influential factor(s) reported in 1-way sensitivity analyses
Shiroiwa et al[19,*] (Japan/ healthcare/ CEA)	49 y (50-60 kg)	1-y adjuvant trastuzumab (LD: 8 mg/kg; MD: 6 mg/kg)	Observational group (adjuvant, neo-adjuvant)	50 y (3%)	$55 994/LYG (2 y) $24 264/LYG (5 y) $16 798/LYG (10 y)	Duration of trastuzumab efficacy, discount rate, recurrence rate, cardiotoxicity costs, and terminal costs
Chen et al[20,*] (China/health insurance/ CEA)	50 y (58 kg)	1-y adjuvant trastuzumab after surgical therapy (LD: 4 mg/kg; MD: 2 mg/kg weekly)	Standard chemotherapy (docetaxel, doxorubicin, cyclophosphamide)	Lifetime (3%)	$8573-$8990	Discount rate, cost of first year in recurrence and metastatic state, probabilities of trastuzumab price, probabilities of DFS progressed to metastatic
Aboutorabi et al[21] (Iran/ healthcare/ CEA)	50 y (70 kg)	1-y adjuvant trastuzumab (dose not stated)	AC-T regimen	20 y (3%)	$56 182	Cost of trastuzumab, discount rate for outcomes and HR in the AC-TH group
Ansaripour et al[10] (Iran/ healthcare/ CUA)	45 y (70 kg)	6 mo, 9 mo, or 1-y adjuvant trastuzumab (dose not stated)	No trastuzumab therapy	Lifetime (3.5%)	$18 235 (6 mo) $20 411 (9 mo) $20 816 (1 y)	Cost of trastuzumab and clinical effectiveness of 1 y of trastuzumab use vs no trastuzumab
Lang et al[22] (Taiwan/ healthcare/ CEA)	50 y[†]	1-y adjuvant trastuzumab (LD: 8 mg/kg; MD: 6 mg/kg)	Common chemotherapy (a combination of docetaxel or paclitaxel, doxorubicin, and cyclophosphamide)	20 y (3%)	$52 371	Transition probabilities of the DFS for both the trastuzumab and nontrastuzumab groups; health utility for the nontrastuzumab group in DFS; utility for trastuzumab in metastasis state
de Lima Lopes[23] (Singapore/ societal/CBA)	48 kg[‡]	1-y adjuvant trastuzumab (dose not stated)	No comparator	(3%)[§]	$19 118-$27 312[§]	Not specified

AC-T indicates doxorubicin and cyclophosphamide followed by docetaxel; AC-TH, doxorubicin and cyclophosphamide followed by docetaxel plus trastuzumab; CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DFS, disease-free state; HR, hazard rate; ICER, incremental cost-effectiveness ratio; LD, loading dose; LYG, life-years gained; MD, maintenance dose; QALY, quality-adjusted life-year.

[*] For studies that did not state the year of costing, the costs were considered 1 y before the publication year.

[†] Body weight of the patient was not reported in the study.

[‡] Age of the patients was not reported in the study.

[§] The value depends on the model used (Kurian et al,[55] Liberato et al,[56] Garrison et al[13]).

Discussion

Adjuvant trastuzumab was reported to be a cost-effective treatment option for patients with early breast cancer in all the economic studies included in this review, consistent with previous systematic reviews.[3,17,30] Nevertheless, the economic evaluations included in the previous systematic reviews[3,17,30] were mainly from developed Western countries and had a great variation in the method and depth of economic evaluation of trastuzumab. Of note, 2 reviews did not perform quality assessment on the methodological aspects of the included economic studies.[3,17] Risk-of-bias assessment is one of the important steps in developing a good systematic review.[31] The validity of the results in economic evaluation can be influenced by biases, and thus its impact on the study findings needs to be assessed.[31] In the present systematic review, the quality assessment on the methodological aspects of each included economic study was conducted using both the Philips and the Drummond checklists. All the studies fulfilled half the components in the structure and data domains as stated in the Philips checklist. The internal and external consistencies of the models, however, were not described in most of the economic studies.[10,19–22]

Table 2 – CHEERS checklist.

Section	Item	Shiroiwa et al[19]	Chen et al[20]	Aboutorabi et al[21]	Ansaripour et al[10]	Lang et al[22]	de Lima Lopes[23]
1	Title	Yes	Yes	Yes	Yes	Yes	Yes
2	Abstract	Yes	Yes	Yes	Yes	Yes	Yes
3	Background and objectives	Yes	Yes	Yes	Yes	Yes	Yes
4	Target population and subgroups	Yes	Yes	Yes	Yes	Yes	Yes
5	Setting and location	Yes	Yes	Yes	Yes	Yes	Yes
6	Study perspective	Yes	Yes	Yes	Yes	Yes	Yes
7	Comparators	Yes	Yes	Yes	Yes	Yes	Yes
8	Time horizon	Yes	Yes	Yes	Yes	Yes	No
9	Discount rate	Yes	Yes	Yes	Yes	Yes	Yes
10	Choice of health outcomes	Yes	Yes	Yes	Yes	Yes	Yes
11a	Measurement of effectiveness: single study	NA	NA	NA	NA	NA	NA
11b	Measurement of effectiveness: model-based	Yes	Yes	Yes	Yes	Yes	NA
12	Measurement and valuation of preference-based outcomes	Yes	Yes	Yes	Yes	Yes	Yes
13a	Estimating resources and costs: single study	NA	NA	NA	NA	NA	Yes
13b	Estimating resources and costs: model-based	Yes	Yes	Yes	Yes	Yes	NA
14	Currency, price date, and conversion	Yes	No	Yes	Yes	No	Yes
15	Choice of model	Yes	Yes	Yes	Yes	Yes	NA
16	Assumptions	Yes	Yes	Yes	Yes	Yes	Yes
17	Analytical methods	Yes	Yes	Yes	Yes	Yes	Yes
18	Study parameters	Yes	Yes	Yes	Yes	Yes	Yes
19	Incremental costs and outcomes	Yes	Yes	Yes	Yes	Yes	Yes
20a	Characterizing uncertainty: single study	NA	NA	NA	NA	NA	No
20b	Characterizing uncertainty: model-based	Yes	Yes	Yes	Yes	Yes	NA
21	Characterizing heterogeneity	Yes	No	No	Yes	No	No
22	Study findings, limitations, generalizability, and current knowledge	Yes	Yes	Yes	Yes	Yes	Yes
23	Source of funding	Yes	Yes	Yes	Yes	Yes	Yes
24	Conflicts of interest	Yes	Yes	Yes	Yes	Yes	Yes

CHEERS indicates Consolidated Health Economic Evaluation Reporting Standards; NA, not applicable.

Table 3 – Drummond checklist.

Criteria	Shiroiwa et al[19]	Chen et al[20]	Abutorabi et al[21]	Ansaripour et al[10]	Lang et al[22]	de Lima Lopes[23]
1. Was a well-defined question posed in answerable form?	Yes	Yes	Yes	Yes	Yes	Yes
2. Was a comprehensive description of the competing alternatives given?	Yes	Yes	Yes	No	Yes	NA
3. Was the effectiveness of the programs or services established?	Yes	Yes	Yes	Yes	Unclear	NA
4. Were all the important and relevant costs and consequences for each alternative identified?	Yes	Yes	No	Yes	Yes	Yes
5. Were costs and consequences measured accurately in appropriate physical units?	Yes	Unclear	Unclear	Yes	Unclear	Yes
6. Were costs and consequences valued credibly?	Yes	Yes	No	Yes	No	Yes
7. Were costs and consequences adjusted for differential timing?	Yes	Yes	Yes	Yes	Yes	Yes
8. Was an incremental analysis of cost and consequences of alternatives performed?	Yes	Yes	Yes	Yes	Yes	Yes
9. Was uncertainty in the estimates of costs and consequences adequately characterized?	Yes	Yes	Yes	Yes	Yes	No
10. Did the presentation and discussion of study results include all issues of concern to users?	Yes	Yes	Yes	Yes	No	Yes

NA indicates not applicable.

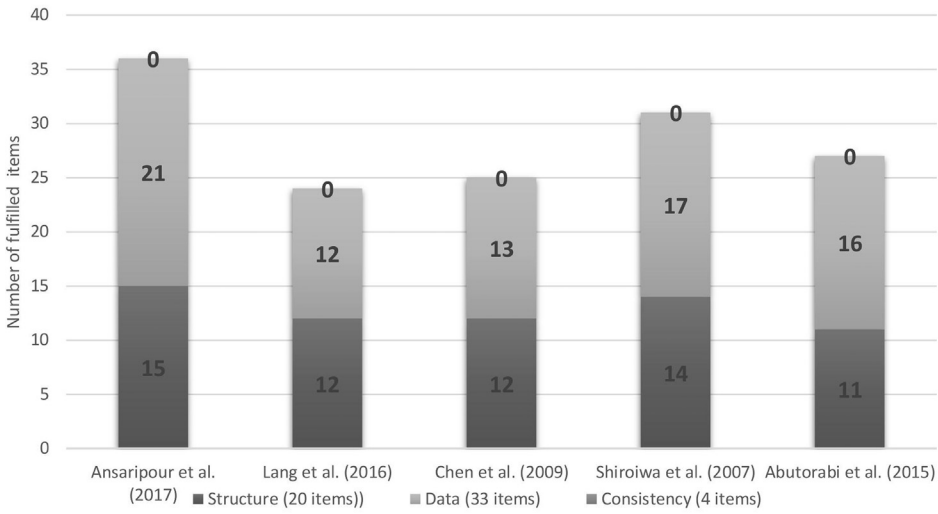

Fig. 2 – Philips checklist—absolute numbers of fulfilled items.

Most of the economic studies included in this review were performed from a healthcare provider perspective,[10,19–22] and only 1 was from a societal perspective.[23] Conducting an economic evaluation from a narrow perspective would significantly undermine the true benefits of an intervention toward the society.[32] According to the recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine, inclusion of informal care in economic evaluations conducted from the societal perspective is essential.[33] Important cost components such as informal care that account for significant cost in many chronic illnesses,[34] however, are seldom included in economic evaluations.[35] Thus, this may lead to suboptimal healthcare policy decision and inefficient allocation of limited resources.[35,36]

The outcome probabilities (ie, input variables for effectiveness data) for all the studies[10,19–23] were obtained from published clinical trials (ie, HERA trial,[37] B31 trial,[38] BCIRG 006 trial,[39] and PHARE trial[40]). In addition, 1 study[22] derived one of the transition probabilities from a cohort study[41] and this may be subject to bias because of incomplete record and loss of follow-up. A pharmacoeconomic analysis may be best performed using data from randomized controlled trials (RCTs) because they provide the most reliable source of data[42] with minimal biases and assumptions needed to be made during the data collection.[43] Nevertheless, this approach has its inherent limitations, such as a shorter length of follow-up and outcome measured in the RCT may not be the patient-level final outcome of treatment.[26] Hence, it is common to use decision-analytical modeling as a means of bringing the evidence together from a range of sources and evaluate the robustness of the economic data with sensitivity analysis,[26] as demonstrated in most of the economic studies[10,19–22] included in the present systematic review.

In the present review, deterministic sensitivity analysis was conducted in handling the uncertainty of the included economic studies.[10,19–22] This method is rather easy to conduct, but may lead to biased estimates of cost-effectiveness data.[26] The nonlinear relationship between the inputs and outputs noted in the Markov models may generate biased cost-effectiveness findings if only deterministic sensitivity analysis was performed for each input parameter to estimate the expected cost, effect, and net benefit.[26] One of the ways to overcome this bias is to conduct probabilistic sensitivity analysis[26]; nevertheless, this was done in only 2 of the economic studies[10,22] included in this review. This concern was also highlighted in the previous review by Ferrusi et al.[44] Probabilistic sensitivity analysis is one of the important tools that aids in decision making especially in highly variable population (ie, age or comorbidity) and treatment settings.[17]

The cost-effectiveness data reported in the economic studies included in this review are influenced by several input parameters. For example, adjuvant trastuzumab was found to be a cost-effective option in patients with early breast cancer who were younger than 59 years.[10] This finding is in line with a previous systematic review[30] that reported that adjuvant trastuzumab was a cost-effective therapy in women with early HER2-positive breast cancer who were younger than 55 years.[30] The ICER value increases when the age of the patients at the onset of the treatment increases.[10] The effect of age-dependent variation in the modeled ICER is mainly due to a decreased life expectancy with an increasing age rather than the result of a difference in the relative treatment effect of trastuzumab among various age groups.[45]

One of the economic studies[19] in this review has explored the robustness of the model outcome against the body weight of the patient. Given that body weight may greatly affect the total administered dose of trastuzumab, the model outcome was generally sensitive to the variation in this input variable. In the economic study by Shiroiwa et al,[19] patients with a body weight of 60 to 75 kg were reported to have a higher ICER compared with those who weighed less than 50 kg.[19] Of note, the average body weights used in the included economic studies[10,19–23] in this review were highly variable. For example, in the Chinese study,[20] the average body weight of the patients was 58 kg, whereas in the Iranian study,[10] it was 70 kg. This variation in body weight may be contributed by a difference in socioeconomic status across Asia. It is reported that the people from low-income countries with a higher socioeconomic status tend to be overweight compared with those from high-income countries.[46] Conversely,

in high-income countries people with higher socioeconomic status reported to have lower body weight because of their active lifestyle.[47]

In the present review, we found that the duration of treatment has an impact on both the costs and the clinical outcomes. The effect of trastuzumab treatment duration (ie, 6 months, 9 months, and 1 year) on the cost-effectiveness data was studied in one of the Iranian studies.[10] A shorter treatment duration (ie, 6 months) of adjuvant trastuzumab was found to be cost-effective when compared with the standard 1-year treatment of adjuvant trastuzumab.[10] The 6-month treatment duration was based on clinical outcomes from the PHARE[40] trial. Currently, there are 2 ongoing RCTs that explore a shorter duration of trastuzumab treatment (ie, SOLD[48] [9 weeks] and short-HER[49] [6 months]). Emerging clinical efficacy data may provide information on whether a shorter treatment duration is as efficacious as the year-long course while achieving greater cost-effectiveness.[23] Once the findings from these ongoing trials[48,49] are available, the impact of duration of treatment on model outcome can be further explored.

We also found that the trastuzumab regimens varied across the included economic studies.[10,19–23] All the studies administered trastuzumab for 1 year on the basis of 2 different schedules: (1) 6 mg/kg every 3 weeks (with a loading dose of 8 mg/kg) was administered sequentially after chemotherapy[10,19,22] and (2) 2 mg/kg weekly doses (with a loading dose of 4 mg/kg) was initiated concurrently with taxane chemotherapy after completion of anthracyclines treatment in the other 2 studies.[20,21] If we compared the ICERs from the 2 Iranian studies,[10,21] the one that used concurrent therapy had a higher ICER[21] value than the one that used sequential chemotherapy.[10] A previous study[50] has shown that total drug cost in concurrent therapy increased two-fold as a result of the high cost of docetaxel and trastuzumab. The efficacy, safety, and cost of drug were not compromised by administering a triple-dose regimen every 3 weeks; instead, it reduced the costs on nursing, pharmacy, and other facilities, as well as improved quality of life by reducing traveling, parking, waiting, and infusion time.[51] Only 1 included economic study[23] did not mention the types of regimens it used.

The choice of time horizon in the included economic studies in this review also has a significant impact on the ICER. The analyses that applied the lifetime horizon reported an ICER between $8573/QALY and $20 816/QALY. The study that applied a shorter time horizon[21] (ie, 20 years) had an ICER of more than 50 000/QALY. In fact, a longer time horizon is crucial to obtain reliable cost-effectiveness estimates of adjuvant treatment on the healthcare budget. A shorter time horizon may underestimate the cost-effectiveness of an intervention because the impact on outcome may become apparent only at a later stage, whereas the treatment costs can often be calculated immediately.[52]

The included economic studies in this review had high levels of heterogeneity because of differences in study setting, study design, and subgroup characteristics. These heterogeneities presented challenges in making direct comparison between the economic studies. The difficulty in directly extrapolating the published economic findings to the appropriate patient populations that reflect the societal benefits remains to be resolved because these economic studies[10,19–22] were mainly conducted from the payer perspective, which resulted in a narrow cost consideration that does not contemplate the true costs and benefits or consequences of health interventions. The local decision maker would face a challenge in interpreting the economic findings because the local data were merely applied in cost category in most of the studies. Apart from that, other factors such as variability in healthcare systems and socioeconomic status pose great challenges to transfer the cost-effectiveness data between countries. Different countries usually have great differences in epidemiology of disease, healthcare settings, clinical practices, relative price levels, patient preferences, and opportunity costs of resources.[53,54]

The present work, however, has limitations. Only studies published in English were included, and thus the number of articles retrieved was small. Despite the use of broad search terms, some of the relevant studies may not have been retrieved. The quality assessment for the included studies was subjected to personal judgment. The high level of the methodological or population heterogeneity, in terms of treatment strategies and patient characteristics, could have affected the findings of this review.

Conclusions

Adjuvant trastuzumab treatment is considered to be a cost-effective treatment option for early breast cancer in Asian countries such as China, Iran, Japan, Singapore, and Taiwan. All studies were generally well conducted with relatively good quality of reporting. Nevertheless, the existing economic evaluations are limited by their great variation in the study design, outcome measure, and population characteristics. Future studies should incorporate the evidence for consistency measurement because it is an important factor in determining the quality of the model. In addition, more economic evaluations that take into account the total societal costs are needed to better aid informed decisions with respect to the adjuvant use of trastuzumab in early breast cancer.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2019.02.003.

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