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Cost Utility of Adjuvant and Neo-Adjuvant Treatment for Breast Cancer: A Systematic Review of Observational Economic Evaluations Studies

Luh Putu Febryana Larasanty[1,4*], Irfanianta Arif Setyawan[2,4], Diah Nurlita[3,4]

[1]Pharmacist Profession Study Program, Department of Pharmacy, Faculty of Mathematics and Basic Science, Udayana University, Bali, Indonesia.
[2]Department of Pharmacy, Faculty of Science, Institut Teknologi Sumatera, Lampung, Indonesia
[3]Department of Pharmacy, Poltekkes Kemenkes Tasikmalaya, Tasikmalaya, Indonesia
[4]Doctor of Pharmacy Study Program, Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia.

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***Corresponding author:**
Luh Putu Febryana Larasanty

email:
febryana@unud.ac.id

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ABSTRACT

This study aimed to perform a systematic review of an observational cost-utility analysis of adjuvant and neo-adjuvant agents in patients with breast cancer. The PRISMA flowchart was used to conduct the literature search and study selection. Through the use of two databases, PubMed and Scopus, a literature search was done. The eligible study was determined based on the established inclusion criteria. To evaluate the quality of the study, Drummond's checklist was used. Data extraction was conducted to assess characteristics, study perspective, cost and outcome measurement, the cost-utility ratio in ICER value, threshold, sensitivity or probability analysis, and the conclusion of the cost-utility study. There was a total of seven studies included for review. Four studies compared chemotherapy regimens as adjuvant or neoadjuvant and three studies included hormone therapy or targeted therapy as an intervention that was compared. Observational characteristics included the use of cohort methods, and a large number of participants, while the comparison was mostly for adjuvant therapy purposes and direct medical cost measured from a payer perspective. Anthracycline-based chemotherapy such as the FAC regimen showed potential cost-effectiveness results. The use of targeted therapy (pertuzumab, trastuzumab) and hormonal therapy (goserelin) is associated with better utility outcomes and an increase in cost burden from intervention. Based to the reviewed studies, anthracycline-containing regimens such as 5-fluorouracil chemotherapy may have pharmacoeconomic properties as adjuvant or neo-adjuvant therapy. While the use of the most recent pharmacological drugs has the potential to improve utility outcomes, however, it is associated with an increase in the intervention's cost burden.

INTRODUCTION

Breast cancer is the most common type of cancer diagnosed among women worldwide, and it was the leading cause of cancer deaths in 11 of 20 regions of the world based on the 2018 GLOBOCAN report (Ferlay *et al*., 2019). Recently, the tremendous improvements in screening techniques, early diagnosis, and therapeutic discoveries, led to an increase in survival in patients with breast cancer. Surgery, radiation, chemotherapy, hormone (endocrine) therapy, and targeted therapy are conventional modalities of treating breast cancer (Nounou *et al*., 2015). Chemotherapy, hormone (endocrine)

therapy, and targeted therapy as pharmacological agents can be used as adjuvant or neo-adjuvant therapy (Spring *et al*., 2016; Wöckel *et al*., 2018).

The continued development of adjuvant and neoadjuvant therapy regimens makes the selection of appropriate regimens more complex. It is necessary to identify which intervention provides the best value or the greatest improvement in health outcomes at the most reasonable and affordable cost (Jayasekera and Mandelblatt, 2020). This can be accomplished by conducting pharmacoeconomic studies. Pharmacoeconomics is a discipline of health economics that examines the costs and benefits of a specific intervention in contrast to an equivalent alternative. This type of analysis is crucial, given the goal of maximizing value for patients, healthcare payers, and society in the face of diminishing resources (Tonin *et al*., 2021).

Cost-utility analysis (CUA), as one of the pharmacoeconomic studies, provides a relevant framework for determining if the advantages of an intervention are worth the additional cost. The cost and quality-adjusted life years (QALYs) are the main outcomes of CUA (Winn *et al*., 2016). Nerich (2016) conducted a large systematic review of cost-utility studies of drug therapies in breast cancer. The review covered studies that were published from 2000 to 2014, but did not discuss the study approach from the literature reviewed.

The pharmacoeconomic study can be developed from three major approaches, one of them was an observational economic evaluation study. The advantages of this approach include external validity of the health economic conclusions and can provide real-world resource utilization and cost data (Bodrodi and Kaló, 2010). The observational approach in the cost-utility study of adjuvant and neo-adjuvant treatment in breast cancer hopefully can improve the generalizability of the therapeutic modality in a real-world setting. Our study's purpose was to conduct a systematic review of the recent cost-utility analysis of the use of adjuvant and neo-adjuvant treatment for patients with breast cancer from an observational pharmacoeconomic study approach.

METHODS

Search strategy

Study reports about cost-utility analysis on the use of pharmacological agents as adjuvant or neo-adjuvant treatment in patients with breast cancer were identified from PubMed and Scopus databases. A literature search was conducted in November 2024 using the population, intervention, comparison, and outcome (PICO) framework to formulate search keywords (Eldawlatly *et al*., 2018). Breast cancer patient (population), OR chemotherapy (intervention), OR cost-utility analysis (outcome) were used as search terms in each database. Searches were limited to those published in January 2012 until November 2024 and full text in the English language. Title and abstracts were then screened for eligibility.

Selection Criteria

The process of database search and selection criteria was arranged as a PRISMA flowchart which can be seen in Figure 1. The study included for review should meet inclusion criteria as follows: (1) all stages of female patients with breast cancer receiving chemotherapy intervention as adjuvant or neo-adjuvant therapy; (2) observational cost-utility analysis study; (3) published in the last 12 years; and (4) access to English language full text. Eligible studies were then assessed with Drummond's checklist to evaluate the quality of the economic study. This checklist consists of 10 main questions (Drummond *et al*., 2015). Each “yes” answer for the question is given 1 point, “no” gets 0 points, while “cannot” tell has the score of 0.5 points.

Data extraction and review

Data extraction was independently performed by the three reviewers. Data collected included study characteristics, study perspective, cost and outcome measurement, cost-utility ratio in incremental cost effectiveness ratio (ICER) value, threshold, sensitivity or probability analysis, and conclusion. The ICER value counts the ratio between incremental cost and incremental utility between intervention and comparator.

RESULTS AND DISCUSSION

Results

Using the search terms in PubMed and Scopus databases, the results in the literature search identified a total of 1365 articles. As seen in Figure 1, by using filters/limitations year published, study trial, and English full-text access eliminated 926 literature. Screening by title and abstracts resulted in 432 studies excluded from eligibility. A total of 7 studies were included for review and assessed with

Drummond's checklist. The result of Drummond's checklist can be seen in Table 1. The range of scores from the checklist assessment was between 8 to 10 points.

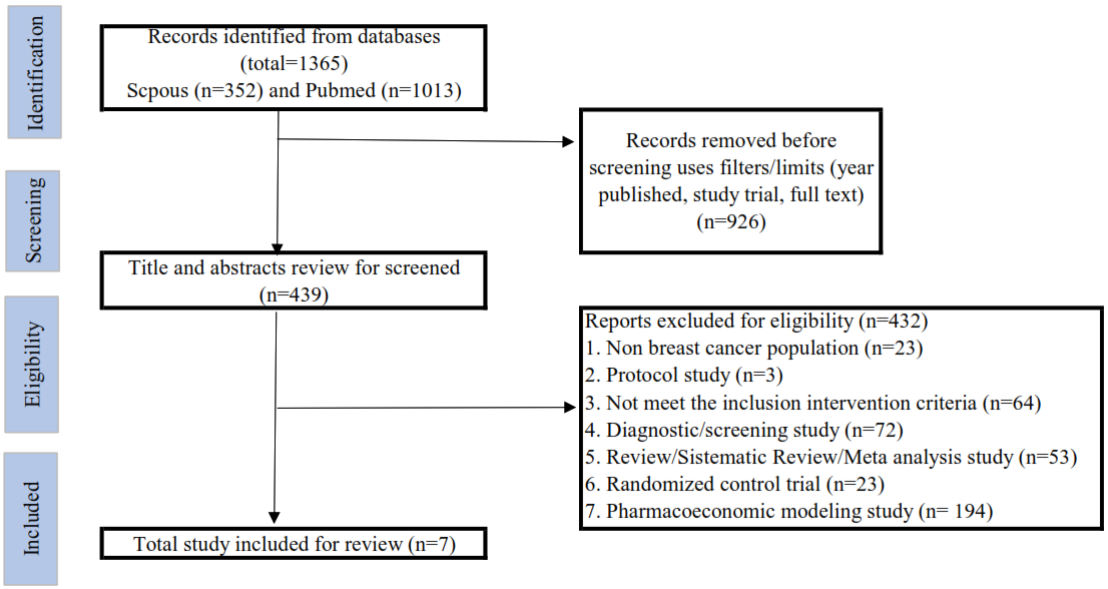


Figure 1. PRISMA flowchart.

Table 1. Drummonds checklist for determine the quality of study

No.	Checklist	Hatam *et al.*, 2015	Lairson *et al.*, 2015	Bastani & Kiadaliri, 2012	Ciruelos *et al.*, 2019	Dai *et al.*, 2021	Sapta-ningsih *et al.*, 2022	Cheng *et al.*, 2012
1	Was a well-defined question posed in an answerable form?	yes	yes	yes	yes	yes	yes	yes
2	Was a comprehensive description of the competing alternatives given?	yes	yes	yes	yes	yes	yes	yes
3	Was the effectiveness of the programmes or services established?	yes	yes	yes	yes	yes	yes	yes
4	Were all the important and relevant costs and consequences for each alternative identified?	yes	yes	yes	yes	yes	yes	yes
5	Were costs and effects measured accurately in appropriate physical units (e.g., QALYs)?	no	no	no	yes	no	no	yes
6	Were costs and effects valued credibly?	yes	yes	yes	yes	can't tell	yes	yes
7	Were costs and effects adjusted for differential timing?	yes	yes	yes	yes	yes	no	can't tell
8	Was an incremental analysis of costs and effects of alternatives performed?	yes	yes	no	yes	yes	yes	yes
9	Were allowances made for uncertainty in the estimates of costs and effects?	yes	yes	yes	yes	yes	yes	yes
10	Did the presentation and discussion of study results include all issues of concern to users?	yes	yes	yes	yes	yes	yes	yes
	Scores	9	9	8	10	8.5	8	9.5

Table 2. Characteristics of included observational cost utility studies

No.	References (Country)	Study Design	Target Population	Treatment Purpose	Study Comparation		Number of Participant	
					Intervention	Comparator	Intervention	Control
1	Hatam *et al.*, 2015 (Iran)	cross-sectional study	woman younger than 65 years old with locally advanced breast cancer	neoadjuvant	doxorubicin and cyclophosphamide (AC)	paclitaxel and gemcitabine (PG)	32	32
2	Lairson *et al.*, 2015 (USA)	Cohort	women 65 to 94 years old with breast cancer stage I, II, or III A	Adjuvant	1. anthracycline [doxorubicin or epirubicin]-based chemotherapy 2. non–anthracycline-based chemotherapy	no chemotherapy	1525 for each group (total 3050 for 2 group)	1525
3	Bastani & Kiadaliri, 2012 (Iran)	Cohort	women younger than 75 years with breast cancer with node-positive (>1)	Adjuvant	docetaxel, doxorubicin, cyclophosphamide (TAC)	5-fluorouracil, doxorubicin, cyclophosphamide (FAC)	32	68
4	Ciruelos *et al.*, 2019 (Spain)	Cohort	women with HER2+ early breast cancer	Adjuvant	trastuzumab plus chemotherapy	chemotherapy	35.851 total patient, there is no information regarding the amount allocated to each group	
5	Dai *et al.*, 2021 (Canada)	Cohort	woman and man with metastasis breast cancer	adjuvant and neoadjuvant	pertuzumab, trastuzumab, and chemotherapy	trastuzumab plus chemotherapy	579	579
6	Saptaningsih *et al.*, 2022 (Indonesia)	not clearly stated	woman with stage I-IIIA breast cancer	Adjuvant	5-fluorouracil, doxorubicin, cyclophosphamide (FAC)	taxane-based chemo-therapies	10	14
7.	Cheng *et al.*, 2012 (Taiwan)	Retro-spective study	woman with stage Ia to IIIa estrogen receptor positive breast cancer before menopause	Adjuvant	Goserelin	1.cyclo-phosphamide, methotrexate, 5-fluorouracil (CMF) 2. 5-fluorouracil, epirubicin, cyclo-phosphamide (FEC) 3. docetaxel, epirubicin (TE) 4. docetaxel, epirubicin, cyclo-phosphamide (TEC)	152 total, there is no information regarding the amount allocated to each group	

Characteristics of the study

Table 2 shows the study characteristics from the seven selected articles reviewed. The studies mostly used Cohort methods as an observational study design (Bastani and Kiadaliri, 2012; Lairson *et al.*, 2015; Ciruelos *et al.*, 2019; Dai *et al.*, 2022). Target population varied between early stages breast cancer (Cheng *et al.*, 2012; Lairson *et al.*, 2015; Ciruelos *et al.*, 2019; Saptaningsih *et al.*, 2022) up to metastatic breast cancer (Dai *et al.*, 2022) with three studies having a large number of participants (Lairson *et al.*, 2015; Ciruelos *et al.*, 2019; Dai *et al.*, 2022). Five studies observed pharmacological agents as adjuvant therapy solely (Bastani and Kiadaliri, 2012; Cheng *et al.*, 2012; Lairson *et al.*, 2015; Ciruelos *et al.*, 2019; Saptaningsih *et al.*, 2022), one study compared neo-adjuvant study (Hatam *et al.*, 2015) while another one discussed both the use of adjuvants and neo-adjuvants therapy (Dai *et al.*, 2022).

Cost and Utility Approach

As an observational cost-utility analysis, certain parameters in a pharmacoeconomic study may not be applied. In the methodology section, data extraction was concerned about study perspectives, currency, price and date, cost coverage, and how to measure cost and outcome.

Table 3. Study perspective, cost and outcome measurements

No.	References (Country)	Study Perspective	Currency, Price Date, and Conversion	Cost Coverage	Cost Measured Methods	Outcome Measured Methods
1	Hatam *et al.,* 2015 (Iran)	societal	US dollars, 2013, conversion calculation not stated	1. direct medical and non-medical cost 2. indirect costs	medical and non-medical direct cost collected from the community, while indirect costs are measured using the Human Capital Approach	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30) are used for measured utility. QALY was calculated by multiplying utility with the treatment period (3 months or 1.4 a year)
2	Lairson *et al.*, 2015 (USA)	US National payer	US dollars, 2013	direct medical cost	cost calculated using Medicare (USA insurance) amount paid	Health state utilities were obtained from the literature. Phase-specific QALYs calculated by multiplying the phase survival time with the associated utility, while total QALYs were obtained from summing phase-specific QALYs.
3	Bastani & Kiadaliri, 2012 (Iran)	third-party payer	US dollars, 2008, conversion rate from Iranian Rial to US dollars (1 Rial = USD 0.0001)	direct medical costs	cost obtained from hospitals records and health insurance organizations	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30) are used for measured utility. Scores then mapped to 15-D and EuroQoL 5D (EQ-5D) using an equations. QALYs calculated by multiplying differences in utility scores between different points of time (0, 4, and 8 months) with it related time period
4	Ciruelos *et al.*, 2019 (Spain)	Patient	Euro, 2017	direct medical costs	cost measured from healthcare costs which included costs of initial treatment and costs after progression (recurrences). During the analytical period, the real use made of trastuzumab according to the market shares	Life Year Gained (LYG) and Disease Free Life Years Gained (DFLYG) measured by an epidemiological model
5	Dai *et al.*, 2021 (Canada)	public payer	Canadian dollars, 2018	direct medical costs	Cost calculated from 5-year total costs for each patient from public healthcare insurance	Life-years (LY) are from the index date until death date or the end of the 5-year follow up. Utility for QALYs obtained from literature and the initial CADTH drug review. QALYs calculated by adjusting 5-year survival with different utilities for patients.
6	Saptaningsih *et al.*, 2022 (Indonesia)	payer, patient	Indonesian rupiah, 2012	direct cost (treatment/ medical cost) and indirect cost (nonmedical cost)	cost estimated from medical claim paid according to clinical pathways (electronic medical records and hospital information systems) and questionnaire to collect information about society cost from patient	Health related quality of life measured using Indonesia Breast Cancer Health-Related Quality of Life (INA-BCHRQoL). The score then mapped to EuroQoL 5D (EQ-5D) index calculator using equations in score utility. Life year gain obtained with breast cancer treatment outcome calculator. QALYs calculated and multiplied using utility scores in a related time period
7	Cheng *et al.*, 2012 (Taiwan)	Payer	US dollars, year not available, currency conversion 1 USD = 32 Taiwan New Dollars	direct medical costs	cost measured based on standard claims submitted to the National Health Insurance a mandatory health insurance employed in Taiwan	QoL using the European Organization for Research and Treatment QoL questionnaire. Utility value by the standard gamble (SG) and visual scale (VS) methods

Table 4. Cost utility ratio in ICER value and study impact

No.	References (Country)	ICER Value	Effectiveness Threshold	Sensitivity Analysis and Probability Test	Conclusion
1	Hatam *et al.*, 2015 (Iran)	ICER was -5535.45 dollars. Doxorubicin and cyclophosphamide saves 5535.45 dollars per each additional QALY compared to paclitaxel and gemcitabine	Not available	Doxorubicin and cyclophosphamide was a dominant strategy	Doxorubicin and cyclophosphamide was a more eminent preference treatment for breast cancer patient for being less costly and more effective
2	Lairson *et al.*, 2015 (USA)	ICER for anthracycline-based group compared to the no chemotherapy group are $12,566 per life-year gained and $7688 per QALY gained, while the non–anthracycline-based group was dominated when compared to anthracycline-based group	$50,000 to $100,000	Cost-effectiveness acceptability curves demonstrate that anthracycline-based chemotherapy was nearly 100% cost-effective	Anthracycline-based chemotherapy was more cost-effective compared to non–anthracycline for treating older age early stages breast cancer
3	Bastani & Kiadaliri, 2012 (Iran)	5-Fluorouracil, doxorubicin, cyclophosphamide is a dominant option compared to docetaxel with doxorubicin and cyclophosphamide regimen	Not available	5-Fluorouracil, doxorubicin, cyclophosphamide dominant results were insensitive to the change in uncertainty variables (cost and utility values)	5-fluorouracil, doxorubicin, cyclophosphamide was a dominant option
4	Ciruelos *et al.*, 2019 (Spain)	Trastuzumab plus chemotherapy versus chemotherapy ICERs was €20,644 /life year gained and €23,960 / disease free life years gained	Not available	The time horizon give a more moderate influence to the clinical output, while variation of the temporal preference rate has less impact upon the economical outcomes	Adding trastuzumab to chemotherapy can improved the survival of patients with HER2 positive early breast cancer along with increased costs of the regimen in a cost-effective manner.
5	Dai *et al.*, 2021 (Canada)	ICERs of pertuzumab, trastuzumab, and chemotherapy versus trastuzumab and chemotherapy was $316.203 per life-year gained and $436.679 per QALY	$50.000 to $100.000	pertuzumab was not cost-effective at the thresholds	Pertuzumab may improved survival for patients with metastatic breast cancer but would not be considered cost-effective, even after 100% price reduction, under conventional thresholds.
6	Saptaningsih *et al.*, 2022 (Indonesia)	ICER of chemotherapy of Taxane compared to FAC in patients without insurance Rp 765,213,092/QALY gained	triple of Indonesian GDP	The FAC was more cost-effective compared to Taxane-based chemotherapy	FAC is a cost-effective option for patients in early node-positive breast cancer compared to Taxane-based chemotherapy.
7	Cheng *et al.*, 2012 (Taiwan)	Goserelin versus CMF had the highest ICERs among the 4 chemotherapeutic drug regimes.	Not available	not performed	Adjuvant goserelin therapy in premenopausal women with breast cancer is particularly cost-effective when compared to TE and TEC adjuvant chemotherapy regimens, but more expensive (at the cost of higher QALY gained) when compared to CMF and FEC.

Data extraction results can be seen in Table 3. About 70% of the selected studies used the payer perspective (Bastani and Kiadaliri, 2012; Cheng *et al.*, 2012; Lairson *et al.*, 2015; Dai *et al.*, 2022; Saptaningsih *et al.*, 2022) so that the most measurable costs are direct medical costs that were calculated from health insurance claims paid. United States Dollar (USD) was used as currency in four studies (Bastani and Kiadaliri, 2012; Cheng *et al.*, 2012; Hatam *et al.*, 2015; Lairson *et al.*, 2015), while three other studies used their country currency (Ciruelos *et al.*, 2019; Dai *et al.*, 2022; Saptaningsih *et al.*, 2022). The cost and quality-adjusted life years (QALYs) were measured in six studies as utility outcomes (Bastani and Kiadaliri, 2012; Cheng *et al.*, 2012;

Hatam *et al*., 2015; Lairson *et al*., 2015; Dai *et al*., 2022; Saptaningsih *et al*., 2022) and one study used Life Year Gained (LYG) and Disease Free Life Years Gained (DFLYG) as outcomes (Ciruelos *et al*., 2019).

Study Impact

The ICER value, effectiveness threshold, interpretation of sensitivity analysis or probability test, and author conclusions are displayed in Table 4. The use of anthracycline-based chemotherapy (doxorubicin or epirubicin) as neo-adjuvant and adjuvant was the dominant strategy based on ICER value and sensitivity/probability interpretations (Hatam *et al*., 2015; Lairson *et al*., 2015). Two studies show 5-fluorouracil chemotherapy (FAC) regimen is more cost-effective compared to taxane-based chemotherapies (Bastani and Kiadaliri, 2012; Saptaningsih *et al*., 2022). Adding one targeted therapy to adjuvant chemotherapy can improve the survival rate for early breast cancer, along with increased cost in a cost-effective manner (Ciruelos *et al*., 2022). In metastatic patients, using a combination of targeted therapy with chemotherapy cannot provide cost-effectiveness even with a 100% price reduction (Dai *et al*., 2022). Lastly, the use of hormone therapy showed cost-effectiveness when compared to taxanes-based chemotherapy, but was not cost-effective when compared to a 5-fluorouracil or anthracyclines regimen.

Discussion

The most crucial parameters considered in determining the need for any type of adjuvant therapy for breast cancer include tumor size, lymph node status, grading, hormone-receptor status, HER2 status, menopausal status, and patient age (Anampa *et al*., 2015; Wöckel *et al*., 2018). Chemotherapy is usually recommended because of the expected benefits outweigh any potential risks (Kerr *et al*., 2022). Besides being given as an adjuvant, chemotherapy can also be given as a neo-adjuvant (Wöckel *et al*., 2018; Kerr *et al*., 2022). Neoadjuvant therapy has many benefits, including allowing response assessment, a higher possibility of finishing chemotherapy, and a larger likelihood of breast conservation therapy (Menon & Alkabban, 2024).

Based on the observational economic studies, anthracycline-containing regiment showed dominant results in CUA. It can be considered an adjuvant or neo-adjuvant treatment for patients with breast cancer. Anthracycline-containing regimens have previously proven to be an essential therapy component for patients with breast cancer, reducing death by 20% to 30% (Peto *et al*., 2012; Ding *et al*., 2018). However, because of the risk of toxicity associated with the use of this regimen, it should be used with caution in patients who may be at high risk of experiencing these adverse effects (Jasra and Anampa, 2018). Another regiment that showed a cost-effectiveness result was the FAC regiment. However, it was not supported by a large number of participants which is one of the advantages of observational research (Bodrogi and Kaló , 2010).

Several studies have examined the advantages of adding a taxane (paclitaxel or docetaxel) to an anthracycline-based adjuvant chemotherapy treatment (Seifter *et al*., 2025). This combination can reduce recurrence rates and breast cancer mortality for women with early-stage breast cancer (EBCTCG, 2023). However, from the pharmacoeconomic study, this TAC regimen is still dominated by the FAC regimen.

Pertuzumab and trastuzumab were new molecular target drugs and regimens that are being developed based on the predicted sensitivity for specific breast cancer histological types (Shien and Iwata, 2020). As a new targeted therapy drug, the cost of pertuzumab and trastuzumab remains high. As an example, adding trastuzumab to chemotherapy increased the cost from € 503,587,698 to € 1,581,553,536 (Ciruelos *et al*., 2019). For that, it is very necessary to identify patients who will greatly benefit from the use of this new type of therapy (Masoud and Pagès, 2017) so that it will be commensurate with the price paid for it.

Study Limitations

One of the limitations of this review was study variability. This study also has various target populations, different interventions, and comparators as pharmacological therapy for patients with breast cancer, different currencies, and non-uniform utility measures approach. This variability makes it difficult to generate the exact conclusion about the impact of pharmacological agents in breast cancer treatment. However, the results of the study can be used as a consideration about the type of adjuvant pharmacological therapy that can provide real-world benefits and the consideration of the economic impact of the use of hormone therapy or targeted therapy with the adjuvant or neo-adjuvant chemotherapy regimen.

CONCLUSIONS

The various intervention and study approaches made it difficult to conclude a clear recommendation of CUA results for the use of pharmacological agents as adjuvant and neo-adjuvant in patients with breast cancer. Our systematic review of CUAs showed an observational study can be one of the approaches to performing real-world pharmacoeconomic studies. The results from the seven eligible studies with various methodological approaches suggest that anthracycline-containing regimens such as 5-fluorouracil chemotherapy have potential pharmacoeconomic properties as adjuvant or neo-adjuvant therapy. While uses of the newest pharmacological agents have the great potential to increase utility outcomes, however, it is accompanied by an increase in the cost burden for using the intervention.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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