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Research Article

COST-EFFECTIVENESS OF COMBINATION ANTI-CANCER DRUG THERAPY IN THE MANAGEMENT OF HER2-POSITIVE BREAST CANCER: A META-ANALYSIS

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ABSTRACT

Objective: The objective of this review article is to conduct a basic meta-analysis to determine the cost-effectiveness of the trastuzumab, pertuzumab, and docetaxel (THP) combination compared to the trastuzumab and docetaxel (TH) alone in the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients. The analysis aims to measure the costs involved and the health outcomes of the therapy to identify the most cost-effective treatment option.

Methods: The researchers collected costs and quality-adjusted life years data from studies that investigated the cost-effectiveness of different treatment regimens for HER2-positive breast cancer. A meta-analysis was conducted using these data, and a probabilistic sensitivity analysis with 1000 iterations was performed using an Excel spreadsheet. The input data used in the analysis were obtained from four studies deemed appropriate for the meta-analysis.

Results: The outputs obtained from the meta-analysis were plotted on an incremental cost-effectiveness ratio (ICER) scatterplot. The ICER scatter plots of the four studies showed that the THP combination was 0% cost-effective at a willingness to pay (WTP) threshold of I$100,000/QALY and 2.38% cost-effective at a WTP of I$200,000/QALY. However, at a higher WTP of I$500,000/QALY, the THP combination was found to be 52.8% cost-effective compared to the TH combination.

Conclusion: Based on the findings of this meta-analysis, the THP combination treatment for HER2-positive breast cancer patients is cost-effective compared to the TH combination at a willingness to pay threshold of I$500,000/QALY. However, at lower WTP thresholds, the THP combination may not be cost-effective. These results provide valuable insights for prescribers in identifying and selecting the most cost-effective treatment option among the alternatives available for HER2-positive breast cancer patients.

Keywords: Cost-effectiveness analysis, Trastuzumab, Pertuzumab, Docetaxel, Quality-adjusted life years, Incremental cost-effectiveness ratio, Probabilistic sensitivity analysis.

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INTRODUCTION

Breast cancer is one of the most frequently diagnosed life-threatening cancers in women and is a leading reason for cancer deaths among women aged 50–69 years. Each year about 15 million new cases are diagnosed worldwide, and over 500,000 women fall fatal to breast cancer. Almost 1 in 5 women diagnosed with breast cancer has human epidermal growth factor receptor 2 (HER2)-positive breast cancer [1]. In HER2-positive breast cancer patients, HER2 overexpression is detected. These tumors are associated with increased tumor aggressiveness, recurrence, and poorer survival rates [2]. A revolutionary change in the prognosis of HER2-positive breast cancer has occurred since the introduction of HER2-targeted therapy with trastuzumab in 1998. It is a monoclonal antibody used with chemotherapeutic drugs such as docetaxel to stop metastatic HER2-positive breast cancer from spreading. However, prolonged usage of trastuzumab leads to drug resistance. New molecules with complementary or synergistic mechanisms of action were developed to address this issue. One such molecule is pertuzumab, a new anti-HER2 humanized antibody that blocks the formation of HER2-dimers. Pertuzumab was approved by the U.S. Food and Drug Administration in 2013 to be utilized in combination with trastuzumab and docetaxel (TH) to treat metastatic breast cancer [3]. These drugs contribute to high health-care utilization and costs since treatment typically continues over the years, and serial treatments are employed for progressive disease.

Cost-effectiveness analysis (CEA) plays a vital role in the economics of cancer drugs by investigating the worth of one intervention compared to another by weighing costs and outcomes together. It helps in assisting a prescriber to identify and select the most cost-effective treatment among available treatment options. Treatment is assumed to be cost-effective when the benefits obtained are worth the price paid for it. Essential elements of a CEA include identifying clinical interventions, calculating all associated costs, and identifying the health outcomes of the treatments for analysis. These economic analyses are helpful to health-care providers in decision-making, and also for payers and health insurance reimbursement organizations [4].

CEA's report their findings using quality-adjusted life years (QALY) and incremental cost-effectiveness ratio (ICER). QALY refers to 1 year of life in perfect health [5]. ICER is determined by distinguishing between the costs of intervention of interest and a comparator divided by health outcomes between the intervention of interest and the comparator. The ICER is compared to a specified economic threshold to determine if an intervention offers "good" value for money. This threshold termed as willingness to pay (WTP) represents the maximum amount a patient is willing to pay for health effects. An intervention can be considered cost-effective if the ICER falls below this WTP threshold. For example, an intervention can be considered cost-effective if a patient is willing to pay $20,000/QALY, and the ICER also falls below $20,000/QALY gained [6].

CEA can be done either by systematic review or meta-analysis. Systemic review is a scientific process where all empirical evidence that fits pre-specified eligibility criteria is collected to answer a specific research question. Meta-analysis is a statistical procedure of combining and

analyzing results from several similar studies. It is an improvement over the systematic review and employs statistical or mathematical approaches to compile the findings of studies [7,8]. Various CEAs have been previously conducted to determine the most cost-effective combination between the intervention and comparator. In this article, data is collected from such studies. A meta-analysis is performed to determine the most cost-effective treatment among TH with and without pertuzumab at various WTP functions using probabilistic sensitivity analysis (PSA).

METHODS

Literature search

Various records have been identified by searching PubMed/Medline and Scopus databases using keywords such as CEA, trastuzumab, pertuzumab, and HER2-positive breast cancer. The search yielded 244 articles for review. Some are excluded based on duplication, irrelevance to the topic, other diseases mentioned, non-availability of full-text articles, etc… Removal of duplicated studies narrowed down the results to 237 articles.

Inclusion and exclusion criteria

Inclusion criteria were as follows: Studies that are original health economic studies specific to HER2-positive breast cancer. The literature includes the total costs involved and QALYs gained by both the intervention and comparator. Exclusion criteria were as follows: Reports or posters for which only abstracts were available; studies in languages other than English; analysis of diagnostic screening, imaging, and therapies for either palliative care or cancer-related side effects. This rounded the number to seven articles whose titles and abstracts were screened. Ultimately, four articles were deemed appropriate for meta-analysis. Fig. 1 presents the outline of the literature search, inclusion, and exclusion criteria.

Overview of studies

Detailed information from each of the four studies was collected. The extraction includes title, authors, year of publication, line of treatment, country/setting, treatment and comparator(s), study design, perspective, and study outcomes. Study outcomes include total costs involved, QALYs gained, incremental costs, and ICER. Table 1 presents the model characteristics of each study and Table 2 presents the overview of outcomes in the studies.

From Diaby *et al*. 2019, only Sequence 1 and Sequence 3, the treatment regimens of our interest along with wastage costs, are taken into consideration [9]. From Attard *et al*. 2015, both the analyses NeoSphere and TRYPHAENA were considered, and data analysis was performed separately for each [10]. Out of the four studies, two studies Attard *et al*. 2015 (NeoSphere and TRYPHAENA) and Garrison *et al*. 2019 concluded that the addition of pertuzumab to TH could be considered cost-effective compared to TH alone [10,11]. The remaining studies, Diaby *et al*. 2019 and Durkee *et al*. 2015 concluded that the addition of pertuzumab to TH combination is unlikely to be cost-effective compared to TH combination [11,12].

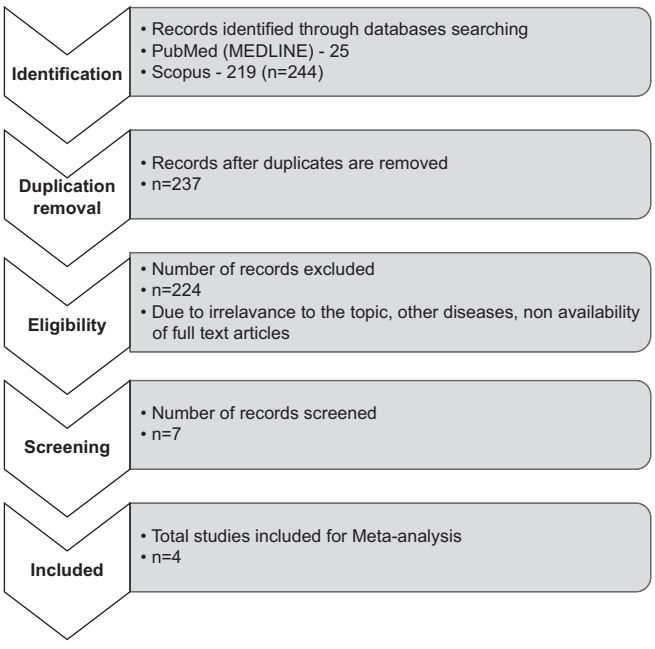

Fig. 1: Outline of literature search and eligibility criteria

In Table 2, the costs involved in the four studies are also mentioned in international dollars (I$). It is to create uniformity between the currencies of different countries. International dollars (I$) are hypothetical currency units with the same purchasing power parity in all countries, that is the purchasing power of 1 I$ is similar around the world. In other words: one can purchase equivalent things in any country with an equivalent amount of I$ [13].

Statistical method

A PSA was performed on an Excel spreadsheet, to determine the probability cost-effectiveness of the intervention in each study. PSA is a strategy used for accounting for parameter uncertainty in cost-effectiveness models. It is a helpful technique to quantify the confidence that a decision-maker has in the conclusions of an economic evaluation [14]. In a PSA, the uncertainty surrounding each parameter is quantified in terms of a probability distribution of that parameter. The input parameter values are picked randomly by sampling from each distribution, and the model is "run" to generate the intended number of outputs (cost and health outcome) for each run. This technique is repeated "N" times, yielding "N" outcome values that form a distribution of the outcomes [15]. The model is run typically over 1,000–10,000 times, resulting in various outputs that can be graphed on the CEA plane and analyzed.

The ICER scatterplot is helpful for a visual demonstration of all different ICERs generated from the "N" number of iterations of the PSA. An ICER scatterplot typically depicts the distribution of PSA samples over the quadrants of a CEA plane [15]. The ICERs are plotted onto a CEA plane, divided into four quadrants. The x-axis represents incremental QALY and the y-axis represents incremental costs of the intervention and comparator. Quadrant 1 has better health outcomes and higher costs of a new medication than a comparator; Quadrant 2 represents less desirable health outcomes and higher total expense; Quadrant 3 represents more vile health outcomes and a lower total expense. In contrast, Quadrant 4 represents better health outcomes and a lower total expense [6].

Excel has a very compliant and easy-to-use macro language known as Visual Basic for Applications (VBA). Using VBA, a probabilistic simulation model that was previously designed was employed to perform 1000 iterations for the given inputs. From each iteration, variable values are randomly sampled from probability distributions. Total costs and QALYs gained for intervention and comparator of each study were given as inputs. Table 3 presents the input data given for PSA.

The Difference in costs (incremental costs) is presented in I$.

For each iteration, the cost and QALY of intervention and comparator are registered to calculate incremental costs and QALYs that form the base for the ICER scatter plot. Each iteration is represented visually on a scatter plot as small blotches. The VBA performed a PSA of 1,000 iterations giving the ICER scatter plot for each study. A WTP, of commonly accepted thresholds I$100,000/QALY, I$200,000/QALY, and I$500,000/QALY was considered to obtain a cost-effectiveness acceptability curve (CEAC) and to determine the probability cost-effectiveness of the intervention at each WTP [16].

RESULTS AND DISCUSSION

All the ICER scatter plots (Figs. 2-6) obtained were within the category Quadrant 1 of the CEA plane denoting that the intervention

Table 1: Model characteristics of the studies

Study	Diaby *et al*., 2019	Garrison *et al*., 2019	Attard *et al*., 2015	Durkee *et al*., 2015
Treatment target	HER2	HER2	HER2	HER2
Country	Taiwan	USA	Canada	USA
Publication year	2019	2019	2015	2015
Treatment line	1st–3rd lines of four sequences	1st line	1st line	1st line
Study design	Markov model	Trial-based cost-utility modeling analysis	Markov model	Markov model
Health states	PFS 1st–3rd lines, death	iDFS Non-metastatic recurrence Remission First-line mBC Subsequent lines in mBC; and Death	Event free, relapsed, and dead	Stable disease, progressing disease, hospice, and dead
Perspective	TNHIA	US payers and stakeholders	Canadian health-care payer	Societal
Currency	USD	USD	CAD	USD
Intervention	Sequence 1: THP→ T-DM1→Cape/Lapat Sequence 2: THP→ Trastuz/Lapat→ Trastuz/Cape	Per+Tra+Doc (THP)	Per+Tra+Doc	Per+Tra+Doc (THP)
Comparator	Sequence 3: Trastuz/Docet T-DM1→Trastuz/Lapat Sequence 4: Trastuz/ Docet→Trastuz/ Lapat→Trastuz/Cape	Tra+Doc (TH)	Tra+Doc	Tra+Doc (TH)

THP: Trastuzumab plus pertuzumab plus docetaxel, TH: Trastuzumab plus docetaxel, T-DM1: Trastuzumab emtansine, Cape: Capecitabine, Lapat: Lapatinib, CAD: Canadian dollars, Per+Tra+Doc: Pertuzumab+trastuzumab+docetaxel, TNHIA: Taiwanese National Health Insurance Administration, PFS: Progression-free survival, iDFS: invasive disease-free survival, mBC: Metastatic breast cancer, HER2: Human epidermal growth factor receptor 2

Table 2: Overview of outcomes in the studies

Study	Diaby *et al*., 2019	Garrison *et al*., 2019	Attard *et al*., 2015	Durkee *et al*., 2015
QALY's gained	Sequence 1: 1.808 Sequence 2: 1.781 Sequence 3: 1.275 Sequence 4: 1.407	THP – 14.98 TH – 14.22	NeoSphere Per+Tra+Doc – 11.042 Tra+Doc – 10.732 TRYPHAENA Per+Tra+Doc – 11.468 Tra+Doc – 11.158	0.62 QALY Incremental benefit
Costs	Sequence 1: 149,759 USD Sequence 2: 147,559 USD Sequence 3: 67,128 USD Sequence 4: 76,487.7 USD	THP – 361,234 USD TH – 294,588 USD	NeoSphere Per+Tra+Doc – 125,518 Tra+Doc – 117,638 TRYPHAENA Per+Tra+Doc – 126,423 Tra+Doc – 112,086	THP – 621,425 USD TH – 326,678 USD
ICER	Sequence 1: $154,848.9 Sequence 2: $158,961.4 Sequence 4: $70,896.37	87,692 USD	NeoSphere – CAD 25,388 TRYPHAENA – CAD 46,196	475,398 USD
Costs in international dollars (I$)	Sequence 1: I$ 149,759 Sequence 2: I$ 147,559 Sequence 3: I$ 67,128 Sequence 4: I$ 76,487.7	THP – I$ 361,234 TH – I$ 294,588	NeoSphere Per+Tra+Doc – I$ 101,132 Tra+Doc – I$ 94,783 TRYPHAENA Per+Tra+Doc – I$ 101,909 Tra+Doc – I$ 90,309	THP – I$ 621,425 TH – I$ 326,678
Study conclusion	Sequence 3 (TH) was the most cost-effective sequence followed by Sequence 1 (THP), among the four sequences considered for treating HER2-positive metastatic breast cancer patients	The model projected improved outcomes (0.76 QALYs) and increased costs (by $66 647) for ICERs of $87,692/QALY gained suggesting that the addition of pertuzumab to the available regimens is likely to be cost-effective for patients in the US at high risk of recurrence	Both NeoSphere and TRYPHAENA analysis suggested addition of pertuzumab resulted in increased QALYs and LYs. The incremental cost per QALY ranged from $25,388 (CAD; NeoSphere analysis) to $46,196 (TRYPHAENA analysis)	THP in patients with metastatic HER2-positive breast cancer is unlikely to be cost-effective in the USA probabilistic sensitivity analysis predicted a 0% chance of cost-effectiveness at a willingness to pay of $100,000 per QALY gained

Per+Tra+Doc: Pertuzumab+Trastuzumab+Docetaxel, THP: Trastuzumab plus pertuzumab plus docetaxel, TH: Trastuzumab plus docetaxel, USD: US dollars, CAD: Canadian dollars, ICERs: Incremental cost-effectiveness ratio, QALYs: Quality-adjusted life years

Table 3: Inputs given for probabilistic sensitivity analysis

Input	Diaby *et al.*, 2019	Garrison *et al.*, 2019	Attard *et al.*, 2015	Durkee *et al.*, 2015
Difference in costs	82,631	66,646	NeoSphere – 6349 TRYPHAENA – 11,600	294,747
Difference in QALYs	0.5	0.8	NeoSphere – 0.3 TRYPHAENA – 0.3	0.6

QALYs: Quality-adjusted life years

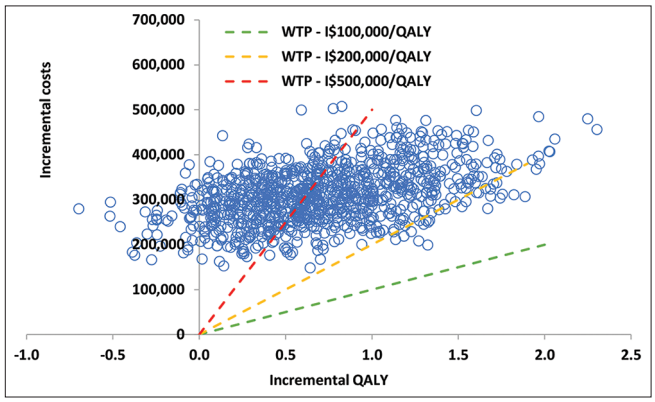

Fig. 2: ICER scatter plot obtained for Diaby *et al*. 2019 study. The diagonal lines represent Willingness to Pay Function ■ WTP – I$500,000/QALY, ■ WTP – I$200,000/QALY, and ■ WTP – I$100,000/QALY) and all virtual blotches located to the right side of specific WTP can be considered cost-effective

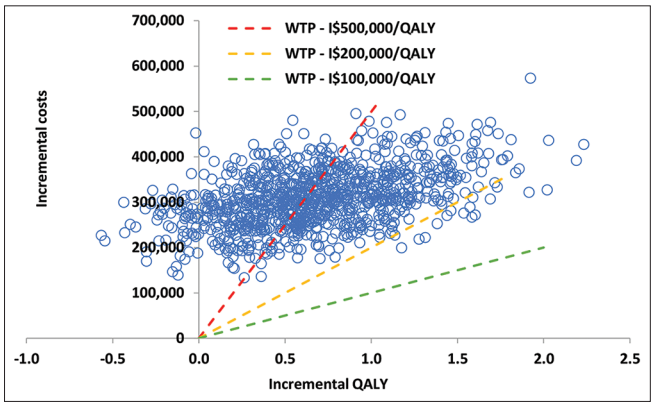

Fig. 3: ICER scatter plots obtained for Garrison *et al*. 2019 study. The diagonal lines represent Willingness to Pay Function ■ WTP – I$500,000/QALY, ■ WTP – I$200,000/QALY, and ■ WTP – I$100,000/QALY) and all virtual blotches located to the right side of specific WTP can be considered cost-effective

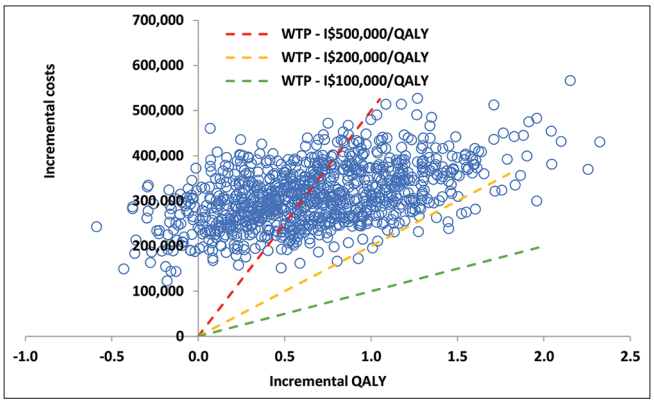

Fig. 4: ICER scatter plots obtained for Attard *et al*. 2015 NeoSphere analysis. The diagonal lines represent Willingness to Pay Function ■ WTP – I$500,000/QALY, ■ WTP – I$200,000/QALY, and ■ WTP – I$100,000/QALY) and all virtual blotches located to the right side of specific WTP can be considered cost-effective

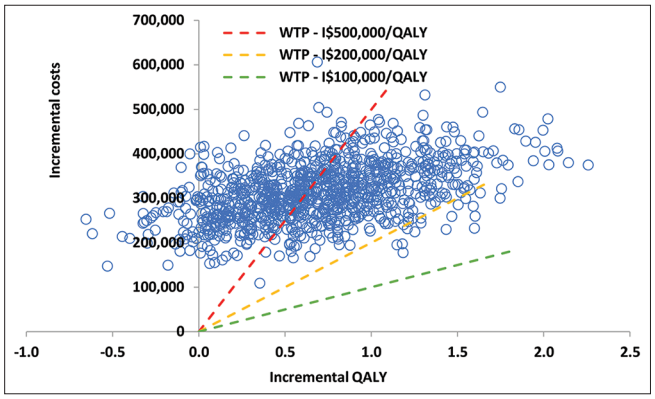

Fig. 5: ICER scatter plots obtained for Attard *et al*. 2015 TRYPHAENA analysis. The diagonal lines represent Willingness to Pay Function ■ WTP – I$500,000/QALY, ■ WTP – I$200,000/QALY, and ■ WTP – I$100,000/QALY) and all virtual blotches located to the right side of specific WTP can be considered cost-effective

trastuzumab, pertuzumab, and docetaxel (THP) combination has better health outcomes and also higher costs compared to TH combination. At a WTP I$100,000/QALY for 1 year of disease-free survival, THP combination showed an average cost-effectiveness of 0%, suggesting that the intervention is not cost-effective compared to TH combination. The conclusion remained the same for the intervention THP even at a WTP I$200,000/QALY for 1 year of disease-free survival, rendering an average of 2.38% cost-effectiveness compared to TH. For a WTP I$500,000/QALY for 1 year of disease-free survival, the intervention THP combination was approximately 52.8% cost-effective compared to TH combination. Fig. 7 showcases the CEAC obtained for all the studies included in the analysis and Table 4 presents the percentage cost-effectiveness of each study at various WTP functions.

Overall, targeted therapies have significantly improved outcomes for patients with HER2-positive breast cancer. Earlier, trastuzumab alone was used in combination with docetaxel (chemotherapy) until the introduction of pertuzumab in 2013. Based on the CLEOPATRA clinical trial, pertuzumab has been approved by the FDA to be used with TH to treat patients with HER2-positive metastatic breast cancer who have not received any prior chemotherapy or anti-HER2 therapy for metastatic disorder [3]. However, these medications come at a very high cost. The high cost of these drugs can be related to various factors such as drug development costs, a tremendous amount of time and expenditure spent on pre-clinical research to describe their mechanism of action, designing dosage forms, and generating pre-clinical data.

Table 4: Summary of probabilistic sensitivity analysis

Study	Quadrant	Incremental effectiveness	Incremental cost	Willingness to pay	Percentage cost-effectiveness
Diaby *et al*., 2019	I	IE >0	IC >0	I$ 100,000/QALY	0
				I$ 200,000/QALY	3
				I$ 500,000/QALY	54.7
Garrison *et al*., 2019	I	IE >0	IC >0	I$ 100,000/QALY	0
				I$ 200,000/QALY	2
				I$ 500,000/QALY	53.3
Attard *et al*., 2015 (NeoSphere analysis)	I	IE >0	IC >0	I$ 100,000/QALY	0
				I$ 200,000/QALY	1.7
				I$ 500,000/QALY	50.7
Attard *et al*., 2015 (TRYPHAENA analysis)	I	IE >0	IC >0	I$ 100,000/QALY	0
				I$ 200,000/QALY	2.5
				I$ 500,000/QALY	52.7
Durkee *et al*., 2015	I	IE>0	IC >0	I$ 100,000/QALY	0
				I$ 200,000/QALY	2.7
				I$ 500,000/QALY	53

QALY: Quality-adjusted life year

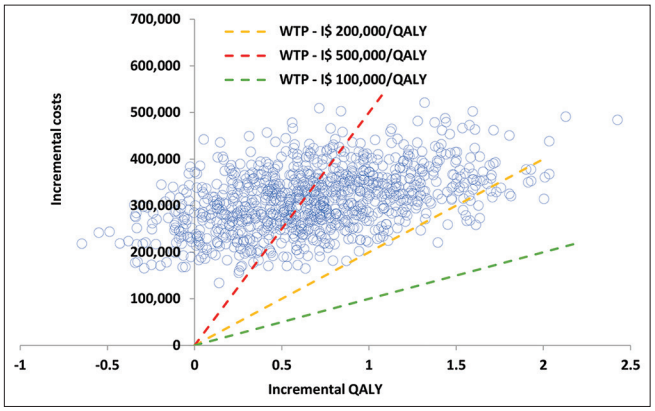

Fig. 6: ICER scatter plots obtained for Durkee *et al*. 2015 analysis. The diagonal lines represent Willingness to Pay Function ■ WTP – I$500,000/QALY, ■ WTP – I$200,000/QALY, and ■ WTP – I$100,000/QALY) and all virtual blotches located to the right side of specific WTP can be considered cost-effective

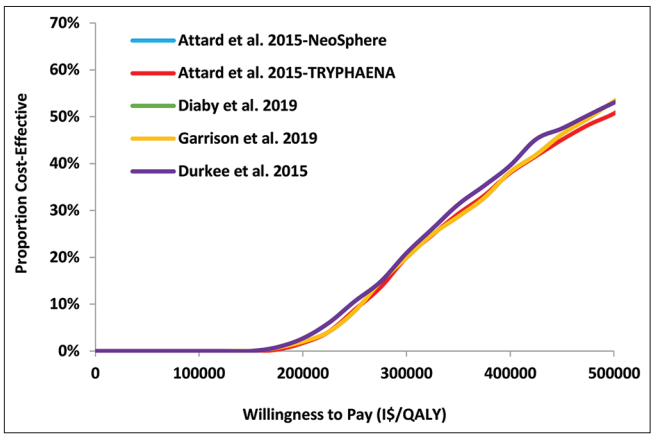

Fig. 7: Cost-effectiveness acceptability curve showing the probability cost-effectiveness of each study at various WTP thresholds

CONCLUSION

The present study analyzed data from previously published CEA studies on THP. Input data from the studies were extracted, and a PSA was performed to determine the cost-effectiveness of THP combination compared to TH alone using ICER scatter plot on CEA plane. The results obtained indicated that though the intervention (THP) is associated with high costs, it results in improved health outcomes compared to the comparator (TH). However, in developing countries such as India, CEA is not in practice due to a lack of proper knowledge of health economics, a non-effective reporting system, and low budget allocation. It will be beneficial to patients if the concerned clinicians create awareness of possible treatment options, associated benefits, risks, and costs involved to patients to provide better health care, especially in diseases requiring longer duration treatments and involving high costs in due course.

AUTHORS CONTRIBUTIONS

Sri Sai Nikitha Kota and Sailaja Bandhakavi contributed equally to this work.

CONFLICTS OF INTEREST

The authors declared no conflict of interest.

AUTHORS FUNDING

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