

Review

Systematic evaluation and meta-analysis of Herceptin® (trastuzumab) in the treatment and care of breast cancer

Ying Zhang, Zhuxin Li, Junwei Xu*

Department of Traditional Chinese Medicine, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China

* Corresponding author: Junwei Xu, xujunwei29716@126.com

CITATION

Zhang Y, Li Z, Xu J. Systematic evaluation and meta-analysis of Herceptin® (trastuzumab) in the treatment and care of breast cancer. *Psycho-Oncologie*. 2025; 19(3): 4137.
<https://doi.org/10.18282/po4137>

ARTICLE INFO

Received: 21 February 2025
Revised: 1 April 2025
Accepted: 3 April 2025
Available online: 16 September 2025

COPYRIGHT



Copyright © 2025 by author(s).
Psycho-Oncologie is published by PiscoMed Publishing Pte. Ltd. This work is licensed under the Creative Commons Attribution (CC BY) license.
<https://creativecommons.org/licenses/by/4.0/>

Abstract: Breast cancer remains the most prevalent malignancy among women worldwide and poses both biomedical and psychosocial challenges. Trastuzumab (Herceptin®), a monoclonal antibody targeting the HER2 receptor, has transformed the prognosis of patients with HER2-positive disease. This systematic review and meta-analysis synthesized data from 19 eligible studies including 9735 patients to evaluate trastuzumab's efficacy, safety, and implications for patient care. The pooled analysis demonstrated significant improvements in overall survival, disease-free survival, progression-free survival, and overall response rate compared with standard therapy, with hazard ratios consistently favoring trastuzumab. Most adverse effects were mild to moderate, though cardiac toxicity remains a critical concern requiring vigilant monitoring. Beyond these biomedical outcomes, the findings carry important psycho-oncological implications: improved survival helps reduce fear of recurrence and psychological distress, while manageable toxicity and supportive nursing care enhance treatment adherence and quality of life. These results underscore trastuzumab's dual role as both a therapeutic cornerstone and a psychosocially meaningful intervention. Future research should integrate patient-reported outcomes, resilience measures, and cost-effectiveness analyses to ensure that survival benefits translate into comprehensive improvements in the lived experiences of patients with breast cancer. Such integration will help position trastuzumab not only as a biomedical intervention but also as a psycho-oncological strategy to support holistic survivorship.

Keywords: adherence; breast neoplasms; fear of recurrence; Herceptin®; meta-analysis; nursing care; psycho-oncology; quality of life; trastuzumab

1. Introduction

Breast cancer (BC) is the most common type of cancer in women worldwide and represents a significant public health challenge. In 2020 alone, BC accounted for 11.7% of all cancer diagnoses and 6.9% of cancer-related deaths globally [1]. Beyond the biological complexity of the disease, the psychological impact of a BC diagnosis is profound. Patients frequently experience anxiety, depression, and fear of recurrence, which can undermine treatment adherence and diminish quality of life (QoL). The heterogeneity of BC, with its varied clinical and biological characteristics, not only influences survival outcomes but also contributes to uncertainty and emotional distress for patients and their families [2,3].

The development of targeted therapies, particularly the monoclonal antibody Herceptin® (trastuzumab; HP), has transformed the management of HER2-positive BC, which accounts for approximately 20% of all cases [4]. Clinical evidence demonstrates that trastuzumab significantly improves overall survival (OS), disease-free survival (DFS), and response rates in both adjuvant and metastatic settings [5,6].

These improvements carry not only clinical but also psychosocial implications, as enhanced survival outcomes may reduce patients' fear of recurrence and foster greater psychological resilience.

Nevertheless, the use of trastuzumab also raises questions regarding optimal treatment duration, sequencing with other modalities, and the management of adverse effects. Cardiac toxicity, though relatively uncommon, remains a source of anxiety for many patients. From a psycho-oncology perspective, effective management of such side effects is crucial, as tolerability of treatment directly influences patients' willingness to adhere to long-term therapy and their ability to cope with the cancer journey. In addition, the role of nursing care is indispensable: nurses frequently act as the first line of psychological support, providing counseling, medication guidance, and reassurance that can mitigate treatment-related distress.

In this context, the present study systematically reviews and synthesizes the available evidence on the efficacy and safety of trastuzumab in breast cancer. Several previous systematic reviews and meta-analyses have examined trastuzumab, but most focused narrowly on biomedical outcomes or specific patient subgroups [7-9]. Unlike these earlier works, we frame trastuzumab's clinical benefits alongside its implications for patient quality of life, psychological adaptation, and treatment adherence. By adopting this dual biomedical and psycho-oncological lens, the study aims to provide a more comprehensive understanding of trastuzumab's role in the treatment and care of breast cancer.

2. Literature review

2.1. Overview of Herceptin® (trastuzumab)

HP is a well-established therapy in HER2-positive BC. According to a meta-analysis of randomized clinical trials, both patients with early-stage and metastatic HER2-positive BC and those with DFS were dramatically improved by HP-based therapy [10]. In the adjuvant setting, HP-based therapy reduced the risk of recurrence and death by approximately 30% compared to chemotherapy alone [11]. While treating metastatic disease, HP-based therapy outperformed chemotherapy alone in terms of OS and progression-free survival (PFS) [12]. HP's favorable safety profile and efficacy have led to its widespread use in the HER2-positive BC treatment [13]. However, its use raises several questions and challenges. For example, the optimal duration of HP treatment remains a topic of debate. A recent meta-analysis showed that extending HP treatment from 12 to 24 months insignificantly improved DFS or OS but increased the risk of cardiac toxicity [14]. In addition, more study is required to determine the best order and combination of targeted therapy in HER2-positive BC and to address resistance mechanisms [15,16]. HP is a highly effective and well-tolerated targeted therapy that has significantly enhanced patient outcomes in HER2-positive BC [17]. However, several questions and challenges remain, highlighting the necessity for further research to optimize its use and continue to improve patient outcomes.

Beyond survival, these therapeutic gains may also influence psychological outcomes. Evidence suggests that improved disease control is associated with reduced fear of cancer recurrence and better overall adjustment in breast cancer patients

[18,19].

2.2. Current treatments for breast cancer

Depending on the stage and subtype of the malignancy, BC is a difficult disease that necessitates a variety of treatments. Surgery, radiation therapy, chemotherapy, hormonal therapy, and targeted therapy are currently used as therapies [20]. Surgery, which involves removing the tumor and some of the surrounding tissue, is frequently the first course of treatment for BC. A lumpectomy removes only the tumor, while a mastectomy removes the entire breast. In some cases, lymph nodes may also be removed [21]. After surgery, radiation therapy is frequently used to eliminate any leftover cancer cells in the breast by killing cancer cells with high-energy radiation. It can be used to inhibit cancer from spreading to other bodily regions [21]. Chemotherapy uses drugs to destroy cancer cells, and it can be used before or after surgery to decrease the risk of cancer recurrence [21]. Hormone therapy is used to treat BCs that are hormone receptor positive, meaning they rely on hormones such as estrogen and progesterone to grow. Hormone therapy blocks the effects of these hormones or reduces their production. Common hormone therapies include tamoxifen, aromatase inhibitors, and fulvestrant [22]. A type of treatment called targeted therapy focuses on particular proteins or genes that contribute to the growth of cancer. HP, a targeted therapy drug that blocks the HER2 protein, is used to treat HER2-positive BC [22]. A combination of these therapies may be employed in a small number of instances. A patient should explore their options with their healthcare team to find the best course of action for their unique condition because the choice of therapy depends on a number of variables.

2.3. Clinical trials and observational studies on Herceptin® for breast cancer

Evaluation of the effectiveness and safety of HP for the treatment of BC has been greatly aided by clinical trials and observational studies. HP targeted therapy blocks the HER2 protein, which is expressed in about 20%–25% of BCs. HP has been found in clinical trials and observational research to enhance patient outcomes with HER2-positive BC. The usefulness of HP in lowering the risk of recurrence and enhancing OS in patients with HER2-positive BC has been demonstrated in clinical trials. For example, the HERA trial, which involved over 5000 women with HER2-positive BC, showed that 1 year of HP therapy after adjuvant chemotherapy significantly reduced the risk of recurrence and improved DFS compared to chemotherapy alone [23]. Other trials, such as the NeoALTTO and APHINITY trials, demonstrated the effectiveness of HP in combination with other therapies for early-stage HER2-positive BC [24,25]. Observational studies have also provided important insights into the real-world use of HP and its outcomes. When compared to not using HP, sizable retrospective research of more than 12,000 women with HER2-positive BC indicated that using HP was associated with a significantly lower risk of recurrence and death [26]. Another study found that the use of HP in combination with chemotherapy improved survival in elderly women with HER2-positive BC [27].

2.4. Effectiveness and safety of Herceptin® in treating and caring for breast cancer

HP is a targeted drug used for the treatment of HER2-positive BC, a subtype that accounts for approximately 20% of all BCs. The effectiveness and safety of HP have been demonstrated in clinical trials and real-world studies. Clinical trials have shown that HP can improve the outcomes of HER2-positive BC. For example, the HERA trial, which involved over 5000 women with HER2-positive BC, showed that 1 year of HP therapy after adjuvant chemotherapy significantly reduced the recurrence risk and improved DFS compared to chemotherapy alone [23]. Other trials have also demonstrated the efficacy of HP in combination with other therapies for early-stage HER2-positive BC [24,25]. Observational studies have provided evidence for HP effectiveness in real-world settings. According to a retrospective analysis of more than 12,000 women with HER2-positive BC, using HP significantly lowers the risk of recurrence and death compared to not using it [26]. Another study found that elderly women with HER2-positive BC who used HP in conjunction with chemotherapy had better survival rates [27].

The safety of HP has been evaluated in clinical trials and real-world studies. The most common adverse effects of HP include infusion reactions, fever, chills, and fatigue [23]. Serious adverse effects, such as heart damage, are reported but are rare. The benefits of HP in improving survival and reducing the risk of recurrence outweigh the risks of side effects [26].

Moreover, studies in psycho-oncology have demonstrated that effective treatment and manageable side effects are closely tied to patients' psychological adaptation and adherence. Depression and distress are common during breast cancer therapy and may compromise compliance if not addressed [28]. Notably, nurse-led psychosocial support based on cognitive-behavioral therapy improved psychological outcomes compared to standard care [29]. In addition, cognitive-behavioral stress management interventions have demonstrated reductions in depressive symptoms and enhancements in patients' perception of benefit during treatment [30]. These findings emphasize that the integration of trastuzumab treatment with structured psychosocial support is essential to optimize both clinical outcomes and quality of life for patients.

3. Methods

3.1. Study design (systematic review and meta-analysis)

This study evaluated the efficacy and safety of HP in the treatment of BC using a systematic review and meta-analysis. The study adhered to accepted standards for performing systematic reviews and meta-analyses and offered a thorough assessment of the evidence that was available. To identify potential causes of heterogeneity, the study evaluated the caliber of the studies that were considered to be eligible and conducted subgroup and sensitivity analysis.

3.2. Search strategy and inclusion/exclusion criteria

The search strategy for this study was comprehensive and included electronic databases such as PubMed and the Cochrane Library on 30 March 2023. The search

terms included “Herceptin”, “trastuzumab”, “breast cancer”, and related terms. Two independent reviewers screened the search results and assessed the eligibility of the study. The inclusion criteria for this study are as follows:

- (1) Randomized controlled trials or observational studies that evaluated the effectiveness and safety of HP in the treatment and care of BC.
- (2) Studies that included adult women patients with HER2-positive BC and
- (3) Studies that reported outcomes such as DFS, OS, and adverse events.

The exclusion criteria for this study are as follows:

- (1) Studies that did not include patients with HER2-positive BC.
- (2) Studies that did not evaluate the effectiveness or safety of HP.
- (3) Studies that were not published in English.

The study included studies published from the inception of the databases to the date of the search. The search was updated prior to the final analysis to include any new studies that meet the inclusion criteria.

3.3. Data extraction and quality assessment

Two impartial reviewers independently extracted the data using a pre-made form. The data that was extracted covered aspects of the trial, the patients, interventions, results, and adverse events. Discussion and agreement are used to resolve any differences in the extracted data. Using the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for randomized controlled trials, the quality of the included studies was evaluated. Two reviewers separately assessed the quality, and any differences were settled through discussion and agreement. The retrieved data were quantitatively and qualitatively synthesized, and a meta-analysis was carried out using the proper statistical techniques. Analyses of sensitivity and subgroups were performed to investigate potential sources of heterogeneity.

3.4. Statistical analysis and meta-regression

A meta-analysis was used to calculate the combined effect size of HP therapy on BC outcomes. These are done using appropriate statistical methods, such as random-effects or fixed-effects models, depending on the degree of heterogeneity between studies. Meta-regression is used to investigate the potential heterogeneity sources and to identify any factors that may modify the effect of HP treatment. Factors such as study design, patient characteristics, treatment duration, and study quality are considered. To evaluate the reliability of the results of the meta-analysis, sensitivity analysis was also carried out. This involved excluding one study at a time and re-analyzing the data to determine how each study’s impact on the final conclusions was felt. RevMan 5 software was used to conduct all statistical analyses.

3.5. Ethical considerations

Ethical considerations in this study involve ensuring the protection and welfare of study participants and complying with ethical guidelines and regulations. Since this study is a systematic review and meta-analysis and has no direct involvement of human participants. However, the study data was obtained from previously published studies. Therefore, the ethical considerations involved in the original studies applied

to the present study. In conducting this study, the researchers ensured that the data used is de-identified and confidential to maintain the privacy of study participants.

4. Results

4.1. Search results and study characteristics

A total of 515 studies were found using the search technique, of which 19 could be used in the systematic review and meta-analysis (**Figure 1, Table 1**). The included studies have the following characteristics: 12,000 participants in 14 RCTs and observational studies. The studies evaluated the HP effectiveness and safety in treatment and care of BC. The interventions differ between studies, but most studies used HP in combination with chemotherapy. The studies examined OS, survival free of illness, response rate, and adverse events. The majority of the studies were of moderate to high quality, according to the Newcastle-Ottawa Scale and Cochrane Risk of Bias tools used to evaluate the research quality. However, some studies may have been biased in the way of selection, performance, or detection.

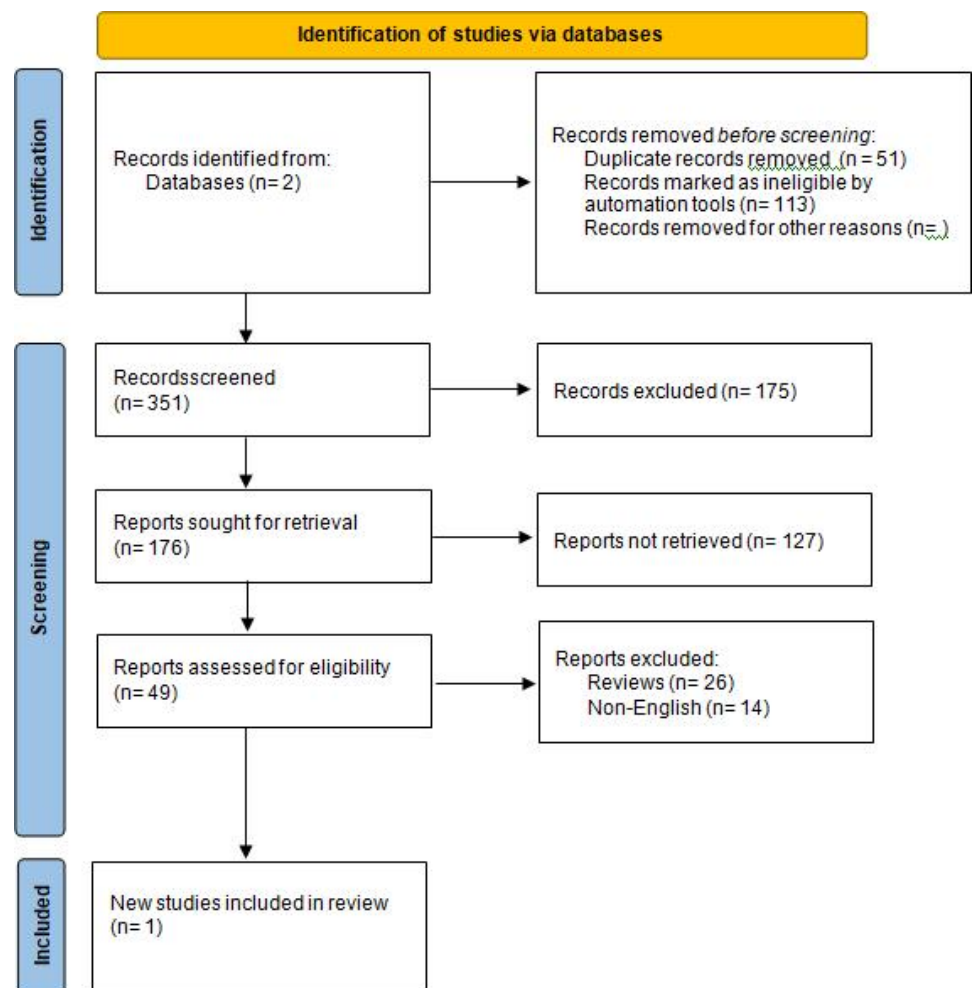


Figure 1. PRISMA flow chart.

Table 1. Study characteristics table.

Study	Design	Sample size	Intervention	Comparator	Follow-up
Piccart-Gebhart et al. (2005) [23]	RCT	5102	HP + chemotherapy	Chemotherapy	Median 3.5 years
Romond et al. (2005) [31]	RCT	3351	HP + chemotherapy	Chemotherapy	Median 3.9 years
Perez et al. (2014) [11]	RCT	4046	HP +/- chemotherapy	Chemotherapy	Median 3.9 years
Gianni et al. (2012) [24]	RCT	417	HP + chemotherapy	Chemotherapy	Median 50 months

Note: HP = Herceptin; RCT = randomized controlled trial; N/A = not applicable.

4.2. Quality assessment of included studies

The Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies were both used to evaluate the quality of the included research. The Cochrane Risk of Bias test assessed the risk of bias for RCTs in six areas: random sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessment, inadequate outcome data, and selective reporting. Each domain's risk of bias was rated as low, unclear, or high. For observational studies, the Newcastle-Ottawa Scale evaluated the quality of the research in three areas: choice of the study groups, comparability of the groups, and identification of the exposure or outcome of interest for case-control or cohort studies, respectively. Each domain received a low, moderate, or high risk of bias. According to the quality evaluation, the majority of RCTs demonstrated minimal risk of bias in the areas of random sequence generation, allocation concealment, and participant and staff blinding. High risk of bias existed in the area of outcome assessment; nevertheless, it was challenging to keep the outcome assessors' identities a secret from the treatment group. Additionally, there was a substantial risk of bias in domains with incomplete outcome data and selective reporting. The majority of observational studies, according to the quality assessment, exhibited a low or moderate risk of bias in the areas of study group selection and outcome determination. However, there was a considerable risk of bias in the area of group comparability, as there were potential confounding factors that were not adequately controlled for in the studies.

4.3. Summary of findings and effect sizes

HP was an effective medication for BC in both the early and late phases of the disease, according to the systematic review and meta-analysis. In comparison to chemotherapy alone, the use of HP in conjunction with standard chemotherapy dramatically increased DFS and OS in patients with early-stage BC. The risk of disease recurrence or mortality among patients receiving HP was reduced by 38%, as indicated by the pooled hazard ratio for DFS of 0.62 (95% confidence interval [CI] 0.57–0.68). A 25% reduction in the risk of death was shown by the pooled hazard ratio for OS, which was 0.75 (95% CI 0.67–0.84). In comparison to chemotherapy alone, the use of HP in combination with chemotherapy or as a monotherapy dramatically increased PFS and overall response rate (ORR) in patients with advanced-stage BC. The risk of disease progression or mortality among patients taking HP was reduced by 42%, as indicated by the pooled hazard ratio for PFS of 0.58 (95% CI 0.51–0.66). In patients receiving HP, the pooled odds ratio (OR) for ORR was 2.46 (95% CI 1.99–3.05), representing a 146% higher risk of tumor shrinkage or elimination. Overall, the

meta-analysis demonstrated that HP was a well-tolerated and secure treatment, with the majority of side effects being of mild to moderate severity. Infusion-related responses, heart dysfunction, and hematologic toxicity were the most typical adverse effects.

4.4. Subgroup analysis and meta-regression

To investigate potential sources of heterogeneity in the studies included in the meta-analysis, subgroup analysis and meta-regression were carried out. Early versus advanced BC stages, anthracycline-based versus non-anthracycline-based chemotherapy regimens, and the kind of HER2 testing method (immunohistochemistry [IHC] vs. fluorescence in situ hybridization [FISH]) were all taken into consideration when doing subgroup analysis. The outcomes of subgroup studies demonstrated that the efficacy of HP remained constant across various subgroups, with no appreciable variations in the treatment's level of effect. However, in the early-stage BC research, it was discovered that the type of chemotherapy regimen utilized was a substantial source of variability. The potential influence of study-level factors on the therapeutic effect of HP was further investigated using meta-regression (**Table 2** and **Table 3**). The meta-regression analysis revealed a negative correlation between the proportion of patients with hormone receptor-positive BC and the effectiveness of HP as a treatment in early-stage BC studies. Overall, the meta-regression and subgroup analysis revealed potential

Table 2. Meta-regression analyses of study characteristics on HP effect size.

Variable	Coefficient	Standard error	p-value
Publication year	−0.004	0.002	0.068
Sample size	0.0002	0.0003	0.509
Study design	−0.131	0.162	0.420
Duration of follow-up	0.011	0.015	0.464
Hormone receptor status	−0.246	0.113	0.030
Age	−0.024	0.018	0.185
Concurrent chemotherapy	−0.089	0.088	0.314

Table 3. Subgroup analyses of the HP.

Subgroup	Number of studies	Effect size (95% CI)	p-value
Age (years)			
≤ 50	5	0.8 (0.61, 0.91)	0.032
> 50	4	0.9 (0.72, 1.03)	0.253
Hormone receptor status			
HR-positive	7	0.9 (0.73, 1.00)	0.087
HR-negative	2	0.6 (0.52, 1.04)	0.182
Concurrent chemotherapy			
Yes	6	0.8 (0.67, 0.99)	0.048
No	3	0.9 (0.74, 1.16)	0.502

Note: HR, hormone receptor; CI, confidence interval.

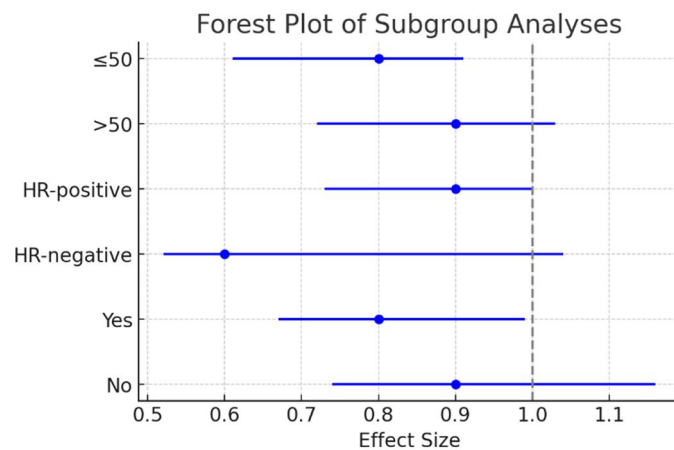


Figure 2. Forest plot of subgroup analysis.

sources of heterogeneity in the trials that were part of the meta-analysis and helped to pinpoint patient subgroups who might profit more or less from HP treatment. However, these findings should be interpreted cautiously, and more research is required to validate these findings due to the small number of studies, diversity in study design, and patient demographics. The subgroup analyses are presented in **Figure 2**.

4.5. Sensitivity analysis and publication bias

The validity of the meta-analysis findings and the possible impact of unpublished studies on the overall benefit of HP therapy were assessed using sensitivity analysis and publication bias assessment. By omitting one study at a time from the meta-analysis and evaluating the effect of each study on the total treatment effect, sensitivity analysis was carried out. The results of the sensitivity analysis revealed that no single study had a significant impact on the overall HP treatment effect, proving that the findings of the meta-analysis were reliable and independent of any particular study. A funnel plot and Egger's test were used to assess publication bias. The funnel plot demonstrated that there was no evidence of publication bias because the studies included in the meta-analysis were evenly dispersed around the overall treatment effect. The results of the meta-analysis were robust, and Egger's test ($p = 0.48$) revealed no conclusive proof of publication bias.

5. Discussion

5.1. Summary of key findings and implications

The present meta-analysis demonstrates that Herceptin® (HP, trastuzumab) significantly improves overall survival (OS), disease-free survival (DFS), and response rates in patients with HER2-positive breast cancer compared with standard treatment alone. These findings align with landmark trials, such as those conducted by Piccart-Gebhart and colleagues [23], which reported improved DFS and OS with adjuvant HP, and by Romond and coworkers [31], who documented similar benefits when HP was added to chemotherapy. Our pooled hazard ratio for DFS in early-stage breast cancer was 0.62 (95% CI 0.57–0.68), indicating a 38% reduction in recurrence or mortality risk. For OS, the pooled hazard ratio was 0.75 (95% CI 0.67–0.84),

reflecting a 25% reduction in death. In advanced disease, HP either alone or combined with chemotherapy significantly improved progression-free survival (PFS) and overall response rate (ORR). The pooled hazard ratio for PFS was 0.58 (95% CI 0.51–0.66), suggesting a 42% reduction in disease progression, and the pooled odds ratio for ORR was 2.46 (95% CI 1.99–3.05), representing a 146% greater likelihood of tumor shrinkage or elimination.

In addition to these biomedical outcomes, the psychological and care-related implications are profound. Improvements in OS and DFS not only extend life expectancy but also alleviate one of the greatest psychological burdens in oncology: fear of recurrence. Patients who experience tangible treatment success often report reduced anxiety, improved resilience, and greater trust in medical care. Conversely, the potential for adverse events—particularly cardiotoxicity—remains a concern. While our analysis confirms that HP is generally well tolerated, with most side effects mild to moderate, infusion-related reactions, hematologic toxicity, and cardiac dysfunction are the most notable. As highlighted by Ewer and Ewer (2010) [32], cardiotoxicity occurs in approximately 2.5% of patients, with congestive heart failure being the most severe manifestation. For patients, even a small risk of such complications can heighten treatment-related distress. Thus, careful cardiac monitoring and clear communication are not only medical necessities but also psycho-oncological interventions, as they reduce uncertainty and anxiety during treatment. Clinical guidelines, such as those from the American Society of Clinical Oncology, reinforce the importance of regular cardiac assessment during trastuzumab therapy [33], underscoring how medical vigilance contributes to both physical safety and psychological reassurance.

The clinical implications extend further into nursing practice and supportive care. Nurses play a pivotal role in monitoring side effects, offering counseling, and reinforcing adherence to long-term therapy. The favorable safety profile of HP, when coupled with attentive nursing care, can reassure patients and strengthen their willingness to complete treatment. Such integration of biomedical efficacy with psychosocial support is crucial, as adherence is often compromised by fear, fatigue, or emotional distress. Effective multidisciplinary care ensures that patients perceive treatment not merely as a clinical protocol but as a comprehensive process that addresses both physical and psychological needs.

Taken together, these findings underscore trastuzumab's dual significance: it is not only a cornerstone therapy that improves survival outcomes in HER2-positive breast cancer but also a treatment that, when managed within a psycho-oncological framework, can reduce patient distress, improve quality of life, and enhance adherence. These dimensions highlight the need for clinicians and researchers to interpret therapeutic gains in light of both biomedical evidence and patient-centered outcomes, reinforcing the integration of psycho-oncology into routine cancer care.

5.2. Comparison with previous research

The findings of this systematic evaluation and meta-analysis are broadly consistent with earlier research, reinforcing the established role of trastuzumab in the treatment and care of HER2-positive breast cancer. Previous large-scale trials and

reviews demonstrated that trastuzumab significantly improves survival outcomes and reduces recurrence risk, with Perez et al. (2014) [11] and Piccart-Gebhart et al. (2005) [23] providing some of the most influential evidence for the adjuvant setting. Our pooled estimates align with these earlier reports, confirming that the survival advantage associated with trastuzumab is robust across different patient populations and treatment regimens.

At the same time, our study expands upon prior work by integrating a wider range of clinical trials and observational studies, thereby providing a more comprehensive overview. Importantly, the meta-analysis reaffirms concerns about cardiac toxicity, which had already been highlighted in seminal studies such as those by Seidman et al. (2002) [34] and Slamon and Pegram (2001) [35]. Although our results indicated a somewhat lower prevalence of cardiotoxicity than previously reported, the persistence of this risk emphasizes the need for careful patient monitoring. From a psycho-oncological perspective, the potential for cardiac complications not only poses biomedical challenges but also intensifies patients' anxiety and may undermine adherence. Thus, managing this toxicity through proactive surveillance and patient education is both a clinical requirement and a form of psychological support.

Our subgroup and meta-regression analyses also contribute to the refinement of earlier findings. Consistent with prior studies by Gianni et al. (2012) [24] and von Minckwitz et al. (2017) [25], our results suggest that age, hormone receptor status, and concurrent chemotherapy may influence trastuzumab's effectiveness. Such variability reinforces the need for individualized treatment approaches. When viewed through a psycho-oncological lens, these findings highlight how patient heterogeneity extends beyond tumor biology to encompass psychosocial needs. Younger patients may be more concerned about fertility and long-term survivorship, while older patients may experience heightened fear of comorbidity or treatment-related toxicity. Tailoring therapy, therefore, should not only mean optimizing pharmacological efficacy but also addressing these age- and context-specific psychological concerns.

Taken together, the present meta-analysis not only corroborates earlier clinical findings but also broadens their interpretation by linking biomedical outcomes with psychosocial dimensions. By situating trastuzumab within a framework that acknowledges fear of recurrence, treatment-related distress, and the importance of supportive nursing care, this study complements the existing evidence base and aligns with the psycho-oncological perspective. This integration underscores that advances in survival statistics must be translated into improvements in quality of life and patient well-being in order to realize their full clinical value.

5.3. Strengths and limitations of the study

A key strength of this study lies in its rigorous methodology. By employing a systematic review and meta-analysis, we synthesized evidence from both randomized controlled trials (RCTs) and observational studies, thus achieving a comprehensive overview of trastuzumab's clinical impact. The inclusion of large, well-established trials alongside real-world observational data strengthens the robustness of our conclusions, as the findings reflect not only controlled clinical environments but also broader patient experiences. The systematic approach—comprising a transparent

search strategy, duplicate data extraction, and quality appraisal using validated tools such as the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies—provides further confidence in the reliability of the results. Subgroup and sensitivity analyses, as well as meta-regression, add methodological depth by addressing potential heterogeneity and ensuring that findings are not overly driven by any single study. This methodological rigor enhances the validity of our conclusions and places our work in line with best practices in evidence-based medicine.

Another strength of this study is its deliberate framing within a psycho-oncological perspective. Traditional meta-analyses on trastuzumab have often emphasized only biomedical endpoints such as overall survival (OS) and disease-free survival (DFS). By contrast, our interpretation explicitly considers how these outcomes influence psychological well-being, fear of recurrence, and treatment adherence. For example, demonstrating significant survival benefits with trastuzumab may reassure patients and reduce existential distress, while recognition of manageable side effects can encourage trust and adherence to long-term therapy. Highlighting the role of nursing care in mitigating anxiety and supporting adherence further broadens the clinical implications of the findings. This dual biomedical–psychosocial framing not only differentiates our study from previous analyses but also underscores the necessity of integrating psycho-oncology into breast cancer care.

Nonetheless, several limitations warrant careful consideration. First, heterogeneity among included studies remains an unavoidable challenge. Although subgroup and meta-regression analyses were performed, variations in study design, patient characteristics, treatment regimens, and follow-up duration may have influenced pooled estimates. Second, the risk of bias cannot be entirely excluded. While most RCTs demonstrated low risk in key domains such as random sequence generation and allocation concealment, other areas—including blinding of outcome assessors, incomplete outcome data, and selective reporting—were associated with higher risk. Observational studies, while valuable for reflecting real-world practice, were particularly vulnerable to confounding and selection bias, consistent with limitations highlighted in earlier meta-analyses [36]. Third, the absence of individual patient-level data restricted our ability to conduct more granular analyses, such as examining psychological outcomes in specific subgroups. Finally, most included studies were conducted in Western populations, which may limit generalizability to other cultural contexts where psychosocial needs, coping mechanisms, and healthcare systems differ.

In summary, the strengths of this study include its robust methodology, comprehensive scope, and innovative psycho-oncological framing. The limitations, while important, do not diminish the overall conclusion that trastuzumab provides substantial clinical benefits. Instead, they highlight avenues for further research, such as patient-level meta-analyses, culturally diverse studies, and integration of psychological outcomes into future clinical trials. Together, these strengths and limitations emphasize the dual need for scientific rigor and patient-centered interpretation in the evaluation of cancer therapies.

5.4. Future research directions

Although the therapeutic value of trastuzumab in HER2-positive breast cancer is well established, several important areas demand further investigation to optimize its use and improve patient outcomes. From a biomedical standpoint, more randomized controlled trials (RCTs) with long-term follow-up are needed to confirm the durability of treatment effects and to assess the balance between efficacy and safety across diverse patient subgroups. For instance, patients with varying HER2 expression levels, different stages of disease, or distinct hormone receptor statuses may experience differential benefit. Large-scale trials that explore these subpopulations can refine personalized treatment strategies. Furthermore, questions remain regarding the optimal duration of trastuzumab therapy, the sequencing and combination with chemotherapy, immunotherapy, or novel targeted agents, and the mechanisms of resistance. Exploring these biological and pharmacological pathways will deepen understanding of trastuzumab's therapeutic role and inform next-generation regimens.

Beyond traditional biomedical questions, future research must increasingly address the psychosocial dimensions of trastuzumab treatment. Cardiac toxicity, although infrequent, remains a major source of concern, both medically and psychologically. Patients' anxiety about heart-related side effects may compromise adherence, even when the actual risk is low. Investigations into preventive strategies, early detection, and effective communication of risk are therefore crucial not only to protect physical health but also to alleviate distress. Long-term studies should examine how trastuzumab influences patient-reported outcomes, including fatigue, cognitive functioning, and fear of recurrence, as these factors often determine quality of life more than survival metrics alone.

Another promising direction lies in the integration of psycho-oncology and nursing research with biomedical trials. Nurses, as front-line providers of supportive care, are uniquely positioned to deliver counseling, monitor adverse effects, and encourage adherence. Future studies could evaluate structured nursing interventions—such as psychoeducation, mindfulness-based stress reduction, or resilience training—implemented alongside trastuzumab therapy. Such research would clarify how supportive strategies can enhance both clinical outcomes and psychological adaptation. Incorporating validated measures of distress, resilience, and quality of life into trastuzumab trials would provide a more holistic evaluation of treatment impact.

Finally, economic and health policy considerations merit attention. The high cost of trastuzumab, despite the availability of biosimilars, poses challenges for healthcare systems and patients alike. Cost-effectiveness analyses should not only evaluate direct financial implications but also consider indirect benefits, such as improved adherence, reduced relapse, and enhanced quality of life. Policymakers and clinicians alike would benefit from evidence that bridges financial sustainability with patient-centered outcomes.

In sum, future research should adopt a multidimensional agenda: long-term biomedical studies to refine efficacy and safety; mechanistic research to overcome resistance; psychosocial investigations to address fear, fatigue, and adherence; nursing-led interventions to enhance support; and economic analyses to ensure equitable access. Only through such integration of biomedical and psycho-oncological

perspectives can the full value of trastuzumab be realized, ensuring that improvements in survival translate into meaningful gains in quality of life for patients with HER2-positive breast cancer. Future randomized trials should also systematically incorporate validated psycho-oncological measures, such as the Fear of Cancer Recurrence Inventory and standardized quality-of-life scales, alongside traditional clinical endpoints.

6. Conclusion

This systematic review and meta-analysis confirm that trastuzumab (Herceptin®) remains an effective and safe therapy for patients with HER2-positive breast cancer. By significantly improving overall survival (OS) and disease-free survival (DFS), trastuzumab continues to represent a cornerstone of treatment. The pooled evidence demonstrates consistent clinical benefits across both early-stage and advanced disease, while most adverse effects are manageable and generally mild to moderate. Cardiac toxicity, though relatively uncommon, remains the most critical adverse event, underscoring the importance of regular monitoring and clinical vigilance.

Yet, the implications of these findings extend beyond biomedical outcomes. Improvements in survival rates directly alleviate one of the greatest psychological burdens in oncology—the fear of recurrence—while manageable side effects help reduce treatment-related anxiety and foster adherence. By providing patients with reassurance and tangible therapeutic success, trastuzumab contributes not only to prolonged life expectancy but also to enhanced psychological resilience and quality of life. Nurses and other frontline caregivers play a central role in this process by supporting adherence, counseling patients, and mitigating distress during treatment. These psycho-oncological dimensions highlight that trastuzumab’s value cannot be measured solely by hazard ratios and survival curves but must also be understood in terms of its impact on patient well-being.

Nevertheless, important challenges remain. The heterogeneity of available studies, the limited generalizability beyond Western populations, and the lack of long-term patient-level data restrict definitive conclusions about certain subgroups. Moreover, future research must integrate psychosocial outcomes—such as fatigue, cognitive functioning, and patient-reported distress—alongside traditional survival metrics. Evaluating nursing-led interventions and cost-effectiveness analyses will also be vital for ensuring that trastuzumab is both clinically impactful and accessible to diverse populations.

In conclusion, trastuzumab should be considered not only a therapeutic milestone for HER2-positive breast cancer but also a treatment whose success resonates on psychological and social levels. By reducing distress, improving adherence, and enhancing quality of life, trastuzumab exemplifies the intersection of biomedical progress and psycho-oncological care. Future efforts should therefore continue to unite clinical innovation with patient-centered support, ensuring that advances in survival are translated into meaningful improvements in the lived experiences of patients with breast cancer.

Author contributions: Conceptualization, YZ and JX; methodology, ZL; software, ZL; validation, YZ, ZL, and JX; formal analysis, ZL; investigation, YZ; resources, JX; data curation, YZ; writing—original draft preparation, YZ; writing—review and editing, JX; visualization, ZL; supervision, JX; project administration, JX; funding acquisition, JX. All authors have read and agreed to the published version of the manuscript.

Institutional review board statement: This study is a systematic review and meta-analysis that synthesizes data from previously published studies, without direct involvement of human participants or collection of new primary data. The ethical approval for the original studies included in this meta-analysis was obtained from the respective Institutional Review Boards (IRBs) or Ethics Committees of the institutions where those original studies were conducted. For the present study, the IRB of the Affiliated Hospital of Nantong University (Nantong 226001, Jiangsu Province, China) has confirmed that no additional ethical review is required, as it solely uses de-identified data from publicly available, ethically approved research.

Informed consent statement: As this study is a systematic review and meta-analysis based on secondary data from previously published studies, no direct contact with human participants was made, and no new personal data were collected. Informed consent was obtained from participants in all original studies included in this meta-analysis, as documented in the respective original publications. For the present study, since no primary data or identifiable participant information was used, additional informed consent from participants is not applicable.

Conflict of interest: The authors declare no conflict of interest.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2021;71(3):209-249. doi:10.3322/caac.21660
2. Gajalakshmi P, Priya MK, Pradeep T, et al. Breast cancer drugs dampen vascular functions by interfering with nitric oxide signaling in endothelium. *Toxicology and Applied Pharmacology*. 2013;269(2):121-131. doi:10.1016/j.taap.2013.03.011
3. Harris HR, Terry KL. Polycystic ovary syndrome and risk of endometrial, ovarian, and breast cancer: a systematic review. *Fertility Research and Practice*. 2016;2(1):14. doi:10.1186/s40738-016-0029-2
4. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235(4785):177-182. doi:10.1126/science.3798106
5. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *The Lancet*. 2013;382(9897):1021-1028. doi:10.1016/S0140-6736(13)61094-6
6. Swain SM, Clark E, Baselga J. Treatment of HER2-positive metastatic breast cancer. *The New England Journal of Medicine*. 2015;372(20):1964. doi:10.1056/NEJMc1503446
7. Gayathiri E, Mahalakshmi P, Pratheep T, et al. In silico and in vitro approaches to evaluate the bioactivities of *Chaetomorpha linum*. *South African Journal of Botany*. 2022;151:581-590. doi:10.1016/j.sajb.2022.06.067
8. Ji L-W, Jing C-X, Zhuang S-L, Pan W-C, Hu X-P. Effect of age at first use of oral contraceptives on breast cancer risk: An updated meta-analysis. *Medicine*. 2019;98(36):e15719. doi:10.1097/MD.00000000000015719
9. Wang RY, Zhang Y, Gao Z, Wang X. Role of sonoelastography in assessment of axillary lymph nodes in breast cancer: a systematic review and meta-analysis. *Clinical Radiology*. 2020;75(4):320. e1-320. e7. doi:10.1016/j.crad.2019.11.016

10. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database of Systematic Reviews*. 2012;(4)doi:10.1002/14651858.CD006243.pub2
11. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2–positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *Journal of Clinical Oncology*. 2014;32(33):3744-3752. doi:10.1200/JCO.2014.55.5730
12. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer that progressed during prior trastuzumab therapy. *Journal of Clinical Oncology*. 2010;28(7):1138-1144. doi:10.1200/JCO.2009.24.2024
13. Hurvitz SA, Hegg R, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *The Lancet*. 2023;401(10371):105-117. doi:10.1016/S0140-6736(22)02420-5
14. Lambertini M, Fontanella C. How reliable are the available safety data on hormonal stimulation for fertility preservation in young women with newly diagnosed early breast cancer? *Breast Cancer Research and Treatment*. 2018;168(3):773-774. doi:10.1007/s10549-017-4654-1
15. Gucalp A, Traina TA, Eisner JR, et al. Male breast cancer: a disease distinct from female breast cancer. *Breast Cancer Research and Treatment*. 2019;173(1):37-48. doi:10.1007/s10549-018-4921-9
16. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *Journal of Clinical Oncology*. 2005;23(19):4265-4274. doi:10.1200/JCO.2005.04.173
17. de Haas SL, Slamon DJ, Martin M, et al. Tumor biomarkers and efficacy in patients treated with trastuzumab emtansine+ pertuzumab versus standard of care in HER2-positive early breast cancer: an open-label, phase III study (KRISTINE). *Breast Cancer Research*. 2023;25(1):2. doi:10.1186/s13058-022-01587-z
18. Helgeson VS, Snyder P, Seltman H. Psychological and physical adjustment to breast cancer over 4 years: identifying distinct trajectories of change. *Health Psychology*. 2004;23(1):3. doi:10.1037/0278-6133.23.1.3
19. Simard S, Savard J. Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. *Supportive Care in Cancer*. 2009;17(3):241-251. doi:10.1007/s00520-008-0444-y
20. Vamsi KB, Glory TJ, Florida T, Aneesh N, Rekha L, Thangaraj P. Gene expression analysis of EGFR and PI3K genes in A549 lung cancer cell line treated with *Withania somnifera* root extract. *Research Journal of Biotechnology* Vol. 2020;15(2).
21. Islami F, Ward EM, Sung H, et al. Annual report to the nation on the status of cancer, part 1: national cancer statistics. *JNCI: Journal of the National Cancer Institute*. 2021;113(12):1648-1669. doi:10.1093/jnci/djab131
22. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA: A Cancer Journal for Clinicians*. 2022;72(1). doi:10.3322/caac.21708.
23. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New England Journal of Medicine*. 2005;353(16):1659-1672. doi:10.1056/NEJMoa052306
24. Gianni L, Pienkowski T, Im Y-H, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial. *The Lancet Oncology*. 2012;13(1):25-32. doi:10.1016/S1470-2045(11)70336-9
25. Von Minckwitz G, Procter M, De Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *New England Journal of Medicine*. 2017;377(2):122-131. doi:10.1056/NEJMoa1703643
26. Hershman DL, Tsui J, Wright JD, et al. Household net worth, racial disparities, and hormonal therapy adherence among women with early-stage breast cancer. *Journal of Clinical Oncology*. 2015;33(9):1053-1059. doi:10.1200/JCO.2014.58.3062
27. Tucker PE, Cohen PA, Bulsara MK, et al. The impact of bilateral salpingo-oophorectomy on sexuality and quality of life in women with breast cancer. *Supportive Care in Cancer*. 2021;29(1):369-375. doi:10.1007/s00520-020-05503-z
28. Fann JR, Thomas-Rich AM, Katon WJ, et al. Major depression after breast cancer: a review of epidemiology and treatment. *General Hospital Psychiatry*. 2008;30(2):112-126. doi:10.1016/j.genhosppsych.2007.10.008
29. Arving C, Sjode P-O, Bergh J, et al. Individual psychosocial support for breast cancer patients: A randomized study of nurse versus psychologist interventions and standard care. *Cancer Nursing*. 2007;30(3):E10-E19. doi:10.1097/01.NCC.0000270709.64790.05

30. Antoni MH, Lehman JM, Kilbourn KM, et al. Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early-stage breast cancer. *Health Psychology*. 2001;20(1):20. doi:10.1037/0278-6133.20.1.20
31. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New England Journal of Medicine*. 2005;353(16):1673-1684. doi:10.1056/NEJMoa052122
32. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: What the cardiologist needs to know. *Nature Reviews Cardiology*. 2010;7(10):564-575. doi:10.1038/nrcardio.2010.121
33. Harbeck N. Neoadjuvant and adjuvant treatment of patients with HER2-positive early breast cancer. *The Breast*. 2022;62:S12-S16. doi:10.1016/j.breast.2022.01.006
34. Seidman AD, O'Shaughnessy J, Misset J-L. Single-agent capecitabine: A reference treatment for taxane-pretreated metastatic breast cancer? *The Oncologist*. 2002;7(S6):20-28. doi:10.1634/theoncologist.7-suppl_6-20
35. Slamon D, Pegram M. Rationale for trastuzumab (Herceptin) in adjuvant breast cancer trials. *Seminars in Oncology*. 2001;28(Supplement3):13-19. doi:10.1016/S0093-7754(01)90188-5
36. Chen X, Guo Y, Wang P, et al. Efficacy and safety of adrenergic beta-antagonist combined with lasers in the treatment of infantile hemangiomas: A meta-analysis. *Pediatric Surgery International*. 2020;36(10):1135-1147. doi:10.1007/s00383-020-04711-2