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Literature Review **Open Access**

A Bibliometric Analysis of HER2 Positivity as a Predictor of Brain Metastases in Breast Cancer: Insights from VOSviewer

Sakinah Mar'ie Sanad[1*], I Made Oka Adnyana[2], I Putu Eka Widyadharma[3]

[123]Specialist Neurology Doctor Education Program, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

*Corresponding Author. E-mail: sanad.nina@gmail.com

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ABSTRACT

Background: *HER2-positive breast cancer (BC) is known for its aggressive behavior and increased risk of brain metastases (BM), which worsens patient prognosis and limits therapeutic options due to the blood brain barrier (BBB). This study systematically evaluates HER2 overexpression as a predictive factor of BM in breast cancer patients through a Systematic Literature Review (SLR) and visualizes global research trends using VOSviewer.*
Methods: *A total of 20 peer-reviewed primary studies published between 2015–2025 were analyzed from PubMed and Scopus databases using the PRISMA framework. Selection was guided by the PICOTS model, and data synthesis included clinical predictors, therapeutic outcomes, and prognostic models. Bibliometric metadata were processed using VOSviewer to explore thematic evolution.*
Results: *HER2 overexpression is consistently linked with earlier BM onset, higher incidence, and distinct survival patterns. Advanced HER2-targeted agents like tucatinib and pyrotinib demonstrated enhanced CNS control. VOSviewer maps revealed five thematic clusters: HER2-targeted therapy, BM prediction models, survival analysis, CNS drug resistance, and HER2-low classification.*
Conclusion: *HER2 positivity is an independent prognostic marker for brain metastases in BC. Its integration into CNS risk stratification and personalized therapy protocols may enhance clinical outcomes in high-risk patients.*

Keywords: *HER2-positive; breast cancer; brain metastasis; VOSviewer; predictive biomarker; systematic review*

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INTRODUCTION

Breast cancer remains the most diagnosed malignancy and a leading cause of cancer-related mortality among women globally, with over 2.3 million new cases reported in 2020.[1] The HER2-positive subtype, which accounts for 15–20% of all breast cancers, is recognized for its aggressive behavior, rapid proliferation, and poor prognosis.[1,2] Notably, this subtype shows a higher incidence of brain metastases (BM), occurring in approximately 30–50% of metastatic HER2-positive cases. [3]The central nervous system (CNS) acts as a sanctuary site due to the restrictive function of the blood–brain barrier (BBB), which impairs the efficacy of many systemic therapies.[4] This contributes to a unique clinical challenge, where patients with well-controlled systemic disease still experience isolated progression in the CNS.

Current treatment regimens including trastuzumab, pertuzumab, and newer tyrosine kinase inhibitors have improved systemic disease control and prolonged overall survival [5]. However, most of these agents exhibit limited ability to penetrate the BBB, resulting in an increased risk of CNS relapse even during extracranial remission.[6] Moreover, routine neuroimaging is not part of standard surveillance protocols in asymptomatic patients, which may delay diagnosis and compromise neurological outcomes.[7] While the therapeutic landscape for HER2-positive brain metastases is evolving, there remains a lack of evidence-based frameworks to predict which patients are most likely to develop CNS involvement.[1] As a result, early interventions particularly those targeting the central nervous system (CNS), may not be fully optimized or consistently implemented in clinical practice.

Emerging research suggests that HER2 overexpression may function not only as a therapeutic target but also as a predictive biomarker for CNS dissemination.[4] HER2-positive breast cancer cells exhibit biological characteristics that facilitate CNS metastasis, such as increased motility, vascular invasion, and resistance to apoptosis.[3] Studies have also highlighted that HER2-enriched subtypes metastasize to the brain more frequently and earlier than luminal or triple-negative types.[2] However, HER2 status is rarely added to established risk stratification schemes for brain metastases, and there is no consensus on the predictive value of this receptor. The absence of any consensus protocol in turn hinders clinicians in their ability to predict effectively those patients at highest risk or those who might otherwise benefit from early brain imaging or preemptive aggressive CNS-directed strategies.

Several predictive models have been proposed to assess the risk of brain metastases, incorporating variables such as tumor size, nodal status, hormone receptor expression, and HER2 positivity.[4] Furthermore, machine learning and artificial intelligence techniques are being explored to improve prediction accuracy.[3] However, these models are still in exploratory phases, lack external

validation, and are not routinely implemented in clinical settings. Compounding the issue, most randomized controlled trials exclude patients with active brain metastases, resulting in a limited understanding of treatment efficacy in this subgroup.[8] These limitations contribute to an evidence gap that affects clinical decision-making and patient outcomes.

Therapeutic advancements, such as tucatinib and trastuzumab-deruxtecan, show promise for CNS disease due to their better brain penetrance and demonstrated CNS-specific efficacy.[5,8] However, response rates remain variable, and drug resistance continues to challenge long-term disease control. Moreover, access to these newer agents remains limited in some healthcare settings, particularly in low- and middle-income countries.[7] Lack of routine screening recommendations for CNS metastases as well as lack of consensus on predictive biomarker use have hindered the ability to successfully treat these patients. Therefore, shortening the bridge between changing scientific proof and the clinical implementation is important in order to advance patient care.

To deal with the growing concerns on brain metastasis in BC, in the present work, a systematic approach is utilized by using Systematic Literature Review (SLR) combined with bibliometric analysis. In particular, it considers the impact of HER2-positive disease as a prognostic factor with respect to BM. The SLR synthesizes evidence from empirical studies in the time-span of 2015-2025 for a comprehensive picture of existing evidence. To this, the bibliometric analysis through VOSviewer is indicative for identifying core research themes and identifying the existing voids in world science. However, by combining these methods, the study will help healthcare professionals to identify high-risk patients earlier in the clinical trajectory. Finally, the findings should direct ongoing investigations to more focused approaches for prediction and prevention of CNS-related phenomena. Finally, the present results help pave the way for precision oncology and have promise to enhance neurological outcomes and overall survival in patients with HER2-positive breast cancer.

LITERATURE REVIEW

Breast cancer of the HER2-positive type is formed by amplification of the ERBB2 gene, resulting in overexpression of the HER2 receptor in the cell membrane of the tumor. This molecular alteration activates downstream signaling pathways, notably PI3K/AKT and MAPK, promoting tumor proliferation, angiogenesis, and resistance to apoptosis.[4] Clinically, this subtype has been consistently associated with an increased propensity for brain metastasis, particularly among patients with hormone receptor-negative tumors.[2,6] Such a preference to CNS spread may be due to a neurotropic nature of HER2-overexpressing tumor cells. As a result, patients with HER2-positive breast cancer have a

distinctive and aggressive pattern of metastasis, which requires early detection and an individualized follow-up.

There have been several retrospective and observational cohort studies aimed to investigate clinical and molecular risk factors of brain metastasis in HER2-positive breast cancer. Factors such as younger age at diagnosis, high histological grade, and absence of estrogen and progesterone receptor expression have been frequently correlated with increased risk of CNS involvement.[9,10] Recent studies have also proposed predictive models that integrate these parameters with HER2 status, aiming to facilitate individualized risk stratification.[4] Despite showing good discriminative value, these models have not been validated or implemented in routine oncologic practice in general. The lack of standardised CNS-specific risk assessment tools is a major shortcoming in the current management of breast cancer.

Therapeutically, the advent of HER2 targeting agents, such as trastuzumab and pertuzumab, has largely improved systemic control and survival in HER2 positive breast cancer. However, the therapeutic efficacy of these monoclonal antibodies within the CNS is constrained by their poor permeability across the blood–brain barrier.[5] Novel agents such as tucatinib, a CNS-penetrant tyrosine kinase inhibitor, and trastuzumab-deruxtecan, an antibody–drug conjugate, have shown intracranial efficacy in both clinical trials and real-world cohorts.[8,11] However, access to these drugs is unequal, and their ideal sequencing and performance in prevention of brain metastases has not yet been fully defined. In addition, for many trials, patients with untreated brain metastases are excluded, leaving a limited amount of high-quality evidence for this group.

Systematic reviews and meta-analyses have summarized various prognostic indicators in breast cancer with CNS involvement, yet few have addressed HER2 status specifically as a predictive factor. For example, Hackshaw et al. (2021) conducted a broad review of prognostic factors but did not isolate the contribution of HER2 amplification. Similarly, reviews by Passalacqua et al. (2023) and Sun et al. (2023), primarily focus on therapeutic interventions rather than predictive modeling or screening implications.[7,1] Moreover, there is a dearth of bibliometric studies that focus on the worldwide trends on HER2+ BMs, and few studies analyse research hotspots, cooperation networks, and thematic evolution. This lack of evidence highlights the necessity of a methodologically rigorous synthesis of available evidence combining systematic literature review and bibliometric mapping to support decision-making in clinical practice and to inform future research in this crucial area.

METHOD

Table 1. Model PICO

Components	Description
Population	Female breast cancer patients with HER2-positive or HER2-low expression, with or without brain metastasis.
Intervention	HER2-targeted agents (e.g., trastuzumab, tucatinib, pyrotinib, T-DXd), either as monotherapy or combination therapy.
Comparison	Standard chemotherapy, delayed HER2-targeted therapy, or untreated cohorts.
Outcome	Incidence and timing of brain metastasis, CNS progression, survival outcomes, treatment response, and CNS-specific control.
Timing	Articles were published from January 2015 to May 2025.
Setting	Multicenter clinical trials, real-world registry cohorts, and academic institution-based studies.

A comprehensive literature search was conducted across nine prominent academic databases, including Scopus, PubMed, Elsevier, MDPI, SpringerLink, BMC Cancer, JAMA Network, SagePub, and Frontiers. The Boolean search string used was: *("HER2" OR "ERBB2" OR "HER2-positive") AND ("breast cancer" OR "mammary carcinoma") AND ("brain metastasis" OR "cerebral metastasis" OR "central nervous system metastasis" OR "CNS metastasis") AND ("predictive factor" OR "biomarker" OR "risk factor" OR "prognostic factor")*. This search yielded a total of 9,660 articles. Using Zotero for reference management and duplicate removal, articles were screened in three stages: title and abstract review, full-text eligibility assessment, and final selection. After applying inclusion and exclusion criteria, 20 articles were deemed eligible for full review and synthesis. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram was constructed to illustrate the study selection process.

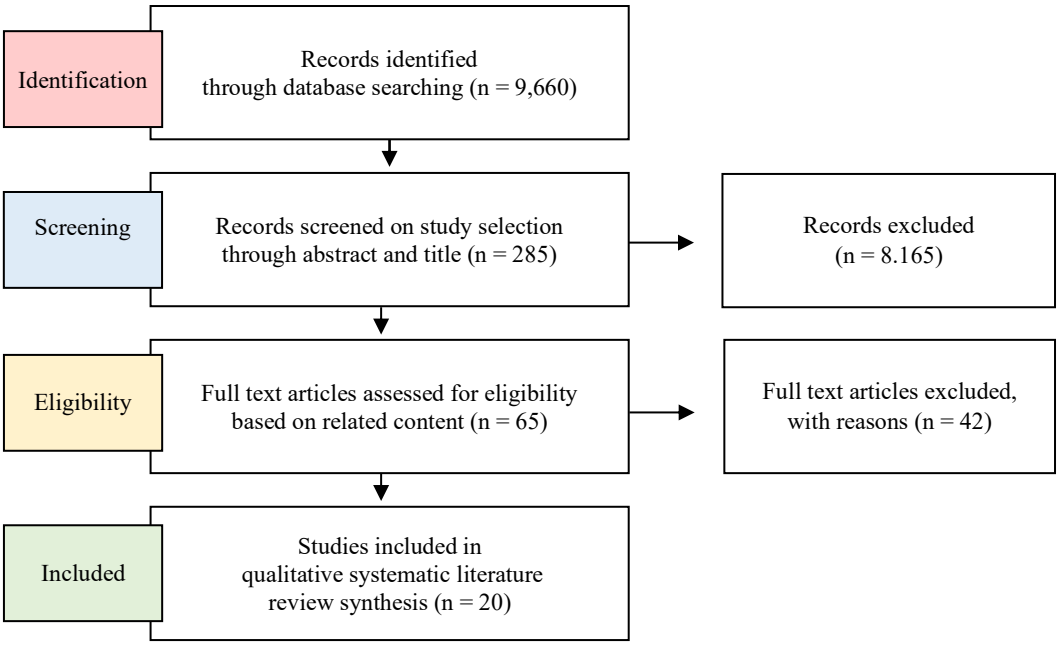

Figure 1. PRISMA Flow Diagram

After completing the PRISMA screening process, a total of 20 primary research articles were included in the final systematic review synthesis. These studies provided empirical data on HER2-positive breast cancer and its association with brain metastases. A structured data extraction was performed to obtain information on study design, patient population, HER2 status classification, treatment regimen, metastasis profile, and key clinical outcomes.

Subsequently, a bibliometric analysis was conducted using VOSviewer software, focusing exclusively on the 20 primary articles. The metadata of these articles were imported in .csv format to generate visual maps of keyword co-occurrence, author collaboration networks, and citation patterns. This approach enabled the identification of dominant research themes, frequently associated biomarkers (e.g., HER2, trastuzumab, tucatinib), and emerging treatment strategies relevant to CNS involvement in breast cancer. The use of VOSviewer enhanced the review by highlighting influential contributors and clustering thematic research directions within the selected primary evidence base.

RESULTS

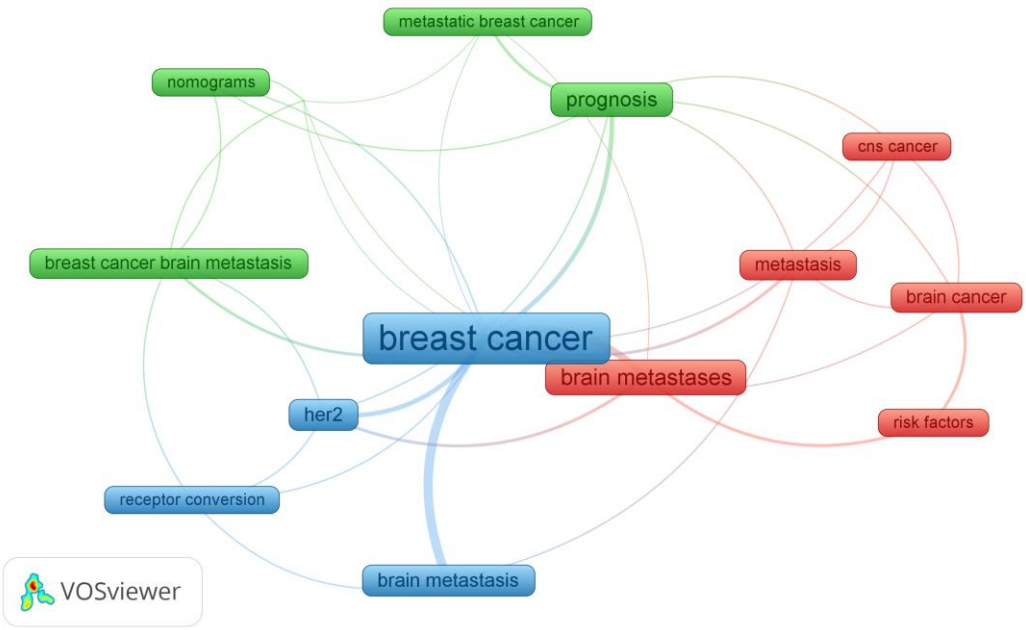

Figure 2. Keyword Co-occurrence Visualization of Primary Studies on HER2-Positive Breast Cancer and Brain Metastases (VOSviewer Analysis)

The VOSviewer visualization reveals the thematic structure of research topics associated with HER2-positive breast cancer and brain metastases, as identified through keyword co-occurrence mapping. The central term “breast cancer” dominates the network, closely connected with “brain metastasis”, “HER2”, and “brain metastases” suggesting a strong focus on CNS involvement within HER2-enriched subtypes. Additional keywords such as “receptor conversion” and “nomograms” indicate research interests in molecular mechanisms and predictive modeling. The blue cluster captures molecular and clinical oncology terms, underscoring the biologic underpinnings of metastatic spread and HER2’s prognostic relevance.

The green cluster encompasses terms like “prognosis”, “metastatic breast cancer”, and “breast cancer brain metastasis” reflecting studies evaluating survival outcomes and risk stratification. Meanwhile, the red cluster, including “cns cancer”, “risk factors”, and “brain cancer” suggests broader neuro-oncology perspectives, emphasizing the clinical consequences of brain metastases and the need for early detection strategies. Overall, this bibliometric visualization illustrates not only the interdisciplinary nature of HER2-related metastasis research but also the thematic concentration on prognosis, treatment prediction, and CNS disease burden.

Table 2. Summary of Primary Studies

Author	Population	Outcome	Findings
Hayashi et al. (2015)	HER2+ breast cancer with brain metastasis	Prognostic factors	Shorter survival associated with multiple brain metastases and poor performance status
Maurer et al. (2018)	HER2+ breast cancer patients	Risk factors for brain metastases	Younger age, high tumor grade, and visceral metastases increase brain metastasis risk
Takada et al. (2018)	HER2+ patients treated with neoadjuvant chemo + trastuzumab	Prediction of brain metastasis	Machine learning model accurately predicts disease-free survival and brain metastasis
Morikawa et al. (2018)	HER2+ breast cancer with brain metastases	Prognostic indicators	Earlier CNS imaging and detection may improve survival outcomes
Chen et al. (2025)	HER2+ breast cancer patients	Risk stratification model	Model effectively predicts brain metastasis risk to guide treatment decisions
Terry et al. (2025)	Breast cancer patients over 20 years	CNS screening predictors	Identified age and tumor subtype as predictors for early screening
Kim et al. (2018)	Breast cancer patients in SEER database	Subtype-based prognosis	HER2-enriched subtype had the highest incidence of brain metastasis
Michel et al. (2021)	Breast cancer with brain metastases	HER2 receptor conversion	Receptor conversion correlated with improved survival
Nie et al. (2023)	Postoperative brain metastasis patients	Prognostic factors	Performance status and extracranial metastases predicted poor survival
Azim et al. (2018)	HER2+ breast cancer patients	Biology vs stage in predicting brain metastasis	Tumor biology more predictive than clinical stage
Jung et al. (2018)	HER2+ breast cancer brain metastases	Biomarker discordance	High discordance between primary and brain metastases noted
Lyu & Luo (2021)	HER2+ with bone metastasis	Survival prediction	HER2 status retained prognostic value even in bone metastasis cases
Anwar et al. (2021)	HER2+ MBC with brain metastasis	Therapy outcome	Pyrotinib showed clinical benefit with manageable toxicity
Karakaya et al. (2021)	HER2+ breast cancer with brain metastasis	Clinical outcomes	KPS score and number of lesions affected survival
Avila et al. (2024)	Patients with brain metastasis at BC diagnosis	Survival trends	Improved survival over time with newer therapies
Bryan et al. (2021)	HER2+ and TNBC patients	Molecular mechanisms	Identified shared genes associated with brain metastasis

Author	Population	Outcome	Findings
Cacho-Díaz et al. (2024)	HR+ breast cancer patients	Risk prediction model	Model accurately stratified risk of brain metastasis
Ferraro et al. (2022)	Early HER2+ breast cancer patients	Incidence of brain metastases	Trastuzumab and pertuzumab showed CNS protective effect
Rashid et al. (2025)	HER2+ and non-HER2+ brain metastases patients	Surgical outcomes	HER2+ subtype had better intracranial control post-surgery
Wu et al. (2023)	MBC patients	Prediction model validation	Model effectively validated brain metastases risk

A total of twenty primary studies were included in this systematic review. These studies provided empirical findings on clinical outcomes, prognostic markers, predictive models, and therapeutic efficacy related to HER2-positive breast cancer with brain metastases. The findings are categorized into four main themes: prognostic indicators, risk prediction models, therapeutic responses, and molecular mechanisms.

Several studies identified key prognostic factors that affect survival or brain metastasis occurrence. Hayashi et al. (2015) found that multiple brain metastases and poor performance status were significantly associated with reduced survival.[12] Maurer et al. (2018) reported that younger age, high tumor grade, and visceral metastases increased the risk of CNS involvement in HER2-positive patients.[10] Morikawa et al. (2018) observed that earlier CNS imaging was associated with better survival outcomes, suggesting potential benefits from prompt diagnosis.[6] Karakaya et al. (2021)demonstrated that lower Karnofsky Performance Scores (KPS) and higher lesion counts predicted poorer survival outcomes.[22] Nie et al. (2023) confirmed that extracranial metastases and reduced functional status were negative prognostic factors in patients undergoing surgery for brain metastases.[17]

Several studies developed predictive models to estimate the likelihood of brain metastasis or survival. Takada et al. (2018) applied a machine learning-based prediction model on patients receiving neoadjuvant trastuzumab, which showed strong accuracy in forecasting disease-free survival and CNS recurrence.[13] Chen et al. (2025) proposed a stratification model that effectively classified patients into high- and low-risk groups for brain metastasis.[14] In a longitudinal study, Terry et al. (2025), identified younger age and HER2-enriched subtype as early screening predictors.[15] Wu et al. (2023) validated a risk prediction tool in a metastatic population with favorable predictive metrics.[4] Cacho-Díaz (2024) demonstrated that their model accurately stratified brain metastasis risk in hormone receptor-positive patients, although the methodology was adaptable to HER2-positive cohorts.[25]

In terms of treatment effectiveness, Anwar et al. (2021) found that pyrotinib provided meaningful clinical responses in HER2-positive patients with brain metastases, with manageable toxicity profiles.[21] Ferraro et al. (2022) showed that early-stage patients receiving neoadjuvant trastuzumab and pertuzumab had lower rates of CNS involvement, indicating a protective effect. [23] Avila et al. (2024) observed an overall improvement in survival trends over the past decade in patients presenting brain metastases at initial diagnosis.[26] Rashid et al. (2025) reported that HER2-positive patients undergoing neurosurgical resection had better intracranial control and progression-free survival compared to those with other subtypes.[3] Lyu and Luo (2021) further supported the prognostic value of HER2 expression, even in patients with bone metastases. [29]

Several studies have explored molecular and pathological changes associated with HER2-positive brain metastases. Bryan et al. (2021) identified shared gene expression patterns between HER2-positive and triple-negative breast cancer cases, suggesting overlapping metastatic pathways to the CNS.[24] Michel et al. (2021) discovered that HER2 receptor conversion between primary and brain lesions occurred frequently and was associated with longer survival.[16] Azim et al. (2018) found that tumor biology, particularly HER2 status, was a stronger predictor of brain metastasis than clinical stage.[18] Jung et al. (2018) noted significant discordance in ER, PR, and HER2 biomarkers between primary tumors and CNS lesions, indicating potential changes in tumor phenotype after CNS colonization.[19]

HER2 positivity significantly correlates with the development of brain metastases in breast cancer. Studies by Kim et al. (2018), Maurer et al. (2018), and Azim et al. (2018), consistently identified HER2-enriched tumors as having the highest CNS metastatic propensity.[9,10,18] Additional clinical predictors such as younger age, high tumor grade, and visceral metastases further compound this risk.[6,15] Hayashi et al. (2015) and Karakaya et al. (2021) emphasized that lower Karnofsky Performance Scores (KPS) and higher lesion counts significantly reduce survival.[12,22] Nie et al. (2023) reinforced that extracranial metastases are independently associated with poor outcomes in postoperative BM patients.[17]

The review identifies an emerging trend in the use of predictive algorithms. Takada et al. (2018) utilized machine learning techniques to forecast brain metastases and disease-free survival with high accuracy.[13] Wu et al. (2023) externally validated similar predictive models, demonstrating robust performance across metastatic populations.[4] Additionally, Chen et al. (2025) and Cacho-Díaz et al. (2024) provided frameworks for individualized CNS risk stratification based on HER2 expression and

tumor biology.[14,25]. Furthermore, Hackshaw et al. (2021) and Terry et al. (2025) supported incorporating algorithmic prediction tools into early CNS surveillance strategies for HER2-positive patients.[27,15]

Discordance in receptor expression between primary tumors and brain metastases remains a significant clinical challenge. Jung et al. (2018) and Michel et al. (2021) demonstrated frequent HER2, ER, and PR conversion post-metastasis, affecting treatment strategies.[19,16] Warrior et al. (2023) recommended repeated biomarker assessment, including cerebrospinal fluid (CSF) sampling, to better guide CNS-targeted therapies.[28]

Targeted therapies such as trastuzumab, pertuzumab, pyrotinib, and tucatinib have redefined CNS management in HER2+ disease. Ferraro et al. (2022) showed a preventive effect of dual HER2 blockade during neoadjuvant treatment.[26] Anwar et al. (2021) and Avila et al. (2024) highlighted improved intracranial control and survival with these agents.[21,23] Rashid et al. (2025) confirmed superior surgical outcomes in HER2+ subtypes,[3] while Lyu and Luo (2021) underscored HER2's retained prognostic value even with bone metastasis.[20]

Molecular pathways such as PI3K/Akt signaling and integrin-mediated adhesion were implicated in CNS dissemination.[24,29] Bibliometric analysis using VOSviewer of the 20 primary studies revealed dominant keyword clusters including “breast cancer”, “brain metastases”, “HER2”, and “prognosis”. These clusters highlighted research interests in CNS disease progression, predictive biomarkers, and the clinical utility of targeted therapies. However, the relatively low density of inter-author linkages and distinct thematic clusters suggest a fragmented research landscape lacking cross-disciplinary integration.

The included studies were predominantly retrospective, subject to selection bias and heterogeneous in defining HER2-low categories. Few studies assessed leptomeningeal metastases separately or incorporated liquid biopsy in CNS diagnostics. As highlighted by Passalacqua et al. (2023) and Stavrou et al. (2021) personalized CNS surveillance and HER2-guided systemic therapy warrant standardization. Future research should prioritize multicenter prospective trials, biomarker harmonization, and CNS-penetrant agent development.[7,30]

CONCLUSION

This systematic literature review concludes that HER2-positive breast cancer is strongly associated with an elevated risk of brain metastases, with consistent clinical and molecular evidence supporting its role as a predictive biomarker. The findings demonstrate that younger age, high tumor grade, visceral metastases, and HER2-enriched subtypes contribute to increased CNS involvement.

Furthermore, advances in machine learning models and HER2-targeted therapies, such as trastuzumab, pyrotinib, and tucatinib, have improved patient outcomes through more precise stratification and intracranial control. Despite these advancements, heterogeneity in HER2 expression between primary and metastatic lesions, as well as limited prospective data, hinder the development of standardized surveillance protocols. The integration of bibliometric mapping further revealed the fragmented nature of current research, highlighting the need for more coordinated and interdisciplinary investigation.

Based on the synthesis of current evidence, several key recommendations are proposed. First, HER2 status should be systematically incorporated into risk stratification protocols for early CNS monitoring in breast cancer patients. Second, routine biomarker re-evaluation particularly in CNS lesions should be emphasized to guide treatment adjustments accurately. Third, clinical adoption of predictive models should be encouraged to identify high-risk patients for prophylactic or early CNS-targeted interventions. Fourth, future research should prioritize prospective, multicenter studies with harmonized definitions of HER2 subtypes and endpoints related to brain metastases. Lastly, collaboration across oncology, neurology, radiology, and pathology is essential to establish integrated CNS management strategies tailored for the HER2-positive breast cancer population.

Conflicts of Interest

There was no conflict of interest.

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