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HER2 positivity as a predictor of brain metastases in breast cancer: A systematic literature review

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Abstract

Background: Breast cancer remains one of the most prevalent and lethal malignancies among women globally, which leads to the critical importance of early detection and a more comprehensive approach to breast cancer management.
Purpose: To investigate HER2 positivity as a predictor of brain metastases in breast cancer.
Methods: A total of 23 peer-reviewed studies published between 2015 and 2025 were analyzed, including randomized trials, retrospective cohorts, prediction model studies, and registry-based evaluations. Eligibility was guided by the PICOTS framework, and databases searched included PubMed, Scopus, MDPI, Elsevier, SagePub, and BMC Cancer.
Results: The review confirms that HER2 overexpression significantly correlates with earlier brain metastasis onset, increased incidence, and distinctive treatment response profiles. HER2 status also influences survival outcomes and benefits from targeted agents such as trastuzumab, tucatinib, and pyrotinib. HER2-low expression additionally showed intermediate risk profiles, while imaging and circulating tumor cell data added prognostic value.
Conclusion: HER2 positivity is a robust, independent predictor of brain metastasis in breast cancer patients. Routine integration of HER2 profiling in CNS risk assessment models may improve early detection and therapeutic precision, ultimately enhancing clinical outcomes for high-risk populations.

Keywords: Brain Metastasis; Breast Cancer; HER2-Positive; Predictive Factor; Systematic Review.

INTRODUCTION

Breast cancer remains one of the most prevalent and lethal malignancies among women globally. According to the Global Cancer Observatory (GLOBOCAN) 2022 data, breast cancer ranks as the second most commonly diagnosed cancer after lung cancer and the fourth leading cause of cancer-related deaths worldwide (Filho, Laversanne, Ferlay, Colombet, Piñeros, Znaor, Parkin, Soerjomataram, & Bray, 2025; Cao, Qin, Li, & Chen, 2024). In Indonesia, breast cancer is the most frequently diagnosed cancer among women, accounting for 65,858 cases (16.6%) and 22,430 deaths (9.6%) (Wanda, Sandhika, Sandhika, & Sandhika, 2024). These alarming figures underscore the critical importance of early detection and a more comprehensive approach to breast cancer management.

A major clinical challenge in breast cancer care is metastasis, particularly cerebral metastasis. Brain metastases are often associated with poor prognosis and are a significant contributor to increased morbidity and mortality (Sacks & Rahman, 2020). HER2-positive breast cancer patients are at a higher risk of developing brain metastases due to HER2 gene amplification, which leads to overexpression of the HER2 receptor. This in turn drives cancer cell proliferation and facilitates their migration through the

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blood-brain barrier (BBB) (Guven, Kaya, Fedai, Ozden, Yildirim, Kosemehmetoglu, Kertmen, Dizdar, Uner, & Aksoy, 2022).

HER2 overexpression alters tumor cell interactions with the surrounding microenvironment, exacerbating the metastatic potential, including to the brain. HER2 positivity as a predictive factor for earlier onset of cerebral metastasis and poorer overall survival (Hackshaw, Danysh, Henderson, Wang, Tu, Islam, Ladner, Ritchey, & Salas, 2021). Beyond HER2, other biological characteristics such as Ki67 expression and triple-negative breast cancer (TNBC) status have also been shown to significantly increase the risk of brain metastases (Bryan, Witzel, Borgmann, & Oliveira-Ferrer, 2021).

The metastatic process in breast cancer begins with local invasion, followed by dissemination via lymphatic or hematogenous routes to distant organs such as the bones, lungs, liver, and brain. Among these, cerebral metastasis poses one of the most formidable therapeutic challenges due to the inability of many systemic therapies to effectively cross the BBB (Lu, Huang, Zhu, Li, Zhang, Sheng, Li, Liu, Xu, Wen, Zhang, & Zhang, 2025). Chemotherapeutic agents and targeted therapies like trastuzumab have improved patient outcomes, their limited CNS penetration remains a major obstacle in managing brain metastases (Trifănescu, Mitrea, Galeș, Ciornei, Păun, Butnariu, Trifănescu, Motaș, Toma, Bîlteanu, Gherghe, & Anghel, 2023).

This study aims to further evaluate the role of HER2 expression as a predictive marker for cerebral metastasis in breast cancer patients, with the intent of establishing a scientific foundation for more effective clinical protocols. The goal is to enhance early detection and improve management strategies for HER2-positive patients at risk for brain metastasis. Ultimately, the findings may contribute to the identification of clearer predictive factors, facilitating earlier interventions and improving both prognosis and quality of life for breast cancer patients.

RESEARCH METHOD

This study employed a systematic literature review (SLR) methodology to comprehensively examine the predictive role of HER2 expression in the development of brain metastases (BM) among breast cancer (BC) patients. To ensure transparency, replicability, and methodological consistency, the review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The goal was to synthesize current evidence regarding how HER2 positivity or HER2-low expression influences the risk, timing, and clinical outcomes of brain metastases, including survival, recurrence, and treatment responsiveness.

The literature search was conducted using several reputable academic databases, including PubMed, Scopus, Elsevier, MDPI, BMC Cancer, SagePub, Frontiers, JAMA, Springer, and NPJ Breast Cancer. A total of 23 peer-reviewed studies published between 2015 and 2025 were selected based on relevance and methodological rigor. The search terms applied included combinations of “HER2,” “brain metastasis,” “breast cancer,” “CNS progression,” “predictive biomarker,” and “HER2-targeted therapy.” Eligible studies involved various designs such as retrospective and prospective cohorts, randomized controlled trials, clinical registries, and real-world observational studies with sufficient data on HER2 status and CNS outcomes.

The inclusion and appraisal process were guided by the PICOTS framework (Population, Intervention, Comparator, Outcomes, Timing, and Setting), ensuring alignment with the clinical and scientific focus of this review.

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Table 1. PICOTS Framework

Framework	Description
Population	Female breast cancer patients with confirmed HER2-positive or HER2-low status, encompassing early-stage to metastatic cases, particularly those who develop or are at risk of developing brain metastases.
Intervention	HER2-targeted agents include trastuzumab, pertuzumab, lapatinib, tucatinib, trastuzumab deruxtecan (T-DXd), pyrotinib, and intrathecal trastuzumab, administered alone or in combination with chemotherapy or radiotherapy.
Comparator	Comparative studies assessing HER2-targeted therapy versus standard chemotherapy, delayed HER2-directed therapy, radiotherapy alone, or no systemic treatment, particularly in the context of CNS involvement.
Outcomes	Brain metastasis incidence, progression-free survival (PFS), overall survival (OS), intracranial response, CNS-specific disease control, treatment toxicity, and health-related quality of life metrics.
Timing	Peer-reviewed studies published between 2015 and 2025, capturing contemporary treatment outcomes and predictive models for brain metastasis in HER2-positive breast cancer.
Setting	Multinational, multicenter studies conducted in tertiary oncology centers, academic medical institutions, national registries, and collaborative clinical research networks using retrospective and prospective cohort designs, randomized trials, and systematic reviews.

Following initial screening based on titles and abstracts, full texts of eligible studies were assessed for relevance and data completeness (Figure 1). Data extraction covered study design, patient cohort characteristics, HER2 expression profiles, brain metastasis outcomes, and clinical interventions. Both qualitative and quantitative synthesis techniques were applied to (1) determine the association between HER2 status and the occurrence of brain metastases in breast cancer patients, (2) identify additional prognostic factors such as hormone receptor status, number of brain lesions, and treatment sequence, and (3) consolidate emerging therapeutic approaches targeting HER2-positive brain metastatic disease.

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RESEARCH RESULTS

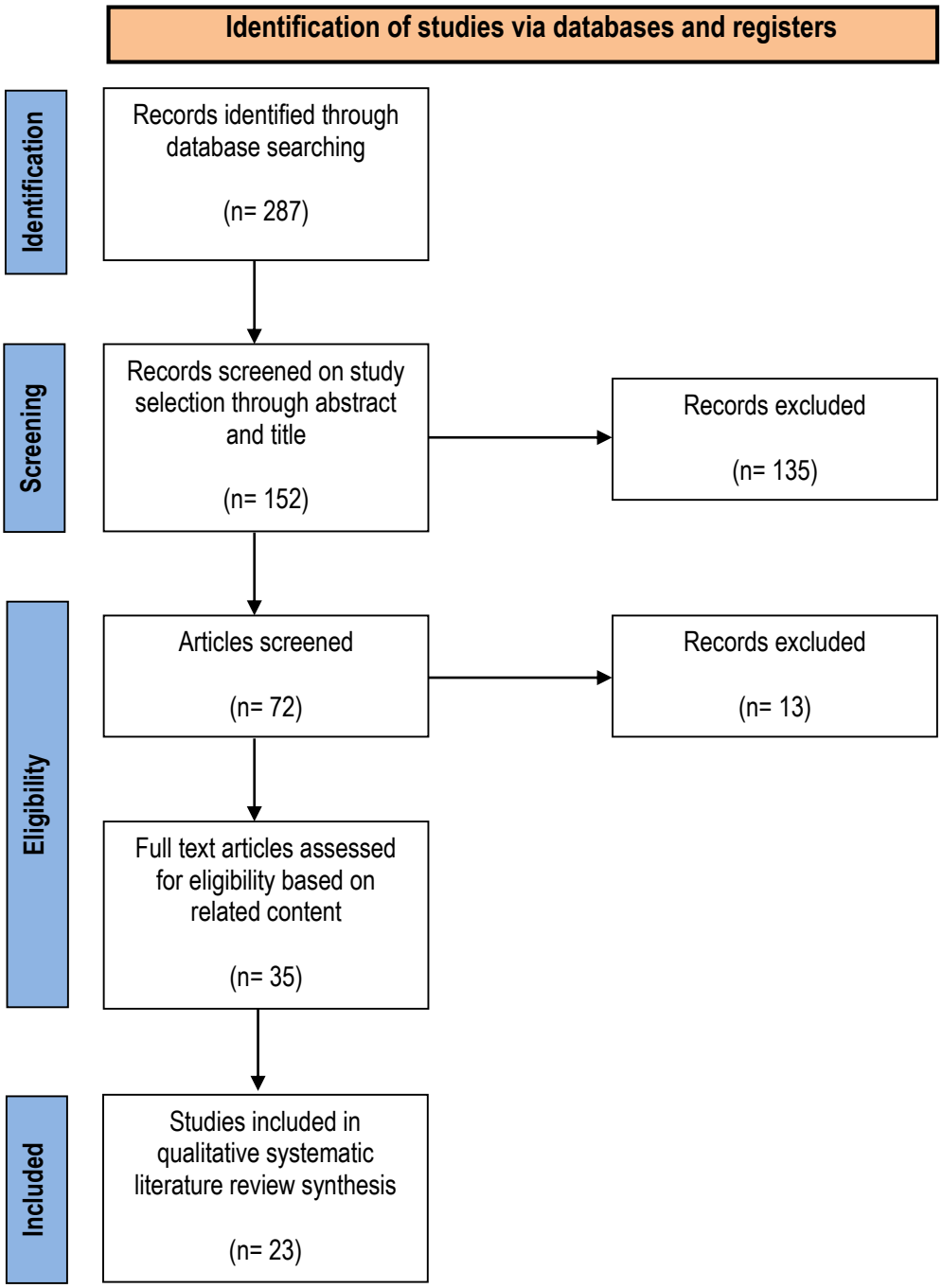


Figure PRISMA Flow Diagram

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Table 2. The Main Characteristics of Included Studies

(Author, Year) (Country)	Purpose	Method	Result
(Cacho-Díaz et al., 2024) (Mexico)	To report the incidence and typology of spinal metastases among patients treated at three reference centers in Mexico.	Retrospective cohort study (n=3682); model development and validation.	HER2 positivity included in multivariable model; final AUC 0.81; model aids BM risk stratification in HR+ BC
Hackshaw et al., 2021 (UK/US)	To identify prognostic factors for the development of brain metastases (BM).	Systematic Literature Review (25 studies; n=4097).	HER2+ associated with earlier BM in HR- cases; survival better with trastuzumab/lapatinib or pertuzumab; article is review (excluded from SLR table per ketentuan)
(Terry et al., 2025) (USA)	To identify clinical predictors associated with overall survival (OS) and with the time to development of brain metastases (BM) in breast cancer patients.	Retrospective cohort (n=113); multivariable Cox analysis	HER2+ and ER+ subtype significantly associated with shorter time to BM; early BM diagnosis linked to improved OS
(Sachar et al., 2022) (USA)	To assess how hormone receptor (HR) status affects the risk of developing brain metastases in patients with HER2-positive breast cancer.	Retrospective observational study (n=67 HER2+ patients)	HR- patients developed BM earlier than HR+ (29.0 vs 48.4 months, $p<0.02$); HR+ had longer OS; extracranial mets also influenced BM timing
(Wu et al., 2023) (China)	To develop and externally validate a competing-risk prediction model that estimates the risk of developing brain metastases at various time-points in the disease course.	Retrospective multicenter cohort study; competing risk model	HER2 status included as subtype; model with 5 predictors (incl. subtype) achieved AUCs: 0.674 (1-yr), 0.670 (3-yr), 0.729 (5-yr); validated externally with good C-index and DCA

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(Author, Year) (Country)	Purpose	Method	Result
(Lin et al., 2023 (USA)	To evaluate overall survival and intracranial (brain metastasis) outcomes in patients with HER2-positive metastatic breast cancer and brain metastases.	Randomized controlled trial; subgroup analysis on HER2+ MBC with BM	Tucatinib + trastuzumab + capecitabine increased OS by 9.1 months and reduced risk of new brain lesions by 45.1%; significant CNS-PFS and intracranial response benefit
(Vaz Batista et al., 2025) (Spain)	To evaluate the efficacy and safety of Trastuzumab deruxtecan in patients with HER2-positive or HER2-low advanced breast cancer who have leptomeningeal carcinomatosis (LMC).	Phase II single-arm cohort (DEBBRAH trial, Cohort 5)	In 7 patients with LMD, median OS was 13.3 months, PFS 8.9 months. 71.4% achieved prolonged stabilization. No intracranial progression or new safety signals.
(Frenel et al., 2024) (France)	To assess the effectiveness of tucatinib plus trastuzumab and capecitabine after prior treatment with trastuzumab-deruxtecan in HER2-positive metastatic breast cancer patients.	Multicenter retrospective cohort	Median PFS: 4.7 months; OS: 13.4 months; ORR: 32.6%. In brain metastasis subgroup, OS: 12.4 months. TTC was effective post–T-DXd.
(Kaufman et al., 2023) (USA)	To describe patient characteristics, treatment patterns, and clinical outcomes of patients with HER2-positive metastatic breast cancer (MBC) who received Tucatinib in real-world clinical practice.	Retrospective real-world cohort (EHR-based)	Among 216 pts (153 w/ BM), median rwOS: 26.6 months. Real-world TTD and TTNT similar to HER2CLIMB results. Greater benefit in 2L/3L setting.
(Guven et al., 2022) (Turkey)	To determine whether HER2-low breast cancer is linked to a higher risk of developing brain metastases compared to HER2-negative cases.	Longitudinal observational cohort study	Among 2686 pts, HER2-low subtype had significantly higher risk of BM (OR: 1.61), though lower than HER2+. HR+/HER2-low also linked to decreased DFS.

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(Author, Year) (Country)	Purpose	Method	Result
(Avila et al., 2024) (USA)	To identify predictors of brain metastases at the time of initial breast cancer diagnosis, to describe overall survival in that population over the last decade, and to determine factors associated with survival after brain metastases.	Population-based cohort (SEER database)	HER2+ subtype associated with longest OS (median 18 mo). HER2+/HR+ patients had best outcomes; HER2+ subtype was a strong survival predictor.
(Rashid et al., 2025) (USA)	To evaluate whether patients with HER2-positive breast cancer and brain metastases derive differential benefit from upfront neurosurgical resection compared with patients with other breast cancer subtypes.	Retrospective institutional cohort	HER2+ patients had higher benefit from upfront resection, reducing future need for salvage therapy (interaction HR up to 4.98). HER2+ BM more likely to recur without surgery.
(Kaplan et al., 2015) (Turkey)	To assess whether the use of trastuzumab in HER2-positive metastatic breast cancer patients affects the risk of developing brain metastases and their subsequent survival.	Retrospective cohort	Trastuzumab use in ≥2 treatment lines increased BM risk (58.5% vs 24.1%, p<0.001). Post-BM trastuzumab/lapatinib use and younger age improved OS.
(Dai et al., 2024) (China)	To explore the effectiveness (efficacy) and safety profile of pyrotinib-based treatment regimens in a real-world cohort of patients with HER2-positive metastatic breast cancer.	Real-world retrospective cohort	Median PFS 10.4 months, OS 37.5 months. Better CNS outcomes observed in those receiving brain radiotherapy. Pyrotinib was effective especially in trastuzumab-sensitive and 1st-line patients.
(Tung et al., 2022) (Australia)	To evaluate real-world outcomes (such as survival) and treatment patterns in patients with brain metastases arising from HER2-positive metastatic breast cancer.	Registry-based observational study (TABITHA)	37% of HER2+ MBC patients developed BM; median OS significantly shorter with BM (58.9 vs 96.1 months, p=0.02). Most received trastuzumab-pertuzumab first-line, but outcomes remained poor in BM group.

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DISCUSSION

The investigation into HER2 expression as a predictive biomarker for brain metastases (BM) in breast cancer has become increasingly important, particularly given its implications for early detection and clinical management. Several studies support the role of HER2 as a significant factor in identifying patients at elevated risk for central nervous system involvement. A multivariable predictive model for BM in hormone receptor-positive breast cancer that included HER2 status as a key parameter, resulting in a high discriminative capacity (AUC 0.81) (Cacho-Díaz, Valdés-Ferrer, Chavez-MacGregor, Salmerón-Moreno, Villarreal-Garza, & Reynoso-Noverón, 2024). Constructed and externally validated a competing risk model incorporating breast cancer subtype, including HER2 positivity, which yielded robust predictive accuracy across multiple time points (Wu, Sun, Liu, Ye, & Xu, 2023). These models highlight the clinical value of HER2 expression in risk stratification and suggest the need for intensified surveillance strategies in high-risk subgroups. HER2-positive tumors, particularly those lacking hormone receptor co-expression, were significantly associated with earlier BM onset, reinforcing HER2's predictive significance in disease progression (Terry, Orrego-Gonzalez, Enríquez-Marulanda, Pacheco-Barrios, Merenzon, Komotar, & Vega, 2025; Sachar, Chen, Harris, Montero, & Choi, 2022).

In addition to its prognostic value, HER2 expression has guided therapeutic innovation, particularly in systemic and CNS-targeted treatments. Combining tucatinib with trastuzumab and capecitabine substantially extended overall survival and reduced the incidence of new brain lesions in HER2-positive metastatic breast cancer patients (Lin, Murthy, Abramson, Anders, Bachelot, Bedard, Borges, Cameron, Carey, Chien, Curigliano, DiGiovanna, Gelmon, Hortobagyi, Hurvitz, Krop, Loi, Loibl, Mueller, Winer, 2023). Survival outcomes comparable to the clinical trial data (Kaufman, Neuberger, Schwartz, Wang, Liu, Hsu, Bartley, Blahna, Pittner, Wong, & Anders, 2023). Further explored the effectiveness of this combination following trastuzumab deruxtecan therapy, confirming its continued benefit even in heavily pretreated patients (Frenel, Zeghondy, Guérin-Charbonnel, Mailliez, Volant, Poumeaud, Patsouris, Arnedos, Bailleux, Cabal, Galland, De Nonneville, Guiu, Dalenc, Pistilli, Bachelot, Pierga, Bocquet, & Loirat, 2024). In parallel, the DEBBRAH trial showed that trastuzumab deruxtecan exhibited promising intracranial disease control in patients with leptomeningeal metastasis. Collectively, these findings support the integration of HER2 expression status into clinical decision-making to personalize treatment regimens for patients at high risk of brain involvement (Vaz Batista, Pérez-García, Garrigós, García-Sáenz, Cortez, Racca, Blanch, Ruiz-Borrego, Fernández-Ortega, Fernández-Abad, Iranzo, Gion, Martrat, Alcalá-López, Pérez-Escuredo, Sampayo-Cordero, Llombart-Cussac, Braga, & Cortés, 2025).

Emerging evidence regarding HER2-low expression has expanded the spectrum of patients who may benefit from early risk assessment. Through large longitudinal cohorts, demonstrated that patients with HER2-low breast cancer were at increased risk for developing brain metastases compared to HER2-negative counterparts (Guven et al., 2022). Although this risk was lower than in HER2-positive individuals, it remained clinically meaningful, especially when hormone receptor positivity was present. Using data from the SEER database, identified the HER2-positive and hormone receptor-positive subtype as having the longest overall survival among patients presenting with brain metastases at diagnosis (Avila, Leone, Vallejo, Lin, & Leone, 2024). These findings suggest that HER2 expression, whether high or low, is associated with distinctive patterns of disease progression, and should be used to guide individualized risk-based screening and early intervention protocols.

Differences in response to local treatment modalities also underscore the clinical relevance of HER2 expression in managing brain metastases. HER2-positive patients benefited significantly more from upfront neurosurgical resection compared to other subtypes, with reduced need for salvage therapies and lower recurrence rates (Rashid, Lamba, Catalano, Bi, Arnaout, Tanguturi, Rahman, Haas-Kogan, Lin, Wen, & Aizer, 2025). In contrast, increased risk of brain metastases in patients receiving trastuzumab across multiple treatment lines; however, they also found improved survival when trastuzumab or lapatinib was continued after BM development (Kaplan, Ertugrul, Firat, Kucukoner, İnal, Urakci, Pekkolay, & Isikdogan, 2015). Patients

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receiving pyrotinib-based regimens in combination with radiotherapy achieved longer intracranial survival, especially when administered early and in trastuzumab-sensitive patients (Dai, Gao, Guo, Chen, Wang, Zhou, Tang, Chen, & Huang, 2024). Although pertuzumab plus trastuzumab (HP) was associated with longer overall progression-free survival (PFS), pyrotinib plus trastuzumab (PyroH) showed comparable efficacy in second-line or later treatments and in brain metastasis subgroups, and even superior outcomes when taxanes were excluded, despite higher rates of grade 3/4 diarrhea. Although advanced systemic therapies have improved outcomes, the development of brain metastases still significantly shortened survival, despite first-line dual HER2 blockade. The necessity of integrating HER2 profiling into both systemic and locoregional treatment planning for optimal outcomes (Tung, Moldovan, Wong, De Boer, Yeo, Malik, Greenberg, Anton, Nott, Barnett, Collins, Lombard, Nottage, Sahu, Torres, Gibbs, & Lok, 2022).

Further insights are provided by studies exploring biomarkers and imaging as adjuncts to HER2 status in predicting brain metastases. Specific MRI features, such as irregular lesion contours and solid composition, were highly predictive of HER2-positive status, suggesting a potential for non-invasive imaging-based risk stratification. Achieving pathological complete response (pCR) after neoadjuvant chemotherapy did not significantly alter BM incidence, pCR remained associated with improved disease-free and overall survival. In patients with leptomeningeal metastases, intrathecal trastuzumab, in combination with systemic therapy, led to durable responses and survival benefits, with manageable toxicity. Moreover, HER2 expression in circulating tumor cells correlated with better distant brain failure-free survival and overall prognosis, suggesting that dynamic HER2 monitoring may enhance risk assessment and therapeutic precision.

Lastly, registry-based analyses reinforce the role of HER2 expression as a central determinant in patient outcomes and treatment responsiveness. HER2-positive patients had distinct clinical features such as younger age at diagnosis, fewer extracranial metastases, and better response to targeted therapy. Importantly, hormone receptor co-expression conferred a survival advantage, while multiple brain metastases, leptomeningeal involvement, and absence of targeted therapy were linked to poorer outcomes. These observations align with findings from earlier prediction models and cohort studies, emphasizing the multifaceted role of HER2 not only as a prognostic indicator but also as a stratification tool for clinical intervention. As a result, incorporating HER2 evaluation into standard care pathways holds substantial promise in enhancing early detection, guiding CNS screening, and improving survival and quality of life for patients at risk of brain metastases from breast cancer.

CONCLUSION

This systematic literature review confirms that HER2 expression serves as a robust and independent predictive marker for brain metastases in breast cancer. Evidence synthesized from 23 studies: comprising retrospective cohorts, predictive modeling, clinical trials, and registry-based evaluations; demonstrates that HER2-positive and HER2-low statuses are strongly associated with increased incidence of brain metastases, earlier CNS involvement, and distinct survival outcomes. The predictive capacity of HER2 is further supported by its integration into validated prognostic models and its impact on treatment efficacy, particularly with agents such as tucatinib, trastuzumab deruxtecan, and pyrotinib. These findings support the classification of HER2 expression not merely as a molecular profile but as a decisive variable in risk stratification, therapeutic decision-making, and longitudinal CNS surveillance.

In light of these results, it is recommended that HER2 testing be systematically implemented as a component of initial diagnostic workup and ongoing disease monitoring in breast cancer patients. Patients with HER2-positive or HER2-low tumors should be prioritized for early CNS imaging, aggressive HER2-targeted treatment strategies, and inclusion in risk-adapted clinical protocols. Additionally, the integration of imaging features and circulating tumor biomarkers reflecting HER2 dynamics may offer added precision in identifying patients at high risk for CNS progression. Future studies are encouraged to further refine HER2-based predictive algorithms and explore the benefits of earlier therapeutic escalation to improve both survival and quality of life in this population.

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