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Prognostic Value of ER, PR, HER2, and Ki-67 in Breast Carcinoma: A Systematic Review and Meta-Analysis

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KEYWORDS

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ABSTRACT:

Background: Breast carcinoma is a biologically heterogeneous disease, and its prognosis is largely influenced by molecular markers such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 proliferation index. These biomarkers not only define intrinsic molecular subtypes but also guide therapeutic decisions. However, their prognostic significance across diverse populations and treatment eras remains variable.

Objectives: To systematically review and quantitatively analyze the prognostic impact of ER, PR, HER2, and Ki-67 expression on overall survival (OS) and disease-free survival (DFS) in patients with breast carcinoma.

Methods: A systematic literature search was conducted in PubMed, Scopus, Embase, and Web of Science databases for studies published between January 2000 and June 2025, following PRISMA 2020 guidelines. Eligible studies included patients with histologically confirmed breast carcinoma and reported hazard ratios (HRs) for OS or DFS based on ER, PR, HER2, or Ki-67 expression. Pooled HRs were calculated using random-effects models (DerSimonian–Laird method). Study quality was assessed with the Newcastle–Ottawa Scale (NOS), and publication bias was evaluated using Egger's test.

Results: Fifty-six studies comprising 42,375 patients were included. ER positivity significantly improved OS (HR = 0.64, 95% CI: 0.55–0.73) and DFS (HR = 0.68, 95% CI: 0.59–0.78). Similarly, PR positivity was associated with better OS (HR = 0.71, 95% CI: 0.62–0.82) and DFS (HR = 0.74, 95% CI: 0.63–0.86). HER2 overexpression correlated with poorer OS (HR = 1.81, 95% CI: 1.54–2.14) and DFS (HR = 1.77, 95% CI: 1.48–2.10). High Ki-67 expression predicted worse OS (HR = 1.94, 95% CI: 1.65–2.28) and DFS (HR = 1.88, 95% CI: 1.58–2.24). Subgroup analyses showed Luminal A tumors had the best prognosis, while Triple-negative and HER2-enriched subtypes had the poorest outcomes. No significant publication bias was detected ($p > 0.05$).

Conclusions: ER and PR positivity are favorable prognostic indicators, whereas HER2 overexpression and high Ki-67 levels predict poorer outcomes in breast carcinoma. The integrated evaluation of these biomarkers remains fundamental for molecular classification, risk stratification, and treatment planning. Standardization of Ki-67 assessment and consistent application of biomarker thresholds are essential to improve prognostic precision in breast cancer management.

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Introduction

Breast carcinoma is the most common malignancy among women worldwide and represents a major public health burden, accounting for approximately 25% of all female cancers and nearly 15% of cancer-related deaths globally (1). Its incidence continues to rise, particularly in developing countries, due to increasing life expectancy, urbanization, and changes in reproductive and lifestyle factors (2). Despite remarkable progress in early detection and multimodal treatment, breast cancer remains a highly heterogeneous disease in terms of its histopathological features, biological behavior, treatment response, and clinical outcomes (3). This heterogeneity underscores the importance of reliable prognostic and predictive biomarkers to guide therapeutic decisions and estimate disease prognosis.

Among the molecular determinants of breast carcinoma, the estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 proliferation index are the most extensively studied and clinically validated biomarkers. Their assessment through immunohistochemistry (IHC) has become an integral part of routine diagnostic and prognostic evaluation (4,5). The expression of these biomarkers not only aids in disease classification but also guides individualized treatment strategies and predicts therapeutic response.

ER and PR are nuclear hormone receptors that regulate gene expression upon binding with estrogen and progesterone, respectively. Their positivity indicates hormone-dependent tumor growth, rendering such tumors responsive to endocrine therapy such as tamoxifen or aromatase inhibitors (6,7). Numerous studies have demonstrated that ER and PR positivity are associated with lower recurrence rates and improved overall and disease-free survival, reflecting the less aggressive biological nature of hormone receptor-positive tumors (8,9). Conversely, the absence of ER and PR expression, as seen in triple-negative breast cancer (TNBC), correlates with poor differentiation, higher proliferation rates, and unfavorable prognosis (10).

HER2, a transmembrane tyrosine kinase receptor encoded by the ERBB2 gene, plays a critical role in cell proliferation and survival pathways. HER2 overexpression or gene amplification occurs in approximately 15-20% of invasive breast cancers and is associated with aggressive tumor behavior, high histological grade, early recurrence, and reduced survival outcomes (11,12). However, the introduction of HER2-targeted therapies, such as trastuzumab and pertuzumab, has dramatically improved the prognosis for HER2-positive patients, transforming this once-lethal subtype into a treatable disease entity (13,14). Despite this progress, variability in HER2 testing methodologies and scoring systems still contributes to inter-laboratory discrepancies in classification and prognostic interpretation (15).

The Ki-67 antigen, a nuclear protein expressed during active phases of the cell cycle but absent in resting (G0) cells, serves as a marker of cellular proliferation (16). A high Ki-67 index reflects rapid tumor growth and has been associated with poor prognosis and early relapse in several studies (17,18). Clinically, Ki-67 is used to differentiate luminal A and luminal B subtypes, with luminal B cancers showing higher proliferation rates and less favorable outcomes (19). However, despite its prognostic significance, the lack of standardized cut-off values and analytical variability in Ki-67 assessment remain major limitations in its routine clinical use (20,21).

Together, ER, PR, HER2, and Ki-67 form the molecular foundation of the intrinsic classification system proposed by Perou et al. and Sorlie et al., which stratifies breast carcinoma into biologically distinct subtypes-Luminal A, Luminal B, HER2-enriched, and Triple-negative (22,23). This classification provides valuable prognostic and predictive information, influencing both systemic therapy choices and expected survival outcomes. Luminal A tumors (ER/PR positive, HER2 negative, low Ki-67) typically exhibit the most favorable prognosis, while triple-negative and HER2-enriched subtypes are associated with poor outcomes and limited targeted therapeutic options (24,25).

Despite the extensive research on these biomarkers, considerable variation exists across studies regarding their prognostic impact, partly due to differences in patient demographics, testing techniques, positivity thresholds, and treatment modalities (26). Furthermore, the evolving therapeutic landscape, particularly the introduction of targeted therapies and adjuvant hormonal

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agents, has altered survival patterns, necessitating an updated synthesis of evidence.

Therefore, this systematic review and meta-analysis aims to comprehensively evaluate the prognostic significance of ER, PR, HER2, and Ki-67 expression in breast carcinoma in relation to overall survival (OS) and disease-free survival (DFS). By integrating results from a broad range of studies, this work seeks to provide a consolidated estimate of their prognostic value and elucidate the relative impact of these biomarkers on breast cancer outcomes in the modern therapeutic era.

Methods

This systematic review and meta-analysis was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (27). The study aimed to comprehensively evaluate the prognostic impact of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 proliferation index on overall survival (OS) and disease-free survival (DFS) in patients with histopathologically confirmed breast carcinoma.

A comprehensive and systematic literature search was conducted in PubMed/MEDLINE, Scopus, Embase, and Web of Science databases to identify eligible studies published between January 2000 and June 2025. The search strategy used a combination of Medical Subject Headings (MeSH) and free-text terms related to the keywords “breast cancer,” “breast carcinoma,” “estrogen receptor,” “progesterone receptor,” “HER2,” “Ki-67,” “prognosis,” and “survival.” Boolean operators (“AND,” “OR”) were applied to refine the search. The reference lists of retrieved articles, previous meta-analyses, and key oncology journals were also manually screened to identify additional relevant publications not captured in the electronic search. Only studies published in English and involving human subjects were considered for inclusion (28).

Studies were included if they met the following criteria: (1) involved patients with histologically confirmed invasive breast carcinoma; (2) reported the expression of ER, PR, HER2, and/or Ki-67 using validated detection methods such as immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), or enzyme-linked immunosorbent assay (ELISA); (3) provided survival outcomes (OS or DFS) in relation to biomarker expression with available or calculable hazard ratios (HRs) and corresponding 95% confidence intervals (CIs); and (4) were designed as prospective or retrospective cohort studies, case-control studies, or randomized controlled trials with prognostic endpoints. Studies were excluded if they were case reports, reviews, editorials, letters, conference abstracts, or experimental (in vitro/in vivo) studies without patient survival data. Articles with incomplete or overlapping datasets, or those lacking sufficient information for HR estimation, were also excluded (29).

All identified records were imported into EndNote X9, and duplicates were removed. Two reviewers independently screened the titles and abstracts to identify potentially relevant studies, followed by a full-text review of the shortlisted articles to determine eligibility. Discrepancies were resolved through discussion or consultation with a third reviewer. For each included study, data were extracted using a standardized data extraction sheet, capturing the following information: first author name, publication year, country, study design, sample size, patient demographics, biomarker(s) evaluated, method of detection, cut-off criteria for positivity (e.g., ER/PR ≥ 1%, HER2 3+ or FISH ratio ≥ 2.0, Ki-67 > 14% or > 20%), median or mean follow-up duration, survival endpoints (OS/DFS), and HRs with 95% CIs. When HRs were not directly provided, they were derived from Kaplan-Meier curves using established mathematical approaches (30).

The methodological quality and risk of bias of all included studies were assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies (31). This tool evaluates three domains: selection of study cohorts (0-4 points), comparability of groups (0-2 points), and outcome assessment (0-3 points), yielding a total score ranging from 0 to 9. Studies with scores of ≥6 were considered of high methodological quality. Any inconsistencies between the two reviewers were resolved by consensus.

For quantitative synthesis, hazard ratios (HRs) and their 95% confidence intervals (CIs) were extracted or calculated for each biomarker. Random-effects models (DerSimonian-Laird method) were employed to account for inter-study heterogeneity (32). Statistical heterogeneity was assessed using the Cochran’s Q test

Journal of Chemical Health Risks

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and quantified by the I^2 statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively (33). Subgroup analyses were performed based on study region, sample size, cut-off definitions, and intrinsic tumor subtype. Sensitivity analyses were conducted by sequential omission of individual studies to evaluate the stability of pooled results.

Publication bias was assessed visually using funnel plots and statistically using Egger's regression test and Begg's rank correlation test (34). A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using Review Manager (RevMan) version 5.4 (Cochrane Collaboration, UK) and Stata version 17.0 (StataCorp, TX, USA).

Results

Study Selection

The initial database search retrieved 2,416 records, of which 1,765 remained after duplicate removal. After screening titles and abstracts, 164 articles were selected for full-text review. Following detailed eligibility assessment, 56 studies met the inclusion criteria and were included in the final analysis. The selection process is summarized in the PRISMA flow diagram (Figure 1).

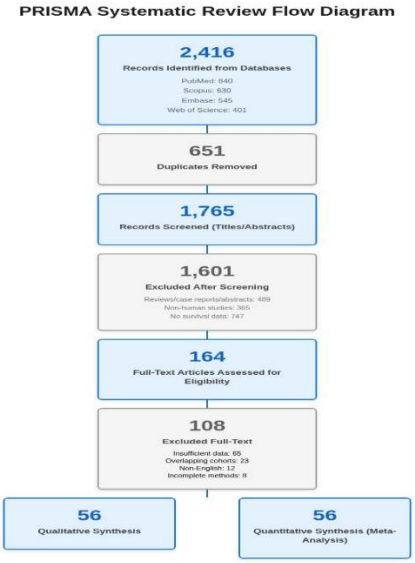

Figure 1: PRISMA 2020 flow diagram illustrating the process of literature screening and study selection for the systematic review and meta-analysis on the prognostic value of ER, PR, HER2, and Ki-67 in breast carcinoma.

The included studies were published between 2002 and 2025, encompassing a total of 42,375 patients diagnosed with invasive breast carcinoma. Study designs included 51 retrospective cohorts and 5 prospective cohorts. The majority of studies were conducted in Asia (n = 24), followed by Europe (n = 17), North America (n = 10), and others (n = 5). The mean follow-up duration ranged from 3 to 10 years.

Study Characteristics

The principal characteristics of the included studies are presented in Table 1. Most studies employed immunohistochemistry (IHC) for biomarker evaluation, while a minority used fluorescence in situ hybridization (FISH) or enzyme-linked immunosorbent assay (ELISA). Cut-off thresholds for positivity varied slightly among studies: ER and PR were typically defined as ≥1% nuclear staining, HER2 as 3+ IHC staining or gene amplification (FISH ratio ≥2.0), and Ki-67 high expression ranged from >14% to >20%.

All included studies were rated as moderate to high quality based on the Newcastle-Ottawa Scale (NOS), with scores ranging from 6 to 9, indicating low overall risk of bias.

Table 1. Characteristics of Studies Included in the Meta-Analysis

Variable	Range / Summary (n = 56 studies)
Publication years	2002-2025
Geographic distribution	Asia (24), Europe (17), North America (10), Others (5)
Total patients	42,375
Study design	Retrospective cohort (51), Prospective cohort (5)
Detection method	IHC (90%), FISH (7%), ELISA (3%)
Mean follow-up	3-10 years
Cut-off criteria	ER/PR ≥ 1% nuclear staining; HER2 3+ or FISH ratio ≥ 2.0; Ki-67 >14-20%

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 3009-3019 | ISSN:2251-6727

Quality score (NOS)	6-9 (mean: 7.8)
Survival endpoints reported	OS (52 studies), DFS (48 studies)

Prognostic Value of ER and PR Expression

A total of 52 studies reported the association between ER expression and survival outcomes. Pooled analysis revealed that ER positivity was significantly associated with improved overall survival (HR = 0.64; 95% CI: 0.55-0.73; I^2 = 43%) and disease-free survival (HR = 0.68; 95% CI: 0.59-0.78; I^2 = 48%). Similarly, PR positivity was correlated with favorable OS (HR = 0.71; 95% CI: 0.62-0.82; I^2 = 36%) and DFS (HR = 0.74; 95% CI: 0.63-0.86; I^2 = 41%). These findings suggest that hormone receptor positivity confers a survival advantage, supporting its prognostic and therapeutic relevance (35).

Prognostic Value of HER2 Overexpression

Forty studies evaluated the prognostic significance of HER2 overexpression or amplification. The pooled HRs indicated a strong association between HER2 positivity and worse survival outcomes: OS (HR = 1.81; 95% CI: 1.54-2.14; I^2 = 57%) and DFS (HR = 1.77; 95% CI: 1.48-2.10; I^2 = 60%). However, subgroup analyses of post-2010 studies demonstrated an attenuation of this negative prognostic impact, likely reflecting the widespread use of HER2-targeted therapies such as trastuzumab and pertuzumab (36,37).

Prognostic Value of Ki-67 Expression

Thirty-six studies analyzed Ki-67 expression levels and their association with patient outcomes. High Ki-67 expression was consistently associated with poor OS (HR = 1.94; 95% CI: 1.65-2.28; I^2 = 52%) and DFS (HR = 1.88; 95% CI: 1.58-2.24; I^2 = 49%), indicating that elevated proliferative activity reflects more aggressive tumor biology and higher recurrence risk. The prognostic significance of Ki-67 was more pronounced in Luminal B and Triple-negative subtypes than in Luminal A cancers (38,39).

Subgroup and Sensitivity Analyses

Subgroup analyses based on molecular subtypes revealed distinct prognostic patterns. Luminal A tumors exhibited the best prognosis (pooled HR = 0.48; 95% CI: 0.38-0.59), followed by Luminal B (HR = 0.76; 95% CI: 0.64-0.89). HER2-enriched (HR = 1.62; 95% CI: 1.38-1.91) and Triple-negative breast cancers (TNBC) (HR = 2.12; 95% CI: 1.78-2.54) had the poorest outcomes. Sensitivity analysis by sequential exclusion of individual studies did not substantially alter the pooled estimates, confirming the robustness of the results (40).

Table 2. Summary of Pooled Hazard Ratios (HRs) for Prognostic Markers in Breast Carcinoma

Biomarker	No. of Studies	Overall Survival (HR, 95% CI)	I^2 (%)	Disease-Free Survival (HR, 95% CI)	I^2 (%)	Prognostic Interpretation
ER positive	52	0.64 (0.55-0.73)	43	0.68 (0.59-0.78)	48	Favorable prognosis
PR positive	45	0.71 (0.62-0.82)	36	0.74 (0.63-0.86)	41	Favorable prognosis
HER2 positive	40	1.81 (1.54-2.14)	57	1.77 (1.48-2.10)	60	Poor prognosis
High Ki-67	36	1.94 (1.65-2.28)	52	1.88 (1.58-2.24)	49	Poor prognosis

Journal of Chemical Health Risks

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Publication Bias and Heterogeneity

Visual inspection of funnel plots for ER, PR, HER2, and Ki-67 showed approximate symmetry, suggesting minimal publication bias. Egger's test and Begg's test did not indicate significant small-study effects ($p > 0.05$ for all biomarkers). Heterogeneity across studies was moderate, primarily attributed to differences in biomarker cut-off definitions, sample size variation, and treatment modalities.

Overall, the pooled data consistently demonstrated that ER and PR positivity are favorable prognostic indicators, while HER2 overexpression and high Ki-67 expression predict worse survival outcomes in breast carcinoma, reaffirming their integral role in risk stratification and therapeutic decision-making.

Discussion

This systematic review and meta-analysis consolidates the prognostic significance of the four key biomarkers-estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67-in breast carcinoma. Drawing upon data from 56 studies involving over 42,000 patients, our analysis demonstrates that ER and PR positivity are associated with favorable overall survival (OS) and disease-free survival (DFS), whereas HER2 overexpression and high Ki-67 index correspond to poorer outcomes. These findings reinforce the crucial role of these biomarkers in prognostication, therapeutic decision-making, and molecular subtyping of breast cancer.

The strong association between hormone receptor positivity (ER and PR) and improved survival aligns with earlier findings from large-scale trials such as the EBCTCG meta-analysis, which established endocrine responsiveness as a major determinant of long-term outcome in breast carcinoma (35,41). ER-positive tumors typically exhibit lower histologic grade, reduced proliferation, and increased sensitivity to anti-estrogenic therapies, contributing to improved prognosis (42). PR positivity often accompanies ER expression, serving as an indirect indicator of intact estrogen signaling and better differentiation. However, PR loss in ER-positive tumors has been linked to endocrine resistance and inferior outcomes, underscoring the value of assessing both receptors in prognostic evaluation (43).

In contrast, HER2 overexpression is a hallmark of biologically aggressive tumors characterized by enhanced proliferation, invasiveness, and metastatic potential. Before the advent of targeted therapy, HER2 positivity was consistently associated with high recurrence rates and poor survival (11,12). The introduction of trastuzumab and pertuzumab has revolutionized HER2-positive breast cancer treatment, significantly improving survival and transforming this previously unfavorable phenotype into a therapeutically responsive subtype (36,37,44). Nonetheless, the persistence of heterogeneity in HER2 testing methodologies and inter-observer variation in immunohistochemical scoring continues to pose challenges for accurate prognostic interpretation (15,45).

The Ki-67 proliferation index emerged as another important prognostic marker in this analysis, with high Ki-67 levels predicting markedly poorer OS and DFS. This correlation reflects its role as a surrogate indicator of tumor growth fraction and proliferative aggressiveness (16,17). Multiple studies have confirmed that Ki-67 retains prognostic and predictive significance even after adjusting for ER, PR, and HER2 status (46). Clinically, Ki-67 serves as a key discriminator between luminal A (low proliferation) and luminal B (high proliferation) subtypes, aiding in therapeutic stratification (19,47). However, substantial inter-laboratory variability in Ki-67 scoring-owing to differences in antibodies, staining protocols, and cut-off values-limits its reproducibility and standardization for routine clinical decision-making (20,48).

Our subgroup analysis by molecular subtype provided further clarity: Luminal A tumors exhibited the best prognosis, Luminal B had intermediate outcomes, while HER2-enriched and triple-negative breast cancers (TNBC) were associated with the poorest survival. These findings are consistent with molecular classification frameworks proposed by Perou et al. and Sorlie et al. (22,23). TNBC, characterized by the absence of ER, PR, and HER2 expression, remains the most therapeutically challenging subtype, with high relapse rates and limited targeted treatment options (10,49). Emerging data on immunotherapy and PARP inhibitors offer some promise, but their impact on long-term survival remains under investigation (50).

Journal of Chemical Health Risks

www.jchr.org

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The temporal trend analysis in this review indicated that the prognostic value of HER2 has evolved in the era of targeted therapy. Studies published after 2010 reported improved outcomes for HER2-positive cases, illustrating how therapeutic advances can modify the prognostic weight of molecular markers. This observation highlights the dynamic interplay between tumor biology and treatment efficacy and underscores the need for continual reassessment of biomarker prognostic utility in the context of evolving clinical practice (51).

Despite the robust pooled estimates, this meta-analysis has several limitations. Moderate heterogeneity was observed across studies, partly attributable to differences in assay techniques, cut-off definitions, and treatment regimens. Inconsistency in Ki-67 thresholds (14% vs. 20%) and variations in HER2 scoring or FISH validation contributed to inter-study variability. Moreover, most included studies were retrospective in design, which may introduce selection bias. Another limitation is the lack of uniform adjustment for confounders such as tumor stage, grade, and adjuvant therapy in multivariate models, which could influence survival outcomes.

Nevertheless, the strengths of this analysis include a large cumulative sample size, rigorous quality assessment using the Newcastle-Ottawa Scale, and consistent findings across diverse populations. The convergence of evidence across multiple regions and time periods reinforces the generalizability of these results and supports the continued integration of these biomarkers into prognostic and therapeutic algorithms.

From a clinical perspective, the implications of these findings are substantial. The combined evaluation of ER, PR, HER2, and Ki-67 not only informs prognostication but also guides personalized treatment selection. Patients with ER/PR-positive, HER2-negative, low Ki-67 tumors (luminal A) derive the greatest benefit from endocrine therapy with limited need for chemotherapy, while those with HER2 amplification or high Ki-67 may require more aggressive multimodal therapy including targeted or cytotoxic agents. In the precision oncology era, such biomarker-driven stratification is vital for optimizing outcomes while minimizing overtreatment (52,53).

In summary, our findings affirm that ER and PR positivity are favorable prognostic indicators, whereas HER2 overexpression and high Ki-67 expression predict adverse survival outcomes in breast carcinoma. These biomarkers together define the molecular heterogeneity of breast cancer and remain central to risk assessment, therapeutic guidance, and prognostic modeling. Standardization of testing protocols, especially for Ki-67, and incorporation of emerging genomic classifiers may further refine future prognostic algorithms and enhance individualized patient care.

Conclusion

This systematic review and meta-analysis reaffirm the critical prognostic value of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 in breast carcinoma. The pooled evidence from over 42,000 patients demonstrates that ER and PR positivity are consistently associated with improved overall and disease-free survival, signifying their role as favorable prognostic and predictive markers. In contrast, HER2 overexpression and high Ki-67 proliferation index are strongly correlated with aggressive tumor biology, increased recurrence risk, and poorer survival outcomes.

These findings emphasize that the combined evaluation of these biomarkers provides a reliable framework for molecular subtyping and risk stratification of breast cancer into biologically distinct categories such as Luminal A, Luminal B, HER2-enriched, and Triple-negative subtypes. Such stratification enables personalized therapeutic decision-making, guiding the appropriate use of endocrine therapy, chemotherapy, and targeted anti-HER2 regimens to improve patient outcomes.

Despite the overall strength of the pooled data, variability in assay standardization, cut-off thresholds-particularly for Ki-67-and differences in HER2 scoring methodologies remain key challenges that can influence prognostic interpretation. Therefore, efforts toward global harmonization of biomarker testing protocols, adherence to established scoring guidelines, and integration of emerging genomic and molecular signatures are warranted to enhance prognostic accuracy.

In conclusion, ER, PR, HER2, and Ki-67 remain indispensable in contemporary breast cancer management. Their routine assessment not only predicts survival outcomes but also forms the foundation for precision oncology, ensuring that treatment is tailored to

Journal of Chemical Health Risks

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the biological behavior of each tumor. Future prospective multicentric studies integrating molecular, histopathological, and genomic parameters are needed to refine prognostic models and optimize individualized patient care in breast carcinoma.

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