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Comparing Biomarkers for Predicting Pathological Responses to Neoadjuvant Therapy in HER2-Positive Breast Cancer: A Systematic Review and Meta-Analysis

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Introduction: The predictive strength and accuracy of some biomarkers for the pathological complete response (pCR) to neoadjuvant therapy for HER2-positive breast cancer remain unclear. This study aimed to compare the accuracy of the HER2-enriched subtype and the presence of PIK3CA mutations, namely, TILs, HRs, and Ki-67, in predicting the pCR to HER2-positive breast cancer therapy.

Methods: We screened studies that included pCR predicted by one of the following biomarkers: the HER2-enriched subtype and the presence of PIK3CA mutations, TILs, HRs, or Ki-67. We then calculated the pooled sensitivity, specificity, positive and negative predictive values (PPVs and NPVs, respectively), and positive and negative likelihood ratios (LRs). Summary receiver operating characteristic (SROC) curves and areas under the curve (AUCs) were used to estimate the diagnostic accuracy.

Results: The pooled estimates of sensitivity and specificity for the HER2-enriched subtype and the presence of PIK3CA mutations, namely, TILs, HRs, and Ki-67, were 0.66 and 0.62, 0.85 and 0.27, 0.49 and 0.61, 0.54 and 0.64, and 0.68 and 0.51, respectively. The AUC of the HER2-enriched subtype was significantly higher (0.71) than those for the presence of TILs (0.59, $p = 0.003$), HRs (0.65, $p = 0.003$), and Ki-67 (0.62, $p = 0.005$). The AUC of the HER2-enriched subtype had a tendency to be higher than that of the presence of PIK3CA mutations (0.58, $p = 0.220$). Moreover, it had relatively high PPV (0.58) and LR+ (1.77), similar NPV (0.73), and low LR– (0.54) compared with the other four biomarkers.

Conclusions: The HER2-enriched subtype has a moderate breast cancer diagnostic accuracy, which is better than those of the presence of PIK3CA mutations, TILs, HRs, and Ki-67.

Keywords: HER2-enriched subtype, breast cancer, biomarker, predict, diagnostic

INTRODUCTION

In approximately 20% of breast cancer cases, the expression of human epidermal growth factor receptor (HER2), which is associated with a poor prognosis, is enhanced (1–3). Neoadjuvant therapy can increase the operability rate for locally advanced diseases and inflammatory subtypes and increase the possibility of breast conservation by reducing tumor bulk or downstaging the tumor (4–6). HER2-targeted therapies such as treatments with trastuzumab, pertuzumab, lapatinib, and trastuzumab emtansine (T-DM1), neratinb, tucatinib, and trastuzumab–deruxtecan, have shown clinically significant efficacy against HER2-positive breast cancer. The National Comprehensive Cancer Network Guidelines, Version 7 (2021), recommend chemotherapy and trastuzumab-based therapy as preoperative systemic therapies for HER2-positive breast cancer. The guidelines also suggest that a pertuzumab-containing regimen is useful for patients with T2 or N1 HER2-positive, early-stage breast cancer in a neoadjuvant setting (7).

Single or dual HER2 blockades in combination with chemotherapy have achieved a pathologically complete response (pCR) of >60% for HER2-positive breast cancer (6, 8, 9). The achievement of pCR has significantly improved the long-term patient outcomes in HER2-positive breast cancer (6, 10–13). However, not all HER2-positive patients can achieve pCR when receiving HER2-targeted neoadjuvant therapy. Selecting patients who can achieve pCR based on biomarkers has thus become a vital clinical issue. To date, multiple potential biomarkers have been investigated among trials involving neoadjuvant therapies. In addition to HER2 overexpression or amplification, the most reported predictive biomarkers for patients with HER2-positive cancer include the HER2-enriched subtype and the presence of phosphatase phosphoinositol-3 (PI3) kinase (PIK3CA) mutations, tumor-infiltrating lymphocytes (TILs), hormone receptors (HRs), and Ki-67.

The HER2-enriched subtype is identified based on the PAM50 signature, which describes the expression profiles of 50 genes; intrinsic typing of PAM50 is now widely used in breast cancer research (14–16). High ERBB2 mRNA and protein levels appear to be associated with activation of the EGFR-HER2 signaling pathway (15–17). PIK3CA is present in the HER2 downstream signaling pathway, and the mutation of PIK3CA or the loss of PTEN can activate the PI3K pathway in breast cancer (18, 19). The PI3K pathway is associated with resistance to HER2-targeted therapy. Activation of PIK3CA mutations and deletion of PTEN (PTEN is a key negative regulator of PI3K signaling) lead to resistance to trastuzumab and lapatinib in breast cancer cell lines, and low PTEN levels are associated with worse patient prognosis (20–22). It was shown that the addition of additional targeted agents for PIK3CA mutations did not show additional benefit in terms of sensitivity to HER2-targeted therapy in the BOLERO-2/3 trial (22, 23). TIL is a stroma component that acts as an important mediator of tumor immunity. It has been shown that TIL is associated with improved distant-metastasis-free survival and increased (pCR) rates of neoadjuvant trastuzumab and chemotherapy in patients with HER2-positive early-stage breast cancer (20, 22). HR engages in crosstalk with HER2-receptor-mediated pathways (24, 25). Ki-67 is a marker of cell proliferation and is specifically expressed in the nucleus in G1 through M phases of the cell cycle (26). All these factors are directly or indirectly involved in the HER2 signaling pathway and may influence the effectiveness of HER2-targeted drugs. Multiple trials and meta-analyses have shown that these five factors can act as biomarkers for predicting pCR to neoadjuvant therapy with HER2-targeted drugs in patients with HER2-positive cancer (27–35).

Our study aimed to perform a systematic review to compare the relative diagnostic accuracy of HER2-enriched subtypes and the presence of PIK3CA mutations, namely, TILs, HRs, and Ki-67, in predicting the degree of pCR to neoadjuvant therapy with HER2-targeted drugs in patients with HER2-positive breast cancer.

METHODS

Study Design

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (36). Two reviewers (FZ and XH) independently performed the literature search, assessed the eligibility criteria of related studies reported in the literature, and performed data extraction.

Search Strategy

To identify clinical trials that assessed the potential of biomarkers in predicting pCR to HER2-targeted therapies, a systematic search was performed in the PubMed/MEDLINE and Embase databases, and reports were obtained from several main congresses of the European Society of Medical Oncology, the American Society of Clinical Oncology, and the San Antonio Breast Cancer Symposium databases. Reports included in this study were published between January 1, 2000 and September 30, 2020. The search strategy was based on the following combination of tags: (a) neoadjuvant OR preoperative, (b) breast cancer OR breast neoplasm OR breast carcinoma, (c) HER2-enriched subtype OR HER2-E, (d) phosphatase phosphoinositol-3 kinase mutation OR PIK3CA mutation, (e) tumor-infiltrating lymphocytes OR TIL, (f) hormone receptor OR estrogen receptor OR progesterone receptor, and (g) Ki-67 index OR Ki-67. The complete search information is presented in **Supplementary Table S1**.

Eligibility Criteria

The inclusion criteria were as follows: (a) pathological results were reported after neoadjuvant therapy and surgery in stage I to stage III HER2-positive breast cancer; (b) patients who received HER2-targeted drugs that were used as part of the neoadjuvant therapy in prospective randomized or single-arm trials that specified the presence of a HER2-enriched subtype, PIK3CA mutation, TILs, HRs, or Ki-67 (retrospective studies were also

included for Ki-67 because few prospective studies reported the results for Ki-67); (c) the presence of a HER2-enriched subtype, PIK3CA mutations, TILs, HRs, or Ki-67 was prospectively or retrospectively used to predict pCR in the abovementioned trials; and (d) articles were written in English. Different definitions of pCR in studies were allowed. Letters to the editor, reviews, editorials, comments, case reports, and studies involving ≤10 patients were excluded. For duplicate publications describing the same populations or overlapping patient cohorts, only the largest, most recent publication was included. Any discrepancies between reviewers were resolved through a discussion until a consensus was reached.

Data Extraction and Quality Assessment

Two reviewers independently extracted patient characteristics and treatment and pathological information from all eligible studies. The primary study outcome was a comparison of the accuracy of the HER2-enriched subtype, PIK3CA mutations, TILs, HRs, and Ki-67 in predicting pCR rates when used as biomarkers. The following data were extracted from each study: study name, first author's last name, study nation, publication year, study design characteristics, participant number, therapy regimens, HER2 status, biomarkers assessed, pCR definition, pCR rate, and, if possible, the cutoff value for biomarkers. Data describing true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) levels were extracted to construct 2 × 2 tables. If the study reported multiple biomarker tests, results describing pCR predictions based on individual biomarkers were extracted separately. The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (37–39).

Statistical Analysis

We calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative LR (LR−) for data obtained from included studies, which were summarized in 2 × 2 tables containing TP, TN, FP, and FN values. Data were pooled together using the Moses–Littenberg model (fixed-effects model) and DerSimonian–Laird model (random-effects model) to generate unweighted and weighted linear regression models, respectively. We also developed summary receiver operating characteristic (SROC) curves and a Q* index. We additionally measured the relationship between test modalities and pCR using the SROC curves and the resultant relative area under the curve (AUC) values. Statistical comparisons of the AUCs were performed using the formula of Hanley and McNeil.

We calculated the pooled sensitivity and specificity for each modality and compared the overall differences in each modality. Random-effects models were used to address the anticipated heterogeneity. To estimate the publication bias for each study, we used the Stata 12.0 software to analyze all eligible studies using Deek's test. All analyses were performed using the Meta-DiSc version 1.4 and Stata 12.0 software. All tests of statistical significance were two-sided, and a p-value of <0.05 was considered significant.

RESULTS

Study Characteristics

In total, 10,530 citations were identified. Of these studies, 51 (40–90) that met the inclusion criteria assessed the relationship between the pCR rate of non-adjuvant therapy with HER2-targeted drugs and either the HER2-enriched subtype (n = 16) (40–55) or the presence of HRs (n = 12) (55–66), Ki-67 (n = 10) (67–76), TILs (n = 5) (46, 77–80), or PIK3CA mutations (n = 11) (54, 81–90) (**Figure 1** and **Supplementary Table S2**). In total, 21 studies examined either multiple-patient cohorts or ≥2 individual predictive biomarkers, which resulted in a total of 94 individual analyses. Among all patients studied, 4,095 achieved pCR and 6,435 did not. **Supplementary Table S2** presents the primary features of these studies, including the study phase, study size, tumor stage, treatment, pCR rate, and pCR definition. Neoadjuvant therapies typically involved anthracycline–taxane combined with HER2-targeted drugs. The main HER2-targeted drugs were trastuzumab, pertuzumab, lapatinib, and T-DM1, which were used as single or dual HER2 blockades. The results of the quality assessment are presented in **Figure 2** (quality assessment results for each study are presented in **Supplementary Figure S1**).

SROC Curves

Supplementary Figure S2 shows a forest plot of the sensitivity and specificity of biomarkers in predicting pCR. The sensitivity of the HER2-enriched subtype and the presence of PIK3CA mutations, TILs, HRs, and Ki-67 ranged from 0.36 to 0.92, 0.71 to 0.92, 0.22 to 0.76, 0.20 to 0.83, and 0.00 to 1.00, respectively. Specificity values for the HER2-enriched subtype and the presence of PIK3CA mutations, TILs, HRs, and Ki-67 ranged from 0.33 to 0.88, 0.17 to 0.43, 0.18 to 0.96, 0.50 to 1.00, and 0.32 to 0.85, respectively.

Figure 3A shows the derived sensitivity and 1 − specificity values for each study. **Figure 3B** shows the forest plot and SROC curves for sensitivity, specificity, and 95% CI for the HER2-enriched subtype and the presence of PIK3CA mutations, TILs, HRs, and Ki-67 of each study. The SROC curves were plotted based on weighting each study based on the number of samples. The weighted SROC curves suggested that the HER2-enriched subtype had better overall diagnostic accuracy; the AUC of the HER2-enriched subtype was significantly higher (0.71) than those of the presence of TILs (0.59, p = 0.003), HRs (0.65, p = 0.003), and Ki-67 (0.62, p =0.005); the presence of TILs had a relatively lower AUC at <0.60. The HER2-enriched subtype also showed a tendency to have better diagnostic accuracy with an AUC significantly higher (0.71) than that of the presence of PIK3CA mutations (0.58, p = 0.220; although the p-value is >0.05, it is clinically significant considering that its line is lower than that of the other four biomarkers and that it may be attribute to the wide 95% confidence interval and limited sample size, resulting in poor statistical efficiency; therefore, the difference between AUC values of the HER2-enriched subtype and the presence of PIK3CA mutations cannot be well identified). Moreover, the presence of PIK3CA mutations,

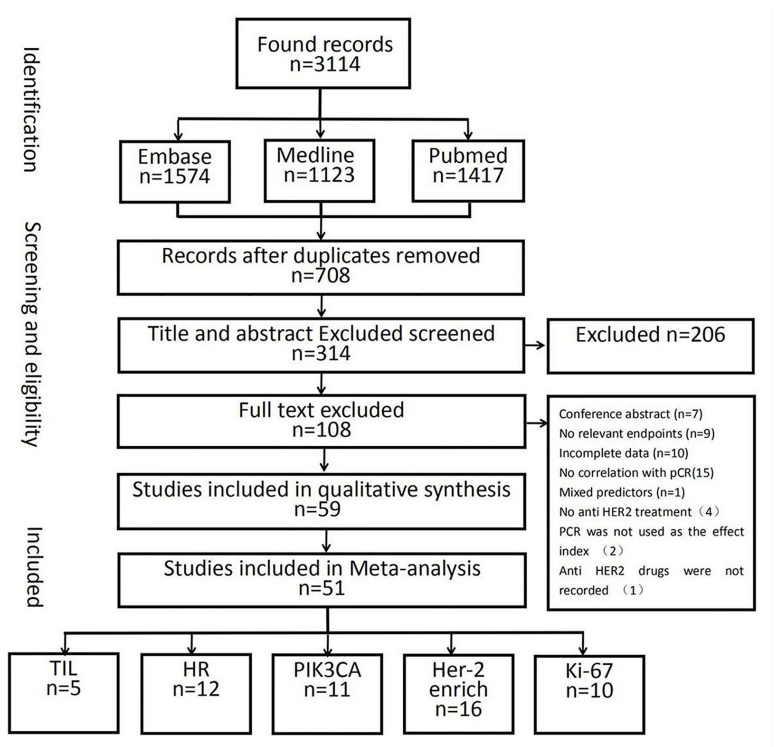

FIGURE 1 | Flowchart illustrating the study-selection strategy.

TILs, and Ki-67 did not have any significantly distinct AUC profiles compared with the presence of HRs (all $p > 0.05$).

PPVs, NPVs, and LRs

The PPVs, NPVs, and LRs are presented in **Table 1**. Most biomarkers had relatively high NPVs, except HRs. The HER2-enriched subtype consistently had relatively high PPVs, the presence of TILs and HRs had moderate PPVs, and the presence of PIK3CA mutations and Ki-67 had relatively low PPVs. The pooled LRs for each biomarker revealed a significantly higher LR+ value of the HER2-enriched subtype and the presence of TILs than those of the presence of PIK3CA mutations, HRs, and Ki-67 (1.77 and 1.72 *vs.* 1.16, 1.60, and 1.37, respectively). In addition, the LR− value of the HER2-enriched subtype was significantly lower than those for the presence of PIK3CA mutations, TILs, HRs, and Ki-67 (0.54 *vs.* 0.57, 0.79, 0.69, and 0.71, respectively).

Pooled Sensitivity and Specificity

Table 1, **Figure 4**, and **Supplementary Figure S2** present the pooled sensitivity and specificity values for predicting pCR. The pooled estimates of sensitivity and specificity for the HER2-enriched subtype and the presence of PIK3CA mutations, TILs, HRs, and Ki-67 were 0.66 and 0.62, 0.85 and 0.27, 0.49 and 0.61, 0.54 and 0.64, and 0.68 and 0.51, respectively. The sensitivity of the HER2-enriched subtype was also higher than those of the presence of PIK3CA mutations ($p < 0.001$), TILs ($p < 0.001$), and HRs ($p < 0.001$); the HER2-enriched subtype showed an improved specificity compared with the presence of PIK3CA mutations ($p < 0.001$) and Ki-67 ($p < 0.001$).

Publication Bias

Supplementary Figure S3 shows the results of a Deek's funnel plot asymmetry test and demonstrates the lack of notable publication biases in the analysis of the HER2-enriched subtype and the presence of PIK3CA mutations, TILs, HRs, and Ki-67 ($p = 0.48$, $p = 0.25$, $p = 0.42$, $p = 0.72$, and $p = 0.48$, respectively).

DISCUSSION

Suitable biomarkers for predicting the pCR to neoadjuvant therapies with HER2-targeted drugs for the treatment of HER2-positive breast cancer can be used to screen patients who are most likely to benefit from such treatment regimens. An increasing number of studies have identified such biomarkers in recent years. The most reported biomarkers for predicting the pCR rates of HER2-targeted drugs include a HER2-enriched subtype and the presence of PIK3CA mutations, TILs, HRs, and Ki-67. To the best of our knowledge, this meta-analysis is the first to compare the relative diagnostic accuracy of these five biomarkers. Our results revealed that the AUC of the HER2-

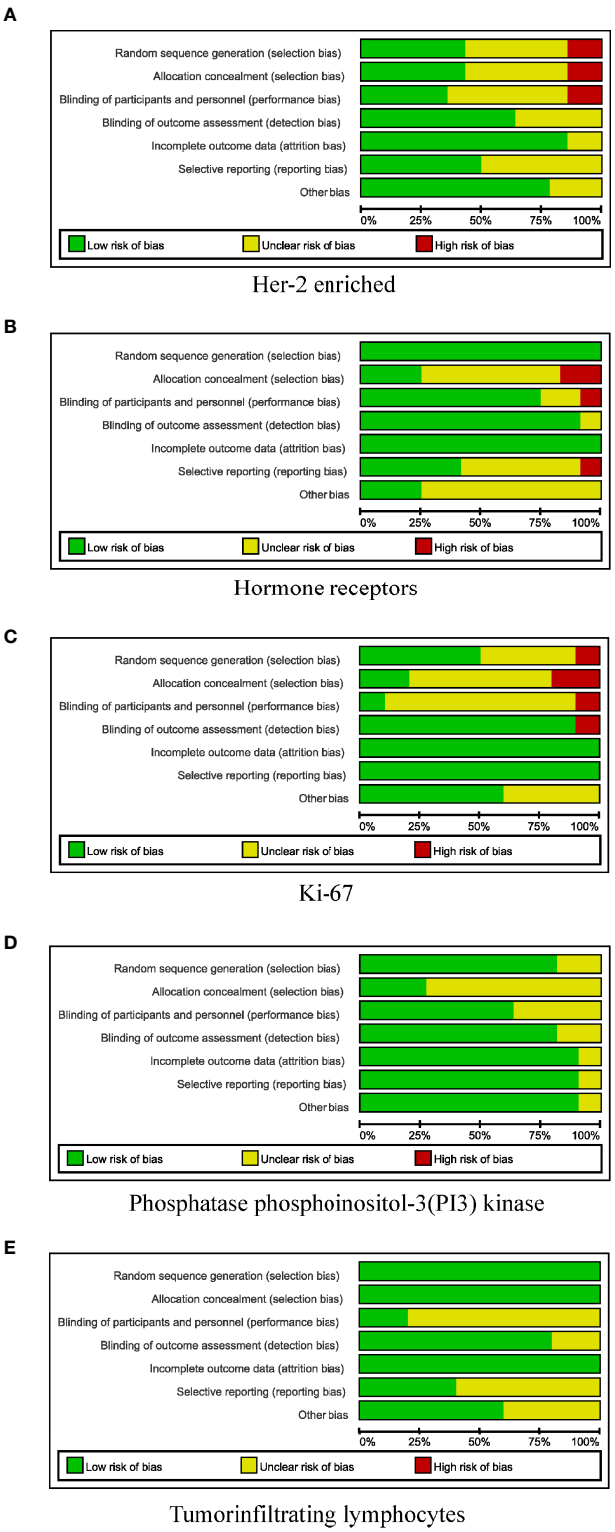

FIGURE 2 | Risk-of-bias review of all included studies. **(A)** HER-2 enriched. **(B)** Hormone receptors. **(C)** Ki-67. **(D)** Phosphatase phosphoinositol-3 (PI3) kinase. **(E)** Tumor-infiltrating lymphocytes.

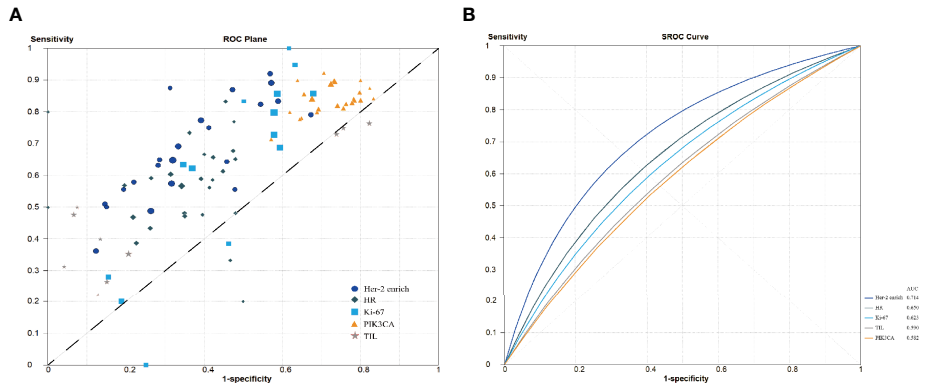

FIGURE 3 | Summary receiver operating characteristic curve analysis. **(A)** Sensitivity and 1 – specificity values from each study. **(B)** Summary receiver operating characteristic curve. HR, hormone receptors; PIK3CA, phosphoinositide 3-kinases; TIL, tumor-infiltrating lymphocytes.

enriched subtype was significantly higher than those of the presence of PIK3CA mutations, TILs, HRs, and Ki-67. The HER2-enriched subtype also exhibited moderate sensitivity and specificity for predicting pCR and improving LR+ and LR– compared with the other four biomarkers. This meta-analysis documents that the HER2-enriched subtype tends to have moderate diagnostic accuracy for determining pCR to neoadjuvant therapy for HER2-positive breast cancer.

HER2-targeting agents have significantly improved the survival of patients with HER2-positive breast cancer. However, many patients do not respond to these agents; thus, there is an urgent need to explore biomarkers that can screen patients who can benefit from HER2-targeted therapy. Although several studies have been conducted to identify such biomarkers, the validation of these biomarkers has generally failed during randomized clinical trials (91–94). To date, only HER2 has been validated in a clinical setting, although its PPV is low (95). In a neoadjuvant setting, the most reported potential biomarkers include the HER2-enriched subtype and the presence of PIK3CA mutations, TILs, HRs, and Ki-67 (6, 8–10, 24).

Although some previous meta-analyses have shown that the presence of a HER2-enriched subtype, high TIL, and high Ki-67 index predict increased pCR, whereas a PIK3CA mutation and positive HR predict decreased pCR (27–35), the discriminatory diagnostic abilities of these biomarkers remain unclear. In this study, we first comprehensively compared the sensitivity and specificity of the abovementioned five biomarkers. According to the pooled results of the 51 studies we assessed, the sensitivity and specificity of the HER2-enriched subtype were relatively higher than those of other biomarkers. In addition, our AUC analysis estimated the overall diagnostic performance of biomarkers compared with their pooled sensitivity and specificity. We generated an SROC plot by weighting each study based on samples that can further enhance SROC to facilitate reporting (96, 97). The AUC of weighted SROC curves for the HER2-enriched subtype was higher than those of the other biomarkers assessed. Although the difference in AUC values between the HER2-enriched subtype and the presence of PIK3CA mutations was not statistically significant, it was likely due to the wide confidence interval and small samples of PIK3CA mutations. To our knowledge, no consensus on an acceptable AUC value for diagnostic applications has been achieved to date. An AUC value of 0.7–0.8 is considered to represent "satisfactory" diagnostic accuracy (98–100). Therefore, an AUC of 0.71 indicates that a HER2-enriched subtype has moderate diagnostic accuracy.

Considering that AUC values may not be frequently applied in clinical settings and that LRs may be more clinically significant, this meta-analysis also calculated LR+ and LR– values as the measures of diagnostic accuracy (101, 102). A higher LR+ value and a lower LR– value mean that a given parameter has better discriminatory power in contributing to a

TABLE 1 | Summary of the pooled sensitivities, specificities, positive and negative predictive values, and likelihood ratios of various biomarkers for predicting pathologically complete response.

Biomarker	Pooled Sensitivity	Pooled Specificity	Pooled PPVs	Pooled NPVs	Pooled Positive LRs	Pooled Negative LRs
HER2-enriched subtype	0.66 (0.63–0.69)	0.62 (0.59–0.64)	0.58 (0.51–0.66)	0.73 (0.67–0.79)	1.77 (1.58–1.98)	0.54 (0.47–0.61)
PIK3CA mutation	0.85 (0.83–0.87)	0.27 (0.25–0.29)	0.37 (0.31–0.43)	0.78 (0.76–0.79)	1.16 (1.12–1.21)	0.57 (0.48–0.67)
TIL	0.49 (0.44–0.54)	0.61 (0.57–0.65)	0.50 (0.36–0.64)	0.71 (0.65–0.78)	1.72 (1.18–2.50)	0.79 (0.69–0.89)
HR	0.54 (0.52–0.57)	0.64 (0.62–0.67)	0.53 (0.46–0.60)	0.64 (0.58–0.71)	1.60 (1.46–1.75)	0.69 (0.63–0.76)
Ki-67	0.68 (0.63–0.73)	0.51 (0.47–0.55)	0.42 (0.29–0.54)	0.76 (0.68–0.84)	1.37 (1.24–1.52)	0.71 (0.55–0.91)

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; HR, hormone receptor; PIK3CA, phosphatase phosphoinositol-3 (PI3) kinase; TIL, tumor-infiltrating lymphocytes.

All data are reported as a proportion [95% confidence intervals (CI)]. Nonoverlapping 95% CIs suggest statistical significance.

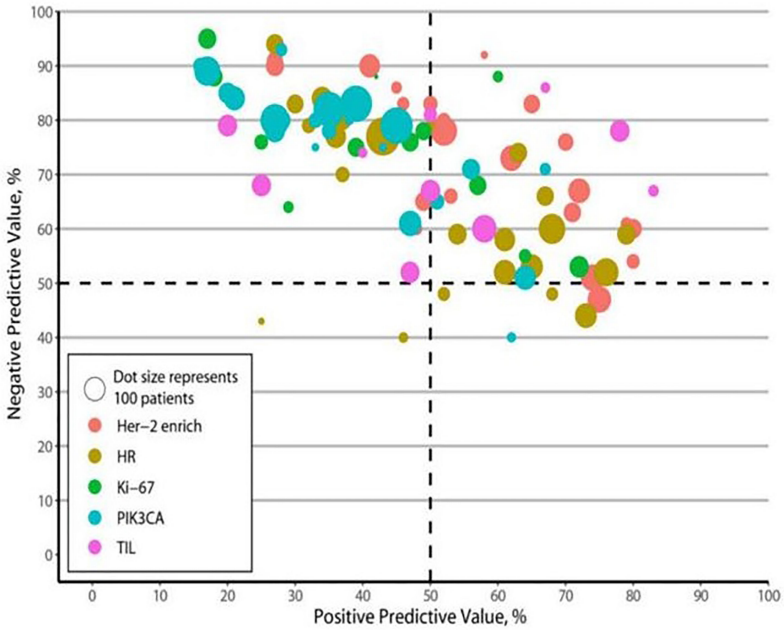

FIGURE 4 | Positive and negative predictive values. HR, hormone receptors; PIK3CA, phosphoinositide 3-kinases; TIL, tumor-infiltrating lymphocytes.

diagnosis. An LR+ value of >10.0 and LR− value of <0.1 indicate a satisfactory diagnostic test (98). Although the HER2-enriched subtype did not meet these criteria, it had the highest pooled LR+ and lowest pooled LR− values among the five biomarkers assessed. An LR+ value of 1.77 (1.58–1.98) indicates that patients who achieve pCR have 1.77 times greater chances of having a HER2-enriched cancer subtype than those who do not achieve pCR, whereas an LR− value of 0.54 (0.47–0.61) indicates that patients who achieve pCR have a 1.85 times greater chance of having a non-HER2-enriched cancer subtype than those who do not achieve pCR.

Although the HER2-enriched subtype has the best diagnostic accuracy of all biomarkers assessed, the remaining markers still have different degrees of diagnostic accuracy in predicting the pCR rate in HER2-positive breast cancer. Notably, HER2-positive breast cancer is a heterogeneous disease and involves heavy crosstalk among various signaling pathways. On the basis of the distribution of intrinsic breast cancer subtypes, the HER2-enriched subtype comprises approximately 75% of HER2-positive/ER-negative and 30% of HER2-positive/ER-positive tumors and exhibits the characteristic HER2/EGFR pathway activation, high proliferation rate, and immune-activated stroma with elevated TIL levels. In addition, approximately 70% of HER2-positive/ER-positive tumors are luminal subtypes that show low HER2/EGFR pathway activation and a high frequency of PIK3CA mutations (24, 82, 103–105). Phosphorylation of the HER2 kinase domain activates the PI3K/AKT signaling pathway, which is central to a growth-regulating pathway in breast cancer (92, 95). Sustained HR signaling is involved in the escape from HER2 blockade (106). Different biomarkers may be clustered together or are inversely correlated with one another (95). Therefore, the exploration of a combination of HER2-enriched subtypes with multiple biomarkers will provide a direction for future trials focusing on predicting patient responses to therapy.

Our meta-analysis has some limitations. First, all assessed data on the HER2-enriched subtype and the presence of PIK3CA mutations, TILs, and HRs were obtained from prospective trials, whereas most data for Ki-67 were obtained from retrospective studies, as few prospective studies reported these. This might have led to potential bias, although no significant publication bias was found. Second, this meta-analysis was based on study-level but not patient-level data, which might have influenced its precision. Third, clinical and methodological heterogeneity might exist among the studies included, such as variations in the baseline characteristics of patients, treatment regimens, detection methods, and cutoff points for biomarker identification. Finally, the definition of pCR varied across studies. Although most studies defined "ypT0/is ypN0" as pCR, some defined pCR as "ypT0/is", "ypT0", and "ypT0 ypN0". Analyses of subgroups distinguished by varying definitions of pCR were not performed, as most included studies defined "ypT0/is ypN0" as pCR.

CONCLUSIONS

With a broad search strategy and large sample size, this meta-analysis comprehensively analyzed the discriminatory diagnostic ability of a HER2-enriched subtype and the presence of PIK3CA mutations and TILs, HRs, and Ki-67 in predicting pCR to

neoadjuvant therapy in patients with HER2-positive breast cancer. The results reveal that the presence of a HER2-enriched subtype has moderate diagnostic accuracy, which is higher than those of the other four biomarkers assessed, although all biomarkers have some degree of diagnostic accuracy. Considering the heterogeneity and the heavy crosstalk among various signaling pathways in HER2-positive breast cancer, combining information about the presence or absence of a HER2-enriched subtype with other biomarkers may help predict patient responses.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

FZ and XH contributed equally to this work. FZ, XH, and JZ had full access to all data used/analyzed in the study and take responsibility for the integrity of the data and the accuracy of data analysis. Conceptualization and design of the study: FZ, XH, MW, GS, and JZ. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: GS and JZ. Statistical analysis: FZ, XH, and JZ. Administrative, technical, and material support: FZ, XH, and JZ. Supervision: JZ. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.731148/full#supplementary-material

Supplementary Table 1 | Systematic review search strategy.

Supplementary Table 2 | Characteristics of the studies included.

Supplementary Figure 1 | Risk-of-bias review of each included study.

Supplementary Figure 2 | Forest plots of sensitivity and specificity. 2A. Sensitivity. 2B. Specificity.

Supplementary Figure 3 | Funnel plot of publication bias.

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