Original Article

Assessing neoadjuvant treatment response through serum human epidermal growth factor receptor 2 (HER2) dynamics

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Background: Human epidermal growth factor receptor 2 (HER2)-positive invasive breast cancer (BC) accounts for 15–20% of all cases, requiring HER2-targeted neoadjuvant therapy (NAT). Despite the success of trastuzumab and other HER2-targeted treatments, many patients still experience inadequate responses, highlighting the need for more accurate and accessible biomarkers to predict treatment outcomes. Serum HER2 (sHER2) levels, as a non-invasive biomarker, have shown promise in monitoring treatment response; however, the role of sHER2 dynamics during treatment remains underexplored. The aim of this study was to investigate the potential of sHER2 dynamics as a predictor of pathological complete response (pCR) in HER2-positive BC patients undergoing NAT.

Methods: This retrospective study analyzed 120 HER2-positive BC patients who underwent standard NAT followed by surgery at Fudan University Shanghai Cancer Center (FUSCC). sHER2 levels were measured at three time points: baseline, after the second cycle of therapy (C2), and at surgery. Logistic regression analysis was used to assess the association between changes in sHER2 levels and the achievement of pCR. The study also examined the influence of other clinicopathological factors such as estrogen receptor (ER) status, Ki67, and tissue HER2 (tHER2) levels on pCR.

Results: During NAT, sHER2 levels showed a significant decline, with a more pronounced reduction observed in patients achieving pCR. The greatest reduction in sHER2 levels after C2 was strongly associated with pCR. Both univariate and multivariate analyses identified significant reductions in sHER2 levels after C2 and ER-negative status as independent predictors of pCR. Notably, sHER2 changes from baseline to C2 demonstrated a stronger predictive value for pCR compared to changes observed later in treatment.

Conclusions: Our study confirms that reductions in sHER2 levels after C2 are a strong indicator of favorable treatment response in HER2-positive BC patients undergoing NAT. Monitoring sHER2 dynamics early in treatment can serve as a useful, non-invasive biomarker to predict pCR and may guide therapeutic decisions in clinical practice.

Keywords: Human epidermal growth factor receptor 2 (HER2); serum HER2 (sHER2); breast cancer (BC); neoadjuvant therapy (NAT); pathological complete response (pCR)

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Introduction

Breast cancer (BC) is one of the most commonly diagnosed malignant diseases in females worldwide (1). Significant advancements in clinical research have ushered BC management into the era of individualized precision medicine (2-5). Human epidermal growth factor receptor 2 (HER2) is a key oncogenic driver in BC, activating downstream tyrosine kinase signaling (6). HER2-positive BC accounts for approximately 15% to 20% of all BCs and is associated with a more aggressive phenotype (7). Since the introduction of trastuzumab, clinical outcomes for HER2-positive BC have improved significantly, thanks to the development of additional HER2-targeting agents over the past decades (8-15). However, despite these advancements, some patients continue to experience inadequate responses to current therapies due to primary or acquired resistance (16).

Neoadjuvant therapy (NAT) has emerged as an effective systemic treatment strategy that facilitates early assessment of therapeutic response (17-19). Pathological complete response (pCR) serves as a strong surrogate endpoint, with patients achieving pCR after NAT demonstrating significantly better clinical outcomes compared to those who do not (19). Despite the substantial improvements in outcomes for HER2-positive patients through HER2-targeted NAT, up to 50% of patients still exhibit residual disease (20). In the era of precision medicine, individualized treatment based on tumor biology and NAT response represents a new therapeutic approach, with numerous factors studied alongside advancements in genomic and transcriptomic sequencing (21,22). However, the high costs of these techniques and the lack of reliable pCR predictors for clinical application hinder the identification of effective interventions, underscoring the need for more accurate and convenient response assessments at this stage (23).

Despite the emergence of new markers defined in recent years, HER2 amplification remains the most reliable predictor of treatment response in HER2-positive BC (24-26). Tissue HER2 (tHER2) and serum HER2 (sHER2) levels, which reflect local and systemic HER2 expression, respectively, have been focal points in research on HER2-positive BC treatment. HER2 amplification in tissue can be assessed through immunohistochemistry (IHC) and in situ hybridization (ISH) (27,28). Previous studies have confirmed that patients with HER2 amplification exhibit higher pCR rates and longer disease-free survival (DFS) after NAT, and low HER2 IHC scores may correlate with reduced pCR rates (29-31). The extracellular domain of HER2 (HER2-ECD) can be shed into the bloodstream, resulting in sHER2, which generates a 95 kDa constitutively active truncated HER2 receptor on the cell membrane (32). As a readily accessible and noninvasive method, several clinical studies have reported significant correlations between sHER2 levels, prognosis, and trastuzumab resistance (33,34).

Given the concerns surrounding the potential clinical value of sHER2 and the underexplored dynamics of sHER2 levels during HER2-targeted NAT (35,36), we retrospectively investigated changes in sHER2 levels in HER2-positive BC patients treated with NAT. We also dynamically assessed the relationship between these changes and treatment efficacy. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-432/rc).

Highlight box

Key findings

- Reductions in serum human epidermal growth factor receptor 2 (sHER2) levels after the second cycle of therapy are strong indicators of pathological complete response (pCR).

What is known and what is new?

- Both tissue HER2 (tHER2) and sHER2 are associated with pCR in HER2-positive patients undergoing neoadjuvant therapy (NAT), and they can even predict long-term prognosis.
- The dynamic changes in sHER2 during the neoadjuvant process are also crucial for predicting pCR.

What is the implication, and what should change now?

- sHER2 dynamics could be used as a non-invasive biomarker to monitor treatment response and guide therapy decisions.

Methods

Clinical cohorts and variables

A retrospective analysis was conducted on 120 patients with HER2-positive BC (BC) without distant metastasis at baseline, diagnosed at Fudan University Shanghai Cancer Center (FUSCC) from 2018 to 2021. The flowchart is presented in *Figure 1*. All participants underwent standard neoadjuvant chemotherapy (NAC) combined with trastuzumab-based HER2-targeted treatment, followed by either mastectomy or breast-conserving surgery. HER2 overexpression was identified using an IHC score of 3+ or ISH positivity. Data collection included social information,

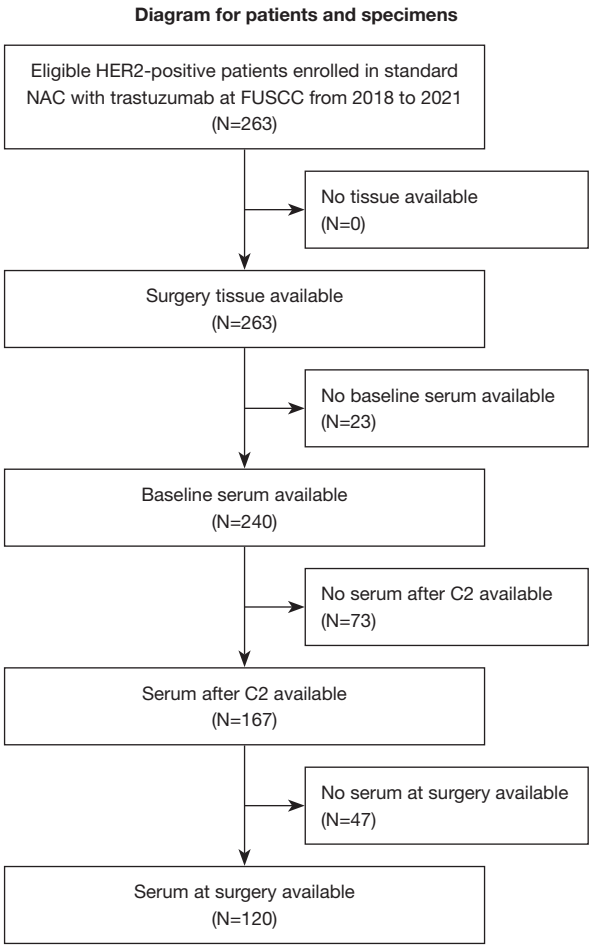

Figure 1 Diagram for patients and specimens. Eligible HER2-positive patients were enrolled in standard NAC with trastuzumab at FUSCC from 2018 to 2021. Patients with available surgical tissue and serum samples at baseline, after C2, and at surgery were included in the study. C2, cycle 2; FUSCC, Fudan University Shanghai Cancer Center; HER2, human epidermal growth factor receptor 2; NAC, neoadjuvant chemotherapy.

clinicopathological characteristics, responses to NAC, and associated outcomes. pCR was defined as ypT0/is ypN0, indicating the absence of invasive cancer in both the breast and axillary nodes, regardless of ductal carcinoma *in situ*, post-NAC. Baseline evaluations consisted of clinical examinations, laboratory tests, and imaging techniques such as ultrasound, mammography, computed tomography (CT) scans of the chest, magnetic resonance imaging (MRI) of the breast or brain, and nuclear imaging methods including emission computed tomography (ECT) and positron emission tomography/CT (PET/CT). Treatment response was assessed after every two therapy cycles via clinical and imaging evaluations. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Review Community of FUSCC (No. 050432-4-2108*), and all patients signed informed consent forms in accordance with institutional guidelines.

Tissue and serum HER2 detection

Prior to initiating NAT, all patients underwent primary tumor biopsies for diagnostic confirmation, including IHC and fluorescence in situ hybridization (FISH) tests. Serum HER2 (sHER2) levels were measured at three points: baseline, post-second treatment cycle (C2), and during surgery.

IHC analysis of paraffin-embedded tumor samples was performed using the SP3 antibody (Thermo Fisher Scientific, Waltham, MA USA) and scored based on the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) 2018 guidelines (28) (scores: 0/1+, 2+, 3+). FISH was conducted using PathVysion HER-2 DNA Probe Kit (Abbott Molecular) with probes for HER2/neu and centromere 17. The HER2/CEP17 ratio and HER2 copy number were evaluated following ASCO/CAP 2018 standards.

Peripheral blood samples were collected to measure sHER2 levels. Plasma was freshly processed immediately after collection to maintain accuracy. Baseline levels were recorded before starting NAT, with additional measurements taken after two therapy cycles and at surgery when applicable. sHER2 concentrations were analyzed using the ADVIA Centaur CP Immunoassay System (Siemens, Germany), ensuring high precision with intra-assay variation <5% and inter-assay variation <10%.

Neoadjuvant treatment

A total of 120 patients received trastuzumab-based NAC. Most patients (n=88) underwent the PCH regimen, which included paclitaxel (80 mg/m^2 on days 1, 8, 15), carboplatin [area under the curve (AUC) =2 on days 1, 8, 15], and trastuzumab (loading dose 4 mg/kg and maintenance dose 2 mg/kg on days 1, 8, 15, 22), administered every four weeks for 4–6 cycles. Smaller groups of patients received alternative chemotherapy protocols: 25 patients were treated with the TCH regimen (docetaxel 75 mg/m^2 on day 1, carboplatin AUC =5 on day 1, and trastuzumab

with an 8 mg/kg loading dose and 6 mg/kg maintenance dose every three weeks for six cycles); 4 patients received the TH regimen (docetaxel 100 mg/m^2 on day 1 and trastuzumab with the same dosing schedule as TCH every three weeks for four cycles); and 3 patients were treated with the ddEC-PH regimen (epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 on day 1 every two weeks for four cycles, followed by paclitaxel 80 mg/m^2 on days 1, 8, 15 and trastuzumab 4 mg/kg loading dose and 2 mg/kg maintenance dose on the same days, administered every three weeks for four cycles).

Statistical analysis

The associations between sHER2 changes and NAT outcomes were evaluated using univariate and multivariate logistic regression analyses. Continuous variables were expressed as mean ± standard deviation or median (interquartile range, 25–75 percentiles) and analyzed using either the Student's *t*-test or the Wilcoxon rank-sum test. Categorical variables were reported as counts and percentages and analyzed with chi-square tests or Fisher's exact tests. Statistical analyses and curve plotting were conducted using SPSS software (version 25.0, SPSS, Chicago, IL, USA) and R software (version 4.1.2). A P value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 120 patients with HER2-positive BC who underwent trastuzumab-based NAT followed by surgery at FUSCC between 2018 and 2021, without evidence of distant metastasis, were included in this analysis. Of these, 60 patients (50%) achieved a total pathological complete response (tpCR). Significant differences are observed in clinical T (P=0.04), pathological T (P<0.001) and N (P<0.001) status. Regarding hormone receptor expression, the pCR group has a higher proportion of ER-negative patients (P=0.002), and HER2+/HR– subtypes (P=0.003). Lower Ki-67 levels are associated with a higher likelihood of achieving pCR (P<0.001) (*Table 1*).

Additionally, we focused on HER2 expression in both tissue and serum. Our findings revealed that the pCR group exhibits elevated baseline sHER2 levels, along with increased HER2 copy numbers and HER2/CEP17 ratios. However, these differences are not statistically significant (*Figure 2A*,*2B*).

sHER2 dynamics during NAT

Furthermore, we assessed the continuous changes in sHER2 levels throughout the NAT process, comparing the pCR and non-pCR groups at key time points: baseline, after cycle 2 (C2), and at surgery. In the pCR group, a significant and progressive decline in sHER2 levels is observed from baseline to after C2 (P<0.001), and from after C2 to at surgery (P=0.009), indicating a strong therapeutic response to NAT. In the non-pCR group, the reductions are less pronounced. The differences between baseline and C2, as well as between after C2 and at surgery, were statistically significant (P<0.001 and P=0.01, respectively), indicating a more moderate reduction compared to the pCR group (*Figure 3A*).

Furthermore, a more precise calculation of the relative changes in sHER2 levels for each patient was performed during the baseline-to-after C2, baseline-to-at surgery, and after C2-to-at surgery phases, respectively, controlling for the influence of preceding sHER2 levels. Significant reductions in sHER2 levels over time from baseline to C2 were observed in the pCR group compared to the non-pCR group (P=0.003). However, possibly due to the limited extent of sHER2 decline or the sample size, no significant difference between the pCR and non-pCR groups was observed from baseline to surgery (P=0.06) and from C2 to surgery (P=0.46) (*Table 1*, *Figure 3B*).

The predictive value of sHER2 dynamics regarding pCR

In the previous analysis, we found that ER status, Ki-67 levels, and changes in sHER2 from baseline to after C2 were strongly associated with pCR. We further investigated whether these variables could predict pCR. In the univariate analysis, changes in sHER2 from baseline to C2 are strongly predictive of pCR in both univariate [odds ratio (OR) 10.324, 95% confidence interval (CI): 2.057–51.806, P=0.005] and multivariate analysis (OR 8.470, 95% CI: 1.608–44.612, P=0.01). ER-positive status is also an independent predictor of pCR, with significant findings in both univariate (OR 0.311, 95% CI: 0.147–0.656, P=0.002) and multivariate analysis (OR 0.340, 95% CI: 0.158–0.735, P=0.006) (*Table 2*). The longitudinal changes in sHER2 levels from baseline to after C2 and at surgery are shown separately for ER-negative and ER-positive groups, demonstrating a significant decrease (ER-negative: baseline

Table 1 Patient characteristics stratified by pCR and non-pCR status

Characteristics	pCR (n=60)	Non-pCR (n=60)	P value
Age (years)	49.78±9.78	48.87±10.83	0.63
BMI (kg/m^2)	22.86 (21.37, 25.65)	23.16 (21.20, 25.24)	0.70
Height (cm)	159.18±4.59	160.52±4.44	0.11
Weight (kg)	60.04±9.07	59.86±7.84	0.91
BC family history			0.41
Negative	51 (42.5)	54 (45.0)	
Positive	9 (7.5)	6 (5.0)	
cT			0.04
I	12 (10.0)	2 (1.7)	
II	28 (23.3)	33 (27.5)	
III	7 (5.8)	7 (5.8)	
IV	13 (10.8)	18 (15)	
cN			0.12
0	8 (6.7)	15 (12.5)	
I	38 (31.7)	32 (26.7)	
II	6 (5)	10 (8.3)	
III	8 (6.7)	3 (2.5)	
Clinical stage			0.36
I	1 (0.8)	0 (0)	
II	33 (27.5)	28 (23.3)	
III	26 (21.7)	32 (26.7)	
pT			<0.001
0	60 (50.0)	13 (10.8)	
I	0 (0)	39 (32.5)	
II	0 (0)	7 (5.8)	
III	0 (0)	1 (0.8)	
pN			<0.001
0	60 (50.0)	27 (22.5)	
I	0 (0)	23 (19.2)	
II	0 (0)	3 (2.5)	
III	0 (0)	7 (5.8)	
Pathological stage			<0.001
0	60 (50.0)	0 (0)	
I	0 (0)	24 (20.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	pCR (n=60)	Non-pCR (n=60)	P value
II	0 (0)	25 (20.8)	
III	0 (0)	11 (9.2)	
ER			0.002
Negative	40 (33.3)	23 (19.2)	
Positive	20 (16.7)	37 (30.8)	
PR			0.08
Negative	44 (36.7)	35 (29.2)	
Positive	16 (13.3)	25 (20.8)	
Ki-67			<0.001
Low	0 (0)	10 (8.3)	
High	60 (50.0)	50 (41.7)	
Molecular subtype			0.003
HER2+/HR−	39 (32.5)	23 (19.2)	
HER2+/HR+	21 (17.5)	37 (30.8)	
HER2 status IHC score			>0.99
2+	5 (4.2)	5 (4.2)	
3+	55 (45.8)	55 (45.8)	
FISH			0.13
Negative	0 (0)	3 (2.5)	
Positive	59 (49.2)	57 (47.5)	
Unknown	1 (0.8)	0 (0)	
HER2 copy number/nucleus	20 (17.5, 20)	17.5 (14, 20)	0.08
HER2/CEP17	8 (5.8824, 8.75)	7 (4.125, 8.1875)	0.11
Baseline sHER2 level (ng/μL)	17.45 (12.75, 28.5)	15 (12.6, 20.025)	0.18
sHER2 level after C2 (ng/μL)	11.5 (9.625, 13.2)	11.7 (10, 12.75)	0.70
sHER2 level at surgery (ng/μL)	10.69±2.34	10.59±2.19	0.81
sHER2 change from baseline to C2 (ng/μL)	0.370±0.240	0.238±0.240	0.003
sHER2 change from baseline to surgery (ng/μL)	0.395±0.280	0.303±0.255	0.06
sHER2 change from C2 to surgery (ng/μL)	0.0614±0.200	0.0868±0.171	0.46
Local therapy			>0.99
Breast-conserving surgery	5 (4.2)	4 (3.3)	
Mastectomy	55 (45.8)	56 (46.7)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	pCR (n=60)	Non-pCR (n=60)	P value
Axillary surgery			0.09
SLNB	14 (11.7)	7 (5.8)	
ALND	46 (38.3)	53 (44.2)	
Neoadjuvant therapy regimen			0.71
PCH	44 (36.7)	44 (36.7)	
TCH	12 (10)	13 (10.8)	
TH	3 (2.5)	1 (0.8)	
ddEC-PH	1 (0.8)	2 (1.7)	
Efficacy after C2			0.06
Partial response	55 (45.8)	48 (40)	
SD	4 (3.3)	12 (10)	
PD	0 (0)	0 (0)	
Unknown	1 (0.8)	0 (0)	
MP grade			<0.001
5	60 (50.0)	10 (8.3)	
4	0 (0)	21 (17.5)	
3	0 (0)	18 (15)	
2	0 (0)	8 (6.7)	
Unknown	0 (0)	3 (2.5)	

Data are presented as mean ± standard deviation or median (IQR) or n (%). "+" indicates positive status, and "–" indicates negative status. ALND, axillary lymph node dissection; BC, breast cancer; BMI, body mass index; cN, clinical nodal stage; cT, clinical tumor stage; ddEC-PH, dose-dense epirubicin, cyclophosphamide, followed by paclitaxel, and trastuzumab regimen; ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IQR, interquartile range; MP grade, Miller-Payne grade; PCH, paclitaxel, carboplatin, and trastuzumab regimen; PD, progressive disease; PR, progesterone receptor; pCR, pathological complete response; pN, pathological nodal stage; pT, pathological tumor stage; SD, stable disease; SLNB, sentinel lymph node biopsy; TCH, docetaxel, carboplatin, and trastuzumab regimen; TH, docetaxel and trastuzumab regimen.

to after C2, P<0.001; after C2 to surgery, P=0.002; ER-positive: baseline to after C2, P=0.001; after C2 to surgery, P=0.006) and exhibiting a similar trend between the two groups (*Figure 3C*). We further compared sHER2 changes between ER-negative and ER-positive patients and found no significant differences between the two groups (*Figure 3D*). Other variables including HER2 signal number/nucleus, HER2/CEP17, sHER2 change from baseline to at surgery, sHER2 change from after C2 to at surgery, PR, and Ki67 do not show consistent or significant associations with pCR.

These results indicate that a reduction in sHER2 levels from baseline to after C2, and ER status are strongly associated with achieving pCR.

Discussion

NAT is a crucial treatment approach for patients with HER2-positive BC (37,38). While previous studies on sHER2 detection have primarily focused on advanced-stage disease, the results have often been conflicting and complex (35,36,39). Previous study has suggested that low sHER2 levels after two cycles of NAT are associated with achieving pCR (40). This raises an important question: Can the relative dynamics of sHER2 provide early insights into

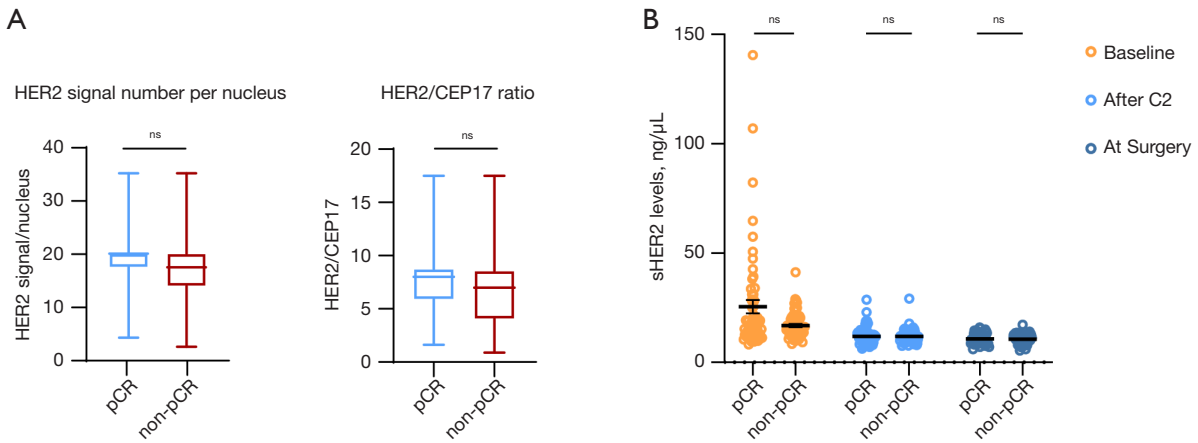

Figure 2 sHER2 levels and tHER2 expression in pCR and non-pCR groups. (A) HER2 signal number per nucleus and HER2/CEP17 ratios in pCR and non-pCR groups. (ns: not significant). (B) sHER2 levels (ng/μL) measured at three time points—baseline, after C2, and at surgery—are shown for both the pCR and non-pCR groups. ns: not significant. C2, cycle 2; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; sHER2, serum HER2; tHER2, tissue HER2.

treatment efficacy for patients undergoing NAT?

Our study included patients undergoing NAT with sHER2 levels measured at three consecutive stages, and we evaluated the value of sHER2 changes throughout the treatment phases. Our study demonstrates the predictive value of sHER2 dynamics in achieving pCR in HER2-positive BC patients receiving NAT. Specifically, our findings underscore the pivotal role of early sHER2 reductions after the second cycle, in predicting therapeutic response.

One of the most notable observations was the significant and progressive decline in sHER2 levels in the pCR group compared to the non-pCR group, particularly from baseline to C2. This early decline in sHER2 may serve as an important biomarker for monitoring treatment efficacy, as patients with greater reductions in sHER2 during this early phase were more likely to achieve pCR. In contrast, the non-pCR group exhibited less pronounced reductions in sHER2, especially from C2 to surgery, suggesting that these patients might benefit from alternative or additional therapeutic strategies to enhance treatment response. These findings are consistent with prior studies that have reported the predictive value of sHER2 monitoring in clinical outcomes (41,42).

Furthermore, the logistic regression analysis further supports the utility of sHER2 changes as a predictive marker. The significant association between a reduction in sHER2 from baseline to C2 and pCR, even after adjusting for confounding factors in multivariate analysis, underscores the importance of early treatment monitoring.

The clinical implications of these findings are substantial. First, the ability to predict pCR early in the NAT process could guide treatment decisions and optimize therapeutic strategies. Patients showing a marked early decline in sHER2 levels could continue with standard HER2-targeted regimens, while those with less pronounced reductions may warrant treatment intensification or the incorporation of alternative therapies. Furthermore, our findings suggest that monitoring sHER2 dynamics could help identify patients who may benefit most from dual HER2-targeted therapy, given the higher pCR rates observed in these patients.

However, this study has certain limitations. The sample size, particularly in subgroup analyses, may limit the generalizability of the findings. Additionally, while we identified significant associations between sHER2 dynamics and pCR, the mechanistic basis for these changes warrants further investigation. It is also important to note that while sHER2 changes provide valuable predictive insights, they should be considered alongside other established biomarkers and clinical factors when making treatment decisions.

Conclusions

In conclusion, our study demonstrates that early reductions in sHER2 levels after C2, are strongly predictive of pCR in patients with HER2-positive BC undergoing NAT. Monitoring sHER2 dynamics could provide clinicians with valuable insights into treatment efficacy and guide

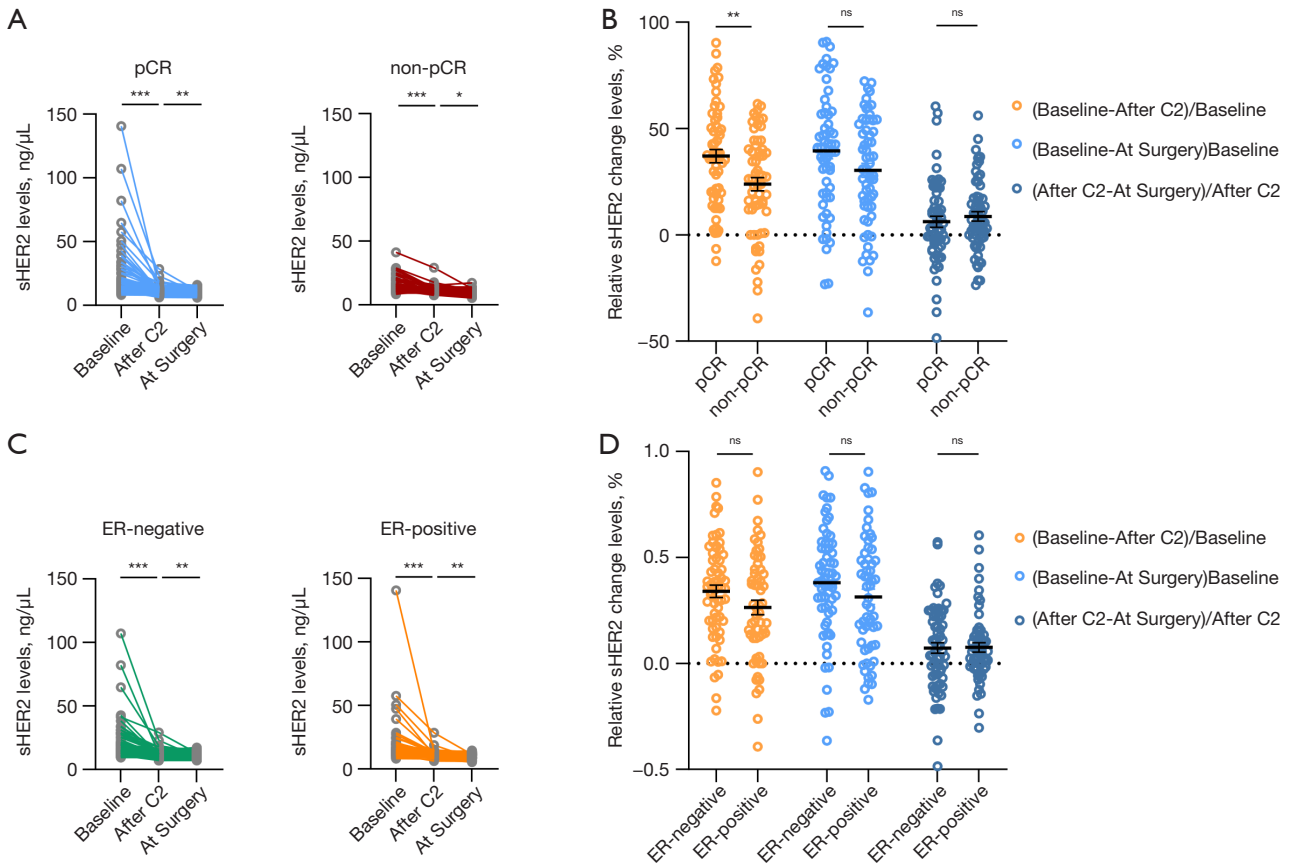

Figure 3 Changes in sHER2 over time in pCR and non-pCR groups or ER-negative and ER-positive groups. (A) The continuous changes of sHER2 levels measured at three time points—baseline, after C2, and at surgery for pCR and non-pCR groups. (B) Relative changes in sHER2 levels (%) in (baseline – after C2)/baseline, (baseline – at surgery)/baseline, and (after C2 – at surgery)/after C2, for pCR and non-pCR groups. (C) The continuous changes of sHER2 levels measured at three time points—baseline, after cycle 2 (C2), and at surgery for ER-negative and ER-positive groups. (D) Relative changes in sHER2 levels (%) in (baseline – after C2)/baseline, (baseline – at surgery)/baseline, and (after C2 – at surgery)/after C2, for ER-negative and ER-positive groups. ***, P<0.001; **, P<0.01; *, P<0.05; ns, not significant. C2, cycle 2; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; sHER2, serum HER2; tHER2, tissue HER2.

Table 2 Logistic regression results of pCR

Characteristics	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
HER2 signal number range/nucleus	1.042 (0.992–1.094)	0.10		
HER2/CEP17	1.088 (0.976–1.212)	0.13		
sHER2 change from baseline to C2	10.324 (2.057–51.806)	0.005	8.470 (1.608–44.612)	0.01
sHER2 change from baseline to surgery	3.644 (0.918–14.460)	0.07		
sHER2 change from C2 to surgery	0.475 (0.067–3.345)	0.46		
ER (positive versus negative)	0.311 (0.147–0.656)	0.002	0.340 (0.158–0.735)	0.006
PR (positive versus negative)	0.509 (0.236–1.098)	0.09		
KI67 (low versus high)	0.000 (0.000–Inf)	0.99		

CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; PR, progesterone receptor; sHER2, serum human epidermal growth factor receptor 2.

more personalized therapeutic approaches. Further studies with larger cohorts are needed to validate these findings and explore the underlying mechanisms that drive the relationship between sHER2 dynamics and therapeutic response.

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None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-432/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Review Community of Fudan University Shanghai Cancer Center (FUSCC) (No. 050432-4-2108*), and all patients signed informed consent forms in accordance with institutional guidelines.

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