Nomogram for Predicting Pathological Complete Response after Neoadjuvant Chemotherapy in Operable Primary Breast Cancer

Yanli Lv, Weimin Mu, Qingzhong Yang, Huiying Xu, Baochen Jin and Yi Li

Breast Centre, Shunyi District Health Care Hospital for Women and Children of Beijing, Beijing, China

ABSTRACT

Objective: To establish a predictive model for pathological complete response (pCR) in operable primary breast cancer after neoadjuvant chemotherapy (NAC).

Study Design: Observational study.

Place and Duration of the Study: Breast Centre, Shunyi District Health Care Hospital for Women and Children of Beijing, Beijing, China, from January 2010 to June 2023.

Methodology: Four hundred and fourteen operable invasive breast cancer patients who received NAC were included in this study. After a random assignment at a ratio of 7:3, 289 patients in the training set were analysed for model building, and the remaining 125 patients in the test set were used for validation. The definition of pCR was the absence of residual invasive disease in either the breasts or the axillary lymph nodes (ypT0 / is ypN0). After multivariate logistic regression analysis, a nomogram was drawn. In the validation phase, the receiver operating characteristic (ROC) curve and AUC were used for evaluation of discrimination, while the calibration plot and Hosmer-Lemeshow test for calibration. Additionally, a decision curve was drawn.

Results: A model containing 8 variables, including BMI, tumour size, histological grade, HR, HER2, axilla status, chemotherapy cycles, and regimens was built. After validation, the model had moderate discriminatory power [AUC, 0.831; 95% CI (0.733, 0.928)]. Calibration curve and Hosmer-Lemeshow goodness of fit (GOF) test ($p = 0.1645$) demonstrated that the model fitted well. Meanwhile, the decision curve analysis revealed that the model was beneficial to patients.

Conclusion: Model containing BMI, tumour size, histological grade, HR, HER2, axilla status, chemotherapy cycles, and regimens showed moderate discrimination and calibration abilities in predicting pCR.

Key Words: *Breast neoplasms, Neoadjuvant therapy, Surgery, Pathology, Nomogram.*

How to cite this article: Lv Y, Mu W, Yang Q, Xu H, Jin B, Li Y. Nomogram for Predicting Pathological Complete Response after Neoadjuvant Chemotherapy in Operable Primary Breast Cancer. *J Coll Physicians Surg Pak* 2025; **35(03)**:324-330.

INTRODUCTION

Neoadjuvant chemotherapy (NAC) has been increasingly used in locally advanced breast cancer for achieving clinical downstaging. Several studies have demonstrated that patients achieving pathological complete response (pCR) have shown better prognoses.[1,2]

Some clinical and pathological characteristics such as low T stage, hormone receptor negativity, high histological grade, and high expression of Ki67 are predictors of pCR.[3,4] Previous studies have shown poorer responses to NAC in overweight and obese women, however, controversy still exists.[5,6]

Correspondence to: Dr. Yi Li, Breast Centre, Shunyi District Health Care Hospital for Women and Children of Beijing, Shunyi District, Beijing, China
E-mail: liyiborui@126.com

Received: August 12, 2024; Revised: January 16, 2025; Accepted: February 14, 2025
DOI: https://doi.org/10.29271/jcpsp.2025.03.324

Besides, peripheral blood inflammatory indicators, for instance, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) may be related to tumour response but also controversial.[4,7,8]

A nomogram is a graphical representation of a multivariable model that integrates multiple predictive factors and can be used to accurately evaluate individual probabilities of a specific endpoint at a certain time.[9] Recently, a nomogram is widely used for predicting the prognosis of different malignancies.[10,11]

The purpose of this study was to establish a predictive model including BMI, clinical and pathological variables, as well as treatment information for pCR after NAC in operable primary breast cancer. Subsequently, the model was evaluated, and a nomogram was plotted.

METHODOLOGY

The patients selected had to meet the following inclusion criteria: (a) Female aged over 18 years; (b) invasive breast cancer confirmed by core needle biopsy (CNB) pathology; (c) clinical stage I-IIIA; (d) received NAC for at least 4 cycles followed by surgery. The exclusion criteria encompassed the

absence of crucial pathological information, including pathological grade, HER2 status, or Ki67 expression. A total of 448 female invasive breast cancer patients met the inclusion criteria at the Breast Centre, Shunyi District Health Care Hospital for Women and Children of Beijing, Beijing, China, during the study period from January 2010 to June 2023. After eliminating the missing data, 414 patients were selected for analysis. All 414 patients were randomly assigned at a ratio of 7:3 to training set (n = 289) for model building and test set (n = 125) for validation (Figure 1). All patients signed written informed consent before treatment. This study was approved by the Research and Ethical Committee of Shunyi District Health Care Hospital for Women and Children of Beijing, Beijing, China.

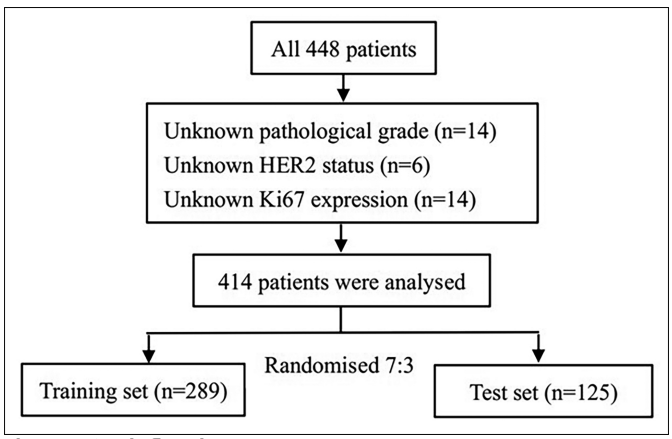

Figure 1: Study flowchart.

Ultrasonic examination and CNB were typically performed prior to admission, while neoadjuvant chemotherapy and surgery were carried out during the hospitalisation period. Consequently, outpatient and inpatient workstations were both utilised for collecting demographic characteristics and clinical and pathological data. In accordance with the Chinese standard of classification criteria for obesity,[12] a BMI ranging from 24.0 to 27.9 was defined as overweight, whereas a BMI of 28.0 or higher was classified as obesity. The cut-off values for neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were set as 2.1 and 150, respectively, consistent with the previous study.[4]

All patients underwent a routine ultrasonic examination before CNB, and the maximum tumour diameter was measured and recorded. The expression status of ER, PgR, HER2, and Ki67 were evaluated through immunohistochemistry (IHC). Tumours with HER2 score ++ were further examined by FISH according to guidelines and expert consensus of China.[13,14] An IHC-based Ki67 index of ≥20% was defined as a high expression. ER or PgR were considered positive if ≥1% of tumour cells showed positive nuclear staining on IHC.[15]

A two-step approach was adopted to assess the baseline status of axillary lymph nodes: Initially, during ultrasonic examination, the ipsilateral axillary region was scanned, and CNB or fine needle aspiration (FNA) was performed if an abnormal morphological lymph node was found; secondly, for patients whose CNB or FNA result of abnormal morphological lymph node turned out negative, as well as those without abnormal lymph node on baseline routine ultrasonic examination, sentinel lymph node biopsy (SLNB) was recommended. Axillary lymph node dissection was exempted for patients without axillary lymph node involvement in SLNB. Conversely, patients with positive results in any one of the biopsies (CNB, FNA, or SLNB), as well as those who did not undergo SLNB, would accept axillary lymph node dissection during surgery.

The relative dose intensity was calculated based on the standard dose of various chemotherapy medicines outlined in the 2008 National Comprehensive Cancer Network (NCCN) guidelines.[14] Anthracycline-included regimens indicated CAF (cyclophosphamide, anthracycline, and 5-fluorouracil), AC (anthracycline and cyclophosphamide), AT (anthracycline and taxane), TAC (taxane, anthracycline, and cyclophosphamide), AC-T (anthracycline and cyclophosphamide followed by taxane). While the anthracycline-excluded regimens indicated TP (taxane and carboplatin), XT (capecitabine and taxane), and TC (taxane and cyclophosphamide). Patients with HER2-positive tumours were recommended synchronous targeted treatment (Trastuzumab, Pertuzumab, and Pyrotinib, either alone or in combination, as per the guidelines and accessibility of anti-HER2 medicines) along with the chemotherapy.

According to the 7th Edition of AJCC Cancer Staging Manual,[16] the standard of pCR was defined as the absence of residual invasive disease in either the breasts or the axillary lymph nodes, while noninvasive breast residuals (such as ductal carcinoma *in situ*) was permitted (ypT0 / is ypN0).

Statistical analysis was performed using the R 4.2.1 software. Frequency (percentage) was used for the description of categorical variables. The association of clinical or pathological characteristics with pCR was analysed using Pearson's χ^2 test, as well as the distribution of baseline characteristics between the training set and test set. A total of 9 variables (BMI, tumour size, histological grade, HR status, HER2 status, axilla status, Ki67 expression, chemotherapy cycles, and regimens) with p-value <0.1 in univariate analysis were included in the initial multivariate logistic regression model using data of the training set. Following the application of a backward stepwise method for filtering variables, a refined model containing 8 variables was established, and a nomogram was drawn. During the validation phase, discrimination, calibration, and decision curve of the model were evaluated using data of the test set. The receiver operating characteristic curve (ROC) was plotted, and area under curve (AUC) was calculated to quantify the discriminatory power of the model. Calibration curve, Hosmer-Lemeshow the goodness of fit (GOF) test was used for evaluation of the calibration performance of the model. Additionally, a decision curve was used to assess the potential benefits for patients derived from model predictions. All statistical tests were two-sided, and statistical significance was defined as a p-value <0.05.

Table I: Association of clinical and pathological characteristics with pCR.

Parameters	pCR (n = 140, %)	non-pCR (n = 274, %)	Statistics	p-value*
Age (year)			1.6104	0.2044
≤50	58 (41.4)	133 (48.5)		
>50	82 (58.6)	141 (51.5)		
BMI			11.866	0.002651
Normal/low weight	56 (40.0)	66 (24.1)		
Overweight	45 (32.1)	122 (44.5)		
Obesity	39 (27.9)	86 (31.4)		
Menopause			2.1989	0.1381
Yes	80 (57.1)	134 (48.9)		
No	60 (42.9)	140 (51.1)		
Family history of malignancy			1.7099	0.191
Yes	23 (16.4)	31 (11.3)		
No	117 (83.6)	243 (88.7)		
Baseline NLR			0.1372	0.7111
<2.1	76 (54.3)	142 (51.8)		
≥2.1	64 (45.7)	132 (48.2)		
Baseline PLR			2.4351	0.1186
<150	84 (60.0)	187 (68.2)		
≥150	56 (40.0)	87 (31.8)		
Tumour size (cm)			6.119	0.01337
≤2	40 (28.6)	48 (17.5)		
>2	100 (71.4)	226 (82.5)		
Grade			26.673	$2.409e^{-7}$
I+II	66 (47.1)	201 (73.4)		
III	74 (52.9)	73 (26.6)		
HR			32.411	$1.248e^{-8}$
Negative	73 (52.1)	65 (23.7)		
Positive	67 (47.9)	209 (76.3)		
HER2			30.595	$3.178e^{-8}$
Negative	58 (41.4)	192 (70.1)		
Positive	82 (58.6)	82 (29.9)		
Ki67			10.555	0.001159
Low expression	8 (5.7)	49 (17.9)		
High expression	132 (94.3)	225 (82.1)		
Axillary lymph nodes			24.713	$6.654e^{-7}$
Negative	79 (56.4)	84 (30.7)		
Positive	61 (43.6)	190 (69.3)		
Chemotherapy cycles			5.7986	0.05506
4~	12 (8.6)	46 (16.8)		
6~	57 (40.7)	92 (33.6)		
8~	71 (50.7)	136 (49.6)		
Chemotherapy regimens			49.06	$2.483e^{-12}$
Anthracycline-included	26 (18.6)	151 (55.1)		
Anthracycline-excluded	114 (81.4)	123 (44.9)		

*BMI, Body mass index; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; HR, Hormone receptor (oestrogen receptor, ER or progesterone receptor, PgR); HER2, Human epidermal growth factor receptor 2. *Pearson's χ^2 test.*

RESULTS

Altogether, 33.8% (140/414) of breast tumours obtained pCR after operation. Notably, a significant difference in pCR rate was seen among different breast cancer subtypes (χ^2 = 22.267, p = $1.461e^{-5}$). Tumours with HER2-positive had demonstrated the highest pCR rate, which was 50.0% (82/164), followed by TN of 44.0% (33/75), while the luminal subtype represented the lowest pCR rate of 14.3% (25/175).

The association of clinical and pathological characteristics with pCR is shown in Table I. After random allocation, 289 breast cancer patients were included in the training set, while the remaining 125 patients in the test set. The patient characteristics between the training set and test set are listed in Table II, and the distribution of all characteristics was balanced between the two groups.

Using the data from the training set, the initial logistic regression model contained nine variables, after backward stepwise methods, eight variables remained in the model, which were BMI, tumour size, histological grade, HR status, HER2 status, axilla status, chemotherapy cycles, and regimens (Table III). Based on this refined model, a nomogram was drawn (Figure 2).

Data of the 125 breast cancer patients from the test set was used for validation. Area under ROC curve (AUC) was 0.831 [95% CI (0.733, 0.928)] (Figure 3), indicating that the model had moderate discriminatory power. Calibration curve (Dxy 0.661, Figure 4), as well as Hosmer-Lemeshow goodness of fit (GOF) test (p-value = 0.1645) demonstrated that the model exhibited well fit and effective calibration. Besides, decision curve analysis (Figure 5) revealed the predictions of the model were beneficial to patients.

Table II: Clinical and pathological characteristics between training set and test set.

Parameters	Training set (n, %)	Test set (n, %)	Statistics	p-value*
Age (years)			0	>0.99
≤50	133 (46.0)	58 (46.4)		
>50	156 (54.0)	67 (53.6)		
BMI			1.4817	0.4767
Normal/low weight	88 (30.4)	34 (27.2)		
Overweight	111 (38.4)	56 (44.8)		
Obesity	90 (31.1)	35 (28.0)		
Menopause			0.036065	0.8494
Yes	148 (51.2)	66 (52.8)		
No	141 (48.8)	59 (47.2)		
Family history of malignancy			0.14445	0.7039
Yes	36 (12.5)	18 (14.4)		
No	253 (87.5)	107 (85.6)		
Baseline NLR			0	>0.99
<2.1	152 (52.6)	66 (52.8)		
≥2.1	137 (47.4)	59 (47.2)		
Baseline PLR			0.00531	0.9419
<150	190 (65.7)	81 (64.8)		
≥150	99 (34.3)	44 (35.2)		
Tumour size (cm)			2.4077	0.1207
≤2	55 (19.0)	33 (26.4)		
>2	234 (81.0)	92 (73.6)		
Grade			0.00067274	0.9793
I+II	187 (64.7)	80 (64.0)		
III	102 (35.3)	45 (36.0)		
HR			0.75781	0.384
Negative	92 (31.8)	46 (36.8)		
Positive	197 (68.2)	79 (63.2)		
HER2			0.77302	0.3793
Negative	170 (58.8)	80 (64.0)		
Positive	119 (41.2)	45 (36.0)		
Ki67			0.50613	0.4768
Low expression	37 (12.8)	20 (16.0)		
High expression	252 (87.2)	105 (84.0)		
Axillary lymph nodes			0.25068	0.6166
Negative	111 (38.4)	52 (41.6)		
Positive	178 (61.6)	73 (58.4)		
Chemotherapy cycles			0.23268	0.8902
4~	39 (13.5)	19 (15.2)		
6~	104 (36.0)	45 (36.0)		
8~	146 (50.5)	61 (48.8)		
Chemotherapy regimens			0.1766	0.6743
Anthracycline-included	126 (43.6)	51 (40.8)		
Anthracycline-excluded	163 (56.4)	74 (59.2)		
Pathological response			0.91598	0.3385
pCR	93 (32.2)	47 (37.6)		
Non-pCR	196 (67.8)	78 (62.4)		

** Pearson's χ^2 test.*

Table III: Multivariate logistic regression model for prediction of pCR.

Parameters	OR (95% CI)	p-value*
BMI (overweight *versus* obesity)	0.55 (0.27, 1.11)	0.0956
BMI (normal *versus* obesity)	1.68 (0.82, 3.51)	0.158
Tumour size (≤2 *versus* >2)	1.78 (0.85, 3.72)	0.127
Grade (III *versus* I+II)	2.42 (1.29 - 4.60)	0.00646
HR (negative *versus* positive)	1.75 (0.94, 3.27)	0.0766
HER2 (positive *versus* negative)	2.98 (1.61, 5.63)	0.000604
Axilla status (negative *versus* positive)	1.90 (1.04, 3.50)	0.0387
Chemotherapy cycles (6 *versus* 4)	2.68 (1.01, 7.91)	0.0585
Chemotherapy cycles (8 *versus* 4)	3.42 (1.29, 10.16)	0.0185
Chemotherapy regimens (anthracycline excluded *versus* anthracycline included)	2.32 (1.17, 4.69)	0.0176

** Multivariate logistic regression model.*

DISCUSSION

NAC is a crucial component of comprehensive treatment for breast cancer, and the ultimate aim is the attainment of pCR. Recently, pCR has emerged as a surrogate endpoint for accelerated approval of anti-tumour medicines in the neoadjuvant setting, which means, achieving pCR may be to a certain extent indicative of improved survival.[17,18]

In this study, a model containing eight variables (BMI, tumour size, histological grade, HR status, HER2 status, axilla status, chemotherapy cycles, and regimens) was built, among which, histological grade, HER2 status, axilla status, chemotherapy cycles, and regimens were independent predictors of pCR. Literature has demonstrated that higher histological grade and positive HER2 status predict better tumour response.[19,20] Ki67 was found to be significantly associated

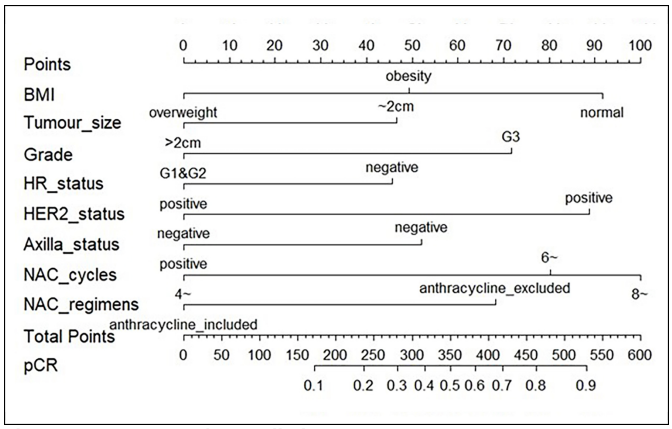

Figure 2: Nomogram for predicting pCR.

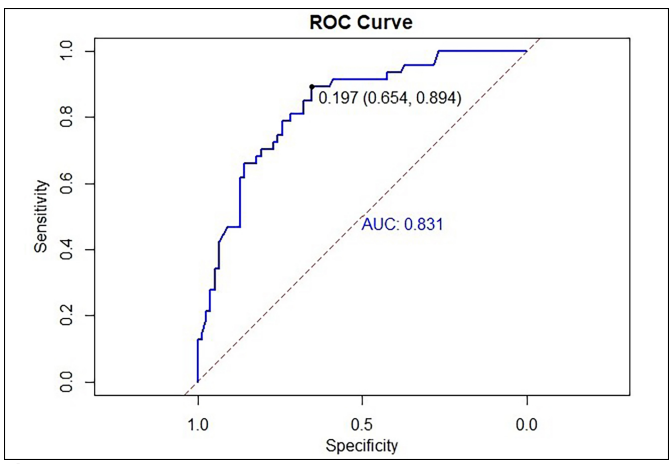

Figure 3: ROC curve.

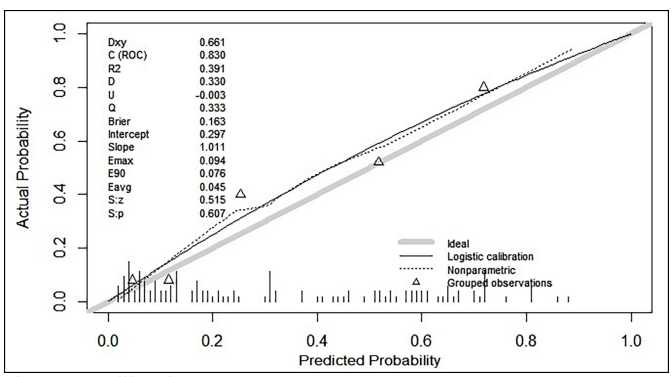

Figure 4: Calibration curve.

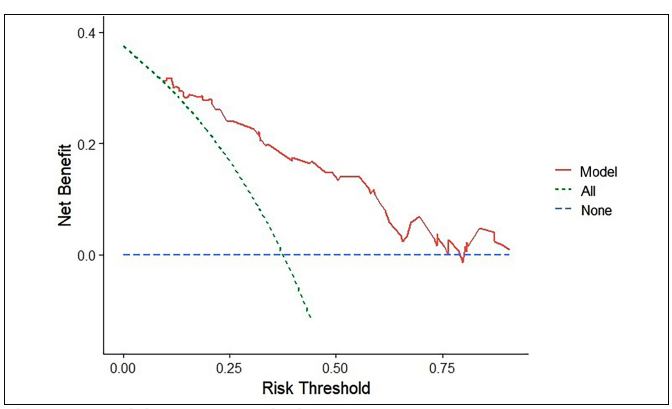

Figure 5: Decision curve analysis.

with histological grade in this study. Specifically, patients with the histological grade III, demonstrated a significantly higher expression rate of high Ki67 compared to those with histological grade I together with II (95.9% *vs*. 80.9%, $\chi^2 = 16.771$, $p = 4.218e^{-5}$), probably as both indices represent faster proliferation. Thus, Ki67 expression was excluded from the refined model. NAC combined with targeted therapy is the preferred recommendation for HER2-positive breast cancer according to guidelines. Notably, HER2 positivity was a favourable predictive factor in both univariable and multivariable analyses. Patients with axillary lymph node uninvolved had relatively early TNM stage, which meant easier to achieve pCR than those with axillary lymph node metastasis. The present study revealed that an increased number of chemotherapy cycles and utilisation of anthracycline-excluded regimens could enhance the pCR rate.

This study failed to verify BMI as an independent predictor of pCR, which was also demonstrated by two other studies recently.[21,22] Besides, tumour size was also not an independent predictor of pCR, which may be ascribed to relatively smaller sample size in comparison to studies based on data from the National Cancer Registry.[23,24] Similarly, a negative HR status would improve the pCR rate without statistically significant [OR = 1.75, 95% CI (0.94, 3.27), p = 0.0766]. Even though, the refined model included the aforementioned three factors in order to enhance the accuracy of predicting pCR. The nomogram was subsequently drawn. Internal validation was done using a test set. The model showed moderate discriminatory power (AUC, 0.831) and calibration (Dxy, 0.661) ability. A decision curve analysis further confirmed the model could bring benefit to patients.

Certainly, this study has some limitations. Firstly, as a retrospective study conducted at a single centre over a relatively extended period, selection bias might have occurred and changes in treatment philosophy concerning NAC might influence the selection of patients. Secondly, external validation using data from other institutions was lacking. Besides, the smaller sample size might lead to instability model.

CONCLUSION

The predicting model which incorporated BMI, tumour size, histological grade, HR, HER2, axilla status, chemotherapy cycles, and regimens performed well in both discrimination and calibration evaluation. A nomogram was a helpful instrument in representing the probability of pCR for a specific patient. It is necessary to conduct further external validation studies before extrapolation of the conclusion.

ETHICAL APPROVAL:

The present study was approved prior to initiation of the research work by the Research and Ethical Committee of Shunyi District Health Care Hospital for Women and Children of Beijing, Beijing, China, and conducted in accordance with the Principles of Helsinki Declaration (Approval No: 2023-01; Dated: 12 January 2023).

PATIENTS' CONSENT:
All patients signed written informed consent before the neoadjuvant treatment. As an observational study, a waiver for informed consent was obtained from the Research and Ethical Committee of Shunyi District Health Care Hospital for Women and Children of Beijing, Beijing, China, and all the data from patients were analysed anonymously.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
YL: Collected the data, performed data analysis, and wrote the paper.
WM, QY, HX, BJ: Contributed to the interpretation of the data and critical revision for important intellectual content.
YL: Designed the study and reviewed the manuscript.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Broglio KR, Quintana M, Foster M, Olinger M, McGlothlin A, Berry SM, *et al*. Association of pathologic complete response to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes: A meta-analysis. *JAMA Oncol* 2016; **2(6)**:751-60. doi: 10.1001/jamaoncol.2015.6113.
2. Haque W, Verma V, Hatch S, Klimberg VS, Butler EB, Teh BS. Response rates and pathologic complete response by breast cancer molecular subtype following neoadjuvant chemotherapy. *Breast Cancer Res Treat* 2018; **170(3)**: 559-67. doi: 10.1007/s10549-018-4801-3.
3. Prete SD, Caraglia M, Luce A, Montella L, Galizia G, Sperlongano P, *et al*. Clinical and pathological factors predictive of response to neoadjuvant chemotherapy in breast cancer: A single center experience. *Oncol Lett* 2019; **18(4)**:3873-9. doi: 10.3892/ol.2019.10729.
4. Lv Y, Li Y, Mu W, Fu H. Factors affecting pathological complete response after neoadjuvant chemotherapy in operable primary breast cancer. *J Coll Physicians Surg Pak* 2020; **30(4)**:389-93. doi: 10.29271/jcpsp.2020.04.389.
5. Usiskin I, Li F, Irwin ML, Cartmel B, Sanft T. Association between pre-diagnosis BMI, physical activity, pathologic complete response, and chemotherapy completion in women treated with neoadjuvant chemotherapy for breast cancer. *Breast Cancer* 2019; **26(6)**:719-28. doi: 10.1007/s12282-019-00974-3.
6. Erbes T, Stickeler E, Rucker G, Buroh S, Asberger J, Dany N, *et al*. BMI and pathologic complete response to neoadjuvant chemotherapy in breast cancer: A study and meta-analysis. *Clin Breast Cancer* 2016; **16(4)**:e119-32. doi: 10.1016/j.clbc.2016.02.018.
7. Acikgoz O, Yildiz A, Bilici A, Olmez OF, Basim P, Cakir A. Pretreatment platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio as a predictor of pathological complete response to neoadjuvant chemotherapy in patients with breast cancer: Single center experience from Turkiye. *Anticancer Drugs* 2022; **33(10)**:1150-5. doi: 10.1097/CAD.0000000000001389.
8. Jin X, Wang K, Shao X, Huang J. Prognostic implications of the peripheral platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in predicting pathologic complete response after neoadjuvant chemotherapy in breast cancer patients. *Gland Surg* 2022; **11(6)**:1057-66. doi: 10.21037/gs-22-244.
9. Touijer K, Scardino PT. Nomograms for staging, prognosis, and predicting treatment outcomes. *Cancer* 2009; **115(13 Suppl)**:3107-11. doi: 10.1002/cncr.24352.
10. Liu Q, Li W, Xie M, Yang M, Xu M, Yang L, *et al*. Development and validation of a SEER-based prognostic nomogram for cervical cancer patients below the age of 45 years. *Bosn J Basic Med Sci* 2021; **21(5)**:620-31. doi: 10.17305/bjbms.2020.5271.
11. Pan X, Yang W, Chen Y, Tong L, Li C, Li H. Nomogram for predicting the overall survival of patients with inflammatory breast cancer: A SEER-based study. *Breast* 2019; **47**:56-61. doi: 10.1016/j.breast.2019.05.015.
12. Zhou B, Coorperative Meta-Analysis Group of China Obesity Task Force. Predictive values of body mass index and waist circumference to risk factors of related diseases in Chinese adult population. *Zhonghua Liu Xing Bing Xue Za Zhi* 2002; **23(1)**:5-10. Available from: https://pubmed.ncbi.nlm.nih.gov/12015100/.
13. Carlson RW, Moench SJ, Hammond ME, Perez EA, Burstein HJ, Allred DC, *et al*. HER2 testing in breast cancer: NCCN Task Force report and recommendations. *J Natl Compr Canc Netw Suppl* 2006; **4(Suppl 3)**:S1-24. Available from: https://pubmed.ncbi.nlm.nih.gov/16813731/.
14. NCCN Clinical Practice Guidelines in Oncology for Breast Cancer (Chinese Version 1). 2008; **26**:35-40.
15. Untch M, Gerber B, Harbeck N, Jackisch C, Marschner N, Mobus V, *et al*. 13th st. Gallen international breast cancer conference 2013: Primary therapy of early breast cancer evidence, controversies, consensus - opinion of a German team of experts (Zurich 2013). *Breast Care (Basel)* 2013; **8(3)**:221-9. doi: 10.1159/000351692.
16. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. ed. 7th, Chicago: American Joint Committee On Cancer Executive Office; 2010.
17. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, *et al*. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: A randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2013; **24(9)**:2278-84. doi: 10.1093/annonc/mdt182.
18. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, *et al*. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): A multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016; **17(6)**:791-800. doi: 10.1016/S1470-2045(16)00163-7.
19. Jarzab M, Stobiecka E, Rybicka AB, Chmielik E, Kowalska M, Bal W, *et al*. Association of breast cancer grade with response to neoadjuvant chemotherapy assessed postoperatively. *Pol J Pathol* 2019; **70(2)**:91-9. doi: 10.5114/pjp.2019.87101.

20. Hou N, Xiao J, Wang Z, Wu Y, Hou G, Guo L, *et al*. Development and validation of a nomogram for individually predicting pathologic complete remission after preoperative chemotherapy in Chinese breast cancer: A population-based study. *Clin Breast Cancer* 2020; **20(6)**:e682-94. doi: 10.1016/j.clbc.2020.06.010.

21. Skarping I, Blaabjerg Pedersen S, Fornvik D, Zackrisson S, Borgquist S. The association between body mass index and pathological complete response in neoadjuvant-treated breast cancer patients. *Acta Oncol* 2022; **61(6)**:731-7. doi: 10.1080/0284186X.2022.2055976.

22. Aguiar D, Ros L, Perez D, Croissier L, Mori M, Hernandez M, *et al*. Impact of body mass index on pathological complete response and survival of breast cancer patients receiving neoadjuvant chemotherapy. *Breast Dis* 2022; **41(1)**:351-61. doi: 10.3233/BD-210071.

23. Goorts B, van Nijnatten TJ, de Munck L, Moossdorff M, Heuts EM, de Boer M, *et al*. Clinical tumour stage is the most important predictor of pathological complete response rate after neoadjuvant chemotherapy in breast cancer patients. *Breast Cancer Res Treat* 2017; **163(1)**:83-91. doi: 10.1007/s10549-017-4155-2.

24. Rosanoff DL, Schumacher J, Walle KV, Drengler TS, Greenberg CC, Neuman H, *et al*. Does tumour size predict response to neoadjuvant chemotherapy in the modern era of biologically driven treatment? A nationwide study of US breast cancer patients. *Clin Breast Cancer* 2019; **19(6)**: e741-7. doi: 10.1016/j.clbc.2019.05.014.