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A logarithmic model for hormone receptor-positive and breast cancer patients treated with neoadjuvant chemotherapy

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the predictive importance of the previously validated log(ER)*log(PgR)/Ki-67 predictive model in a larger patient population.

METHODS: Patients with hormone receptor positive/HER-2 negative and clinical node positive before chemotherapy were included. Log(ER)*log(PgR)/Ki-67 values of the patients were determined, and the ideal cutoff value was calculated using a receiver operating characteristic curve analysis. It was analyzed with a logistic regression model along with other clinical and pathological characteristics.

RESULTS: A total of 181 patients were included in the study. The ideal cutoff value for pathological response was 0.12 (area under the curve=0.585, p=0.032). In the univariate analysis, no statistical correlation was observed between luminal subtype (p=0.294), histological type (p=0.238), clinical t-stage (p=0.927), progesterone receptor level (p=0.261), Ki-67 cutoff value (p=0.425), and pathological complete response. There was a positive relationship between numerical increase in age and residual disease. As the grade of the patients increased, the probability of residual disease decreased. Patients with log(ER)*log(PgR)/Ki-67 above 0.12 had an approximately threefold increased risk of residual disease when compared to patients with 0.12 and below (odds ratio: 3.17, 95% confidence interval: 1.48–6.75, p=0.003). When age, grade, and logarithmic formula were assessed together, the logarithmic formula maintained its statistical significance (odds ratio: 2.47, 95% confidence interval: 1.07–5.69, p=0.034).

CONCLUSION: In hormone receptor-positive breast cancer patients receiving neoadjuvant chemotherapy, the logarithmic model has been shown in a larger patient population to be an inexpensive, easy, and rapidly applicable predictive marker that can be used to predict response.

KEYWORDS: Patients. Breast neoplasms. Neoadjuvant therapy. Antineoplastic agents. Receptors, progesterone. Receptors, estrogen.

INTRODUCTION

Breast tumors show different behaviors based on the biological characteristics of the cells from which they originate[1]. Frequently used markers in tumor biology classification are estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor (HER-2). Generally, hormone receptor (HR)-negative tumors (ER and PgR negative) or HER-2-positive tumors are sensitive to chemotherapy and respond well to neoadjuvant chemotherapy (NACT)[2]. NACT enables axillary downstaging, breast conserving surgery, and evaluation of early in vivo response to chemotherapy in most of these patients[3]. However, HR-positive/HER-2-negative breast cancer (ER or PgR positive) cases respond poorly to NACT, pathological complete response rate (pCR) is significantly lower, and there is a relationship between residual tumor characteristics and survival after treatment[4]. Nevertheless, some subgroups of HR-positive patients may have good responses to NACT; therefore, the establishment of methods which can aid treating physicians to distinguish patients will benefit from NACT is of utmost importance[5].

At present, there is no inexpensive, reliable, and easily accessible predictive marker for the HR-positive/HER-2-negative patient group for obtaining pCR with NACT. Although genome sequencing tests such as Mammaprint and Oncotype can be used as validated methods for predicting benefit from NACT, they are expensive, and the cost of their application makes them inaccessible for large patient populations. On the contrary, relative cost-effective methods such as immunohistochemical determination of Ki-67 levels still remain far from standardization, and there can be significant differences between the immunohistochemical methods and pathology laboratories in the evaluation processes of Ki-67; there is still a need for predictive methods that are cost-effective, are easily reproducible, and can be validated.

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The European Society for Medical Oncology (ESMO) divides HR-positive breast tumors into two as luminal A-like and luminal B-like according to receptor percentages. In patients with ER >1, a PGR of less than 20% or a high Ki-67 (an indeterminate cutoff) is referred to as luminal B-like[6]. In contrast, ASCO defines ER between 1 and 10% as low ER positivity and does not accept Ki-67 as a tumor marker[7]. Due to such uncertainties, there is a need for a new classification using important markers such as ER, PgR, and Ki-67 to classify HR-positive/HER-2-negative patients according to NACT responses.

In a previous study, we found that the formula log(ER)*log(PgR)/Ki-67 was predictive of NACT response in 126 HR-positive/HER-2-negative patients. In this study, we aimed to investigate the predictive value of our logarithmic index in a larger patient population and confirm its accuracy[8].

METHODS

In our study, the data of HR-positive/HER-2-negative breast cancer patients who received NACT between February 1, 2014, and May 1, 2022 were evaluated retrospectively. Inclusion criteria were as follows: receiving a standard chemotherapy regimen [four cycles of cyclophosphamide+epirubicin (or doxorubicin) followed by either docetaxel (75 mg/m^2) every 3 weeks for 4 cycles or paclitaxel (80 mg/m^2) every 12 cycles week], and being clinically node positive before treatment. Patients who were metastatic, male, and unable to complete the neoadjuvant regimen and who received different chemotherapy regimens were excluded from the study (Figure 1). Clinical and pathological tumor staging was based on the TNM Classification of Malignant Tumors, 8th edition. Polymerase chain reaction (PCR) was defined as ypT0/ypTis, ypN0. The cutoff value for Ki-67 was determined as 18 in the separation of luminal A-like and luminal B-like.

In the formula log(ER)*log(PgR)/Ki-67, log(ER) defines the base 10 logarithm of the ER level, log(PgR) defines the base 10 logarithm of the PgR level, and Ki-67 defines the proliferation index without "%." Values with ER zero (0) or PgR zero (0) are considered 0, as they do not cut the logarithm curve.

The SPSS Statistical version 24 (SPSS Inc., Chicago, III) software was used for all statistical analyses. The specificity-sensitivity along with the ideal cutoff value for PCR and non-PCR discrimination of the logarithmic formula were determined by receiver operating characteristic (ROC) analysis. The relationships between logarithmic formula, pCR, and other clinical-pathological characteristics were assessed with the chi-square test. Univariate and multivariate analyses were calculated using binary logistic regression analysis. Odds ratio (OR) was reported with the corresponding 95% confidence intervals (CIs), and $p<0.05$ was considered statistically significant.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and approved by the Non-Interventional Ethics Committee (Approval no. 2022.86.05.13).

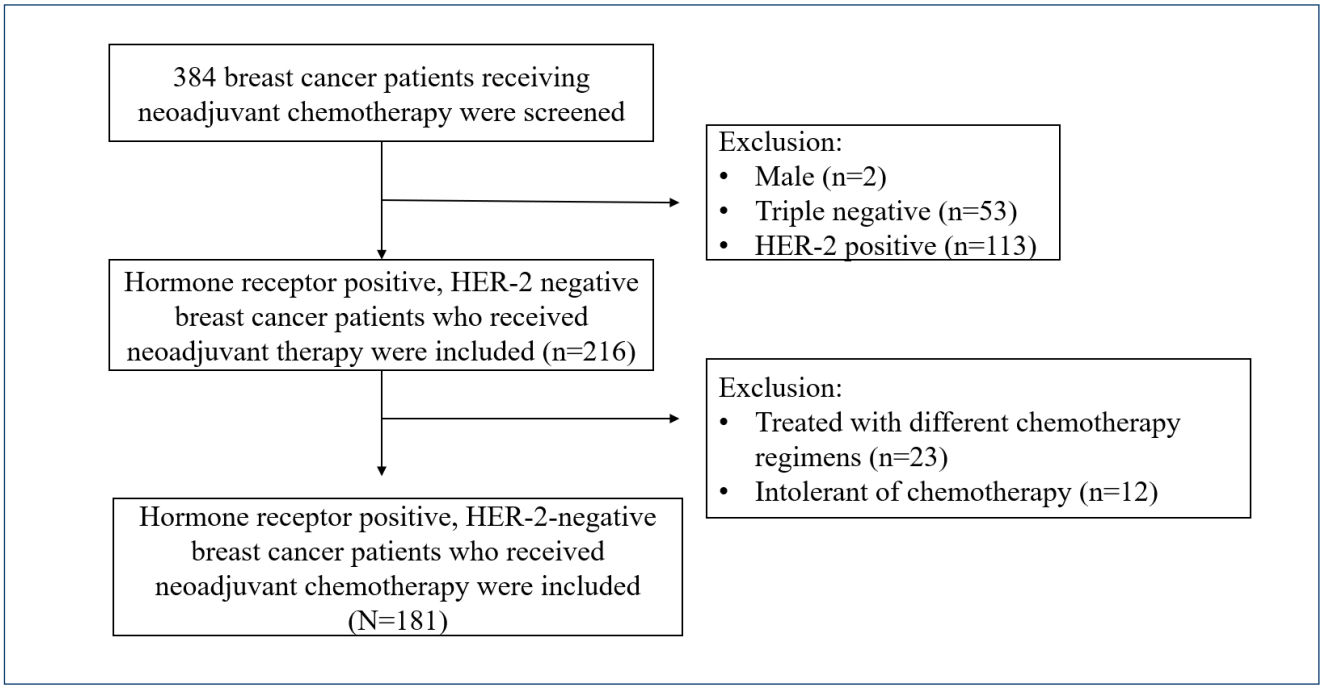

Figure 1. Flow chart documenting selection criteria for patients.

RESULTS

Patient characteristics and treatment responses by characteristics

The data of 181 patients were analyzed. The median age of the patients was 50 (min–max: 25–79) years. When the patients were separated according to their molecular subtypes, 39 (21.5%) patients were luminal A-like and 142 (78.5%) patients were luminal B-like. Histologically, 151 (83.4%) patients had invasive ductal carcinoma and 30 (16.6%) patients had other histological subtypes; 142 (78.5%) patients were found to have residual tumor (non-pCR) and 39 (21.5%) patients were found to have pCR among the patients who underwent surgery after NACT. The highest pCR was observed in patients aged less than 50 (27.4%) years, and the least pCR was observed in grade 1 tumors (0%) (Table 1).

Pathological and clinical characteristics according to log(ER)*log(PgR)/Ki-67

The ideal cutoff value, which distinguishes patients who had pCR and those who did not, was determined as 0.12 using the ROC analysis (Figure 2). This value allows identifying two separate populations: cutoff ratio^{low} (<0.12), 86 (47.5%) patients and cutoff ratio^{high} (≥0.12), 95 (52.5%) patients (n=181, AUC=0.585, p=0.032). The sensitivity and specificity of this value to identify non-PCR patients were 58.5 and 69.2%, respectively.

When treatment responses were analyzed using the univariate logistic regression analysis, no statistical relationship was found between pCR and luminal subtype (0.294), histological subtype (0.238), clinical t-stage (0.927), PgR receptor level (0.261), and Ki-67 cutoff value (0.425). There was

Table 1. Comparison of treatment responses according to patients' clinical and pathological characteristics.

Variables	Total (n=181)	Non-pCR (n=142)	Non-pCR (%) (78.5%)	pCR (n=39)	pCR (%) (21.5%)	p-value
Age						
<50	68	61	72.6	7	27.4	0.076
≥50	113	81	83.5	32	16.5	
Molecular subtype						
Luminal A-like	39	33	84.6	6	15.4	0.291
Luminal B-like	142	109	76.8	33	23.2	
Histological type						
Ductal	151	116	76.8	35	23.2	0.231
Others	30	26	86.7	4	13.3	
PgR						
<20	54	40	74.1	14	25.9	0.350
≥20	127	102	80.3	25	19.7	
Ki-67						
<18	51	42	82.4	9	17.6	0.424
≥18	130	100	76.9	30	23.1	
Grade						
Grade 1	8	8	100	0	0	0.072
Grade 2	121	98	81.0	23	19.0	
Grade 3	52	36	78.5	16	21.5	
Clinical T stage						
T1	50	39	78.0	11	22.0	0.927
T2-T3	131	103	78.6	28	21.4	
Log(ER)*log(PgR)/Ki-67						
Cutoff ^{low} (<12%)	86	59	68.6	27	31.4	0.002
Cutoff ^{high} (≥12%)	95	83	87.4	12	12.6	

pCR: pathological complete response; Non-pCR: non-pathological complete response; PgR: progesterone receptor.

a positive relationship between numerical increase in age and residual disease (OR 1.032, 95%CI 1.000–1.065, p=0.048). Probability of residual disease decreased as the grade of the patients increased (OR 0.457, 95%CI 0.230–0.908, p=0.025). Patients with log(ER)*log(PgR)/Ki-67 above 0.12 (cutoff ratio^{high}) had an approximately threefold increased risk of having residual disease (OR 3.17, 95%CI 1.48–6.75, p=0.003) compared to patients with a value of 0.12 and below (cutoff ratio^{low}). When age, grade, and logarithmic formula were evaluated together, the logarithmic formula maintained its statistical significance (OR 2.47, 95%CI 1.07–5.69, p=0.034) (Table 2).

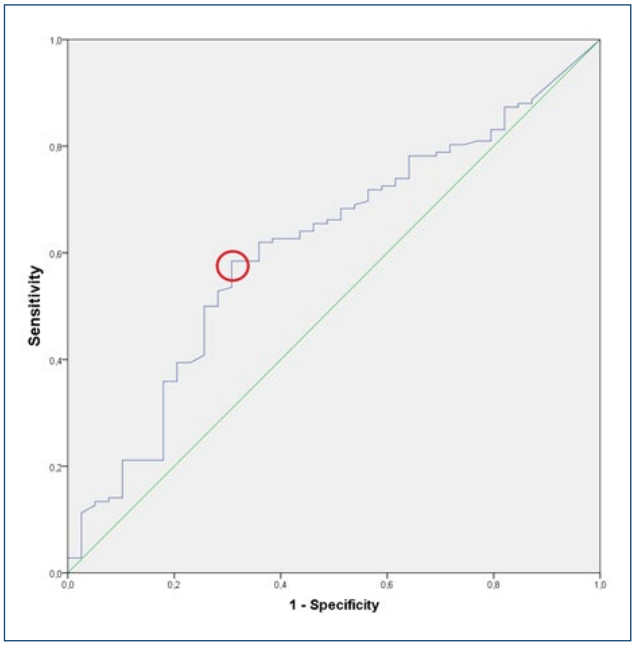

Figure 2. Receiver operating characteristic curve to determine the ideal cut-off value for the logarithmic model (the red circle indicates the cut-off value).

DISCUSSION AND CONCLUSION

Luminal-like breast cancer is considered chemotherapy resistant relative to triple-negative and HER-2-positive subtypes. However, NACT is being increasingly utilized as a method for increasing the rate and improving the outcome of breast and axillary conserving surgery; therefore, it is important to be able to delineate the patients who can most benefit from NACT[6]. pCR can be chosen as a decisive parameter for the description of HR-positive/HER-2-negative BC patients who have an increased chance of showing a response to NACT. As a result of the investigation of tumor genetics, such as Oncotype DX® and Mammaprint® along with the next generation sequencing method, the selection of the right patients to be the candidates for chemotherapy is beneficial[9,10]. However, the use of these tests for NACT is limited and sometimes cannot give clear results in the selection of patients who may benefit from chemotherapy. In addition, it is expensive and the results can be obtained only after a long time[11]. Therefore, these markers cannot be used routinely, especially in developing countries.

In a previous study, we developed an easily accessible model in all clinics, which demonstrated its predictive effectiveness[8]. In this study, it was aimed to investigate the clinical and pathological characteristics of the patients, along with the predictive importance of the log(ER)*log(PgR)/Ki-67 formula in a larger patient population (n=181) in HR-positive/HER-2-negative patients. When assessed with a univariate analysis, patients with cutoff ratio^{high} had approximately three times more complete responses than those with cutoff ratio^{low}.

Table 2. Univariate and multivariate logistic regression analysis of clinical and pathological markers for residual disease after neoadjuvant chemotherapy in HR-positive/HER-2-negative breast cancer patients (n=181).

Variable	Category	Univariate analysis		Multivariate analysis	
		OR (95%CI)	p-value	OR (95%CI)	p-value
Age	Continuous	1.03 (1.00–1.07)	**0.048**	1.02 (0.99–1.05)	0.276
Luminal type	Luminal A/B (HER-2 negative)	0.60 (0.23–1.56)	0.294		
Histological type	Ductal/others	1.96 (0.64–6.00)	0.238		
Clinical T stage	t1/t2/t3	1.04 (0.47–2.28)	0.927		
Log(ER)*log(PgR)/Ki-67	Low/high	3.17 (1.48–6.75)	**0.003**	2.47 (1.07–5.69)	**0.034**
Ki-67	<18/≥18	0.71 (0.31–1.63)	0.425		
PgR	Continuous	1.01 (1.00–1.02)	0.261		
Nuclear grade	1/2/3	0.46 (0.23–0.91)	**0.025**	0.72 (0.34–1.53)	0.390

Significant values are indicated in bold.

Age and histological grade are known as predictive factors for NACT in breast cancer[12]. In this study, in accordance with the literature, age and grade predicted residual disease after NACT. The logarithmic formula maintained its statistical significance as an independent predictor of response to NACT even when age and grade were included in the multivariate analysis.

In the 2011 Gallen Consensus, it was reported that the luminal classification can be used to predict prognosis, risk of recurrence, and pCR in HR-positive/HER-2-negative breast cancer patients[13]. However, current studies show that the luminal A and B breast cancer classification alone is inadequate to identify patients who might benefit from NACT[14,15]. Consistently, luminal classification was not found to be predictive for pCR in our study, which included only luminal breast cancer patients. In addition, the logarithmic formula was predictive for the NACT response, while also detecting residual disease with higher accuracy than the classical luminal classification.

In many studies, it has been reported that an increase in Ki-67 and a decrease in ER caused a higher rate of pCR as well[16,17]. There is a mathematically inverse relationship between Ki-67 proliferation index and ER and PR HR expression levels in terms of treatment response, and these three biomarkers can be evaluated in the context of a continuum within a formula. The reference ranges of these three biomarkers are between 1 and 100, and the pathologists still specifying the level manually, despite automated systems, make standardization difficult. The literature also proposes logarithmic transformation of predictively skewed data in breast cancer[18,19]. The standardization of reporting of HR depression levels and reduction of inconsistencies between different centers of ER levels and reducing differences between centers can be achieved with application of log-transformation formulas[20]. In our study, besides hormone expression levels, the Ki-67 expression levels were also included in the formula. This innovative approach helped eliminate the Ki-67 cutoff uncertainty problems and enabled the categorization of continuous variables such as ER-PgR.

There are some limitations to our study. First is the retrospective analysis of the data. Second, our study could not exclude the possibility of neoadjuvant selection bias, even though the choice of treatment for all patients in the study was decided by the multidisciplinary breast cancer tumor board. The strengths of our study were that all patients received a single NACT regimen and that the data were homogeneous because the pathology specimens were assessed by the same pathologist.

In conclusion, we confirmed that the log(ER)*log(PgR)/Ki-67 formula can be used as a predictive marker for pCR in a larger patient population. We think that our new predictor formula, which is easily accessible, inexpensive, and powerful, may have a decisive role in the selection of patients who can benefit from NAC.

ETHICS STATEMENT

Approval no: 2022.86.05.13 (Non-Interventional Ethics Committee of Tekirdağ Namık Kemal University).

AUTHORS' CONTRIBUTIONS

EŞŞ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration. **Yİ:** Conceptualization, Writing – original draft, Writing – review & editing. **EÇ:** Conceptualization, Writing – original draft, Writing – review & editing. **KK:** Conceptualization, Writing – original draft, Writing – review & editing. **OA:** Conceptualization, Writing – original draft, Writing – review & editing. **AY:** Conceptualization, Writing – original draft, Writing – review & editing. **SÖG:** Conceptualization, Writing – original draft, Writing – review & editing. **MÖ:** Conceptualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Yersal O, Barutca S. Biological subtypes of breast cancer: prognostic and therapeutic implications. World J Clin Oncol. 2014;5(3):412. https://doi.org/10.5306/wjco.v5.i3.412
2. Pennisi A, Kieber-Emmons T, Makhoul I, Hutchins L. Relevance of pathological complete response after neoadjuvant therapy for breast cancer. Breast Cancer (Auckl). 2016;10:103-6. https://doi.org/10.4137/BCBCR.S33163
3. Piato JR, Andrade RD, Chala LF, Barros N, Mano MS, Melitto AS, et al. MRI to predict nipple involvement in breast cancer patients. AJR Am J Roentgenol. 2016;206(5):1124-30. https://doi.org/10.2214/AJR.15.15187
4. Gomes Cunha JP, Goncalves R, Silva F, Aguiar FN, Mota BS, Chequim BB, et al. Validation of the Residual Cancer Burden Index as a prognostic tool in women with locally advanced breast cancer treated with neoadjuvant chemotherapy. J Clin Pathol. 2021; jclinpath-2021-207771. https://doi.org/10.1136/jclinpath-2021-207771
5. Torrisi R, Marrazzo E, Agostinetto E, Sanctis R, Losurdo A, Masci G, et al. Neoadjuvant chemotherapy in hormone receptor-positive/HER2-negative early breast cancer: when, why and what? Crit Rev Oncol Hematol. 2021;160:103280. https://doi.org/10.1016/j.critrevonc.2021.103280
6. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(8):1194-220. https://doi.org/10.1093/annonc/mdz173

7. Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol. 2020;38(12):1346-66. https://doi.org/10.1200/JCO.19.02309
8. Iriagac Y, Cavdar E, Karaboyun K, Tacar SY, Taskaynatan H, Avci O, et al. A new predictive marker for predicting response after neoadjuvant chemotherapy in hormone receptor positive/HER2-negative patients: a logarithmic model. J BUON. 2021;26(6):2274-81. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85123687967&partnerID=40&md5=c1ca8222edc33d471241f8e685fdc766
9. Carlson JJ, Roth JA. The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013;141(1):13-22. https://doi.org/10.1007/s10549-013-2666-z
10. Mook S, Van't Veer LJ, Rutgers EJ, Piccart-Gebhart MJ, Cardoso F. Individualization of therapy using Mammaprint®: from development to the MINDACT Trial. Cancer Genomics Proteomics. 2007;4(3):147-55. PMID: 17878518
11. Chandler Y, Schechter CB, Jayasekera J, Near A, O'Neill SC, Isaacs C, et al. Cost effectiveness of gene expression profile testing in community practice. J Clin Oncol. 2018;36(6):554-62. https://doi.org/10.1200/JCO.2017.74.5034
12. Huober J, Minckwitz G, Denkert C, Tesch H, Weiss E, Zahm DM, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat. 2010;124(1):133-40. https://doi.org/10.1007/s10549-010-1103-9
13. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ; Panel members. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011;22(8):1736-47. https://doi.org/10.1093/annonc/mdr304
14. Collins PM, Brennan MJ, Elliott JA, Abd Elwahab S, Barry K, Sweeney K, et al. Neoadjuvant chemotherapy for luminal a breast cancer: factors predictive of histopathologic response and oncologic outcome. Am J Surg. 2021;222(2):368-76. https://doi.org/10.1016/j.amjsurg.2020.11.053
15. Zhang Z, Zhang H, Li C, Xiang Q, Xu L, Liu Q, et al. Circulating microRNAs as indicators in the prediction of neoadjuvant chemotherapy response in luminal B breast cancer. Thorac Cancer. 2021;12(24):3396-406. https://doi.org/10.1111/1759-7714.14219
16. Fasching PA, Heusinger K, Haeberle L, Niklos M, Hein A, Bayer CM, et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer. 2011;11:486. https://doi.org/10.1186/1471-2407-11-486
17. Chen X, He C, Han D, Zhou M, Wang Q, Tian J, et al. The predictive value of Ki-67 before neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis. Futur Oncol. 2017;13(9):843-57. https://doi.org/10.2217/fon-2016-0420
18. Chapman JW, Murray D, McCready DR, Hanna W, Kahn HJ, Lickley HL, et al. An improved statistical approach: can it clarify the role of new prognostic factors for breast cancer? Eur J Cancer. 1996;32(11):1949-56. https://doi.org/10.1016/0959-8049(96)00232-8
19. Feng C, Wang H, Lu N, Chen T, He H, Lu Y. Log-transformation and its implications for data analysis. Shanghai Arch psychiatry. 2014;26(2):105-9. https://doi.org/10.3969/j.issn.1002-0829.2014.02.009
20. Chapman JA, Mobbs BG, Hanna WM, Sawka CA, Pritchard KI, Lickley HL, et al. The standardization of estrogen receptors. J Steroid Biochem Mol Biol. 1993;45(5):367-73. https://doi.org/10.1016/0960-0760(93)90005-h