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The predictive value of preoperative serum neutrophil-to-lymphocyte ratio and tumor markers for early breast cancer patients

A retrospective study

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Abstract

Peripheral blood of Neutrophil-to-Lymphocyte ratio (NLR), carcinoma embryonic antigen (CEA), cancer antigen 125 (CA125) and cancer antigen 15–3 (CA15-3) could be used as prognostic indicators for several types of tumors. The purpose of this study was to evaluate the predictive value of inflammatory cell ratio and tumor markers for postoperative breast cancer patients. Clinical data concerning 190 breast cancer patients who underwent radical surgery in Zhejiang Provincial Hospital of Chinese Medicine from 2013 and 2016 were retrospectively analyzed. The effects of NLR, CEA, CA125, and CA153 on the disease-free survival (DFS) of patients with breast cancer were analyzed by χ^2 test and Cox regression analyses. There were totally 32 of 190 patients had local or distant metastases within 5 years after surgery. The peripheral blood NLR, CEA, CA125, and CA15-3 areas under the curve (AUC) were 0.8272, 0.667, 0.702, and 0.715, and the optimal cutoff values were 2.65, 1.47, 10.55, and 10.55, respectively. Univariate analysis and Kaplan-Meier survival analysis revealed that the serum NLR, CEA, CA125, and CA15-3 were related to postoperative 5-year DFS ($P < .05$). In addition, multivariate survival analysis identified the following independent prognostic factors: NLR ($P < .001$), CA125 ($P = .045$) and ki-67 ($P = .020$). Preoperative serum inflammatory biomarker of NLR and tumor marker of CA125 have potential prognostic value for breast carcinoma.

Abbreviations: AJCC = American Joint Committee on Cancer, AUC = areas under the curve, CA125 = cancer antigen 125, CA15-3 = cancer antigen 15-3, CEA = carcinoma embryonic antigen, DFS = disease-free survival, LMR = lymphocyte-to-monocyte ratio, NLR = Neutrophil-to-Lymphocyte ratio, OS = overall survival, PLR = platelet-to-lymphocyte ratio, ROC = receiver operating characteristic, TNM = tumor-node-metastasis.

Keywords: breast cancer, disease-free survival, neutrophil-to-lymphocyte ratio, prognostic indicator, tumor marker

1. Introduction

Female breast cancer has taken place of lung cancer as the highest incidence of human malignant tumors worldwide according to the GLOBOCAN 2020 database.[1] Although for early breast cancer group, receiving a standard systemic therapy such as chemotherapy, endocrinotherapy, immunotherapy and molecular targeted therapy usually leads to favorable outcomes like longer disease free survival (DFS) and overall survival (OS), sometimes recrudesce is still inevitable.[2–4] For facilitating the identification of patients who are most likely to benefit from the treatment, there is a need to identify easily accessible biomarkers

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which can provide relatively specific predictive information about therapeutic effects and postoperative survival of patients with different initial conditions.

The connection between chronic inflammation with malignancies was first proposed by Rudolf Virchow in the mid-19th century.[5] Since then, a growing body of researches have shown that inflammation predisposes to the development of cancer and promotes all stages of tumorigenesis.[6–8] In recent years, the elevated peripheral blood neutrophil-to-lymphocyte ratio (NLR) has been proved to be an effective indicator for predicting poorer prognosis of various cancers.[9] A previous meta-analysis comprising fifteen studies reported that the presence of high NLR had great effect on adverse DFS and OS, especially for the luminal subtype.[10]

The carcinoembryonic antigen (CEA), cancer antigen 125 (CA125) and cancer antigen 15-3 (CA15-3) are extensively used serum tumor markers for monitoring the occurrence, development and therapeutic effects of carcinoma.[11] A previous retrospective investigation verified that the serum level of CA15-3 and CEA were associated with breast tumor burden and reflected independent prognostic parameters.[12] A recent cohort study of 10,836 Chinese breast cancer patients revealed that the negative correlation effect of preoperative CA15-3 and CEA expression on survival and tumor progression.[13]

To further evaluate the prognostic efficacy of preoperative inflammatory and tumor markers in early breast cancer patients, we retrospectively investigated the baseline and clinicopathologic information of the patients in our center and performed a 5 years of follow-up.

2. Patients and Methods

2.1. Patients selection

This study included a total of 190 patients who received standard surgical treatment after being diagnosed pathologically as invasive breast cancer between January 1st, 2013 to 2016, at Zhejiang Provincial Hospital of Chinese Medicine. Before starting any specialized treatment, complete clinicopathological data including age, menopausal status, NLR, tumor size, pathological staging, ER, PR, HER-2, Ki67, and operation mode were collected for analyzing. The tumor-node-metastasis (TNM) staging were stratified according to the American Joint Committee on Cancer (AJCC) version 8. Since none of the patients in this study died during follow-up, the main prognostic indicator DFS was defined as the time between the onset of surgical treatment and disease recurrence. Absolute value of neutrophil and lymphocyte counts were measured by using automated blood cell analyzer. Peripheral blood of CEA, CA125, and CA15-3 levels were measured by automated chemiluminescence immunoassay analyzer.

Systemic postoperative management of all patients was performed on the basis of international breast cancer guidelines and clinical follow-up was carried out every 6 months to detect whether there existed local or distant relapse, which included physical examination, complete blood count, breast, axillary lymph nodes and abdominopelvic ultrasonography, chest, head and bone scans. For a period of 5 years, we calculated the DFS of these patients based on patients' records of disease relapse or the last follow-up.

2.2. Inclusion criteria

(1) All patients were pathologically diagnosed as invasive breast cancer and underwent mastectomy or breast-conserving surgery and axillary lymph node management in our hospital. Immunohistochemical examination was completed for all postoperative specimens. (2) All patients were confirmed to have no distant metastasis by preoperative imaging examinations. (3) Postoperative standard systemic therapy and regular follow-up checks were received at our medical center. (4) No infection or other malignancy at first visit.

2.3. Exclusion criteria

(1) Less than 18 years old. (2) Standard postoperative systemic treatment was not received or interrupted. (3) Bilateral breast cancer. (4) Distant metastasis or other sites of primary malignancy existed. (5) Loss of preoperative blood indicators. (6) Perioperative infections.

2.4. Statistical analysis

Receiver operating characteristic (ROC) curve was used for analyzing raw data and the area under the curve (AUC) was calculated. Selecting the best cutoff values of NLR, CEA, CA125, and CA15-3 by sensitivity and specificity. Stratifying all dependent variables that might be associated with prognosis.

The Statistical Product and Service Solutions (SPSS, version 25.0) was used for analyzing the correlation between every independent variable and conclusion factors. Normality test was adopted on the 2 sets of data, independent-samples T test will be used if conformed to normal distribution. Relevance of clinicopathologic factors to NLR, CEA, CA125, and CA15-3 levels was determined by Chi-square test. DFS were estimated using the Kaplan-Meier method and the group differences in event-free survival time were tested using the log-rank test. Multivariate Cox regression was carried out to identify independent prognostic factors for DFS. The P value <0.05 was considered statistically significant.

3. Results

All data were from the medical record database of Zhejiang Hospital of Traditional Chinese Medicine. After strict review of the above inclusion and exclusion criteria, a total of 190 female patients were included in this study. The general characteristics of 2 groups were summarized in Table 3. Based on the expression status of ER, PR, and HER2 proteins in immunohistochemistry for molecular classification, 107 patients (56.3%) were categorized as luminal type, 53 patients (27.9%) as HER2-positive type, and 30 patients (15.8%) as triple-negative type breast cancer. The median age of the study population was 51 years old (range 24–86 years) and postoperative distant recurrence and metastasis occurred in 32 patients (16.84%). On a telephone or outpatient follow-up visit, all patients were alive at the fifth year of time point. The median DFS time of relapse group was 38 months (range 12–59 months). As described in Figure 1, the expression level of NLR, CEA, CA125, and CA15-3 in patients suffering from recurrence or metastasis was higher than that in the tumor-free survivors ($P < .05$), respectively.

ROC curve and corresponding AUC were shown in Figure 2. The AUC of NLR, CEA, CA125, CA15-3 were 0.8272, 0.6670, 0.7017, and 0.7145 (Table 1), respectively. Meanwhile, the interrelated optimal cut-off value was set as 2.65 for the NLR (sensitivity = 71.88%, specificity = 86.08%), 1.47 for CEA (sensitivity = 87.50%, specificity = 43.04%), 10.55 for CA125 (sensitivity = 84.38%, specificity = 56.96%), and 10.55 for CA15-3 (sensitivity = 78.13%, specificity = 61.39%).

Hierarchical processing relevant data on the basis of the optimal truncation value was calculated above along with clinicopathologic feature. Study population with more advanced T-stage and N-stage present an elevated level of NLR, CA125, and CA15-3 compared to the normal group ($P < .05$). Nevertheless the elevated-CEA level was influenced by age ($P < .001$), menopausal status ($P = .039$), and surgical options ($P < .001$) (Table 2).

Univariate analysis suggested that the ending of postoperative recurrence or metastasis were associated with level of NLR

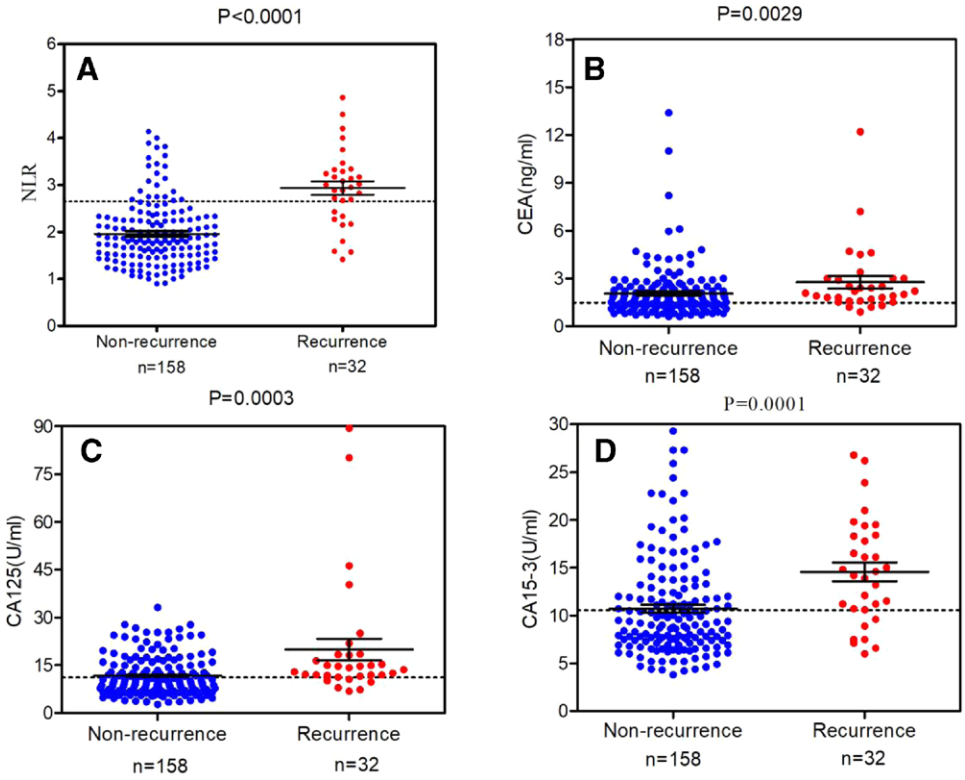


Figure 1. The levels of NLR, CEA, CA125, and CA153 in the nonrecurrent and recurrent groups.

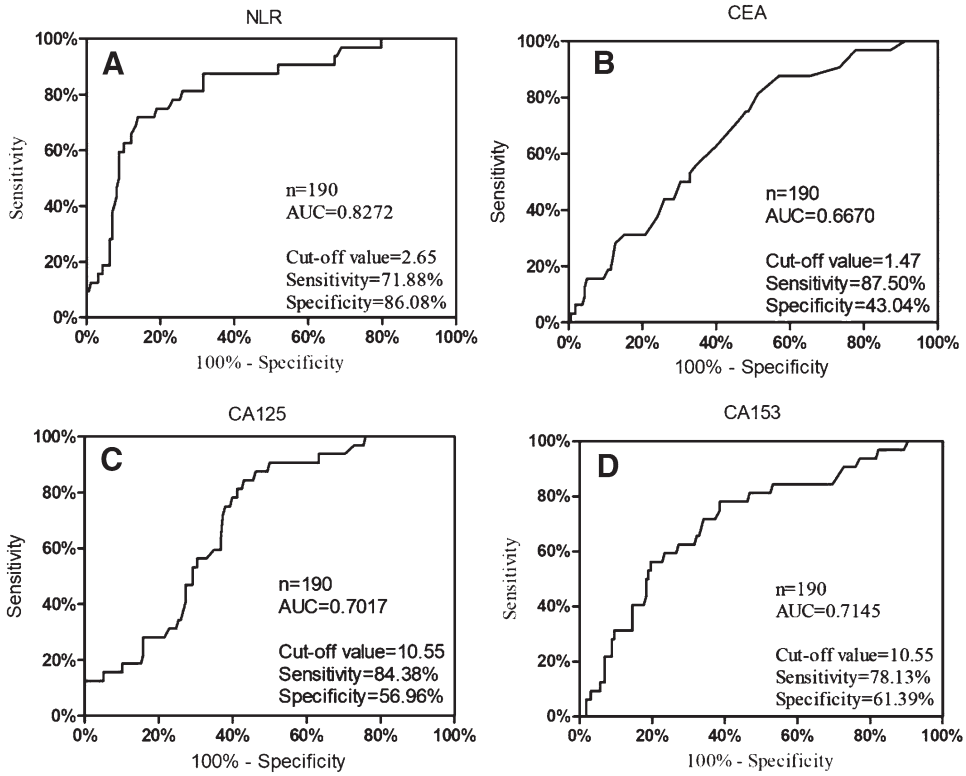


Figure 2. The ROC curves of NLR, CEA, CA125, and CA153. (A) The optimal cutoff value was 2.65 for the NLR (sensitivity 71.88%, specificity 86.08%, AUC 0.8272). (B) The optimal cutoff value was 1.47 for the CEA (sensitivity 87.50%, specificity 43.04%, AUC 0.6670). (C) The optimal cutoff value was 10.55 for the CA125 (sensitivity 84.38%, specificity 56.96%, AUC 0.7017). (D) The optimal cutoff value was 10.55 for the CA125 (sensitivity 78.13%, specificity 61.39%, AUC 0.7145).

Table 1

The optimal cutoff values and corresponding AUC based on DFS.

Peripheral Blood Index	Median	Minimum Value	Maximum Value	Cut-off value	AUC
NLR	1.97 (2.58–1.54)	0.90	4.86	2.65	0.8272
CEA (ng/ml)	1.80 (2.50–1.30)	0.60	13.40	1.47	0.6670
CA125 (U/ml)	10.55 (16.00–7.30)	2.70	89.40	10.55	0.7017
CA15-3 (U/ml)	9.85 (14.05–7.50)	3.80	29.30	10.55	0.7145

Table 2

Baseline characteristics of the patients according to the NLR, CEA, CA125 and CA153.

		NLR ≤ 2.65	NLR > 2.65		CEA ≤ 1.47	CEA > 1.47		CA125 ≤ 10.55	CA125 > 10.55		CA153 ≤ 10.55	CA153 > 10.55	
		N (%)	N (%)		N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	*P*
Characteristics	Total	145 (76.3)	45 (23.7)	*P* value	72 (37.9)	118 (62.1)	*P* value	95 (50.0)	95 (50.0)	*P* value	104 (54.7)	86 (45.3)	value
Age (yr)				0.794			<0.001			0.055			0.649
≤40	30	24 (80.0)	6 (20.0)		21 (70.0)	9 (30.0)		10 (33.3)	20 (66.7)		18 (60.0)	12 (40.0)	
41–59	127	97 (76.4)	30 (23.6)		41 (32.3)	86 (67.7)		64 (50.4)	63 (49.6)		70 (55.1)	57 (44.9)	
≥60	33	24 (72.7)	9 (27.3)		10 (30.3)	23 (69.7)		21 (63.6)	12 (36.4)		16 (48.5)	17 (51.5)	
Menopausal status				0.928			0.056			0.001			0.652
Premenopausal	94	72 (76.6)	22 (23.4)		42 (44.7)	52 (55.3)		36 (38.3)	58 (61.7)		53 (56.4)	41 (43.6)	
Postmenopausal	96	73 (76.0)	23 (24.0)		30 (31.2)	66 (68.8)		59 (61.5)	37 (38.5)		51 (53.1)	45 (46.9)	
pT stage				0.009			0.437			0.009			0.008
T1	104	87 (83.7)	17 (16.3)		42 (40.4)	62 (59.6)		61 (58.7)	43 (41.3)		66 (63.5)	38 (36.6)	
T2-T3	86	58 (67.4)	28 (32.6)		30 (34.9)	56 (65.1)		34 (39.5)	52 (60.5)		38 (44.2)	48 (55.8)	
pN stage				0.048			0.214			0.840			0.001
N0-1	161	127 (78.9)	36 (21.1)		64 (39.8)	97 (60.2)		81 (50.3)	80 (49.7)		96 (59.6)	65 (40.4)	
N2-3	29	18 (62.1)	11 (37.9)		8 (27.6)	21 (72.4)		14 (48.3)	15 (51.7)		8 (27.6)	21 (72.4)	
Molecular subtype				0.509			0.783			0.248			0.746
Luminal	107	85 (79.4)	22 (20.6)		42 (39.3)	65 (60.7)		59 (55.1)	48 (44.9)		58 (54.2)	49 (45.8)	
HER2-positive	53	38 (71.7)	15 (28.3)		18 (34.0)	35 (66.0)		22 (41.5)	31 (58.5)		31 (58.5)	22 (41.5)	
Triple-negative	30	22 (73.3)	8 (26.7)		12 (40.0)	18 (60.0)		14 (46.7)	16 (53.3)		15 (50.0)	15 (50.0)	
ER				0.576			0.896			0.635			0.567
Negative	57	42 (73.7)	15 (26.3)		22 (38.6)	35 (61.4)		27 (47.4)	30 (52.6)		33 (57.9)	24 (42.1)	
Positive	133	103 (77.4)	30 (22.6)		50 (37.6)	83 (62.4)		68 (51.1)	65 (48.9)		71 (53.4)	62 (46.6)	
PR				0.838			0.648			0.547			0.691
Negative	70	54 (77.1)	16 (22.9)		28 (40.0)	42 (60.0)		33 (47.1)	37 (52.9)		37 (52.9)	33 (47.1)	
Positive	120	91 (75.8)	29 (24.2)		44 (36.7)	67 (63.3.)		62 (51.7)	58 (48.3)		67 (55.8)	53 (44.2)	
HER2				0.225			0.628			0.198			0.641
Negative	136	107 (78.7)	29 (21.3)		53 (39.0)	83 (61.0)		72 (52.9)	64 (47.1)		73 (53.7)	63 (46.3)	
Positive	54	38 (70.4)	16 (29.6)		19 (35.2)	35 (64.8)		23 (42.6)	31 (57.4)		31 (57.4)	23 (42.6)	
KI-67				0.676			0.476			1.000			0.992
≤14%	64	50 (78.1)	14 (21.9)		22 (34.4)	42 (65.6)		32 (50.0)	32 (50.0)		35 (54.7)	29 (45.3)	
>14%	126	95 (75.4)	31 (24.6)		50 (39.7)	76 (60.3)		63 (50.0)	63 (50.0)		69 (54.8)	57 (45.2)	
Surgical method				0.310			<0.001			0.246			0.084
Mastectomy	141	105 (74.5)	36 (25.5)		43 (30.5)	98 (69.5)		74 (52.5)	67 (47.5)		72 (51.1)	69 (48.9)	
Lumpectomy	49	40 (81.6)	9 (18.4)		29 (59.2)	20 (40.8)		21 (42.9)	28 (57.1)		32 (65.3)	17 (34.7)	

($P < .001$), 3 tumor markers ($P \leq .001$), Ki-67 ($P = .018$), pathological T-stage ($P < .001$), N-stage ($P = .001$) and operation choosing ($P = .006$) to a great extent (Table 3). By means of the Kaplan-Meier and log-rank methods, breast cancer patients group with higher level of NLR, CEA, CA125, and CA15-3 had shorter DFS ($P < .001$) (Fig. 3). Considering the definite difference in prognosis of diverse molecular subtypes of breast cancer indicated by previous studies, above univariate analysis ($P < .05$) as well as pathological classification were included into Multivariate Cox regression model. Preliminary results showed the expression levels of NLR, CA125, and Ki-67 acted as independent prognostic factors for the 5 years DFS (Table 3).

4. Discussion

Chronic inflammation and cancer interacts with each other: cancer lesions may lead to the upregulation of inflammatory mediators throughout the body and recruitment of some immune cells with tumor-promoting properties. Simultaneously, the presence of pro-tumorigenic inflammation will affect the plasticity of tumor and stromal cells, thus forming a tumor microenvironment which is prone to evade antitumor immunity and promote malignant progression of nascent cancer.[6,14] The signs of up-regulated inflammation-associated cytokines had been observed in patients with distant metastasis of multiple types of malignant tumors in previous researches, including breast cancer.[15,16] Except for those regular significant positive systemic inflammatory indicators such as C-reaction protein and serum helper T cell type 1/2 cytokines, some negative prognostic biomarkers like NLR, lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) have been shown to be novel independently prognostic scores for some tumors in recent years.[16–20]

The forecast value in suggesting therapeutic efficacy and prognostic survival of NLR has been widely confirmed in the clinical field of breast cancer. In a previous retrospective study of the relationship between neutrophil-to-lymphocyte ratio and axillary lymph node invasion, NLR level was higher in

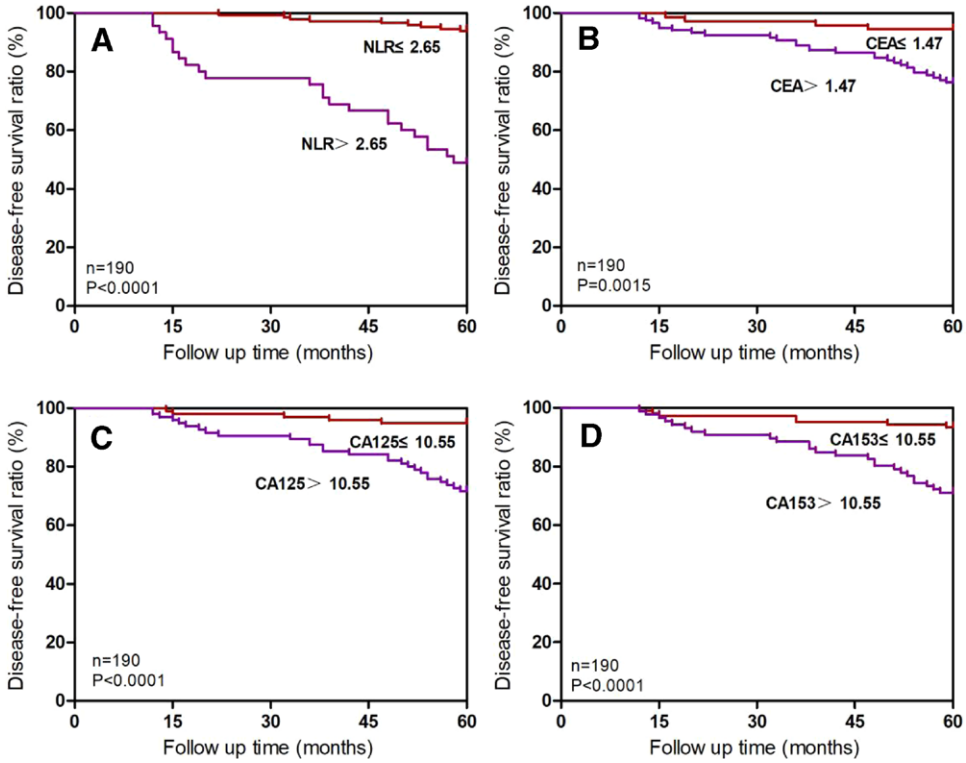


Figure 3. Kaplan–Meier analyses for DFS of all 190 early breast cancer patients. An up-regulated NLR, CEA, CA125 and CA153 indicating poor DFS following surgical resection.

cT1N0 breast cancer patients group with sentinel lymph node metastasis.[21] As for those who receiving neoadjuvant chemotherapy, especially with luminal and triple-negative tumors, high pretreatment NLR level usually meant lower pathological complete response rate and worse survival.[22–24] The predictive value of this negative correlation was also expressed in breast cancer patients who underwent local surgical treatment directly. Kim et al[25] found that NLR was associated with poor prognosis among triple-negative breast cancer patients, while the increasement of NLR during treatment compared to the preoperative status may suggest the need for additional treatment besides the routine medical therapy. HER2 positive group with a high NLR usually had shorter OS and breast cancer specific survival; however, molecular targeted drug was still beneficial for those patients.[26]

Similar to above studies, our retrospective study verified that the preoperative high NLR level was an independent factor indicating the increased risk of recurrence among breast cancer patients. Baseline NLR status have prognostic value analogous to other different clinicopathologic factors such as T stage, N stage, and Ki-67 in this analysis. Meanwhile the pathological staging was also associated with elevated NLR levels in some degree.

Serum tumor markers are usually tested as routine indicators before diagnosis of malignant tumors, but generally considered to be nonspecific and nonsensitive for breast cancer.[27] Although the consensus has not been reached on the clinical significance of tumor marker elevation, current studies have confirmed the relevance of elevated tumor markers level to more advanced tumor burden.[28,29] Through summarization and statistics of recent literature data, CA125, CA15-3, and CEA all have abilities in predicting distant metastasis of breast carcinoma.[30–32] And the joint dynamical detection of above markers would be more sensitive than single tumor marker index. Moreover, for young breast cancer patients, preoperative serum CEA and CA125 levels showed independent prognostic significance for OS.[33]

CA125, a glycoprotein encoded by the MUC16 gene, is particularly sensitive in the diagnosis and therapeutic effect evaluation of gynecological malignancies.[34,35] In our study, CA125 in early breast cancer patients presented a better independent predictive value on ROC curve analysis than CEA and CA15-3 in multivariate analysis, and the calculated optimal cutoff value was 10.55 U/mL. Based on previous studies of ovarian malignancies, CA125 fluctuation was influenced by estrogen receptor, progesterone receptor status along with menopausal state.[36,37] We additionally analyzed whether CA125 level was related to ER, PR, and menopausal status, and the final result displayed that menopausal status was its only influencing factor ($P < .05$).

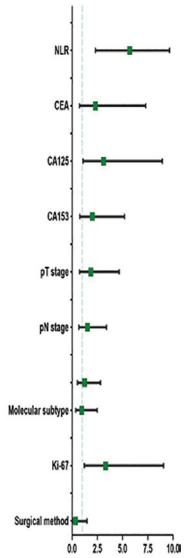
Since Ki-67 is usually active during cell division, its protein expression is often used to evaluate cell proliferation in pathological practice. Based on the consensus guidance of the 2011 St Gallen Conference, Ki-67 has been recommended not only as 1 of the classification criteria for Luminal breast cancer, but holds a promising role in the prediction of animation prognosis of multiple malignancies.[38] Tracing past research experience, the cutoff value for Ki-67 was set as 14% in this study to further explore its intrinsic interaction with disease prognosis. Unlike pT and pN, Ki-67 level presented significant independent prognosis in the regression analysis of influencing factors. In response to this phenomenon, the size of primary lesions and axillary lymph node metastasis are affected by the time of diagnosis and treatment, while some high-risk breast cancer patients may also obtain lower T and N grades through timely detection and treatment. The expression of Ki-67 represents the original characteristics of cancer cell proliferation, which leads to its more prognostic consequence.

Although a comprehensive survey was performed, there are still some limitations as relatively small sample size, insufficient follow-up time, lack of subgroup analysis, and so forth. At the same time, the possibility of long-term drug use affecting peripheral blood data cannot be ruled out. Our data in this study will offer some references to clinical field of breast cancer, but further exploration and data mining are still needed.

Table 3

Univariate and multivariate prognostic analysis for Postoperative DFS.

Characteristics	Total	Nonrecurrent n (%)	Recurrent n (%)	Univariate analysis		Multivariate analysis		Forest map
				χ^2	*P*	HR (95%CI)	*P*	
Age (yr)				1.266	0.531			
≤40	30	23 (76.7)	7 (23.3)					
41–59	127	108 (85.0)	19 (15.0)					
≥60	33	27 (81.8)	6 (18.2)					
Menopausal status at diagnosis	94	80 (85.1)	14 (14.9)	0.504	0.478			
Premenopausal	96	78 (81.3)	18 (18.7)					
Postmenopausal								
NLR				49.443	<0.001			
≤2.65 (reference)	145	136 (93.8)	9 (6.2)					
>2.65	45	22 (48.9)	23 (51.1)			5.695 (2.313–9.649)	<0.001	
CEA				10.545	0.001			
≤1.47 (reference)	72	68 (94.4)	4 (5.6)					
>1.47	118	90 (76.3)	28 (23.7)			2.305 (0.729–7.290)	0.155	
CA125				18.188	<0.001			
≤10.55 (reference)	95	90 (94.7)	5 (5.3)					
>10.55	95	68 (71.6)	27 (28.4)			3.116 (1.086–8.943)	0.045	
CA153				16.773	<0.001			
≤10.55 (reference)	104	97 (93.3)	7 (6.7)					
>10.55	86	61 (70.9)	25 (29.1)			1.995 (0.767–5.191)	0.157	
pT stage				16.773	<0.001			
T1 (reference)	104	97 (93.3)	7 (6.7)					
T2-T3	86	61 (70.9)	25 (29.1)			1.851 (0.735–4.662)	0.192	
pN stage				12.113	0.001			
N0-1 (reference)	161	141 (87.6)	20 (12.4)					
N2-3	29	17 (58.6)	12 (40.0)			1.510 (0.669–3.411)	0.321	
Molecular subtype				2.561	0.278			
Luminal (reference)	107	93 (86.9)	14 (13.1)					
HER2-positive	53	42 (79.2)	11 (20.8)			1.225 (0.532–2.820)	0.633	
Triple-negative	30	23 (76.7)	7 (23.3)			0.949 (0.362–2.489)	0.915	
Ki-67				5.618	0.018			
≤14% (reference)	64	59 (92.2)	5 (7.8)					
>14%	126	99 (78.6)	27 (21.4)			3.310 (1.211–9.049)	0.015	
Surgical method								
Mastectomy (reference)	141	111 (78.7)	30 (21.3)					
Lumpectomy	49	47 (95.9)	2 (4.1)	7.677	0.006	0.323 (0.070–1.477)	0.145	
ER				2.069	0.150			
Negative	57	44 (77.2)	13 (22.8)					
Positive	133	114 (85.7)	19 (14.3)					
PR				0.789	0.374			
Negative	70	56 (80.0)	14 (20.0)					
Positive	120	102 (85.0)	18 (15.0)					
HER2				0.671	0.413			
Negative	136	115 (84.6)	21 (15.4)					
Positive	54	43 (79.6)	11 (20.4)					
Pathological type								
Invasive ductal carcinoma	179							
Mucinous carcinoma	7							
Apocrine carcinoma	1							
Invasive micropapillary carcinoma	3							
Recurrence and metastasis								
Ipsilateral breast	2							
Lung	4							
Liver	3							
Bone	14							
Chest wall	3							
Combination	8							



5. Conclusions

This study was conducted to assess the peripheral blood NLR and tumor markers as significant guidelines in selecting low-stage breast cancer patients with more substantial prognosis after surgery and systemic treatment. Results showed that the preoperative rising of NLR and CA125 were independent prognostic factors for 5-year DFS, which indicating aggressive characteristics and worse survival. Relevant data in this analysis could be used to screen those potential patients with poor prognosis, and inform clinicians whether additional treatment is necessary and how frequently follow-up should be conducted.

Author contributions

Fan SY, Yao ZY, and Gu XD conceived the idea, wrote the initial draft of the manuscript, and sorted out the materials; Wang WJ and Shen Y provided the data; Yao ZY, Gu XD, and Xie XH contributed to the revisions.

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