



Original Research

Correlation analysis of lymphocyte-monocyte ratio with pathological complete response and clinical prognosis of neoadjuvant chemotherapy in patients with breast cancer

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ABSTRACT

Purpose: Inflammation plays an important role in tumor proliferation, metastasis, and chemotherapy resistance. Peripheral blood lymphocyte-monocyte ratio (LMR) has been reported to be closely associated with the prognosis of many tumors, such as certain hematologic malignancies and gastric cancer. However, the association in breast cancer is still not clear. This study investigated the relationship between LMR with pathological complete response and clinical prognosis of neoadjuvant chemotherapy in patients with breast cancer, to provide convenient and accurate predictive indicators for pathological complete response (pCR) and prognosis.

Methods: The clinicopathological data of 192 female breast cancer patients who received neoadjuvant chemotherapy and surgery in Harbin Medical University Tumor Hospital from January 2013 to August 2017 were retrospectively analyzed. Blood lymphocytes and monocytes were obtained by peripheral venous punctures.

Results: Compared with the low LMR group, pCR was more easily obtained in the high LMR group ($P=0.020$); Subgroup analysis showed that patients with the high LMR and HER-2(+) group were more likely to obtain pCR ($P=0.011$). Univariate and multivariate results showed that the overall survival (OS) and disease free survival (DFS) of the high LMR group were longer than that of the low LMR group.

Conclusion: LMR and HER-2 status are correlated with pCR of neoadjuvant chemotherapy in breast cancer patients and are independent predictors of pCR after neoadjuvant chemotherapy in breast cancer patients. Meanwhile, both LMR and T stage of tumor are independent prognostic factors of breast cancer patients, with good predictive value.

Introduction

Breast cancer is the most common malignant tumor in the world, which seriously affects people's quality of life and endangers people's health. Although major advances in cancer treatment over the past few decades have significantly reduced mortality rates among women worldwide, breast cancer is still one of a leading cause of death among women today [1]. Surgery-based comprehensive treatment has been recognized as the best treatment for patients with early breast cancer [2]. However, tumor cells are characterized by diffusion from the primary site and early metastasis to other tissues or organs, resulting in unsatisfactory treatment results, and a considerable number of patients

will have local recurrence or distant metastasis within a period after surgical resection [3]. Therefore, the identification of reliable biomarkers to predict prognosis and choose a treatment plan has become the key to the treatment of breast cancer.

Many studies have confirmed that inflammation plays a crucial role in the occurrence, development, and prognosis of cancer [4]. Changes in inflammatory cells can significantly affect tumor progression, including tumor proliferation, angiogenesis, metastasis, and resistance to chemotherapy [5,6]. Inflammatory responses related to cancer are divided into local responses and systemic responses, which can be detected unlike local responses [7]. Studies have confirmed that inflammatory indicators such as inflammatory cytokines, white blood cell count and

Abbreviation: LMR, lymphocyte-monocyte ratio; pCR, pathological complete response; OS, overall survival; DFS, disease free survival; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor.

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platelet count in peripheral blood have been used to evaluate the inflammatory state of the body [8,9]. Some immunological and histological indicators are closely related to the prognosis of breast cancer [10], but the acquisition of these indicators is time-consuming and expensive, which greatly limits their clinical application. Compared with them, routine peripheral blood examination is simple to operate, easy to evaluate, cheap, and has a good promotion effect.

According to the number of inflammatory cells in peripheral blood, previous researchers established some combined indicators [11,12] and used them as relevant parameters to evaluate systemic inflammatory response. Among them, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been reported as prognostic factors of various cancers [13–15]. Previous studies have found that NLR is not only associated with the prognosis of patients with breast cancer, lung cancer, colorectal cancer, esophageal cancer and cervical cancer [14–18] elevated preoperative NLR is also associated with poor prognosis of breast cancer. PLR is considered as a prognostic marker for gastric cancer, ovarian cancer, colorectal cancer, bile duct cancer and other cancers as well[17,19-21]. In breast cancer, some studies have found that increased PLR has an adverse effect on survival [22]. The

value of LMR as a prognostic indicator has been validated in several cancer types, including head and neck cancer, lymphoma and pancreatic cancer [23–25]. Although it has been reported that LMR has predictive value for neoadjuvant chemotherapy for breast cancer [26], there are still few studies on the correlation between LMR and prognostic value of neoadjuvant chemotherapy for breast cancer patients.

Based on previous studies, we concluded that LMR is likely to play an important role in the prognosis of neoadjuvant chemotherapy in breast cancer. Therefore, we conducted a retrospective cohort study to investigate the relationship between lymphocyte monocyte ratio with a pathological complete response and clinical prognosis of neoadjuvant chemotherapy in patients with breast cancer, to provide convenient and accurate predictive indicators for pCR and prognosis.

Material and methods

Clinical sample and data collection

A retrospective study was performed on 217 female breast cancer patients who received neoadjuvant chemotherapy and mastectomy from

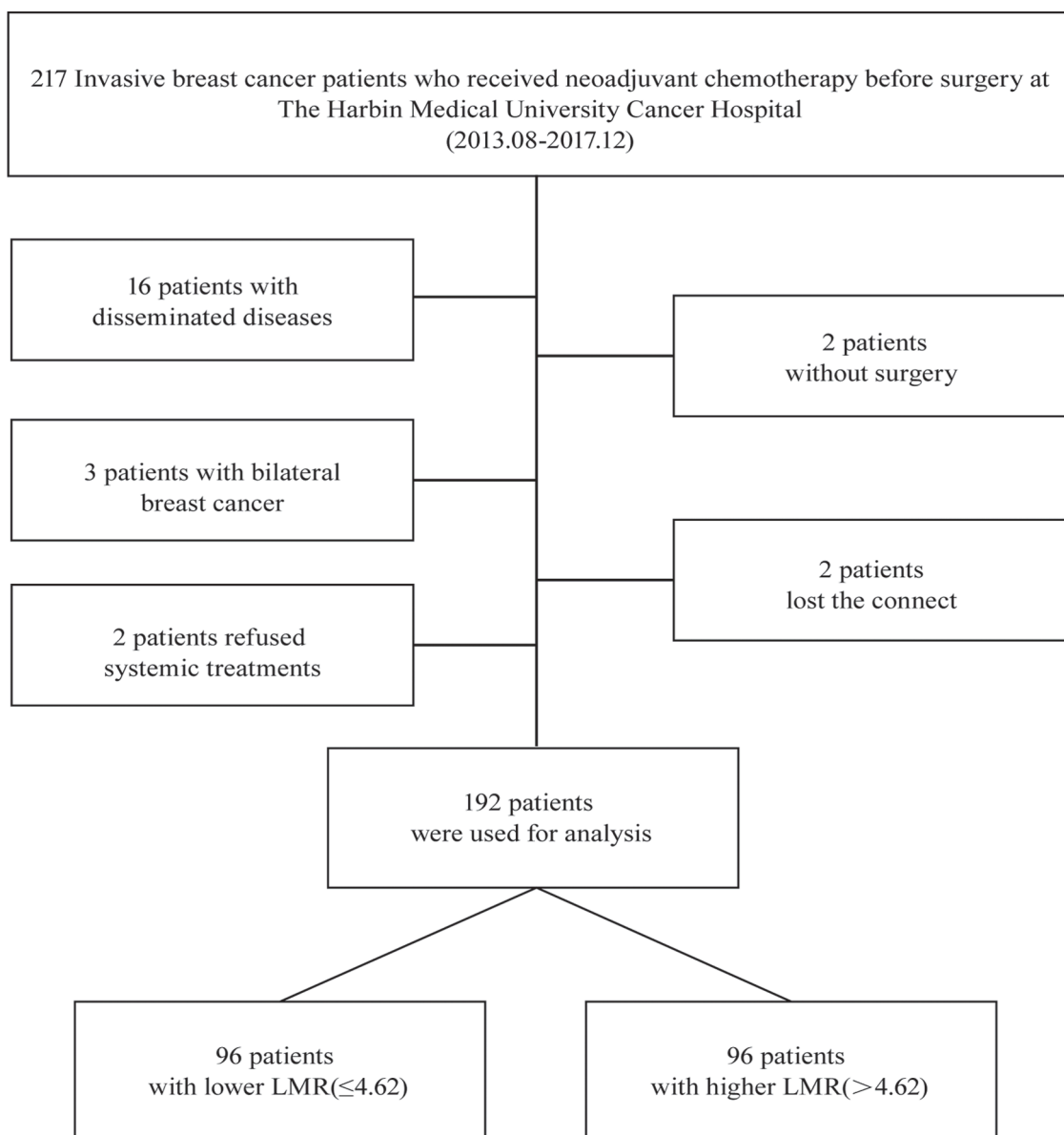


Fig.1. Grouping flow chart of 217 breast cancer patients collected.

August 2013 to December 2017 in Harbin Medical University Cancer Hospital.

Inclusion criteria:

- (1) Female patients
- (2) Neoadjuvant chemotherapy was performed before surgery, and radiotherapy and endocrine therapy were not given before chemotherapy
- (3) Patients with invasive breast cancer confirmed by biopsy pathology before chemotherapy
- (4) Patients with sufficient detailed clinicopathological data.

Exclusion criteria:

- (1) Patients with incomplete clinical data
- (2) Patients with multiple tumors
- (3) Patients who have inflammatory diseases, infectious diseases, autoimmune diseases, immune deficiency diseases, or other diseases which affect blood components (such as blood diseases, liver dysfunction, chronic kidney diseases, etc.)
- (4) Patients taking drugs that have obvious effects on blood cells. A retrospective analysis was performed of 192 patients who met the inclusion criteria (Fig. 1).

Clinicopathological data including age, Body Mass Index (BMI), tumor stage according to the AJCC Cancer Staging Manual, Edition 8, chemotherapy cycle, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2) and KI-67 status. Lymphocyte count, monocyte count, lymphocyte count and monocyte count ratio were assessed based on laboratory data.

All enrolled patients had signed the Informed Consent for Secondary Use of Medical Data/Biological specimens before treatment, and all procedures involving human participants in the study met the Committee's standards, as well as the declaration of Helsinki of 1964 and other ethical standards amendments.

Treatment plan

All enrolled patients who received neoadjuvant chemotherapy after chemotherapy regimens were selected according to immunohistochemical results and patient wishes. Including 15 cases of AC-T; EC-T scheme in 32 cases; TA scheme in 15 cases; TAC scheme in 29 cases; TE scheme in 50 cases; TEC scheme in 51 cases. The efficacy was evaluated by Miller-Payne (MP) pathological evaluation system. All the enrolled patients received surgical treatment and necessary follow-up treatment in Harbin Medical University Tumor Hospital.

AC-T scheme: Doxorubicin 60mg/m², cyclophosphamide 600mg/m², 1/21d × 4, sequential docetaxel 80-100mg/m², 1/21d × 4;

EC-T scheme: Epirubicin 90mg/m², cyclophosphamide 600mg/m², 1/21d × 4, sequential docetaxel 80-100mg/m², 1/21d × 4;

TA scheme: Docetaxel 75mg/m², Doxorubicin 60mg/m², 1/21d × 4;

TAC scheme: Docetaxel 75mg/m², Doxorubicin 50mg/m², cyclophosphamide 500mg/m², 1/21d × 6;

TE scheme: Docetaxel 75mg/m², Epirubicin 75mg/m², 1/21d × 4;

TEC scheme: Docetaxel 75mg/m², Epirubicin 75mg/m², cyclophosphamide 500mg/m², 1/21d × 6;

Evaluation methods

According to the Miller-Payne (MP) pathological evaluation system, the rough needle biopsy specimens before chemotherapy were compared with the surgical specimens after chemotherapy. According to the reduction of tumor cells, the tumor cells were divided into five grades: Grade 1 (G1): the invasive cancer cells did not change or only a few cancer cells changed, but the number of cancer cells did not decrease

overall (pNR); Grade 2 (G2) showed a slight decrease in invasive cancer cells, but the total number was still high, and the number of cancer cells was less than 30% (pPR). Grade 3 (G3) is a 30% to 90% reduction in invasive cancer cells (pPR). Grade 4 (G4) is a significant reduction of more than 90% in invasive cancer cells, with only scattered small clusters or single cancer cells remaining (almost pCR); Grade 5 (G5) refers to the presence of ductal carcinoma *in situ* (pCR) despite the absence of invasive cancer cells in the original tumor bed. G1, G2, and G3 were classified as a pathological invalid group, G4 and G5 were classified as a pathological effective group, and G5 was pathological complete response (pCR).

Pathological features and molecular subtypes

ER, PR, HER-2 and Ki67 states are assessed by immunohistochemistry (IHC) staining or *in situ* hybridization (ISH), and ER and PR nuclear ≥1% are defined as positive. Ki-67 positive nuclear ≥14% was defined as high expression, <14% as low expression. HER-2 immunohistochemical staining was divided into positive HER-2, low HER-2 expression and negative HER-2. IHC 0 was defined as HER-2 negative, IHC 2+ and ISH negative or IHC 1+ was defined as HER-2 low expression, and IHC 3+ or IHC 2+ and ISH positive were defined as positive.

Follow-up

Follow-up in this study was from the time of the first diagnosis to October 1, 2021. Patients were followed up by outpatient review and telephone contact. Disease free survival (DFS) was defined as the interval from the first diagnosis to first recurrence or distant metastasis and contralateral breast malignancy. Overall survival (OS) was defined from the date of diagnosis to the date of death or the end of follow-up.

Statistical Treatment

SPSS 21.0 statistical software was used for data analysis and processing. Analysis between different LMR groups and HER-2 subgroups was evaluated by Pearson's χ^2 test. The logistic regression model was used to conduct univariate and multivariate analysis on the relationship between clinicopathological features and pCR. Cox regression model was used to conduct univariate and multivariate analysis on the relationship between clinicopathological features and patients' OS and DFS. Kaplan-Meier method was used to draw a survival curve. P<0.05 was considered to be statistically significant.

Result

Patient characteristics

A total of 192 women with breast cancer were enrolled in this study. All of them have been pathologically confirmed as breast cancer and received surgical treatment and necessary follow-up treatment in Harbin Medical University Cancer Hospital. Patients ranged in age from 24 to 65 years, with a median age of 49 years. Among them, 99 cases (51.6%) were ≤49 years old and 93 cases (48.4%) were >49 years old. The LMR value of the patients ranged from 1.27 to 92.50, and the median LMR value was 4.62, among which 96 cases (50%) were ≤4.62 and 96 cases (50%) were >4.62. There were 117 cases (60.9%) with negative HER-2, 13 cases (6.8%) with low HER-2 expression and 62 cases (32.3%) with positive HER-2. 30 cases (15.6%) reached pCR after neoadjuvant therapy, and 162 cases (84.4%) did not (Table 1).

Univariate and multivariate analysis of pCR

Among 192 patients, a total of 30 patients (15.6%) obtained pCR. Logistic univariate analysis showed that: (1) Compared with negative HER-2 patients and patients with low HER-2 expression, the pCR of

Table 1
Clinicopathological characteristics of patients with different LMR groups

Variable	N (n=192)	LMR≤4.62 (n=96)	LMR>4.62 (n=96)	χ^2	p value
Age(years-old)				3.005	0.083
≤49	99 (51.6%)	56(58.3%)	44(45.8%)		
>49	93 (48.4%)	40(41.7%)	52(54.2%)		
BMI				0.795	0.672
<25	116 (60.4%)	55(57.3%)	61(63.5%)		
25–30	67 (34.9%)	36(37.5%)	31(32.3%)		
≥30	9(4.7%)	5(5.2%)	4(4.2%)		
T stage				1.298	0.730
cT1	16(8.3%)	6(6.3%)	10(10.4%)		
cT2	139 (72.4%)	70(72.9%)	69(71.9%)		
cT3	31 (16.1%)	17(17.7%)	14(14.6%)		
cT4	6(3.1%)	3(3.1%)	3(3.1%)		
Nstage				2.599	0.458
N0	14(7.3%)	5(5.2%)	9(9.4%)		
N1	72 (37.5%)	33(34.4%)	39(40.6%)		
N2	59 (30.7%)	32(33.3%)	27(28.1%)		
N3	47 (24.5%)	26(27.1%)	21(21.9%)		
HER-2				1.965	0.374
Negative	117 (60.9%)	63(65.6%)	54(56.3%)		
Low expression	13(6.8%)	5(5.2%)	8(8.3%)		
Positive	62 (32.3%)	28(29.2%)	34(35.4%)		
Cycle				2.970	0.227
≤4	65 (33.8%)	28 (29.2%)	37 (38.5%)		
5–6	80 (41.7%)	40 (41.7%)	40 (41.7%)		
≥7	47 (24.5%)	28 (29.2%)	19 (19.8%)		
Ki-67				0.837	0.360
≤14%	37 (19.3%)	21(21.9%)	16(16.7%)		
>14%	155 (80.7%)	75(78.1%)	80(83.3%)		
pCR				5.689	0.017
No	162 (84.4%)	87(90.6%)	75(78.1%)		
Yes	30 (15.6%)	9(9.4%)	21(21.9%)		

positive HER-2 patients was higher (OR=5.302, CI 95% 2.225-12.634, $P<0.001$). Compared with the low LMR group, pCR was more easily achieved in the high LMR group (OR=2.707, CI 95% 1.169-6.268, $P=0.020$), and the difference was statistically significant (Table 2). (2) Indexes with statistical differences in univariate analysis were included in multivariate analysis. Logistic regression analysis showed that pCR was more easily obtained in the high LMR group than in the low LMR group (OR=2.579, CI 95% 1.077-6.176, $P=0.033$). The pCR rate of positive patients was higher than that of negative and low HER-2 expression patients (OR=5.132, CI 95% 2.129-12.372, $P<0.001$), and the difference was statistically significant. The results showed that LMR and HER-2 status were independent predictors of pCR (Table 3).

Her-2 subgroup analysis

According to univariate and multivariate analysis of clinicopathological features and pCR, LMR and HER2 status were independent predictors of pCR in breast cancer patients. To further understand the

relationship between them, we conducted a subgroup analysis. In the high LMR group, the pCR rate of HER-2(+) subgroup was 44.1% (15 cases), The pCR rate of HER-2(-) subgroup was 9.3% (5 cases), and the pCR rate of HER-2 low expression subgroup was 12.5% (1 case). The pCR rate of positive HER-2 subgroup was significantly different ($P=0.011$). In the low LMR group, the pCR rate of HER-2(+) subgroup was 14.3%(4 cases), the pCR rate of HER-2(-) subgroup was 6.3%(4 cases), and the pCR rate of patients with low HER-2 expression subgroup was 20.0% (1 case). There was no significant difference in the pCR rate among different subgroups (all $P>0.05$). That is, patients with the high LMR and HER-2(+) group were more likely to obtain pCR. (Table 4)

Univariate and multivariate analysis of OS

The mean survival time of 192 patients to the deadline of follow-up was 56.8 months. Cox regression model was used for univariate analysis: (1) compared with the low LMR group, the high LMR group had longer OS. (OR=0.501, CI 95% 0.261-0.959, $P=0.037$), the difference was statistically significant. The OS of cT1/cT2 group was longer than that of cT3/cT4. (OR=2.466, CI 95% 1.287-4.724, $P=0.007$), the difference was statistically significant (Table 5). (2) LMR and tumor T stage with the statistical difference in univariate analysis were included in multivariate Cox regression analysis: patients in the high LMR group had a longer survival trend than those in the low LMR group (OR=0.532, CI 95% 0.277-1.022, $P=0.058$). Although it failed to reach statistical significance, this may be caused by the long survival cycle of breast cancer patients after standardized treatment and the relatively small sample size of this study. Therefore, we still need a larger sample size to confirm the effect of LMR on OS in breast cancer patients. Compared with cT3/cT4, The OS of cT1/cT2 group was longer (OR=2.324, CI 95% 1.210-4.464, $P=0.011$), and the difference was statistically significant. LMR is one of the factors affecting OS in breast cancer patients. Tumor T stage was an independent predictor of OS (Table 6).

Univariate and multivariate analysis of DFS

The mean DFS of 192 patients to the deadline of follow-up was 48.5 months. Cox regression model was used for univariate analysis: (1) compared with the low LMR group, the high LMR group had longer DFS. (OR=0.422, CI 95% 0.220-0.808, $P=0.009$). Compared with cT3/cT4, cT1/cT2 group had a longer DFS. (OR=2.513, CI 95% 1.311-4.819, $P=0.006$), the difference was statistically significant (Table 7). (2) LMR and tumor T stage with the statistical difference in univariate analysis were included in multivariate Cox regression analysis: compared with low LMR group, DFS in high LMR group was longer (OR=0.441, CI 95% 0.230-0.846, $P=0.014$); Compared with cT3/cT4, cT1/cT2 group had longer DFS. (OR=2.379, CI 95% 1.239-4.568, $P=0.009$), the difference was statistically significant. Therefore, we believe that LMR and tumor T stage are independent predictors of DFS (Table 8).

Influence of LMR on prognosis

192 patients with breast cancer were followed up for 12-98 months, with an average follow-up of (56.78±17.20) months. Local recurrence or metastasis occurred in 65 patients (33.9%) during follow-up. Kaplan-Meier survival analysis showed that there was a significant correlation between LMR and OS, and patients with high LMR before treatment had higher OS than those with low LMR (Fig. 2 A), the difference was statistically significant ($P=0.033$). LMR was significantly correlated with DFS, and patients with high LMR before treatment had higher DFS than those with low LMR (Fig. 2 B), the difference being statistically significant ($P=0.007$).

Discussions

In recent decades, studies on the relationship between inflammation

Table. 2
Univariate analysis between clinical characteristics and pCR.

Variable	N	pCR (n=30)	B	S.E.	Wals	OR	CI(95%)	p
Age(years-old)								
≤49	99(51.6%)	17(17.2%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>49	93(48.4%)	13(14.0%)	-0.244	0.401	0.370	0.784	0.357-1.719	0.543
BMI								
<25	116(60.4%)	19(16.4%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
25~30	67(34.9%)	10(14.9%)	-0.110	0.425	0.067	0.896	0.390-2.060	0.795
≥30	9(4.7%)	1(11.1%)	-0.449	1.090	0.170	0.638	0.075-5.404	0.680
T stage								
cT1/cT2	155(80.7%)	27(17.4%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
cT3/cT4	37(19.3%)	3(8.1%)	-0.872	0.638	1.864	0.418	0.120-1.462	0.172
Nstage								
N0	14(7.3%)	2(14.3%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
N1-3	178(92.7%)	28(15.7%)	0.113	0.791	0.021	1.120	0.238-5.279	0.886
HER-2								
Negative	117(60.9%)	9(13.8%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Low expression	13(6.8%)	2(15.4%)	0.780	0.843	0.856	2.182	0.418-11.395	0.355
Positive	62(32.3%)	19(30.6%)	1.668	0.443	14.179	5.302	2.225-12.634	<0.001
Cycle								
≤4	65 (33.9%)	9(13.8%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
5~6	80 (41.7%)	16(20.0%)	0.442	0.455	0.943	1.556	0.638-3.795	0.332
>7	47 (24.5%)	5(10.6%)	-0.300	0.594	0.255	0.741	0.231-2.373	0.613
Ki-67								
≤14%	37(19.3%)	3(8.1%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>14%	155(80.7%)	27(17.4%)	0.872	0.638	1.864	2.391	0.684-8.355	0.172
LMR								
≤4.62	96(50.0%)	9(9.4%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>4.62	96(50.0%)	21(21.9%)	0.996	0.428	5.401	2.707	1.169-6.268	0.020

Table. 3
Multivariate analysis between clinical characteristics and pCR.

Variable	B	S.E.	Wals	OR	CI(95%)	p value
LMR						
≤4.62	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>4.62	0.947	0.446	4.520	2.579	1.077-6.176	0.033
HER-2						
Negative	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Low expression	0.657	0.854	0.593	1.930	0.362-10.280	0.441
Positive	1.635	0.449	13.271	5.132	2.129-12.372	<0.001

and tumor have been more and more extensive, and it has been confirmed that cancer-related inflammation plays a crucial role in tumor growth, invasion and metastasis [4]. Many inflammatory indicators, including NLR, PLR and LMR are prognostic factors for a variety of malignant tumors including breast cancer [14–22]. Lymphocytes play a crucial role in tumor immunity, such as cytotoxic cell death, tumor cell proliferation and migration’s inhibition, etc. [27]. The decrease in the number of lymphocytes is considered to be the cause of the body’s low immune response to tumors, leading to tumor progression and metastasis [28]. In addition, the association between lymphocytopenia and reduced overall survival has been demonstrated in several prospective studies, such as metastatic breast cancer and non-Hodgkin’s lymphoma [29,30]. Monocytes, especially tumor-associated macrophages differentiated in the tumor microenvironment, can promote tumor proliferation, invasion, metastasis, neovascularization and recurrence [31,32]. Thirdly, Tumor-associated macrophages (TAMs) and Tumor-infiltrating lymphocytes (TILs) are immune cells that have been found to exist in a

variety of malignant tumor tissues and play an important role in the prediction of tumor prognosis [33]. TAMs are monocytes originating from circulating blood and are active around tumor tissues to secrete tumor chemokines. TAMs can also accelerate tumor progression by generating growth factors and cytokines to promote tumor angiogenesis and generate anti-immune responses. Relevant studies have confirmed that patients with high TAMs infiltration have a poor prognosis [34,35]. Studies have confirmed that the absolute value of peripheral blood monocytes is a biological marker that can replace TAMs [36]. TILs controls tumor progression by participating in cellular and humoral immunity. Low lymphocyte count may indicate poor immune function. The decrease of immune function will lead to the weakening of tumor tissue growth control function, resulting in poor prognosis [37–39]. Thus, the immune response to cancer is dependent on lymphocytes, and the high level of tumor-associated macrophages from monocytes is significantly associated with tumor aggressiveness and outcome. The LMR obtained by combining these two parameters can effectively reflect the immune status of the host and the degree of tumor progression. Low lymphocyte count and high monocyte count can reflect the deficiency of anti-tumor immunity and increased tumor load.

The mechanism of the correlation between LMR and prognosis in breast cancer patients is thought to be related to tumor-infiltrating immune cells such as TILs or tumor-associated macrophages. Circulating lymphocytes affect TILs formation and are involved in immune responses in tumors. TAMs can induce specific immunity by promoting the activation and recruitment of T and B TILs and inducing an appropriate immune response [40]. The increase of LMR may be due to stronger anti-tumor immunity mediated by lymphocytes than by monocytes. Thus, patients with elevated LMR may have a better prognosis.

Many pieces of literature have reported the prognostic value of LMR in a variety of cancers [23–25]. A meta-analysis showed that LMR was

Table. 4
Relationship between LMR and HER-2 subgroup of breast cancer patients.

Variable	HER-2 (-) (n=117)				HER-2 Low expression(n=13)				HER-2 (+) (n=62)			
	non-pCR	pCR(%)	χ^2	P	non-pCR	pCR(%)	χ^2	P	non-pCR	pCR(%)	χ^2	P
LMR≤4.62	59	4(6.3%)	0.347	0.556	4	1(20%)	0.133	0.715	24	4(14.3%)	6.429	0.011
LMR>4.62	49	5(9.3%)			7	1(12.5%)			19	15(44.1%)		

Table. 5
Univariate analysis between clinical characteristics and OS.

Variable	N	B	S.E.	Wald	OR	CI(95%)	p
Age(years-old)							
≤49	99(51.6%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>49	93(48.4%)	-0.088	0.318	0.077	0.916	0.491-1.708	0.782
BMI							
<25	116(60.4%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
25~30	67(34.9%)	-0.336	0.321	1.093	1.399	0.745-2.628	0.296
≥30	9(4.7%)	-0.415	1.025	0.164	0.661	0.089-4.924	0.686
T stage							
cT1/cT2	155(80.7%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
cT3/cT4	37(19.3%)	0.903	0.332	7.402	2.466	1.287-4.724	0.007
Nstage							
N0	14(7.3%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
N1-3	178(92.7%)	1.200	1.013	1.405	3.322	0.456-24.182	0.236
HER-2							
Negative	117(60.9%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Low expression	13(6.8%)	0.319	0.539	0.349	1.375	0.478-3.954	0.555
Positive	62(32.3%)	-0.165	0.362	0.208	0.848	0.417-1.725	0.648
Cycle							
≤4	65 (33.9%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
5~6	80 (41.7%)	0.512	0.359	2.028	1.668	0.825-3.373	0.154
>7	47 (24.5%)	-0.201	0.502	0.161	0.818	0.306-2.185	0.688
Ki-67							
≤14%	37(19.3%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>14%	155(80.7%)	0.523	0.478	1.194	1.686	0.660-4.305	0.275
LMR							
≤4.62	96(50.0%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>4.62	96(50.0%)	-0.669	0.332	4.353	0.501	0.261-0.959	0.037

Table. 6
Multivariate analysis between clinical characteristics and OS.

Variable	B	S.E.	Wals	OR	CI(95%)	p value
LMR						
≤4.62	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>4.62	-0.631	0.333	3.590	0.532	0.277-1.022	0.058
T stage						
cT1/cT2	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
cT3/cT4	0.843	0.333	6.420	2.324	1.210-4.464	0.011

Table. 8
Multivariate analysis between clinical characteristics and DFS.

Variable	B	S.E.	Wald	OR	CI(95%)	p value
LMR						
≤4.62	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>4.62	-0.819	0.333	6.057	0.441	0.230-0.846	0.014
T stage						
cT1/cT2	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
cT3/cT4	0.867	0.333	6.779	2.379	1.239-4.568	0.009

Table. 7
Univariate analysis between clinical characteristics and DFS.

Variable	N	B	S.E.	Wald	OR	CI(95%)	p
Age(years-old)							
≤49	99(51.6%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>49	93(48.4%)	-0.139	0.318	0.190	0.870	0.467-1.623	0.663
BMI							
<25	116(60.4%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
25~30	67(34.9%)	0.387	0.321	1.453	1.473	0.785-2.766	0.228
≥30	9(4.7%)	-0.575	1.024	0.316	0.563	0.076-4.183	0.574
T stage							
cT1/cT2	155(80.7%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
cT3/cT4	37(19.3%)	0.922	0.332	7.700	2.513	1.311-4.819	0.006
Nstage							
N0	14(7.3%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
N1-3	178(92.7%)	1.120	1.013	1.223	3.065	0.421-22.310	0.269
HER-2							
Negative	117(60.9%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Low expression	13(6.8%)	0.508	0.539	0.890	0.345	0.578-4.778	1.662
Positive	62(32.3%)	-0.162	0.362	0.200	0.655	0.418-1.729	0.850
Cycle							
≤4	65 (33.9%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
5~6	80 (41.7%)	0.514	0.359	2.043	1.671	0.826-3.379	0.153
>7	47 (24.5%)	-0.272	0.500	0.295	0.762	0.286-2.032	0.587
Ki-67							
≤14%	37(19.3%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>14%	155(80.7%)	0.500	0.478	1.094	1.649	0.646-4.211	0.296
LMR							
≤4.62	96(50.0%)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>4.62	96(50.0%)	-0.863	0.332	6.767	0.422	0.220-0.808	0.009

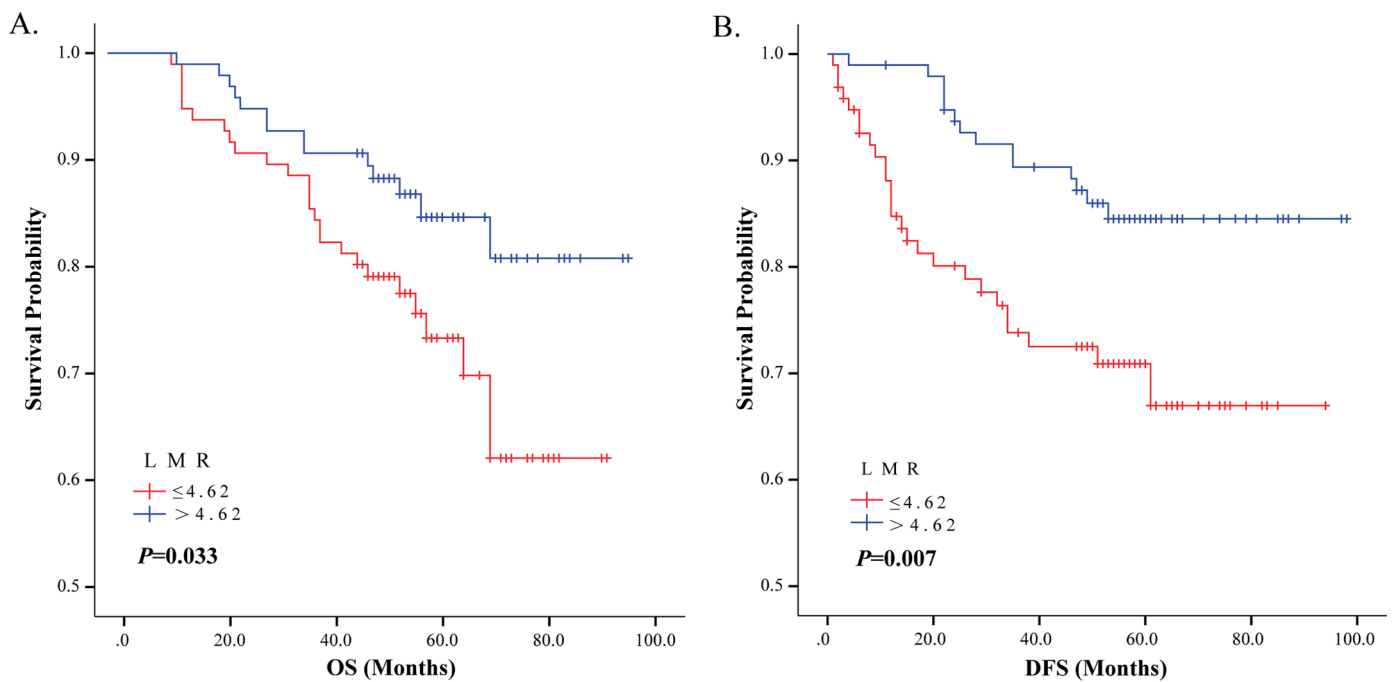


Fig.2. Kaplan-Meier analysis of the relationship between LMR and OS and DFS in 192 breast cancer patients. (A) LMR was significantly correlated with OS ($P=0.033$). Patients with high LMR before treatment had higher OS than those with low LMR. (B) LMR was significantly correlated with DFS ($P=0.007$), and patients with high LMR before treatment had higher DFS than those with low LMR.

significantly correlated with tumor invasion depth and tumor size, and high LMR suggested better OS and DFS for colorectal cancer [41]. Hirahara et al. found that LMR was related to the prognosis of patients with esophageal cancer [42]. Mandaliya et al confirmed the prognostic value of LMR for patients with non-small cell lung cancer [43]. Our study also confirmed that LMR was significantly correlated with OS and DFS in breast cancer patients. There have been some pieces of literature confirming the prognostic value of LMR in breast cancer, Ni et al. conducted a retrospective cohort study of 542 patients with locally advanced breast cancer who received neoadjuvant chemotherapy and reported for the first time that the high level of LMR in peripheral blood before neoadjuvant chemotherapy is a favorable factor for the prognosis of patients with locally advanced breast cancer [44]. In this study, univariate and multivariate analyses showed that LMR was an independent factor affecting the prognosis of breast cancer patients, and the prognosis of the high LMR group was better than that of the low LMR group. This is also consistent with the results of Ni et al. Hu RJ et al also pointed out that preoperative LMR was related to DFS and OS of breast cancer patients and can be used as a reference indicator of breast cancer prognosis [45]. In addition, several studies have assessed the predictive value of LMR or NLR for progression and sensitivity to chemotherapy in breast cancer patients treated with NAC. For example, Marin Hernandez C et al found that preoperative LMR was significantly correlated with the prognosis of breast cancer patients receiving neoadjuvant chemotherapy [46]. The results of this study are similar to the above conclusions. We found that LMR before neoadjuvant chemotherapy was significantly associated with pathological complete response and prognosis of breast cancer patients. Since breast cancer patients have a better prognosis and longer survival cycle after systematic treatment, in this study, although The OS of breast cancer patients after receiving neoadjuvant chemotherapy was not statistically significant, we still believed that the OS of patients in the high LMR group was relatively better. Subsequent studies with large sample sizes are still needed to confirm this result. In conclusion, LMR may play an important role in the occurrence and development of a variety of malignant tumors including breast cancer, and its specific mechanism needs to be further explored.

HER-2 is a transmembrane protein with tyrosine kinase activity and

is a member of the EGFR family [47]. Participating in signal transduction pathways leading to cell growth and differentiation can inhibit cell apoptosis, promote cell proliferation, promote blood vessel and lymphatic regeneration, and increase the invasiveness of tumor cells [48–50]. Previous studies have confirmed that the overexpression of HER-2 is significantly correlated with the occurrence, development and metastasis of breast cancer, and is one of the most important prognostic indicators in its progression [51]. In previous studies, HER-2 status was usually only divided into negative HER-2 group and positive HER-2 group. In this study, HER-2 was divided into negative HER-2 group, positive HER-2 group and low HER-2 expression group according to the 2021 CSCO breast cancer diagnosis and treatment Guidelines. According to the results of subgroup analysis, in the high LMR group, The pCR rate of the HER-2 (+) subgroup was 44.1% ($P=0.058$). It indicates that patients with the high LMR and HER-2(+) group are more likely to obtain pCR.

The limitations of this study: 1. This study is a retrospective study of single-center, samples from single provinces and regions, including in the sample size are small, may increase the heterogeneity between samples, there is a risk of bias, the future would still need a large sample of prospective cohort studies, and long-term follow-up, so as to achieve better results; 2. For the determination of the critical value of LMR, the critical value selected by different studies is not exactly the same, and the prognostic value is also different. The median was used as the cut-off value of LMR in this study, but whether its accuracy and sensitivity can meet the requirements of the application of clinical biomarkers remains to be further verified.

Conclusion

The results of this study suggest that LMR and HER-2 status are independent predictors of pathological complete response after neoadjuvant chemotherapy in breast cancer patients. More importantly, LMR was significantly associated with OS and DFS in breast cancer patients. LMR is a ratio based on peripheral blood lymphocytes and mononuclear cells of a joint index, compared with the imaging examination and histopathologic examination, it can provide a non-invasive,

easy to obtain, feasible and low price method to evaluate the curative effect of neoadjuvant chemotherapy and the prognosis of patients with breast cancer, and offers the choice of treatment for patients with strong support.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

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CRediT authorship contribution statement

Xiangyu Meng: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Xueying Wang:** Data curation, Formal analysis. **Cong Jiang:** Data curation, Formal analysis. **Shuai Zhang:** Data curation, Formal analysis. **Shaoqiang Cheng:** Data curation, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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