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Original Article

Correlation of serum NLR, PLR and HALP with efficacy of neoadjuvant chemotherapy and prognosis of triple-negative breast cancer

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Abstract: Objective: To investigate the correlation of blood neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) with the efficacy of neoadjuvant chemotherapy (NAC) and the prognosis of triple-negative breast cancer (TNBC). Methods: In this retrospective study, clinical data of 92 patients with TNBC were analyzed. The patients were treated with NAC in the Department of Gynecology of the People's Hospital of Zhuji from January 2015 to December 2018. According to treatment efficacy of NAC, patients were divided into a pathologic complete response (pCR) group (n=37) and a non-pathologic complete response (non-pCR) group (n=55). The pathological and clinical data of patients were collected, and the efficacy of NAC and influencing factors were statistically analyzed. The predicting performances of NLR, PLR and HALP for the efficacy of NAC in patients with TNBC were investigated. Patients were followed up for 3 years to obtain the all-cause mortality so as to analyze the correlation of NLR, PLR and HALP with survival time. Results: Multivariate regression analysis showed that TNM stage III (OR (95% CI): 1.742 (1.209-2.631), P=0.003), lymph nodes metastasis (OR (95% CI): 1.922 (1.492-2.983), P =0.005), high NLR (OR (95% CI): 2.261 (1.625-2.754), P<0.001), high PLR (OR (95% CI): 2.062 (1.692-2.791), P<0.001) and low HALP (OR (95% CI): 0.518 (0.365-0.734), P<0.001) were risk factors of poor NAC efficacy for TNBC. The mortality of patients in the non-pCR group was higher than that in the pCR group within 3 years (P<0.05). Survival analysis showed that the 3-year survival rate of the non-pCR group was lower than that of the pCR group (P<0.05). Furthermore, patients with high NLR, high PLR and low HALP had a lower 3-year survival rate than those with low NLR, low PLR and high HALP (P<0.05). Conclusions: Lymph node metastasis, TNM stage III, high NLR, high PLR and low HALP are risk factors for the poor efficacy of NAC for TNBC. High expression of NLR, PLR and low expression of HALP may indicate a poor prognosis of TNBC patients who failed NAC.

Keywords: Triple-negative breast cancer, neoadjuvant chemotherapy, efficacy, prognosis, correlation

Introduction

Breast cancer is a public health problem that threatens women's health. According to a worldwide report in 2018, breast cancer has one of the highest incidence and mortality in women [1]. Triple-negative breast cancer (TNBC) is a special subtype of breast cancer, with clinical manifestations of strong local tissue infiltration and invasion, easy recurrence, early metastasis and high mortality, accounting for 10-30% of all breast cancers [2]. Neoadjuvant chemotherapy (NAC) is a standard method for treating locally advanced breast cancer. This therapy can shrink the tumor and create an opportunity for surgery, thereby improving the prognosis of patients. Previous studies have shown that pathological complete response (pCR) achieved during NAC can indicate a better long-term prognosis [3, 4]. Although there are corresponding precise and individualized treatment plans for different pathological types of breast cancer, not all patients can benefit from NAC. Therefore, to predict the efficacy of NAC through clinical indicators has become a new research orientation.

Previous studies have shown that the systemic inflammatory response plays an important role

in the occurrence and development of tumors, and have pointed out that peripheral blood inflammatory markers have certain value in cancer treatment and prognosis prediction [5, 6]. Blood neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) are indicators of systemic inflammation. Previous studies have shown certain correlations of systemic inflammation indicators with the occurrence, development and prognosis of tumors [7, 8]. However, controversies still exist in the correlation of systemic inflammatory indicators with the treatment efficacy and prognosis in patients with breast cancer [9, 10], and there are limited reports on the correlation of those indicators with the treatment efficacy and prognosis in TNBC patients after NAC. Based on this, we investigated the correlation of the pre-NAC systemic inflammatory indicators (NLR, PLR and HALP) with the efficacy of NAC and the long-term prognosis of TNBC.

Materials and methods

General data

A retrospective study was conducted in 92 patients with TNBC treated with NAC in the Department of Gynecology of the People's Hospital of Zhuji from January 2015 to December 2018. The patients were 29-67 years old, with an average age of 52.3±8.9 years old. This study was approved by the Ethical Committee of The People's Hospital of Zhuji.

Inclusion & exclusion criteria

Inclusion criteria: (1) Patients with pathologically confirmed TNBC [11]. Patients with at least one measurable tumor lesion with TNM stage II-III; (2) patients with an age over 18 years old; (3) patients with no indication for surgery; (4) patients who received NAC; (5) patients with no acute or chronic inflammation, hematological and autoimmune diseases before NAC; (6) patients who had their systemic inflammatory indicators collected before radiotherapy and chemotherapy; (7) patients with complete clinical data including NLR, PLR and HALP; (8) patients who completed the 3-year follow-up.

Exclusion criteria: (1) patients without an evaluable clinical result regarding the treatment; (2) patients with other malignant tumors; (3) patients with severe heart, brain or kidney diseases; (4) patients who could not tolerate NAC or received non-standard NAC; (5) patients with metastatic tumors.

Methods

The data related to NLR, PLR and HALP of the patients were collected before NAC (with paclitaxel liposome (H20030357, dosage: 175 mg/m^2, Nanjing Luye Pharmaceutical Co., Ltd.) and carboplatin (H20020180, dosage: 0.3-0.4 g/m^2, Shandong Qilu Pharmaceutical Co., Ltd.) as the main treatment drugs). The therapy was performed weekly with 4 weeks as one course of treatment.

According to the response evaluation criteria in solid tumors and the results of color Doppler ultrasound before and after NAC, the efficacy was divided into complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD) [12]. The patients were then divided into a pCR group (CR+PR) and a non-pCR group (SD+PD) based on the treatment efficacy.

All included patients completed a 3-year telephone or outpatient follow-up until December 2021. The overall survival (OS) of the patients was recorded as the time from surgery to death or the end of the follow-up.

Outcome measures

The NLR, PLR and HALP were calculated and compared between the two groups. NLR = neutrophil/lymphocyte, PLR = platelet/lymphocyte, HALP = hemoglobin (g/L) * albumin (g/L) * lymphocyte (/L) * platelet (/L). NLR and PLR were used to evaluate the systemic inflammation, and HALP was used to evaluate the nutritional status in patients.

The predicting performances of NLR, PLR and HALP for the efficacy of NAC in patients with TNBC were investigated.

The OS of the included patients was observed through a 3-year follow-up.

The correlation of NLR, PLR and HALP with the survival time was evaluated in patients with TNBC.

Table 1. Comparison of general data between the two groups ($\bar{x} \pm sd$, n (%))

Item	pCR group (n=37)	non-pCR group (n=55)	χ^2/t/Z	P
Age (years old)				
≥50	25 (67.57)	35 (63.64)	0.151	0.698
<50	12 (32.43)	20 (36.36)		
Menopause (n)	15 (40.54)	22 (40.00)	0.003	0.959
BMI (kg/m^2)	22.53±2.54	23.29±2.78	1.330	0.187
TNM stage				
Stage II	20 (54.05)	12 (21.82)	10.133	0.001
Stage III	17 (45.95)	43 (78.18)		
Lymph node metastasis (n)	12 (32.43)	37 (67.27)	10.786	0.001
Tumor diameter (cm)	3.2±0.6	4.0±0.6	6.271	<0.001
NLR	2.43±0.58	3.49±0.76	7.183	<0.001
PLR	115.11±22.82	159.03±30.62	7.878	<0.001
HALP (points)	37.92±13.92	18.33±4.92	8.221	<0.001

Note: χ^2 is the statistical value of Chi-square test; t is the statistical value of t test; Z is the statistical value of rank sum test. BMI: body mass index; pCR: pathologic complete response; NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, HALP: hemoglobin and albumin levels and lymphocyte and platelet counts.

Statistical analyses

SPSS 22.0 statistical software was used to analyze the data. Continuous variables with a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm sd$), and processed by independent sample t test, denoted as t. Those did not meet a normal distribution were presented by median (lower quartile, upper quartile), and compared using the Mann-Whitney U test between the two groups. The enumeration data were subjected to Pearson's chi-square test, and the variables with differences between groups (P<0.05) were included in a binary logistic regression to further analyze the influencing factors for NAC efficacy in patients with TNBC. The predicting performances of NLR, PLR and HALP for the efficacy of NAC in patients with TNBC was analyzed by receiver operating characteristic (ROC) curve. An area of 0.5-0.7 indicated a low predicting value, 0.7-0.9 indicated a medium predicting value, and over 0.9 indicated a high predicting value. Kaplan-Meier method and log-rank test were used for survival analysis. A difference of P<0.05 was considered statistically significant.

Results

General data

Among the included patients, 37 of them benefited from NAC and belonged to the pCR group, and the other 55 did not benefit from NAC and belonged to the non-pCR group. Comparison of general data showed that the pCR group showed less cases with TNM stage III and lymph node metastasis, smaller tumor diameter, lower NLR and PLR, and higher HALP as compared with those in the non-pCR group (all P<0.01). See **Table 1**.

Logistic regression analysis of influencing factors for NAC efficacy in patients with TNBC

Taking pCR as the dependent variable (1= yes, 0= no), the indicators with differences in univariate analysis were subjected to multivariate binary logistic regression. It was found that TNM stage III (OR (95% CI): 1.742 (1.209-2.631), P=0.003), lymph node metastasis (OR (95% CI): 1.922 (1.492-2.983), P=0.005), high NLR (OR (95% CI): 2.261 (1.625-2.754), P< 0.001), high PLR (OR (95% CI): 2.062 (1.692-2.791), P<0.001) and low HALP (OR (95% CI): 0.518 (0.365-0.734), P<0.001) were factors related to NAC efficacy. See **Table 2**.

Predicting performances of NLR, PLR and HALP for the efficacy of NAC in patients with TNBC

The area under the curve for NLR in predicting the efficacy of NAC was 0.837, and when the NLR was at the cut-off value of 3.16, its Youden index was 0.745, with a specificity of 0.946 and a sensitivity of 0.745. The area under the curve for PLR was 0.845, and when the PLR was at

Table 2. Logistic regression analysis of factors related to NAC efficacy in patients with TNBC

Variable	OR value (95% CI)	P
Constant	-	<0.001
TNM stage III	1.742 (1.209-2.631)	0.003
Lymph node metastasis	1.922 (1.492-2.983)	0.005
Tumor diameter (cm)	1.062 (0.585-1.582)	0.072
NLR	2.261 (1.625-2.754)	<0.001
PLR	2.062 (1.692-2.791)	<0.001
HALP	0.518 (0.365-0.734)	<0.001

Note: TNM stage III =1, stage II =0; lymph node metastasis =1, negative lymph node metastasis =0; For numerical indicators, the median of the corresponding indicator of all patients was set as the division. Tumor diameter ≥3.6 cm =1, tumor diameter <3.6 cm =0; NLR ≥3.06 =1, NLR <3.06 =0; PLR ≥141.36 =1, PLR <141.36 =0; HALP ≤26.21 =1, HALP >26.21 =0. NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, HALP: hemoglobin and albumin levels and lymphocyte and platelet counts; NAC: neoadjuvant chemotherapy; TNBC: triple-negative breast cancer.

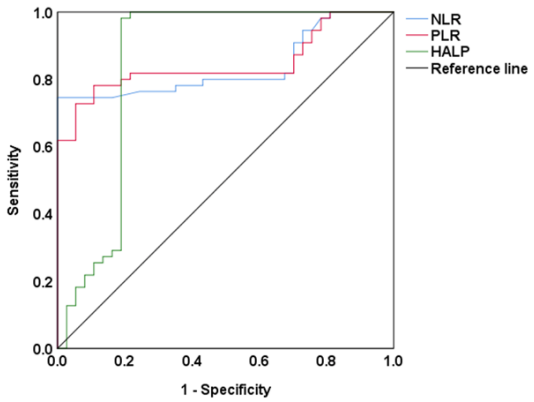

Figure 1. Diagnostic value of NLR, PLR and HALP in the efficacy of NAC for TNBC. NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; HALP: hemoglobin and albumin levels and lymphocyte and platelet counts; NAC: neoadjuvant chemotherapy; TNBC: triple-negative breast cancer.

the cut-off value of 129.52, its Youden index was 0.674, with a specificity of 0.782 and a sensitivity of 0.892. The area under the curve for HALP was 0.847, and when the HALP was at the cut-off value of 24.14, its Youden index was 0.745, with a specificity of 0.982 and a sensitivity of 0.811. See **Figure 1**.

Comparison of 3-year mortality rate between two groups

Among the 37 patients in the pCR group, 16 patients died within 3 years, with a mortality of 43.24%, while 39 out of the 55 patients in the non-pCR group died within 3 years, with a mortality of 70.91%, showing a statistically significant difference (χ^2=7.042, P=0.008). The mean overall survival time in the non-pCR group was 29.5 months, which was lower than 40.3 months in the pCR group (χ^2=6.687, P=0.001). See **Table 3** and **Figure 2**.

Correlation of NLR, PLR and HALP with prognosis of TNBC

According to the predicating cut-off value (3.16) of NLR, 41 patients were included in the high NLR group and 51 in the low NLR group. Survival analysis showed that the survival rate of the high NLR group was lower than that of the low NLR group, with a statistical difference (χ^2=15.441, P<0.001). According to the PLR predicating cut-off value (129.52) of PLR, 46 patients were included in the high PLR group and 46 in the low PLR group. The survival analysis showed that the survival rate of the high PLR group was lower than that of the low PLR group, with a statistical difference (χ^2=5.337, P=0.021). According to the predicating cut-off value (24.14) of HALP, 67 patients were included in the high HALP group and 25 in the low HALP group. The survival analysis showed that the survival rate of the low HALP group was lower than that of the high HALP group, with a statistical difference (χ^2=31.002, P<0.001). See **Figure 3**.

Discussion

In this study, patients with TNBC were included to explore the predicting factors of the efficacy of NAC. The regression analysis showed that lymph node metastasis, TNM stage, NLR, PLR and HALP were influencing factors of NAC efficacy. Lymph node metastasis and TNM stage III as risk factors suggested that NAC was insensitive to tumors with strong proliferation and invasion ability, which is consistent with previous results [13]. NLR, PLR and HALP are all systemic inflammatory factors, which play an important role in the occurrence and development of tumors, including breast carcinoma. Previous study on breast cancer cells and animal experiments confirmed that inflammatory factors played an important role in breast cancer cell proliferation, invasion and metastasis [14]. Another study showed that the massive release of inflammatory factors in the circulatory system had an adverse effect on the prog-

Table 3. Comparison of death rate within 3 years between the two groups (n (%))

Group	Death within 1 year	Death within 2 years	Death within 3 years
pCR group (n=37)	6 (16.22)	10 (27.03)	16 (43.24)
non-pCR group (n=55)	13 (23.64)	25 (45.45)	39 (70.91)
χ^2	0.743	3.187	7.042
P	0.389	0.074	0.008

Note: χ^2 is the statistical value of Chi-square test.

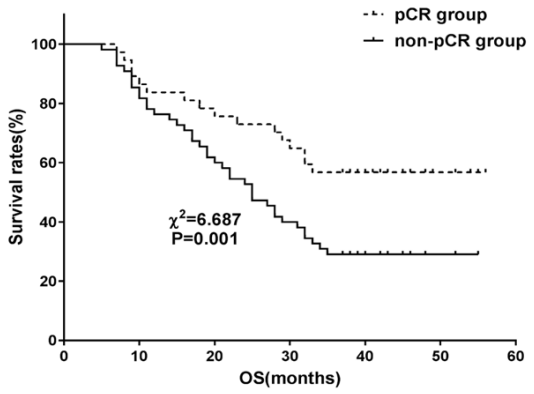

Figure 2. The 3-year survival curve of the two groups. OS: overall survival.

nosis of breast cancer [15]. It is shown that systemic inflammatory factors are closely related to the tumor microenvironment [16]. Systemic inflammatory factors increased the invasion and proliferation of cancer cells, thereby promoting tumor growth and stage progression. This study showed that lymph node metastasis and TNM stage III may be related to the high inflammatory state of patients.

We further analyzed the correlation of NLR, PLR and HALP with the efficacy of NAC. The results showed that the optimal cut-off value was 3.16 for NLR, 129.52 for PLR and 24.14 for HALP. At present, peripheral blood inflammatory factors have been shown to be related to chemotherapy efficacy and prognosis in different tumor studies [17, 18]. However, the prediction value of peripheral blood inflammatory factors on chemotherapy efficacy and survival rate is still in an exploratory stage, and there is no widely-recognized cut-off value yet.

The prognosis of tumors is a clinical concern. It is shown in clinical practice that the treatment efficacy greatly impacts the prognosis. As an important treatment for TNBC, NAC can improve the surgical resection rate and is of great significance in improving the prognosis [19]. This study showed that patients with better efficacy after NAC had higher 3-year survival rate.

Correlation analysis of NLR, PLR and HALP with prognosis showed that patients with high NLR, high PLR and low HALP had a lower 3-year survival rate than those with low NLR, low PLR and high HALP. A previous study involving 8563 patients showed that the overall survival was significantly decreased when the NLR was greater than a cut-off value of 3.0 [20]. A meta-analysis used NLR as a risk predictor for breast cancer [21]. Another study showed that the NLR and PLR before NAC were correlated with chemotherapy efficacy and prognosis [22]. Study also showed that patients with lower PLR before NAC had a higher pCR rate [23]. HALP is a comprehensive index that can reflect the nutritional, immune and inflammatory status of the body. Study showed that in patients with small cell lung cancer receiving first-line chemotherapy, a HALP score >25.8 before treatment is an independent risk factor for progression-free survival [24]. A study in patients with prostate cancer showed that pre-treatment HALP >32.4 were significantly associated with prolonged progression-free survival [25]. In patients with esophageal cancer treated with chemotherapy, a significant prolongation of progression-free survival was also observed when HALP >48.34 [26]. Currently, there is no report on the correlation between HALP and prognosis in patients with breast cancer.

The ROC and survival analyses of this study showed that patients with high inflammatory response had worse chemotherapeutic efficacy and prognosis. Tumor cell-associated neutrophils, which are mainly derived from peripheral blood, are considered to be key mediators of tumor progression. They can promote tumor growth, stimulate angiogenesis, cause genetic instability and enhance tumor invasiveness [27]. Tumor-associated macrophages are mainly derived from circulating monocyte precur-

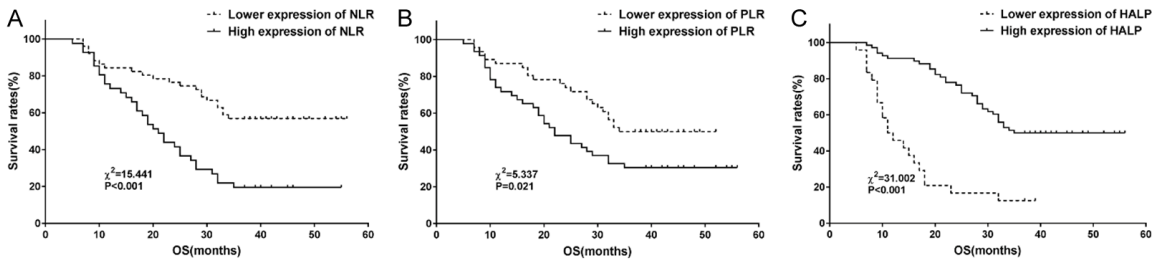

Figure 3. Correlation of NLR, PLR and HALP with prognosis of TNBC. A: Survival curves of patients with different NLR; B: Survival curves of patients with different PLR; C: Survival curves of patients with different HALP. OS: overall survival; NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, HALP: hemoglobin and albumin levels and lymphocyte and platelet counts; TNBC: triple-negative breast cancer.

sors and play a key role in the tumor microenvironment. They can produce pro-angiogenic factors, growth factors and proteases, promote extracellular matrix degradation and tumor cells proliferation, induce angiogenesis, and are beneficial to invasion and metastasis [7]. In the process of tumor progression, platelets mainly promote angiogenesis through adhering on tumor blood vessels and release granules containing angiogenesis-stimulating factors such as platelet-derived endothelial cell growth factor [28]. Lymphocytes play an important role in the immune regulation of host cells. They help to destroy residual malignant tumor cells and related micrometastases in host cells. In the local tumor inflammatory environment, more neutrophil and platelet infiltration and less lymphocyte infiltration can be observed [29].

Limitations and prospects: The sample size can be expanded to further observe the correlation of NLR, PLR and HALP with the efficacy of NAC and the prognosis of TNBC. Further studies could also explore the mechanisms and influencing factors that lead to the changes of NLR, PLR and HALP in patients with TNBC.

In conclusion, lymph node metastasis, TNM stage III, NLR (≥3.16), PLR (≥129.52) and HALP (≤24.14) are the risk factors for the poor efficacy of NAC in patients with TNBC. High NLR, high PLR and low HALP suggest a poor prognosis in patients who did not benefit from NAC.

Disclosure of conflict of interest

None.

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