Original Article

# Prognostic significance of preoperative serum inflammation markers in patients with male breast cancer

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**Background:** There were no predictive prognosis factors of serum in male breast cancer, while breast cancer is a heterogeneous disease. The purpose of our study was to determine the prognostic implications of the pretreatment neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) in the serum of patients with male breast cancer.

**Methods:** We retrospectively identified a random cohort of male breast cancer patients treated at the Sun Yat-sen University Cancer Center between Jan 1, 1996 and Dec 31, 2016. A number of 108 patients had different inflammation markers recorded pre-operation. Survival status was retrieved from our cancer center registry and phone follow-up. Cox proportional hazards regression model was used to analyze the disease-free survival (DFS) and overall survival (OS).

**Results:** Among these patients in this study, 13 (12.0%) had disease recurrence, and 7 (6.5%) patients appeared distant metastasis. No statistically significant association of the preoperative NLR, PLR or LMR level with patients' different outcomes was found.

**Conclusions:** In short, we were unable to establish a connection between preoperative inflammation biomarkers and male breast cancer patients' survival. Neither NLR, PLR nor LMR is useful for predicting prognosis in male breast cancer patients, and prospective studies to evaluate the above biomarkers as a simple prognostic trail is necessary.

**Keywords:** Male breast cancer (MBC); neutrophil-to-lymphocyte ratio (NLR); platelet-to-lymphocyte ratio (PLR); lymphocyte-to-monocyte ratio (LMR); disease-free survival (DFS)

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## Introduction

Human male breast cancer (MBC) is an infrequent cancer and fewer than 1% of all breast cancers are found in men (1). Compared with female breast cancer (FBC), researchers have focused relatively little attention on MBC. Therefore, standard treatment for men have usually been derived from clinical trials of female patients (2). Even in the same stage or similar pathological features, the prognosis is usually very unpredictable and heterogeneous. It would be of great value to identify simple and useful markers to stratify MBC patients with high risk and to improve individualized therapy.

Recent studies consider that inflammation is a known

major driver for the development and progression of cancer (3). Various immunologic-based score markers, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) might provide survival information on different cancers, including gastric, colorectal, pancreas, lung, and esophageal cancers (4-7). Even in FBC, previous meta-analyses have also confirmed that preoperative NLR may be an effective predictive biomarker for prognosis (8). The prognostic role of NLR, PLR or LMR in MBC has not been evaluated yet. These blood parameters are easy to perform and inexpensive, and they are readily performed in daily routine. Consequently, the purpose of our study was to evaluate whether the preoperative NLR, PLR or LMR is an independent prognostic indicator in MBC patients. We present the following article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-693).

## Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committees of Sun Yat-sen University Cancer Center (GZR2019-254). Each patient had written informed consent.

### *Patient selection and clinical data collection*

From an institutional database, a number of 108 male patients diagnosed with breast cancer who were undergoing operation at our Cancer Center between 1995 and 2016 were collected in our study. These patients were included in the cohort if they had blood routine examination before their surgery treatment modality. Patients who had the following situation were excluded from this study: (I) received preoperative chemotherapy; (II) had chronic inflammatory disease including autoimmune disorder and infection; (III) had distant metastases at diagnosis; (IV) had secondary malignancies; (V) had incomplete clinical pathological data; and (VI) lost to follow-up. All patients included in this study received treatment according to the standard treatment guidelines. The data regarding patient-related clinical pathology, such as age, TNM stage, estrogen (ER)/progesterone (PR) receptor [hormone receptor (HR)] status, and human epidermal growth factor receptor 2 (HER-2) status were collected and analyzed. Our study design was approved by the local institute research ethics committee. Each patient had written informed consent.

### *Patients follow-up*

The primary endpoint was disease-free survival (DFS), which was defined as the time interval from operation to the date of any recurrence (local, regional, or distant) of breast cancer, or a second primary cancer, or death due to any cause. The secondary end point was overall survival (OS), which was defined as the time interval from diagnosis to death or the last follow-up. We had followed up all patients by medical records review or telephone interview until Dec 1, 2016.

### *Statistical analysis*

All statistical analyses were performed using SPSS (version 22.0) software. Cox proportional hazards model, including NLR, PLR and LMR was fit to determine these inflammation parameters that were significantly statistically associated with DFS or OS. Binary logistic regression analyses were respectively performed to assess the influence of NLR, PLR and LMR in different groups. Odds ratio (OR) estimated from logistic regression was reported relative risks with 95% confidence interval (95% CI). A $P<0.05$ was considered statistically significant.

## Results

### *Clinicopathological characteristics among the patients of MBC*

We identified 108 male patients who had been diagnosed and underwent breast surgery. The mean age of the patients was 57.7±13.9 years, with an age distribution of 28–91 years. Tumor size after surgery was classified as pT1–2 in 87.1%, pT3–4 in 8.3%. Lymph node status positive were diagnosed in 33.3%, negative in 66.7%, whereas HR was positive in 75% of patients, negative in 25%. The HER-2 expression was positive in 20.4% and negative in 79.6% patients. Until last follow-up, local recurrence or distant metastasis were confirmed in 20 (18.5%) patients, however there were 42 patients confirmed dead. All patients' characteristics are presented in *Table 1*.

### *Comparison of blood parameters among the patients of MBC*

The mean preoperative serum NLR, PLR and LMR were 2.15±0.93 (range, 0.21–4.77) 125.94±58.22 (range, 38.80–440.77) and 4.61±2.21 (range, 1.25–13.50), respectively. The

 

**Table 1** Clinicopathological characteristics in patients with male breast cancer (n=108)

| Characteristic | Value |
|---|---|
| Age | |
| Median (range) | 58 (28–91) |
| Age in years, n (%) | |
| <50 | 31 (28.7) |
| ≥50 | 77 (71.3) |
| T classification, n (%) | |
| T1–2 | 94 (87.1) |
| T3–4 | 9 (8.3) |
| Unknown | 5 (4.6) |
| N classification, n (%) | |
| N0 | 72 (66.7) |
| N1–3 | 36 (33.3) |
| TNM stage, n (%) | |
| I + II | 83 (76.9) |
| III | 21 (19.4) |
| Unknown | 4 (3.7) |
| HR status, n (%) | |
| Negative | 27 (25.0) |
| Positive | 81 (75.0) |
| HER-2 status, n (%) | |
| Negative | 86 (79.6) |
| Positive | 22 (20.4) |

HR, hormone receptor; HER-2, human epidermal growth factor receptor 2.

median DFS time was 81 months (range, 1–287 months). There were 13 patients with recurrence, and 7 patients appeared distant metastasis. The average preoperative serum NLR, PLR and LMR levels in patients without disease recurrence, with disease recurrence and with metastasis are shown in *Figure 1*. There were no significant differences between groups regarding these data.

### *The prognostic impact of serum NLR, PLR or LMR on survival of MBC*

In the Cox proportional hazards regression model analysis, whether DFS or not OS, the serum NLR or

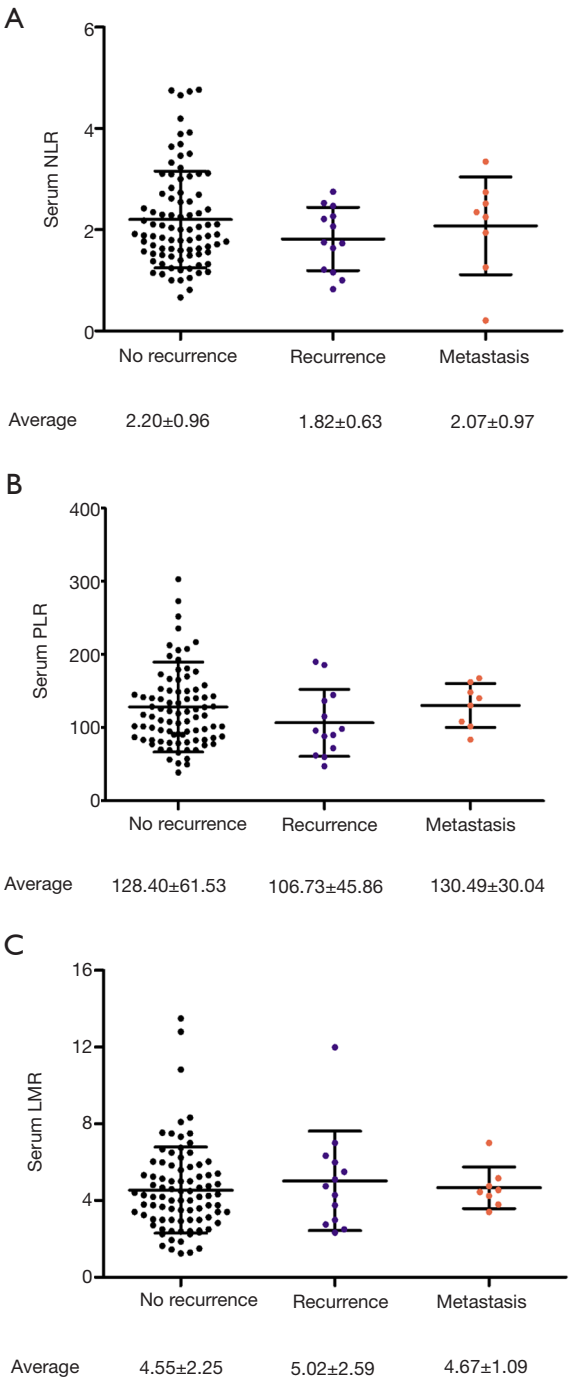


**Figure 1** The average preoperative level of serum NLR (A), PLR (B) and LMR(C) in patients without disease recurrence, with disease recurrence and in patients with metastasis. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

**Table 2** Univariate logistic regression model of NLR, PLR or LMR with regard to DFS

| Risk factor | β | OR (95 % CI) | P |
|---|---|---|---|
| NLR | –0.291 | 0.747 (0.461–1.212) | 0.237 |
| PLR | –0.003 | 0.997 (0.988–1.005) | 0.412 |
| LMR | –0.001 | 0.999 (0.876–1.141) | 0.992 |

NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; DFS, disease-free survival; OR, odds ratio; CI, confidence interval; β regression coefficient.

**Table 3** Univariate logistic regression model of NLR, PLR or LMR with regard to OS

| Risk factor | β | OR (95 % CI) | P |
|---|---|---|---|
| NLR | –0.046 | 0.955 (0.774–1.177) | 0.664 |
| PLR | 0.000 | 1.000 (0.995–1.005) | 0.875 |
| LMR | –0.084 | 0.920 (0.815–1.038) | 0.173 |

NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; OS, overall survival; OR, odds ratio; CI, confidence interval; β regression coefficient.

**Table 4** Univariate logistic regression model of blood parameters ratio with regard to HR status

| Risk factor | HR negative (n=27) | | | HR positive (n=81) | | |
|---|---|---|---|---|---|---|
| | β | OR (95% CI) | P | β | OR (95% CI) | P |
| NLR | –0.184 | 0.832 (0.414–1.672) | 0.605 | –0.417 | 0.659 (0.344–1.261) | 0.208 |
| PLR | –0.014 | 0.986 (0.954–1.018) | 0.389 | –0.003 | 0.997 (0.986–1.007) | 0.517 |
| LMR | 0.087 | 1.091 (0.650–1.833) | 0.742 | –0.017 | 0.983 (0.843–1.148) | 0.832 |

NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; HR, hormone receptor; OR, odds ratio; CI, confidence interval; β regression coefficient.

PLR or LMR were not statistically significant with these patients' prognosis. Therefore, no multivariate analyses were calculated. They were not independent prognostic indicators in these male patients. This data was respectively summarized in *Tables 2,3*.

### *Relationship between different HR or HER-2 status and clinical blood parameters*

Additional analysis was made according to different HR or HER-2 status. Even in subtypes, NLR, PLR or LMR were not a predictive parameter for prognosis. P value for ER or PR positive tumors (n=81), were 0.208, 0.517, 0.832 respectively; and for HER2-positive tumors (n= 22), P value was 0.180, 0.747, 0.322 respectively. These results were summarized in *Tables 4,5*. In summary, we were unable to establish a connection between preoperative NLR, PLR or LMR and various clinical features, including recurrence, metastasis, HR and HER-2 status.

## Discussion

Our study was to determine whether inflammatory markers were predictive factors in MBC patients. However, we could not find a predictive or prognostic value of NLR, PLR and LMR in this retrospective analysis. Recently, many articles have investigated blood indicators in patients with malignant tumors, the relationship between them is usually a multifactorial and complex process, still poorly understood. They concluded that tumor-associated neutrophil promotes remolding of the extracellular matrix, which results in the release of fibroblast growth factor, migration of endothelial cells and the split of tumor cells; in addition, neutrophil-derived reactive oxygen species

 

**Table 5** Univariate logistic regression model of blood parameters ratio with regard to HER-2 status

| Risk factor | HER-2 negative (n=86) | | | HER-2 positive (n=22) | | |
|---|---|---|---|---|---|---|
| | β | OR (95% CI) | P | β | OR (95% CI) | P |
| NLR | –0.183 | 0.833 (0.52–1.324) | 0.440 | –0.887 | 0.412 (0.113–1.504) | 0.180 |
| PLR | –0.004 | 0.996 (0.987–1.006) | 0.442 | –0.003 | 0.997 (0.982–1.013) | 0.747 |
| LMR | –0.035 | 0.966 (0815–1.146) | 0.691 | 0.168 | 1.183 (0.848–1.651) | 0.322 |

NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; HER-2, human epidermal growth factor receptor 2; OR, odds ratio; CI, confidence interval; β regression coefficient.

could inhibit the cytotoxic activity of lymphocytes, reduce the promoting of the extracellular matrix, suppress apoptosis of cancer cells. These events finally enhanced angiogenesis, and tumor growth and influenced survival outcomes in patients with cancer (9,10). Hile lymphocytes play an important role in the immune reaction against tumors, patients with cancer had higher densities of tumor-infiltrating lymphocytes, they could advance responses to treatments and improve outcome (11-13). As systematic inflammatory markers, serum low lymphocyte and high neutrophil, platelet, macrophage counts have been recognized as worse prognosis in solid tumors. When coupled with these indicators, such as NLR, PLR, and LMR, the predictive effect on cancer prognosis may be enhanced. Several studies consistently had found that NLR was an unfavorable prognostic indicator in patients with gynecological, lung, gastrointestinal, and renal cancers (14-19). A meta-analysis including 8,586 esophageal squamous cell carcinoma patients had reported that high NLR, PLR and low LMR were associated with poorer prognosis (7).

There was also lots of research in breast cancer, Azab *et al.* studied 465 FBC patients and demonstrated significantly worse prognosis in patients with higher NLR (20). Several other studies have also shown similar findings (21,22). A recent meta-analysis which included eight researches published has shown that higher NLR may be associated with poor survival (22-24). It is worth noting that the available data mainly concern female patients.

For the first time, it enrolled amounts of male patients to investigate the prognostic role of these inflammatory markers in MBC patients. In our study, we identified 108 male patients who were diagnosed and underwent breast surgery. After mean follow-up of 86 months, we found that whether DFS or not OS, the serum NLR or PLR or LMR were not statistically significant with these patients' prognosis. This was not the same as in the women's study. As breast cancer is a complicated and heterogeneous disease, lots of clinical parameters or biomarkers have been confirmed to be associated with the prognosis of patients, such as hormone status, HER-2 status, and TNM stage. Studies had found that NLR, PLR, and LMR were just systemic inflammatory response related markers and may affect the prognosis in different cancers. In some cases, these inflammatory markers may even contradict each other. Subsequently, we did a subgroup analysis, whether in HR positive group or in HR negative group, we could not find these marks related to the prognosis of patients. It was different in female patients, Orditura *et al.* showed that higher NLR could lead to worse prognosis in female patients with early breast cancer (8), while Asano *et al.* reported that lower NLR may cause higher efficacy and better outcome after neoadjuvant chemotherapy in triple negative breast cancer patients (25). An additional analysis was made according to different HER-2 status, even in different groups we could not identify NLR, PLR, LMR as a predictive factor for prognosis. For MBC patients is rare, treatment standards or prognostic indicators for them have generally been derived from female patients. However, breast cancer is a highly heterogeneous disease, some inflammatory biomarkers could predict the prognosis of patients with a woman, not suitable for male patients. Moreover, gender differences may affect patient preferences and survival factors. Therefore, it could need more studies independent in male patients to improve their therapy and prolong survival.

There are some limitations in our analysis. Firstly, this is a retrospective study with manual data extraction and analysis. However, data concerning laboratory values and survival data were not missed. Meanwhile, this was a mono-center study, all male patients eligible were included, it may also have the risk of a patient selection bias. Secondly, serum samples of patients were collected uniformly before treatment to avoid false blood parameters. Furthermore,

 

in accordance with national treatment guidelines for advanced women with breast cancer, some patients in T3–T4 should be offered neoadjuvant chemotherapy to reduce the risk for recurrence and death. However, in our study, some patients underwent surgical treatment if operable. Because it is unclear whether neoadjuvant therapy improves male patient outcomes (26). In addition, the number of patients and events were relatively small and did not allow comprehensive multivariable analysis and preclude definitive conclusions, further multiple center and prospective studies still required.

## Conclusions

Although the systemic inflammatory response is closely related to cancer, especially serum NLR or PLR may have clinical role in predicting survival in various cancers. However, this retrospective study failed to show an impact of NLR, PLR, LMR on prognosis in MBC patients. Due to the different influencing factors of hematological components measurement and the heterogeneity of breast cancer, the role of these inflammation markers in MBC should be further evaluated.

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## Footnote

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*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committees of Sun Yat-sen University Cancer Center (GZR2019-254). Each patient had written informed consent.



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