Original Article

Association between platelet-to-lymphocyte ratio and outcomes in HER2-positive advanced breast cancer patients treated with pyrotinib: a retrospective study

Li Hao[1,2#], Jie Dong[2#], Haiyang Yu[2#], Jian Chen[2], Xinghua Han[2], Yueyin Pan[1,2]

[1]Cheeloo College of Medicine, Shandong University, Jinan, China; [2]Department of Medical Oncology, The First Affiliated Hospital of USTC, Division of Life Science and Medicine, University of Science and Technology of China, Hefei, China

Contributions: (I) Conception and design: L Hao, Y Pan; (II) Administrative support: X Han, Y Pan; (III) Provision of study materials or patients: L Hao, J Dong; (IV) Collection and assembly of data: L Hao, H Yu; (V) Data analysis and interpretation: L Hao, J Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jian Chen, MD, PhD. Department of Medical Oncology, The First Affiliated Hospital of USTC, Division of Life Science and Medicine, University of Science and Technology of China, No. 17 Lujiang Road, Hefei 230000, China. Email: chenjianustc@sina.com; Xinghua Han, MD, PhD. Department of Medical Oncology, The First Affiliated Hospital of USTC, Division of Life Science and Medicine, University of Science and Technology of China, No. 17 Lujiang Road, Hefei 230000, China. Email: hanxhustc@163.com; Yueyin Pan, MD, PhD. Cheeloo College of Medicine, Shandong University, Jinan, China; Department of Medical Oncology, The First Affiliated Hospital of USTC, Division of Life Science and Medicine, University of Science and Technology of China, No. 17 Lujiang Road, Hefei 230000, China. Email: panyyustc@163.com.

Background: Peripheral blood biomarkers have been reported to be associated with the prognosis of breast cancer (BC) patients, but a few findings remain controversial. This study aimed to explore the correlation between peripheral blood indicators and treatment outcomes in human epidermal growth factor receptor 2 (HER2)-positive advanced BC patients treated with pyrotinib.

Methods: This was a retrospective cohort study including 156 HER2-positive advanced BC patients who treated with pyrotinib between March 2019 and May 2021. The baseline clinical characteristics including age, hormone receptor (HR) status, Ki-67, sites of metastasis, antitumor therapies and peripheral blood parameters including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), the product of neutrophil, platelet, and monocyte counts divided by lymphocyte count [pan-immune-inflammation value (PIV)] were collected. Tumor response was assessed every two cycles during treatment period. Follow-up was performed every 2 months to record survival status. All patients were followed up until death or time of data lock.

Results: Low PLR was associated with better disease control rate (P=0.005). Univariate analysis showed that high MLR (P=0.004), PLR (P=0.003), or PIV (P=0.02), low lymphocyte count (P=0.025), more than two metastatic sites (P<0.001), and presence of liver metastasis (P<0.001) or brain metastasis (P<0.001) were associated with poor progression-free survival (PFS). Multivariate analysis showed that only high PLR was an independent factor for poor PFS [hazard ratio =0.63; 95% confidence interval (CI): 0.41–0.97; P=0.038]. For overall survival (OS), univariate analysis showed that high NLR (P=0.001), MLR (P=0.005), PLR (P<0.001), or PIV (P=0.018), more than two metastatic sites (P=0.001), presence of liver metastasis (P=0.004) or brain metastasis (P=0.007), and pyrotinib monotherapy (P=0.036) were associated with worse OS. Multivariate analysis showed that PLR (hazard ratio =0.37; 95% CI: 0.14–0.94; P=0.037), number of metastatic sites (hazard ratio =2.84; 95% CI: 1.02–7.94; P=0.046) and treatment regimens (hazard ratio =0.15; 95% CI: 0.03–0.73; P=0.019) were independent factors.

Conclusions: High PLR is associated with poor treatment response and is an independent unfavorable prognostic factor in HER2-positive advanced BC patients treated with pyrotinib. The findings herein indicate that patients with higher PLR are less likely to benefit from pyrotinib-based therapy and may be

helpful in identifying the effective population in clinical practice.

Keywords: Platelet to lymphocyte ratio (PLR); breast cancer (BC); pyrotinib; prognosis

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Introduction

Breast cancer (BC) is the most common malignancy worldwide (1). Human epidermal growth factor receptor 2 (HER2) positive BC is a special subtype of BC, which accounts for approximate 15% to 20% of BC (2). It is characterized by amplification of the erb-B2 oncogene, and hyperactivation of HER2-related signaling pathway that stimulates tumor cell proliferation and survival (3). Historically, HER2-positive BC was considered to be a more aggressive subtype with a worse prognosis (4). Since the introduction of the first anti-HER2 drug trastuzumab, outcomes of HER2-positive BC patients have been significantly improved (5).

In recent years, a number of anti-HER agents have been approved for HER2-positive BC patients. Pyrotinib is an orally administered, irreversible, small-molecule, tyrosine kinase inhibitor targeting HER family receptors including HER1, HER2, and HER4 (6). It can covalently bind to the adenosine triphosphate (ATP)-binding sites of HER1 or HER2 receptor intracellular kinase domain, inhibit the formation of homodimer or heterodimer, block the activation of downstream signaling pathway (7). The antitumoral effect of pyrotinib has been demonstrated in several clinical studies. In a phase III clinical trial, compared with placebo, pyrotinib combined with capecitabine can significantly improve objective response rate (ORR; 68.6% *vs.* 16.0%, P<0.001) and prolong progression-free survival (PFS; 11.1 *vs.* 4.1 months, P<0.001) in advanced HER2-positive BC patients (8). Another phase III study showed advanced HER2-positive BC patients received pyrotinib plus capecitabine had longer PFS than those received lapatinib plus capecitabine (12.5 *vs.* 5.7 months, P<0.0001) (9). Currently, pyrotinib has been approved for the treatment of advanced HER2-positive BC patients.

However, there are multiple treatment options for HER2-positive BC patients at the advanced stage, especially after progression of first-line therapy, and there are no uniform standards for the sequence of drug usage. Although pyrotinib is effective, there are still some patients who fail to benefit from pyrotinib-based therapy due to primary resistance. Therefore, it is necessary and important to identify patients who may obtain better outcomes from pyrotinib-based therapy at the advanced stage. Effective prognostic factors can help guide treatment selection. Prognostic factors of BC reported in previous studies include tumor size, stage, histological grade, lymph node status, hormone receptor (HR) status, Ki-67 and age (10,11). However, they are generally used to predict the prognosis of patients with resectable BC and are not appropriate to guide the selection of chemotherapy or targeted agents for metastatic or recurrent BC. For HER2-positive advanced BC patients receiving pyrotinib-based therapies, a phase I clinical trial suggested that patients harboring PIK3CA or TP53 mutation, detected through circulating tumor DNA (ctDNA), showed lower ORR and were less sensitive to pyrotinib (12). Another phase I study demonstrated that recurrence or persistence of HER2 amplification, and mutation of tumor protein p53 (TP53) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR)

Highlight box

Key findings

- High platelet to lymphocyte ratio (PLR) was associated with poor treatment response and prognosis in human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer (BC) patients treated with pyrotinib.

What is known and what is new?

- Peripheral blood biomarkers have been reported to be correlated with the prognosis of BC patients, but some findings remain controversial.
- High PLR was associated with lower disease-control rate and was an independent prognostic biomarker for poorer progression-free survival and overall survival in HER2-positive advanced BC patients treated with pyrotinib.

What is the implication, and what should change now?

- PLR may be helpful in identifying the effective population that is more likely to benefit from pyrotinib-based therapy. Larger studies are needed to explore the clinical value of PLR in the future.

pathway-related genes may be associated with the resistance to pyrotinib (13). It was also found that tumor heterogeneity determined by ctDNA can be used for predicting and monitoring response to pyrotinib, and the predictive power of molecular tumor burden index (mTBI) was superior to that of single-gene mutation alone (14). The patients with high tumor mutation burden (TMB) tended to have shorter PFS (15). Although these molecular biomarkers may be more intrinsic and reasonable, genetic testing usually requires invasive procedures, and it sometimes cannot be performed because of insufficient pathological tissues. For ctDNA, they are generally found in low concentrations in the blood and currently there is a lack of standardization in sample collection and analysis, thus affecting the accuracy of results. Moreover, due to the high cost of genetic testing, it is difficult to get popularized in clinical practice.

Recently, various studies have evaluated the prognostic value of biomarkers in BC and other solid malignancies based on peripheral blood cell characteristics, such as neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and platelet to lymphocyte ratio (PLR). Most studies have demonstrated that high NLR, PLR, and/or MLR are associated with poor prognosis in BC patients (16-20), but due to the small sample size, the results of current studies are inconsistent. These studies were not further analyzed by specific BC molecular subtypes and therapies, so it is unclear whether peripheral blood biomarkers have prognostic value in HER2-positive advanced BC patients treated with pyrotinib. Peripheral blood biomarkers are simple and convenient, it could help to identify the effective population for pyrotinib-based therapy if its prognostic value is being proven.

The current study analyzed the clinicopathological features and peripheral blood cell to explore the prognostic value of peripheral blood biomarkers in HER2-positive advanced BC patients receiving pyrotinib-based therapy. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1078/rc).

Methods

Participants and study design

This was a multicenter, retrospective study. A total of 179 patients with advanced HER2-positive BC who received pyrotinib-based therapy at The First Affiliated Hospital of University of Science and Technology of China and the First Affiliated Hospital of Bengbu Medical College from March 2019 to May 2021 were enrolled. The eligibility criteria included: (I) age ≥18 years; (II) pathologically or cytologically confirmed diagnosis of advanced HER2-positive BC, as defined as 3+ positive for HER2 overexpression by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH/CEP17 ≥2.0) positive; (III) receiving pyrotinib-based therapy, including pyrotinib monotherapy or combined with chemotherapy; (IV) available for absolute counts of peripheral blood neutrophil, monocyte, lymphocyte, and platelet counts determined within seven days prior to initiation of pyrotinib-based treatment; (V) complete medical records, objective response, PFS and overall survival (OS) information; (VI) no acute infections within 14 days before or after the detection of peripheral blood cell. A total of 23 patients were excluded based on the above criteria, of which 4 patients were treated with pyrotinib for less than 3 weeks due to serious adverse events, 13 patients could not be evaluated for efficacy due to lack of measurable lesions, and 6 patients had no peripheral blood data collected within 7 days prior to pyrotinib-based treatment. Therefore, 156 patients were included in the final analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was carried out with approval from the ethics committee of The First Affiliated Hospital of University of Science and Technology of China (No. 2022-RE-028). Informed consent was waived because of the retrospective nature of the research.

Outcome evaluation and follow-up

The objective response was evaluated every 2 cycles (42±7 days) according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. In addition, long-stable disease (SD) was defined as SD conditions lasting for more than 24 weeks. PFS was defined as time from initiation of pyrotinib-based therapy to disease progression or death, and OS was defined as time from initiation of pyrotinib-based therapy to death. Patients were followed up regularly every 2 months to assess survival status. No patients were lost to follow-up in this study. All patients were followed up until death or time of data lock (1 September 2021).

Data collection and assessment

Clinicopathologic data such as patient age, HR status, Ki-67, metastatic site, and antitumor therapies were collected,

as well as absolute counts of peripheral neutrophils, lymphocytes, monocytes, and platelets measured within 7 days prior to initiation of pyrotinib-based treatment. NLR was defined as the ratio of neutrophil count to lymphocyte count, MLR was defined as the ratio of monocyte count to lymphocyte count, PLR was defined as the ratio of platelet count to lymphocyte count, pan-immune-inflammation value (PIV) was defined as neutrophil count multiplied by platelet count and monocyte count, and the result was divided by lymphocyte count. Optimal cutpoints for these continuous variables were determined by the surv_cutpoint function of the survminer package to distinguish between the high and low groups. The cut-off values of neutrophil, lymphocyte, monocyte and platelet counts were 2.77×10^9/L, 1.62×10^9/L, 0.52×10^9/L and 216×10^9/L, respectively. The cut-off values of NLR, MLR, PLR and PIV were 3.25, 0.38, 234.72 and 369.42, respectively. During the treatment period, computed tomography (CT) scan and/or magnetic resonance imaging (MRI) were performed every 2 cycles (42±7 days) to evaluate the tumor response according to the RECIST 1.1 criteria, and PFS was recorded if the patient experienced disease progression. After failure of pyrotinib-based treatment, patients were followed up by telephone every 2 months to assess and record survival status until death or time of data lock (1 September 2021).

Statistical analysis

All statistical analyses were implemented with R 4.0.5. The chi-square test and Mann-Whitney *U*-test were used to compare the categorical and continuous data in different groups. Spearman's correlation tests were used to evaluate the associations. The area under receiver operating characteristic (ROC) curve (AUC) was estimated by the pROC package. Prognostic factors affecting PFS and OS were first assessed in univariate analysis, and then significantly correlated prognostic factors (P<0.05) were identified for further assessment of their independent association with survival in multivariable Cox proportional hazard model. The following clinically relevant covariates were evaluated: age (≥53 *vs.* <53 years), HR status (positive *vs.* negative), Ki-67 (>30% *vs.* ≤30%), number of metastasis sites (>2 *vs.* ≤2), presence of visceral metastasis (yes *vs.* no), presence of liver metastasis (yes *vs.* no), presence of lung metastasis (yes *vs.* no), presence of brain metastasis (yes *vs.* no), pyrotinib-based treatment regimens (combined with capecitabine *vs.* combined with other chemotherapeutics *vs.* single drug), lines of systematic therapy of pyrotinib (1st *vs.* 2nd *vs.* ≥3rd), lines of anti-HER2 therapy of pyrotinib (1st *vs.* ≥2nd). Results were considered statistically significant at a two-sided P value of <0.05.

Results

Patient characteristics

A total of 156 patients were enrolled finally (*Table 1*). The median age of them was 52 years (range, 27–75 years). 105 (67.3%) patients had HR-positive tumor. 131 (84.0%) patients had visceral metastasis. 94 (60.3%) patients were treated with pyrotinib plus capecitabine. 23 (14.7%) patients received pyrotinib-based therapy as first-line anti-HER2 treatment. For peripheral blood markers, the mean lymphocyte count was 1.27±0.546 ($\times10^9$/L), the mean NLR was 3.53±4.59, the mean MLR was 0.404±0.304, the mean PLR was 196±107, and the mean PIV was 335±390. Interestingly, NLR, MLR, PLR and PIV were moderately to strongly correlated with each other (Figure S1). Other clinicopathological characteristics are also presented in *Table 1*.

Clinical responses and clinicopathological features

Of these patients, 1 (0.6%), 49 (31.4%), 92 (59.0%) and 14 (9.0%) achieved complete response (CR), partial response (PR), SD and progressive disease (PD) respectively. The overall ORR and disease-control rate (DCR) were 32% and 91% respectively (*Table 1*). Forty-eight out of 92 SD patients experienced long-SD. No correlation with ORR other than the number of metastatic sites and the lines of systemic treatment was observed (*Figure 1A*,*1B*, Figures S2,S3). Similar to ORR, no peripheral blood markers nor clinicopathological characteristics were observed to be associated with CR/PR/long-SD except for the number of metastatic sites, regimens, and the lines of systemic treatment (*Figure 1C-1E*, Figures S4,S5). However, only PLR was found to be related to DCR and patients with low PLR had significantly higher DCR (*Figure 1F*, Figures S6,S7), which might imply that high PLR was associated with ineffective pyrotinib treatment. The AUC for PLR predicting resistance to pyrotinib was 0.726 (*Figure 2*). These results suggested that PLR may be a predictor of primary resistance to pyrotinib.

Survival and clinicopathological features

For PFS, the median follow-up time was 13.4 months [95%

Table 1 Baseline clinicopathological characteristics of 156 patients

Characteristic	Values
Hormone receptor status*	
Negative	51 (32.7)
Positive	105 (67.3)
Ki67	
≤30%	65 (41.7)
>30%	79 (50.6)
Missing	12 (7.7)
No. of metastatic sites	
≤2	82 (52.6)
>2	74 (47.4)
Visceral metastases	
No	25 (16.0)
Yes	131 (84.0)
Liver metastasis	
No	85 (54.5)
Yes	71 (45.5)
Lung metastasis	
No	75 (48.1)
Yes	81 (51.9)
Brain metastases	
No	104 (66.7)
Yes	52 (33.3)
Regimens	
Monotherapy	7 (4.5)
With capecitabine	94 (60.3)
With others	55 (35.3)
Lines of systematic therapy of pyrotinib	
1st	23 (14.7)
2nd	36 (23.1)
≥3rd	97 (62.2)
Lines of anti-HER2 therapy of pyrotinib	
1st	23 (14.7)
≥2nd	133 (85.3)
Objective response	
CR	1 (0.6)
PR	49 (31.4)
SD	92 (59.0)
PD	14 (9.0)
Age (years)	52 [27–75]
Neutrophil count ($\times10^9$/L)	3.53±2.14
Lymphocyte count ($\times10^9$/L)	1.27±0.546
Monocyte count ($\times10^9$/L)	0.430±0.202
Platelet count ($\times10^9$/L)	212±74.1
NLR	3.53±4.59
MLR	0.404±0.304
PLR	196±107
PIV	335±390

Data are presented as n (%), median [range], or mean ± standard deviation. *, defined positive if >1% of tumor cells express hormone receptors. HER2, human epidermal growth factor receptor 2; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PIV, pan-immune-inflammation value.

confidence interval (CI): 12.0–15.9], and 103 events were observed. The median PFS for all cases was 8.1 months (95% CI: 6.5–10.1). Log-rank test showed that MLR, PLR, and PIV were associated with PFS. The patients with low lymphocyte count, high MLR, PLR or PIV had poor PFS (all P<0.05, *Figure 3*). As expected, other clinicopathological characteristics, such as the number of metastatic sites, liver metastasis, brain metastasis, regimens, lines of systematic treatment were also related to PFS (Figure S8A-S8E). Univariate Cox regression analysis confirmed that MLR (hazard ratio =0.56; 95% CI: 0.38–0.83; P=0.004), PLR (hazard ratio =0.53; 95% CI: 0.35–0.80; P=0.003), and PIV (hazard ratio =0.60; 95% CI: 0.39–0.92; P=0.02) were the risk factors of PFS. Multivariate Cox regression analysis demonstrated that PLR was an independent prognostic biomarker for PFS (hazard ratio =0.63; 95% CI: 0.41–0.97;

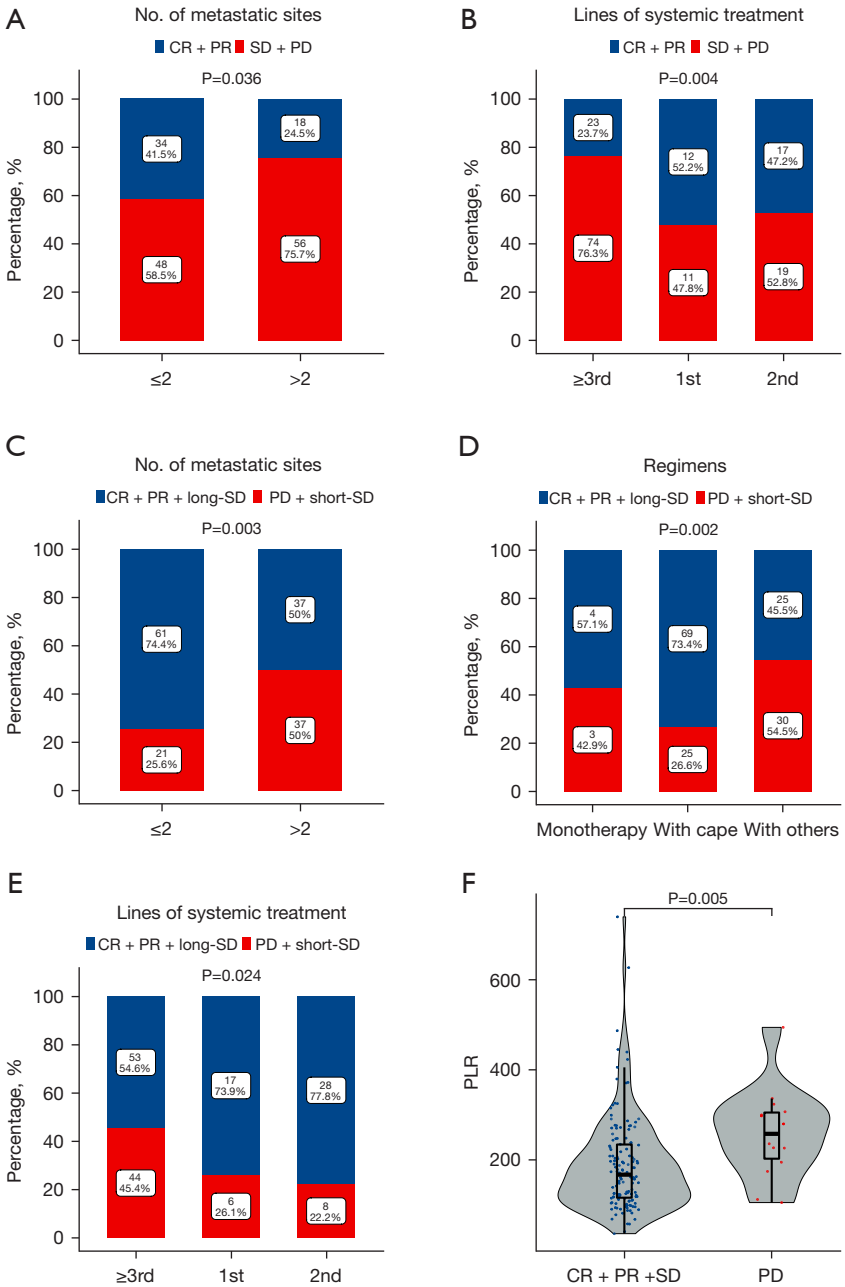

Figure 1 Clinical responses according to clinicopathological features: CR + PR (ORR) according to (A) number of metastatic sites and (B) lines of systemic treatment; CR + PR + long-SD according to (C) number of metastatic sites and (D) regimens and (E) lines of systemic treatment; CR + PR + SD (DCR) according to (F) PLR. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; long-SD, stable disease lasting more than 24 weeks; short-SD, stable disease lasting less than 24 weeks; PLR, platelet to lymphocyte ratio; ORR, objective response rate; DCR, disease control rate.

P=0.038) (*Table 2*).

As for OS, the median follow-up time was 8.6 months (95% CI: 7.2–10.1). The median OS was not reached since the number of patients (24 patients) who passed away during the follow-up period was limited. The log-rank test showed that all peripheral blood markers were associated with OS. High NLR, MLR, PLR or PIV led to worse OS (*Figure 4*). Meanwhile, the number of metastatic sites,

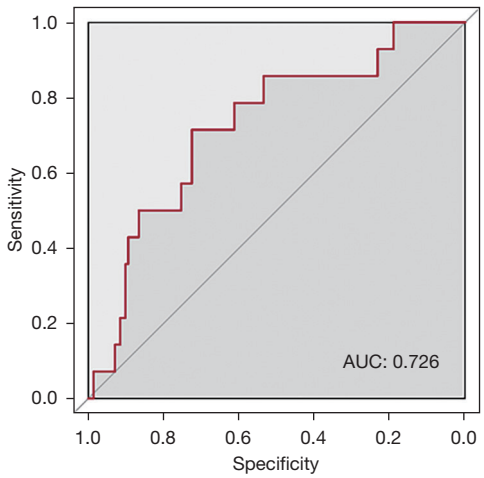

Figure 2 Evaluation of PLR as a predictor of primary resistance to pyrotinib using ROC curves. AUC, area under receiver operating characteristic curve; PLR, platelet to lymphocyte ratio; ROC, receiver operating characteristic.

liver metastasis, brain metastasis, and regimens were also related to OS (Figure S8F-S8I). Cox regression suggested that the high levels of peripheral blood markers affected OS unfavorably. Among these peripheral blood markers, only PLR was an independent prognostic biomarker for OS (hazard ratio =0.37; 95% CI: 0.14–0.94; P=0.037) (*Table 3*).

Discussion

In this study, PLR was found to be associated with the treatment response and prognosis of patients with HER2-positive advanced BC receiving pyrotinib. Patients with high PLR had low response to the treatment, they were more likely to develop disease progression, and high PLR was associated with worse PFS and OS, which was an independent prognostic factor.

According to the 2022 Chinese Society of Clinical Oncology (CSCO) BC treatment guidelines, for HER2-positive advanced BC patients who have failed first-line anti-HER2 treatment with trastuzumab, pyrotinib combined with capecitabine or T-DM1/T-Dxd antibody-drug conjugate is recommended as second-line treatment. All three regimens are recommended as class IA, but choosing the optimal treatment regimen for patients remains a clinical conundrum. The present study found that patients with low PLR prior to pyrotinib-based therapy had significantly higher DCR and better prognosis. As a simple and economical marker, PLR may be helpful in identifying the effective population that is more likely to benefit from pyrotinib-based therapy, thereby providing guidance for selecting anti-HER2 agents after first-line treatment failure.

Current research shows that inflammation and the abnormalities of immune microenvironment are closely related to tumor cell survival, apoptosis, proliferation and migration, and tumor microvascular formation (21). For example, neutrophils secrete cytokines such as chemokines and growth factors in the tumor microenvironment to inhibit the activity of lymphocytes and cause immunosuppression (22). At the same time, these cytokines can also promote tumor angiogenesis and tumor cell proliferation and migration (23); M2 tumor-associated macrophages (TAMs) derived from circulating monocytes that exert immunosuppressive effects can suppress tumor immunity and promote tumor cell migration (24,25). The activity of natural killer (NK) cells can be inhibited by activated platelets, thereby suppressing tumor immunity (26). Meanwhile, platelets can promote tumor cell proliferation and angiogenesis by secreting vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β) (27,28). In contrast, lymphocytes are the primary effector cells for the immune system to clear tumor cells (29). Lymphocytes can induce cytotoxic cell death and inhibit tumor cell proliferation and migration, thereby controlling tumor growth, and this tumor defense role makes lymphocytes a key player in tumor immune surveillance (30,31). All the above may explain for the reasons why the lymphocyte counts, NLR, MLR, PLR and PIV are associated with prognosis in this study.

These inflammatory markers have been shown in several studies to be associated with prognosis in patients with HER2-positive BC. In an analysis of 57 patients with HER2-positive advanced BC treated with first-line trastuzumab, pertuzumab, and paclitaxel, high baseline MLR, PLR, and PIV, similar to the findings of this study, were predictive of poorer PFS, high PIV and MLR were associated with significantly poorer OS in patients (32). A study by Ding *et al.* showed that in patients with HER2-positive BC treated with trastuzumab, lower NLR before treatment was associated with better DFS (33). Imamura *et al.* found a strong correlation between high NLR, PLR and poorer PFS and OS in patients with HER2-positive metastatic BC treated with second-line TDM-1, which was consistent with the current findings (34). A study by Blanchette *et al.*, which analyzed factors influencing survival in patients with HER2-positive metastatic BC treated

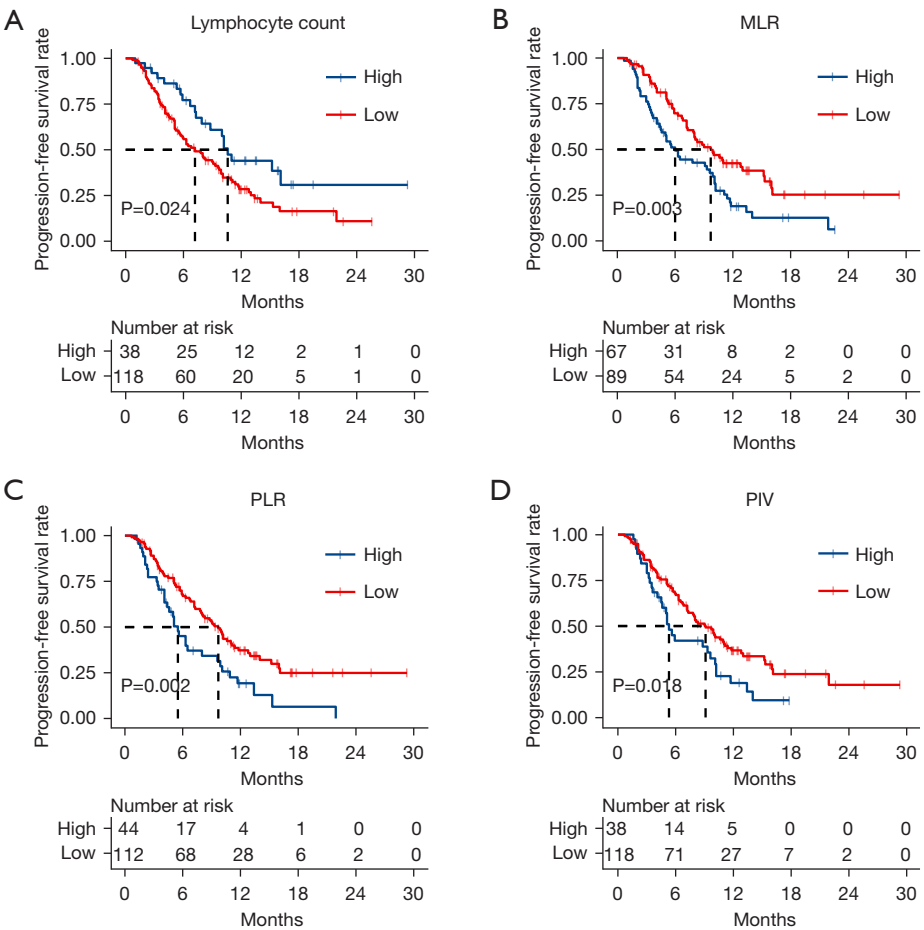

Figure 3 PFS according to baseline lymphocyte count, MLR, PLR and PIV values. Kaplan-Meier curves representing patient PFS according to baseline lymphocyte count (A), MLR (B), PLR (C), and PIV (D) categories. The optimal cutpoint determined by the surv_cutpoint function of the survminer package is used as a threshold to define the parameter categories (high *vs*. low). MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PIV, pan-immune-inflammation value; PFS, progression-free survival.

with trastuzumab, also found that pretreatment PLR was an important prognostic factor (35). Previous studies have shown that approximately 55% of HER2-positive BCs had >10% stromal tumor-infiltrating lymphocytes (sTILs), and TILs were associated with better survival prognosis in HER2-positive BCs (36-38). Peripheral blood counts, which reflect systemic inflammatory or immune status, are more readily available than TILs. Our study suggested that baseline PLR may replace TILs as a simpler and more effective prognostic biomarker.

There are few studies on inflammatory indicators as biomarkers for predicting the efficacy of treatments for BC. A retrospective study involving 104 patients with metastatic BC treated with eribulin-based treatment showed that high baseline NLR was associated with poorer treatment response (39). In addition, another study showed that high NLR and PLR were risk factors for poor response to neoadjuvant chemotherapy for triple-negative BC. For HER2-positive BC, the data are even scarcer. Our study explored and found that high PLR was associated with poorer DCR in patients with HER2-positive advanced BC who received pyrotinib-based therapy. Although the efficacy may be determined by a variety of factors, the conclusions herein may be helpful for clinical medication guidance to some extent. However, further studies are needed to confirm the findings.

Pyrotinib is an irreversible small-molecule tyrosine kinase inhibitor targeting HER1/EGFR, HER2 and HER4. At present, there are few studies on the correlation between

Table 2 Univariate and multivariable Cox proportional hazards model for PFS

Variables	N	Univariable			Multivariable		
		Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Neutrophil count							
Low	64	1.36	0.92–2.01	0.122			
High	92	1 (reference)					
Lymphocyte count							
Low	118	1.75	1.07–2.85	0.025**			
High	38	1 (reference)					
Monocyte count							
Low	110	0.7	0.46–1.05	0.086			
High	46	1 (reference)					
Platelet count							
Low	85	0.76	0.52–1.12	0.17			
High	71	1 (reference)					
NLR							
Low	107	0.68	0.46–1.02	0.065			
High	49	1 (reference)					
MLR							
Low	89	0.56	0.38–0.83	0.004**	0.83	0.50–1.37	0.461
High	67	1 (reference)			1 (reference)		
PLR							
Low	112	0.53	0.35–0.80	0.003**	0.63	0.41–0.97	0.038**
High	44	1 (reference)			1 (reference)		
PIV							
Low	118	0.60	0.39–0.92	0.02**	0.84	0.50–1.43	0.524
High	38	1 (reference)			1 (reference)		
Age							
Low	83	1.11	0.75–1.65	0.599			
High	73	1 (reference)					
Hormone receptor status*							
Positive	105	1.45	0.94–2.23	0.091			
Negative	51	1 (reference)					
Ki67							
>30%	79	0.94	0.62–1.41	0.75			
≤30%	65	1 (reference)					

Table 2 *(continued)*

Table 2 *(continued)*

Variables	N	Univariable			Multivariable		
		Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
No. of metastatic sites							
>2	74	2.37	1.60–3.52	<0.001**	1.62	0.97–2.72	0.065
≤2	82	1 (reference)			1 (reference)		
Visceral metastasis							
Yes	131	1.2	0.69–2.07	0.522			
No	25	1 (reference)					
Liver metastasis							
Yes	71	2.14	1.43–3.21	<0.001**	1.56	1.00–2.45	0.051
No	85	1 (reference)			1 (reference)		
Lung metastasis							
Yes	81	0.93	0.63–1.37	0.72			
No	75	1 (reference)					
Brain metastases							
Yes	52	2.05	1.38–3.04	<0.001**	1.3	0.79–2.15	0.302
No	104	1 (reference)			1 (reference)		
Regimens							
With capecitabine	94	0.8	0.32–2.00	0.63			
With others	55	1.79	0.70–4.55	0.224			
Monotherapy	7	1 (reference)					
Lines of systematic therapy of pyrotinib							
1st	23	0.56	0.30–1.06	0.076			
2nd	36	0.63	0.38–1.04	0.07			
≥3rd	97	1 (reference)					
Lines of anti-HER2 therapy of pyrotinib							
1st	23	0.84	0.47–1.51	0.57			
≥2nd	133	1 (reference)					

**, statistically significant; *, defined positive if >1% of tumor cells express hormone receptors. PFS, progression-free survival; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PIV, pan-immune-inflammation value; HER2, human epidermal growth factor receptor 2.

inflammatory indicators and the outcome of small-molecule drug therapy. Results from a study of 150 patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors (TKIs) suggested that PLR was an independent determinant of OS (40). Another study demonstrated that NLR and MLR were important markers for evaluating the efficacy of EGFR TKI therapy in NSCLC patients, and elevated NLR was also an independent prognostic factor for poor PFS (41). In addition, studies have shown that the tumor immune microenvironment of EGFR/anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer can be remodeled by TKIs (42). By inhibiting the EGFR

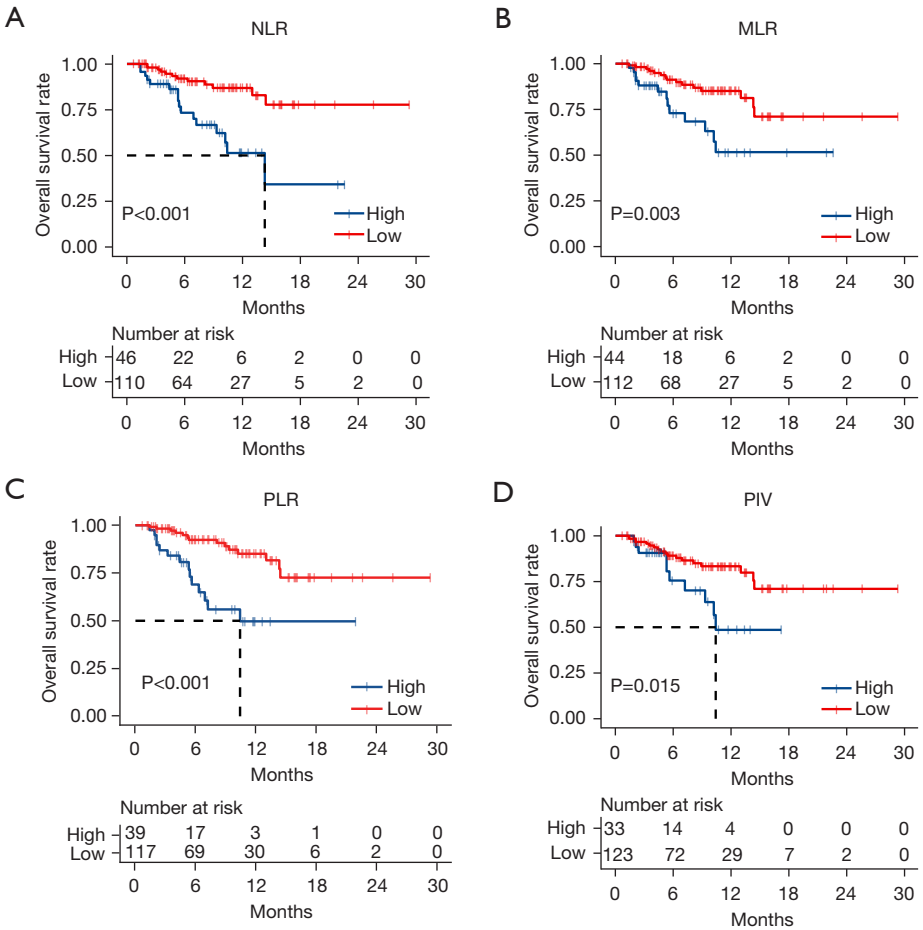

Figure 4 OS according to NLR, MLR, PLR, and PIV. Kaplan-Meier curves representing patient OS according to baseline NLR (A), MLR (B), PLR (C) and PIV (D) categories. The optimal cutpoint determined by the surv_cutpoint function of the survminer package is used as a threshold to define the parameter categories (high *vs*. low). NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PIV, pan-immune-inflammation value; OS, overall survival.

pathway, EGFR-TKIs increased the expression of MHC-I and decreased the recruitment of T cells to tumors, and anti-tumor active cells such as $CD8^+$ T cells and NK cells were significantly increased after TKIs treatment (43). Therefore, it is reasonable to use inflammatory/immune markers to predict the efficacy and prognosis of pyrotinib in HER2-positive advanced BC.

The main limitations of this study are the relatively small number of patients included in the analysis, the retrospective nature of the investigation, the short follow-up time, and PLR should be conducted in randomised studies to assess clinical responses.

Conclusions

Data from this study suggested that PLR has predictive value in estimating the efficacy and prognosis of pyrotinib in the treatment of HER2-positive advanced BC. High PLR was associated with lower DCR and was an independent prognostic biomarker for poorer PFS and OS. PLR can be used to help screen for the effective population with pyrotinib treatment clinically and to identify patients with

Table 3 Univariate and multivariable Cox proportional hazards model for OS

Variables	N	Univariable			Multivariable		
		Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Neutrophil count							
Low	123	0.52	0.24–1.13	0.098			
High	33	1 (reference)					
Lymphocyte count							
Low	45	1.82	0.85–3.89	0.122			
High	111	1 (reference)					
Monocyte count							
Low	91	0.55	0.26–1.16	0.117			
High	65	1 (reference)					
Platelet count							
Low	99	0.53	0.25–1.12	0.096			
High	57	1 (reference)					
NLR							
Low	110	0.26	0.12–0.56	0.001**	0.65	0.22–1.93	0.436
High	46	1 (reference)			1 (reference)		
MLR							
Low	112	0.34	0.16–0.73	0.005**	1.16	0.41–3.31	0.775
High	44	1 (reference)			1 (reference)		
PLR							
Low	117	0.24	0.11–0.51	<0.001**	0.37	0.14–0.94	0.037**
High	39	1 (reference)			1 (reference)		
PIV							
Low	123	0.39	0.18–0.85	0.018**	0.66	0.26–1.70	0.394
High	33	1 (reference)			1 (reference)		
Age							
Low	56	0.53	0.22–1.24	0.14			
High	100	1 (reference)					
Hormone receptor status*							
Positive	105	0.72	0.34–1.52	0.39			
Negative	51	1 (reference)					
Ki67							
>30%	79	1.48	0.62–3.54	0.379			
≤30%	65	1 (reference)					

Table 3 *(continued)*

Table 3 *(continued)*

Variables	N	Univariable			Multivariable		
		Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
No. of metastatic sites							
>2	74	4.2	1.83–9.62	0.001**	2.84	1.02–7.94	0.046**
≤2	82	1 (reference)			1 (reference)		
Visceral metastasis							
Yes	131	1.67	0.51–5.55	0.399			
No	25	1 (reference)					
Liver metastasis							
Yes	71	3.31	1.47–7.45	0.004**	2.03	0.80–5.18	0.139
No	85	1 (reference)			1 (reference)		
Lung metastasis							
Yes	81	0.83	0.39–1.74	0.616			
No	75	1 (reference)					
Brain metastases							
Yes	52	2.82	1.33–5.97	0.007**	1.79	0.70–4.60	0.226
No	104	1 (reference)			1 (reference)		
Regimens							
With capecitabine	94	0.25	0.07–0.91	0.036**	0.15	0.03–0.73	0.019**
With others	55	0.82	0.24–2.88	0.763	0.53	0.11–2.50	0.425
Monotherapy	7	1 (reference)			1 (reference)		
Lines of systematic therapy of pyrotinib							
1st	23	0.56	0.17–1.90	0.354			
2nd	36	0.58	0.22–1.53	0.27			
≥3rd	97	1 (reference)					
Lines of anti-HER2 therapy of pyrotinib							
1st	23	0.72	0.22–2.38	0.59			
≥2nd	133	1 (reference)					

**, statistically significant; *, defined positive if >1% of tumor cells express hormone receptors. OS, overall survival; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PIV, pan-immune-inflammation value; HER2, human epidermal growth factor receptor 2.

a predicted longer survival. Larger studies are needed to explore the clinical value of PLR in the future.

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Footnote

Reporting Checklist: The authors have completed the

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1078/coif). The authors have no conflicts of interest to declare.

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 carried out with approval from the ethics committee of The First Affiliated Hospital of University of Science and Technology of China (No. 2022-RE-028). Informed consent was waived because of the retrospective nature of the research.

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