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Single Center Study: Using Pre-Treatment Neutrophil to Lymphocyte Ratio as a Predictor of Outcome in Metastatic Breast Cancer Patients Treated with Cyclin Dependent Kinase 4/6 Inhibitors

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ABSTRACT

Introduction: Breast cancer is the most prevalent cancer among women worldwide, and prognostic markers are vital for predicting outcomes. Systemic inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and lymphopenia, have been associated with tumor progression and prognosis. This study aimed to assess the predictive effects of NLR, LMR, and lymphopenia in Pakistani women receiving CDK4/6 inhibitors alongside endocrine therapy for metastatic breast cancer. **Materials and Methods:** We conducted a retrospective study at Aga Khan University Hospital, Karachi, from January 2018 to September 2024. Blood tests conducted within one week before treatment initiation were analyzed for NLR, LMR, and lymphopenia. **Results:** Among 53 evaluable patients, those with pre-treatment NLR <2.5 had a median progression-free survival (PFS) of 14 months versus 8 months for NLR ≥2.5. Median overall survival (OS) was 24 months (95% CI: 18.4–29.0) for NLR <2.5 and 20 months (95% CI: 14.7–25.2) for NLR ≥2.5. Patients with LMR >3.3 had a median OS of 14 months (95% CI: 9.71–18.29) compared to 12 months (95% CI: 8.4–15.96) for LMR ≤3.3. Lymphopenia patients had a median PFS of 8.0 months (95% CI: 1.78–14.22), while those with normal lymphocyte counts had a PFS of 14.0 months (95% CI: 11.20–16.81). **Conclusion:** NLR, LMR, and lymphopenia are accessible, cost-effective biomarkers that may aid in prognostication and treatment planning for metastatic breast cancer patients receiving CDK4/6 inhibitors.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women worldwide (1). In 2022, globally 2.3 million new cases of breast cancer has been reported and there has been 666,000 reported deaths due to breast cancer (1). In Pakistan one in four female cancer-related deaths is attributed to breast cancer (2). In 2020, approximately 25,928 breast cancer cases and 13,725 deaths were reported in Pakistan (3).

Despite increased awareness and improved screening programs to aid earlier diagnoses, approximately 6% of breast cancer patients present with metastatic stage IV disease, which remains incurable. Additionally, around 20% of early-stage breast cancer patients eventually develop distant metastases (4).

Estrogen receptor (ER)-positive, HER2-negative tumors institute the biggest chunk of breast cancer cases accounting for nearly 70% of all breast cancers and they are attributable to breast cancer-related deaths as well (5,6). The use of cyclin-dependent kinase (CDK) 4/6 inhibitors, including all three agents Palbociclib, Ribociclib, and Abemaciclib, along with the endocrine treatment, has been the current standard treatment option in first as well as second line in ER-positive, HER2-negative advanced and metastatic breast cancer and it has significantly improved the progression-free survival (PFS) and overall survival (7–9).

Prognostic aspects are essential for forecasting results and choosing the best course of action. Low Eastern Cooperative Oncology Group performance status (ECOG-PS), high tumor grade, negative progesterone receptor (PR) status, prior treatments, number of metastases, and a shorter time to progression to metastatic disease are among the clinical and histological indicators of poor outcome in HR+/HER2- metastasized breast cancer and these have been authenticated. However, predictive

factors of response to CdK4/6i and ET have been evaluated in very few studies (10). Furthermore, no comparable study has been carried out among the Pakistani population.

Studies have demonstrated the role of host systemic inflammatory response on tumour growth, invasion, progression and prognosis (11–13). This inflammation can be assessed using lymphocyte, neutrophil, and monocyte counts to calculate scores such as the neutrophil–lymphocyte ratio (NLR), lymphocyte-to- monocyte ratio (LMR) and absolute lymphocyte count. These ratios have been proposed as prognostic markers in different solid cancers (14,15). Nonetheless, the importance of these biomarkers in breast cancer prognosis, especially those for predicting outcomes in CDK 4/6 inhibitors are not calculated as such in many studies (16,17).

According to a prospective study examining the relationship between survival and the pre-treatment NLR and PLR, both ratios are independently linked to a higher risk of death in all-stage BC. (18). Though, most of these inflammatory biomarkers have been evaluated in early breast cancer settings where (neo) adjuvant chemotherapy is being delivered. Ma et al. shown that in patients with ER/PR-positive HER2-negative breast cancer, LMR may serve as a marker to forecast the effectiveness and prognosis of neo-adjuvant chemotherapy (NAC) (19). High pretreatment NLR was identified in prior meta-analysis as a self-determining poor predictive factor for both progression-free survival (PFS) and overall survival (OS) in all-stage BC. (20–22) However, for mBC, the data is still sparse and inconsistent. Our study's objective was to evaluate the predictive effects of NLR, lymphopenia, and LMR on response proportions and survival in Pakistani women receiving CdK4/6i in conjunction with ET for mBC. These ratios can be determined from the complete blood count (CBC), and may thus offer a more straight forward and affordable method for predicting the prognosis of breast cancer, particularly in low middle income countries and considering the fact that pre-treatment CBC is always attained before starting treatment with CDK 4/6i, this simple test may just be beneficial if parameters like NLR, LMR and lymphopenia are determined upfront and hence help in prognosticating the disease as well as the survival outcomes associated with these drugs.

MATERIALS AND METHODS

Population

We conducted a retrospective single center study at the Aga Khan University Hospital's oncology department in Karachi, Pakistan. All female patients above 18 years of age with histo-pathological and radiological diagnosis of hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer (MBC) who had received CDK 4/6 inhibitors on any line of treatment from January 2018 to September 2024 at our institution were included. Patients files which lacked complete information were not included in the research. We went over the case records of all these patients.

Endpoint

We collected data regarding demographic characteristics (age, ECOG, menopausal status) their disease (e.g. tumour grade and subtype, site of metastasis, ER/PR/Her 2 status of the tumor. Toxicity profiles were also recorded. Statistical analysis was done using SPSS version 20.4. Clinical and pathologic variables were reported using descriptive analyses. Categorical variables were reported as frequency distributions, whereas continuous variables were summarized as median and standard deviation (SD) reported with 95% confidence intervals (CI).

PFS was assessed using the Kaplan–Meier method. HR and 95% confidence interval (CI) were derived from a Cox proportional hazards regression model.

The blood test results were gathered no later than the week prior to the start of treatment. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, and LMR was defined as the absolute lymphocyte count divided by the absolute monocyte count. Lymphopenia was defined by absolute lymphocyte count (ALC) below 1500 cells/ mm^3. The period of time between the start of CdK4/6i and radiographic progression, death, or loss to follow-up was referred to as PFS. The period of time from CdK4/6i commencement and death from any cause was known as overall survival (OS).

Objectives

The objectives included assessment of PFS according to pretreatment NLR, LMR and absolute lymphocyte count (ALC) and OS according to pretreatment NLR and LMR.

Statistical Analysis

Data was analyzed in SPSS VERSION 20.4. The study population's baseline characteristics were compiled using descriptive statistics. For continuous variables, means and standard deviations were computed, whereas frequencies and percentages were computed for categorical variables. Survival analysis was conducted using the Kaplan–Meier method to estimate overall survival (OS) and progression-free survival (PFS) rates. Survival curves were generated, and comparisons between groups were made using the log-rank test where appropriate.

RESULTS

Patient's Characteristics

A total of 53 patients were included in the analysis. Regarding performance status**,** 50.9% had an ECOG score of 1, 28.3% had ECOG 2, 18.9% had ECOG 3, and only 1.3% had ECOG 4. The majority of patients were postmenopausal (75.5%), while 24.5% were premenopausal. Comorbid conditions were present in a significant proportion of patients, with 34.0% having no comorbidities, 15.1% with hypertension, 5.7**%** with diabetes, 17.0% having both hypertension and diabetes, 1.9% with hypothyroidism, and 26.4% reporting other comorbidities. Tumor grading revealed 43.4% had Grade II tumors, 28.3% had Grade III, 22% were ungraded (Grade 0), and 5.7% had Grade I tumors. The most frequent occurring tumor subtype was invasive ductal carcinoma (IDC) in 62.3% of patients, followed by invasive lobular carcinoma (ILC) in 17.0%, and IDC with neuroendocrine features in 1.3%. In 18.9%, the histological subtype was not applicable or reported. In terms of metastatic presentation, 52.8% had de novo metastatic disease, while 47.2% developed metastases later on after initial

diagnosis of early breast cancer. Regarding metastatic burden, 43.4% had a single site of metastasis, 26.4% had two sites, 18.9% had three, and 11.3% had four sites involved. Most patients were receiving first-line treatment (56.6%), while 30.2% were on second-line, 7.5% on third-line, and a minority were on fourth-line (3.8%) or beyond (1.9%). Ribociclib was administered to 50.9% patients, Palbociclib to 47.2%, and Abemaciclib to 1.3%. Hormonal agents included Letrozole (49.1%), Fulvestrant (28.3%), Exemestane (11.3%), Tamoxifen (7.5%), and Anastrozole (3.8%). (Table 1)

Table 1

Patient's Characteristics

Variables	Total (n)	Percentages (%)
ECOG	53	100
• 1	27	50.9
• 2	15	28.3
• 3	10	18.9
• 4	1	1.3
Menopausal Status	53	100
• Premenopausal	13	24.5
• Postmenopausal	40	75.5
Comorbidities	53	100
• Non	18	34.0
• Hypertension	08	15.1
• Diabetes	03	5.7
• Hypertension+Diabetes	09	17.0
• Hypothyroidism	01	1.9
• Others	14	26.4
Grade	53	100
• 0	12	22
• I	03	5.7
• II	23	43.4
• III	15	28.3
Tumor Subtype	53	100
• IDC	33	62.3
• ILC	09	17.0
• IDC with neuroendocrine	01	1.3
• Not applicable	10	18.9
Timing of Metastasis	53	100
• DE novo	28	52.8
• Metastatic later	25	47.2
Site of Metastasis	513	100
• Only one site involved	23	43.4
• Two sites involve	14	26.4
• Three sites involve	10	18.9
• Four Sites Involved	06	11.3
Line of Treatment	53	100
• First line	30	56.6
• Second Line	16	30.2
• Third Line	04	7.5
• Fourth Line	02	3.8
• Cell cycle inhibitor used	53	100
• Ribociclib	27	50.9
• Palbociclib	25	47.2
• Abemaciclib	01	1.3
Hormonal agent used	53	100
• Tamoxifen	04	7.5
• Letrozole	26	49.1
• Anastrozole	02	3.8
• Fulvestrant	15	28.3
• Excmestane	06	11.3

Hematological Profile of Patients

The hematological parameters of the 53 patients enrolled in the study are summarized in Table 2. The cohort's mean age was 55 years, and its standard deviation (SD) was 10.5 years. The mean total leukocyte count was 6.7 $\times 10^9$/L (SD 2.6), and the neutrophil count averaged 60.1% (SD 10.2). The lymphocyte count had a mean of 28.3% (SD 9.8), while the platelet count was 264.2 $\times 10^9$/L (SD 116.9).

The monocyte percentage was 8.1% (SD 2.8). In terms of derived immune-inflammatory indices, the neutrophil-to-lymphocyte ratio (NLR) was 1.8 (SD 0.9), and the lymphocyte-to-monocyte ratio (LMR) was 4.0 (SD 2.4). The absolute lymphocyte count (ALC) was 1940 cells/µL (SD 1009), and the absolute monocyte count (AMC) was 526.9 cells/µL (SD 216.5).

These hematologic parameters provide a baseline immune-inflammatory profile of the patient population prior to treatment and are relevant for correlating with treatment response and survival outcomes. (Table 2)

Table 2

Patient's Hematological Values

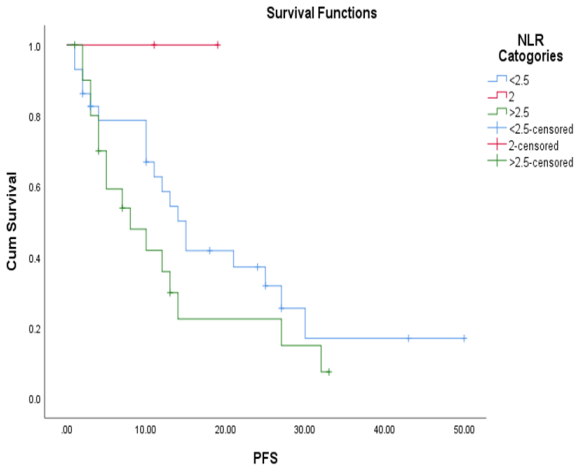
Variables	Mean	Standard Deviation
Age	55 years	10.5
Total Leukocytes Count	6.7	2.6
Neutrophil count	60.1	10.2
Lymphocyte count	28.3	9.8
Platelet	264.2	116.9
Monocyte	8.1	2.8
NLR	1.8	0.9
ALC	1940	1009
AMC	526.9	216.5
LMR	4.0	2.4

Survival Analysis

Prognostic Impact of Neutrophil-to-Lymphocyte Ratio on Progression-Free Survival

Patients were stratified based on a neutrophil-to-lymphocyte ratio (NLR) cut-off value of 2.5. The median progression-free survival (PFS) for patients with an NLR <2.5 was 14 months. While those with an NLR ≥2.5 had a significantly shorter median PFS of 8 months.

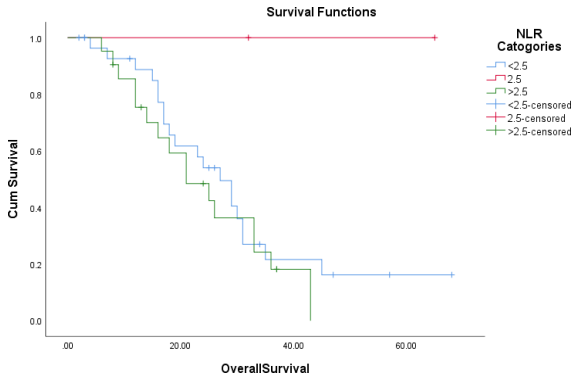
Figure 1



Prognostic Impact of Neutrophil-to-Lymphocyte Ratio on Overall Survival

The median overall survival (OS) for Neutrophil to Lymphocyte ratio less than the cut off was 2.5 had median OS of 24 months, with a confidence interval (18.4 to 29 months). Whereas patients with NLR >2.5 had a median OS of 20 months (95% CI 14.7-25.2).

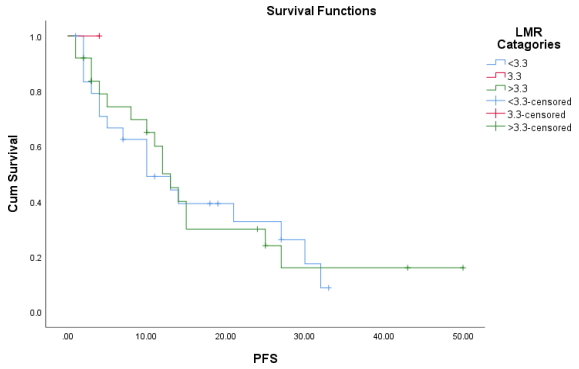
Figure 2



Prognostic Impact of Lymphocyte-to-Monocyte Ratio on Progression Free Survival

Patients were stratified based on a lymphocyte-to-monocyte ratio (LMR) cut-off of 3.3. The median progression free survival (PFS) for patients with LMR ≤3.3 was 12 months, with the 95% confidence interval of 8.4 and 15.96. However, those with LMR >3.3 demonstrated a longer median OS of 14 months, with 95%confidence interval of 9.71 and 18.29 months.

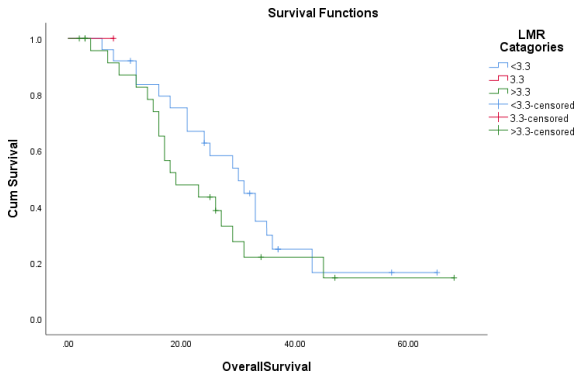
Figure 3



Prognostic Impact of Lymphocyte-to-Monocyte Ratio on Overall Survival

Patients were stratified based on a lymphocyte-to-monocyte ratio (LMR) cut-off of 3.3. The median overall survival (OS) for patients with LMR ≤3.3 was 26 months, with the 95% CI: 19.7 and 32.2. However, those with LMR >3.3 demonstrated a longer median OS of 21 months with the 95% CI of 15.4 and 26.4. These findings suggest a potential prognostic role of higher LMR in predicting improved overall survival.

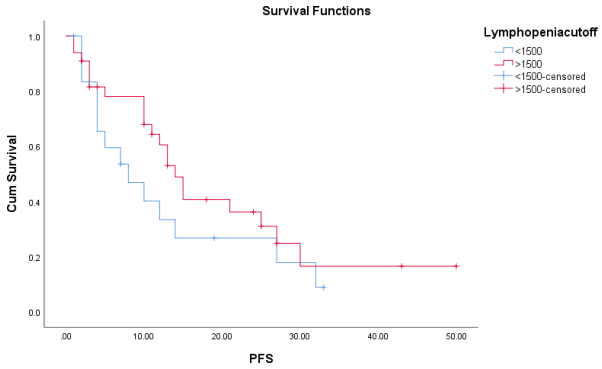
Figure 4



Prognostic impact of Lymphopenia on Progression Free Survival

The median progression-free survival (PFS) for patients with lymphopenia <1500 was 8.0 months (95% CI: 1.78–14.22), whereas patients with normal lymphocyte counts >1500 had a longer median PFS of 14.0 months (95% CI: 11.20–16.81). The overall median PFS for the entire cohort was 13.0 months (95% CI: 10.05–15.95).

Figure 1



DISCUSSION

Our study reported that in Pakistani women treated with CdK4/6i and ET for metastatic HR+/HER2- breast cancer, pretreatment high NLR (>2.5), low LMR (< 3.3) and lymphopenia (<1500) was associated with worse PFS. Additionally, a high NLR (>2.5), low LMR (< 3.3) and lymphopenia (<1500) was associated with worse OS.

It has been established by studies that lymphopenia is present in around 20–25% of those patients with advanced stage cancers, including 20% of untreated metastatic breast cancer (MBC) patients (23). The numbers of B lymphocytes, NK cells, and CD4+ and CD8+ T lymphocytes are all affected (24). In a prospective study conducted by Coquard et al when patients with metastatic breast cancer are receiving chemotherapy, lymphopenia has been identified as an independent predictor of overall and progression-free survival. (25). Manuel et al investigated lymphopenia as a prognostic factor in metastatic breast cancer patients and found it to be associated with shorter OS (23). A recent study conducted on HR+ HER2- mBC patients treated with first line CdK4/6i, reported that lymphopenia group had a shorter median PFS of 21 months versus 36 months for patients with normal absolute lymphocyte count (10). The median OS for the normal ALC group was 51 months, whereas the lymphopenia group's was 41 months (10). Our study reported similar trends with a shorter median PFS of 8 months in lymphopenia group versus a longer median PFS of 14.0 months in normal ALC group.

Ma et al. demonstrated that HR+/HER2- breast cancer patients receiving neoadjuvant chemotherapy with low LMR showed poor disease-free survival and thus worse prognosis (19). Similarly, in our study, low LMR (< 3.3) was associated with worse PFS and OS in women treated with CdK4/6i and ET for metastatic HR+/HER2- breast cancer.

It is crucial to comprehend how the immune system regulates tumors micro-environment. While certain

immune cells—such as neutrophils, B lymphocytes, and some subsets of CD4+ T cells—can promote tumor growth, other immune components play a protective role (10). These include cytotoxic CD8+ T cells, T helper 1 (TH1) cells, TH17 cells, CD4+ T cells, and Natural Killer (NK) cells which inhibit tumor growth by producing interferon gamma (10). Mahmoud et al. demonstrated that a high total and peripheral CD8+ T cell count was linked to a noticeably prolonged breast cancer-specific survival in a research involving 1,902 eBC patients (26). Tumour-induced neutrophils in breast cancer acquire the ability to suppress cytotoxic T lymphocytes and thus promote metastasis (27). In addition to inducing tumour cell cycle arrest, CDK4/6 inhibitors promote anti-tumour immunity by enhancing tumour antigen presentation, increasing tumor infiltration and activation of effector T cells and by suppressing the proliferation of regulatory T cells (28, 29). When combined, these processes support the removal of tumor cells by cytotoxic T-cells. This could help to explain why NLR might be a useful biomarker for predicting survival and better responsiveness to CDK4/6i.

Pretreatment high NLR (≥ 2.53) was linked to lower PFS and OS, according to a recent trial of women with metastatic HR+/HER2-breast cancer treated with CDK4/6i and ET (10). Meta-analyses have shown that in addition to a worse disease-specific survival, patients with a greater NLR also had shorter overall and disease-free survival (17, 21, 22). Wariss et al. conducted a study in Brazil in 2,374 eBC and mBC patients and reported an association between high NLR and worse OS (30). Our study reported high NLR was associated with worse PFS and OS which corroborates the results of previous studies. The overall lower PFS and OS in our population, however, can be explained by multiple associated factors including co-morbidities, poor ECOG performance, those patients were also included who received CDK4/6i in later lines of treatment, multiple prior treatment lines received and also the presence of visceral metastasis. The cut-off values for lymphopenia, LMR, and NLR are not yet agreed upon. In our study, we determined these thresholds using ROC curve. A meta-analysis on breast cancer (BC) found that 10 out of 15 studies reported a median NLR cut-off of 2.5 (20). The NLR cut-off determined in our study was similar to the values reported in the available literature (between 2 and 5).

Limitations

Since the breast cancer diagnosis and data for this study were gathered solely by looking through patient files, the primary weakness of this research is its retrospective approach, which may result in an incomplete history. Moreover, some values of inflammatory and immune response indicators (albumin, CRP, B cells, T cells, and CD4/CD8 ratio) could not be obtained due to retrospective design. Patients were also disqualified because they had missed follow-up appointments, the drugs were unavailable or inaccessible, the treatment was too expensive, or they had stopped because of negative effects. Additionally, this represents the small sample size from patients treated at a single tertiary care facility.

CONCLUSION

In conclusion, our study emphasizes the potential of simple, cost-effective blood-based markers—such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and lymphopenia—as valuable tools for prognostication in metastatic breast cancer patients receiving CDK4/6 inhibitors. This is especially important in nations with low and moderate incomes, where access to refined molecular testing is frequently restricted. These routinely available parameters can help clinicians make more informed decisions about treatment, better stratify patients by risk, and monitor outcomes more effectively. By leveraging accessible and affordable biomarkers, we can take meaningful steps toward more personalized and equitable cancer care in resource-constrained settings.

List of Abbreviations

Hormone receptor (HR)
Human epidermal growth factor receptor 2 (HER2)
Estrogen receptor (ER)
Progesterone receptor (PR)
Breast cancer (BC)
Complete blood count (CBC)
Cyclin-dependent kinase 4 and 6 inhibitors (CDK 4/6i)
Neo-adjuvant chemotherapy (NAC)
Progression-free survival (PFS)
Overall survival (OS)
Metastatic breast cancer (mBC)
Standard deviation (SD)
Confidence intervals (CI)
Invasive ductal carcinoma (IDC)
Hazard Ratio (HR)
Eastern Cooperative Oncology Group (ECOG)
Hormone therapy (HT)
Neutrophil to lymphocyte ratio (NLR)
Lymphocyte to monocyte ratio (LMR)
Absolute lymphocyte count (ALC)
Platelet to lymphocyte ratio (PLR).

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