ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 10 | October - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PREDICTIVE IMPACT OF PAN-IMMUNE INFLAMMATION VALUE ON RADIOLOGICAL RESPONSE IN METASTATIC BREAST CANCER PATIENTS ON PALBOCICLIB

ONCOLOGY

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ABSTRACT

Background: Hormone receptor–positive (HR+), HER2-negative metastatic breast cancer (MBC) is the most common subtype of advanced breast cancer. CDK4/6 inhibitors combined with endocrine therapy significantly improve survival outcomes, but resistance frequently develops, emphasizing the need for reliable predictive biomarkers. The Pan-Immune Inflammation Value (PIV), a composite index calculated from complete blood counts, reflects systemic inflammation and immune status. Although high PIV has been linked with poor prognosis across multiple cancers, its predictive role in radiological response to palbociclib-based therapy in HR+/HER2− MBC remains unexplored. **Methods:** We conducted a retrospective–prospective observational study at a tertiary cancer center in Bangalore, India, from 2019 to 2024. A total of 129 patients with HR+/HER2− MBC who received palbociclib with endocrine therapy were included. PIV was calculated as (neutrophils × platelets × monocytes) / lymphocytes. Radiological response was assessed at 6 months using RECIST v1.1. Statistical analyses included ANOVA to compare PIV values across response groups and receiver operating characteristic (ROC) analysis to establish an optimal cut-off. **Results:** Baseline clinical and treatment characteristics were similar between low and high PIV groups. At 6 months, the overall radiological outcomes were: complete response (CR) in 13.1%, partial response (PR) in 38.7%, stable disease (SD) in 28.6%, and progressive disease (PD) in 19.3%. Disease control (CR/PR/SD) was achieved in 54.2% of low PIV patients versus 26.3% of high PIV patients, while PD was more frequent in the high PIV group (13.1% vs. 6.2%; $p < 0.001$). Mean PIV values were lowest in CR (267.6) and progressively higher in PR (599.3), SD (601.4), and PD (1276.1) ($p < 0.001$). ROC analysis defined ≤530.8 as the optimal cut-off (AUC 0.702, 95% CI 0.615–0.779, sensitivity 76.1%, specificity 66.1%). Toxicity profiles were consistent with previous CDK4/6 trials, with neutropenia (52.7% grade ≥3) as the most common adverse event. **Conclusion:** Baseline PIV is an inexpensive, reproducible, and clinically relevant biomarker that predicts radiological response to palbociclib in HR+/HER2− MBC. Integrating PIV into clinical practice may allow for improved patient stratification and personalized treatment strategies.

KEYWORDS

Pan-Immune Inflammation Value (PIV), Predictive Biomarker, Radiological Response, Hormone Receptor-positive (HR+) Breast Cancer, HER2-negative Metastatic Breast Cancer, CDK4/6 inhibitors

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide, with HR-positive, HER2-negative disease representing the most frequent subtype of metastatic breast cancer (MBC)[1]. The introduction of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, such as palbociclib, ribociclib, and abemaciclib, in combination with endocrine therapy has significantly improved clinical outcomes by prolonging progression-free survival (PFS) and delaying disease progression[2-3]. Despite these advances, a considerable proportion of patients develop resistance, highlighting the urgent need for predictive biomarkers to refine patient stratification and optimize treatment strategies[4].

Systemic inflammation has been recognized as a hallmark of cancer progression, influencing tumor biology, immune evasion, and therapeutic response[5]. Various blood-based inflammatory indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and C-reactive protein to albumin ratio (CRP/Alb) have been investigated as prognostic markers in breast cancer[6]. However, these parameters are limited by inconsistent predictive performance across clinical settings.

To address this gap, Fucà et al. introduced the Pan-Immune Inflammation Value (PIV), a composite biomarker derived from routine blood counts, calculated as (neutrophils × platelets × monocytes) / lymphocytes[7]. PIV reflects the balance between systemic inflammation and host immune competence. High PIV levels have been associated with poor prognosis in colorectal cancer, HER2-positive breast cancer treated with targeted therapy, and patients undergoing neoadjuvant chemotherapy[7-9].

In HR+/HER2− MBC, Kayıkçıoğlu et al. reported that high baseline PIV was independently associated with shorter PFS among patients treated with CDK4/6 inhibitors, establishing PIV as a promising prognostic biomarker[10]. More recently, composite indices incorporating PIV, such as the PILE score, have also demonstrated potential predictive utility for treatment efficacy with CDK4/6 inhibitors[11]. However, limited evidence exists regarding the ability of PIV to predict radiological response to palbociclib-based therapy, which could provide oncologists with an early and non-invasive tool to guide personalized treatment.

In this context, our study aims to evaluate the predictive role of pre-treatment PIV in determining radiological response among HR+/HER2− MBC patients receiving palbociclib with endocrine therapy. By integrating a simple and inexpensive biomarker into clinical decision-making, we aim to enhance treatment individualization and improve patient outcomes.

OBJECTIVE

To evaluate the Pan-Immune Inflammation Value (PIV) as a predictive biomarker of radiologic treatment response in patients with hormone receptor-positive, HER2-negative metastatic breast cancer receiving palbociclib-based therapy.

METHODOLOGY

This was a retrospective–cum–prospective observational study conducted between 2019 and 2024 at a tertiary cancer center in Bangalore, India. A total of 129 patients with hormone receptor-positive, HER2-negative metastatic breast cancer (MBC) who received palbociclib in combination with endocrine therapy were included. Prior to treatment initiation, all patients underwent complete blood count (CBC) evaluation, and the pan-immune-inflammation value (PIV) was calculated by multiplying the neutrophil count (10^3/μL) by the platelet count (10^3/μL) and monocyte count (10^3/μL), and dividing the product by the lymphocyte count (10^3/μL).

Palbociclib was administered as per institutional protocol in combination with an appropriate endocrine agent. Radiological response was assessed six months after treatment initiation using RECIST (version 1.1)

The pan-immune-inflammation value (PIV) was calculated by multiplying the neutrophil count (10^3/μL) by the platelet count (10^3/μL) and monocyte count (10^3/μL), and dividing the product by the lymphocyte count (10^3/μL).

Statistical analyses included comparison of mean PIV values across different response groups using one-way analysis of variance (ANOVA), and receiver operating characteristic (ROC) curve analysis was employed to determine the optimal PIV cut-off for predicting treatment response. A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

A total of 129 hormone receptor-positive, HER2-negative metastatic breast cancer patients were analyzed and stratified into low and high Pan-Immune Inflammation Value (PIV) groups based on pre-treatment CBC.

The baseline characteristics were similar between low and high PIV groups. No significant differences were noted in median age, comorbidities such as diabetes and hypertension, BMI, or menopausal status (p-values >0.05). The majority of patients were postmenopausal, and comorbidities were evenly distributed. (Table 1)

Table 1. Baseline Clinical Characteristics of Patients According to PIV Status.

Characteristic	Low PIV	High PIV	P Value
AGE (28-80)			0.75
< 50	30(23.2%)	21(16.2%)	
≥ 50	48(37.2%)	30(23.2%)	
CO-MORBIDITIES			0.624
Diabetes	17(13.1%)	6(4.6%)	
Hypertension	12(9.3)	8(6.2%)	
Both	8(6.2%)	4(3.1%)	
BMI (median) (range)	24.67 (15.24–41.11)	24.43 (14.49–32.88)	
Menopausal Status			0.385
Pre menopause	6(4.6%)	2(1.5%)	
Post menopause	72(55.8%)	49(37.9%)	

Treatment patterns were also were similar across groups. Most patients received palbociclib as first-line therapy combined with endocrine agents, mainly aromatase inhibitors (51.9% in low PIV vs. 33.3% in high PIV). Tamoxifen and fulvestrant were used less frequently and similarly distributed. Prior chemotherapy and endocrine therapy exposure were 21.7% in low PIV vs. 12.4% in High PIV and 6.2% in low PIV vs. 4.6% in High PIV.(Table 2)

Table 2. Treatment Characteristics of Patients in the Low and High PIV Groups.

Treatment Variable	Low PIV	High PIV	P Value
No of Lines of Treatment			
1 Line of Treatment	42(32.5%)	29(22.4%)	0.786
>1 Line of Treatment	36(27.9%)	22(17%)	
Prior Chemotherapy	28(21.7%)	16(12.4%)	0.66
Prior Endocrine Therapy	8(6.2%)	6(4.6%)	
Palbociclib Drug Combination			
Aromatase Inhibitor	67(51.9%)	43(33.3%)	0.86
Tamoxifen	3(2.3%)	3(2.3%)	
Fulvestrant	8(6.2%)	5(3.8%)	

Radiological outcomes showed a clear and statistically significant relationship with baseline PIV values (p < 0.001). In the low PIV group, 54.2% of patients achieved complete response (CR), partial response (PR), or stable disease (SD), compared with only 26.3% in the high PIV group. Progressive disease (PD) was more common in the high PIV group (13.1% vs. 6.2%). This highlights the predictive role of PIV in determining disease control under palbociclib therapy. (Figure 1, Table 3):

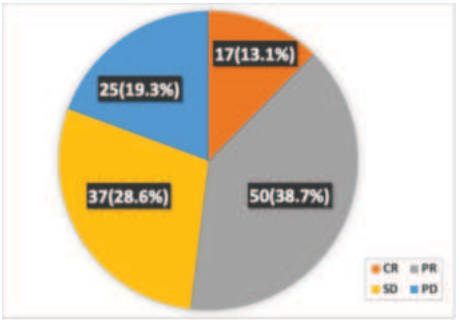

Figure 1. Distribution of Radiological Response According to PIV Groups.

Table 3. Radiological Response Outcomes by PIV Status.

RADIOLOGICAL RESPONSE	LOW PIV	HIGH PIV	P VALUE
PRESENT(CR,PR,SD)	70(54.2%)	34(26.3%)	<0.001
ABSENT(PD)	8(6.2%)	17(13.1%)	

The safety profile of palbociclib was consistent with prior CDK4/6 inhibitor studies. Neutropenia was the most frequent adverse event, observed in 52.7% of patients at grade ≥3 severity. Other hematological events included leukopenia (30.2%, with 0% at grade ≥3) and thrombocytopenia (10.8%, with 3.8% grade ≥3). Non-hematological toxicities were generally mild, with fatigue (34.1%) and myalgia (26.3%) most common. Nausea, anorexia, alopecia, and rash were infrequent and manageable.Infections were reported in only 2.3%. No unexpected safety concerns emerged.(Figure 2)

Figure 2. Adverse Events in Patients Receiving Palbociclib-based Therapy.

Detailed hematological toxicities demonstrated that grade ≥3 neutropenia was the most significant laboratory abnormality (52.7%), followed by thrombocytopenia (3.8%). These events were generally reversible and managed with dose interruptions or supportive care, with no major morbidity.(Figure 3)

Figure 3. Distribution of Metastatic Sites Between Low and High PIV Groups.

The distribution of metastatic sites was broadly similar between the low and high PIV groups. Bone was the most common site of metastasis, observed in 31% of patients with low PIV and 26.3% of those with high PIV. Lymph node involvement was also frequent (27.1% vs. 23.7%), followed by liver metastases (20.9% vs. 8.5%). Lung metastases occurred in 11.6% of patients in the low PIV group and 9.3% in the high PIV group. Less common sites included the brain (5.4% vs. 1.5%) and skin (6.9% vs. 3.1%). Overall, the distribution of metastatic burden was balanced between groups, with bone and lymph nodes being the predominant sites, while visceral and CNS involvement were less frequent.(Figure 3)

Receiver operating characteristic (ROC) analysis confirmed PIV as a reliable predictor of treatment response. Mean PIV values were lowest in patients with CR (267.6) and progressively higher in PR (599.3), SD (601.4), and PD (1276.1) groups ($p < 0.001$). The optimal cut-off of ≤530.80 yielded a sensitivity of 76.1% and specificity of 66.1% (AUC 0.702, 95% CI: 0.615–0.779, $p < 0.0001$). These results reinforce the role of PIV as an inexpensive, easily measurable biomarker for early prediction of response in metastatic breast cancer patients receiving palbociclib.

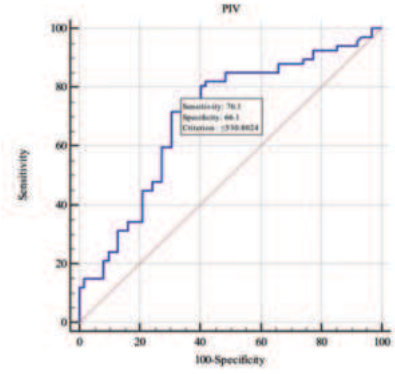

Figure 4. ROC Curve of Pan-Immune Inflammation Value (PIV) for Predicting Radiological Response in HR+/HER2− Metastatic Breast Cancer Patients Receiving Palbociclib.

DISCUSSION

The present study highlights the potential role of the pan-immune inflammation value (PIV) as a predictive marker in patients with hormone receptor–positive (HR+), HER2-negative metastatic breast cancer (MBC) treated with palbociclib and endocrine therapy. By demonstrating that lower baseline PIV values correlated with superior radiological outcomes, our findings emphasize the impact of systemic inflammation on treatment response. This discussion integrates our results with published evidence from clinical trials and real-world datasets.

The age of the patients in this study ranged between 28–80 years, with 93.7% postmenopausal. Comorbidities were recorded in 33.2% of patients. The median body mass index (BMI) was 24.67kg/m² in low PIV(15.24-41.11) and 24.43 in High PIV (14.49-32.88). When compared with pivotal CDK4/6 inhibitor trials, differences emerge. In PALOMA-2, which assessed palbociclib plus letrozole as first-line therapy, the median age was 62 years (range 30–89), with 40.8% aged ≥65 years, and nearly all patients had ECOG performance status 0–1[2]. In PALOMA-3, the median age was 57 years (range 30–88), also restricted to ECOG 0–1, but all patients had prior endocrine therapy and 33% had prior chemotherapy[12]. By contrast, real-world cohorts tend to include older and more heterogeneous populations. In the Dutch multicenter study by Hackert et al. (n=229), the median age was 65 years (range 38–87), with 10% ECOG ≥2[13]. Taken together, these comparisons demonstrate that our population lies between rigorously selected trial cohorts and more heterogeneous real-world populations, enhancing the generalizability of the findings.

In this study, 84% of patients received palbociclib in combination with an aromatase inhibitor, 10% with fulvestrant, and 4.6% with tamoxifen. A total of 34.1%. of patients had received prior chemotherapy, and 10.8% had prior endocrine therapy.

In PALOMA-2, no patients had received systemic therapy for advanced disease, but 48% had received adjuvant chemotherapy and 56% adjuvant endocrine therapy[2]. By contrast, PALOMA-3 included exclusively endocrine-resistant patients: all had prior endocrine therapy, and 33% had prior chemotherapy[12]. Real-world series reveal even heavier pre-treatment exposure. Hackert et al. reported that 47% of patients had ≥3 prior endocrine lines, and 37% had prior chemotherapy[2]. Thus, our patient population was more pretreated than PALOMA-2 but less heavily exposed than real-world cohorts, making it well-suited for assessing predictive biomarkers such as PIV.

At six months, radiological outcomes were as follows: complete response (CR) in 17 patients (13.1%), partial response (PR) in 50 patients (38.7%), stable disease (SD) in 37 patients (28.6%), and progressive disease (PD) in 25 patients (19.3%).

These results align with published evidence. In PALOMA-2, the objective response rate (ORR) was 42% with palbociclib plus letrozole compared with 35% with letrozole alone[2]. In PALOMA-3, ORR was 19% with palbociclib plus fulvestrant[12]. Real-world evidence confirms similar results, with ORRs between 40–55% and clinical benefit rates around 80%[14]. Notably, in the current study, patients with low baseline PIV were more likely to achieve CR or PR, whereas high PIV values were enriched among progressors, underscoring the predictive capacity of this biomarker.

Hematological toxicities were frequent, consistent with trial data. Neutropenia occurred in 88 patients (68%), with 66 patients (52.7%) experiencing grade ≥3 neutropenia. Leukopenia was reported in 39 patients (30.2%), thrombocytopenia in 19 (14.7%). Non-hematological toxicities included fatigue (35.6%), alopecia (9.3%), and gastrointestinal events such as nausea or diarrhea (6.2%).

These findings mirror those in PALOMA-2, where 66% of patients developed grade ≥3 neutropenia and 25% grade ≥3 leukopenia[2]. In PALOMA-3, grade ≥3 neutropenia occurred in 65% of patients[13]. Real-world studies report similar toxicity but greater variation in management strategies: Hackert et al. described more frequent cycle delays (54% vs 36% in PALOMA-3) and fewer dose interruptions (26% vs 54%), without adverse impact on progression-free survival[13]. Importantly, toxicity incidence did not differ significantly between low and high PIV groups in our cohort, suggesting PIV reflects prognosis and treatment response rather than toxicity risk.

ROC analysis identified an optimal baseline PIV cut-off of 530.8, with an AUC of 0.702 (95% CI 0.615–0.779, $p < 0.0001$). Sensitivity and specificity were 76.1% and 66.1%, respectively. Patients with PIV ≤530.8 achieved markedly higher CR/PR rates, confirming the discriminatory capacity of PIV.

These results are consistent with previous reports linking systemic inflammatory markers to treatment outcomes. Kayıkçıoğlu et al. showed that elevated PIV independently predicted inferior survival in HR+/HER2− MBC patients treated with CDK4/6 inhibitors[10]. Fucà et al. reported similar findings in metastatic colorectal cancer, where high PIV was associated with poor outcomes in pooled analyses of the Valentino and TRIBE studies[7]. Peng et al. confirmed PIV as a prognostic biomarker in advanced non-small cell lung cancer[15]. Collectively, these studies reinforce the role of PIV as a broadly applicable marker of systemic immune dysregulation.

High PIV represents elevated neutrophils, platelets, and monocytes with reduced lymphocytes. Neutrophils and monocytes contribute to tumor progression via cytokine release, angiogenesis, and immune evasion; platelets protect circulating tumor cells and facilitate metastasis; while lymphopenia reflects impaired adaptive immunity. Beyond cell cycle arrest, CDK4/6 inhibitors enhance antigen presentation and T-cell activation. However, in the context of high systemic inflammation, these immune-modulatory benefits may be blunted, reducing therapeutic efficacy[14].

Neutropenia itself has been investigated as a pharmacodynamic marker of palbociclib efficacy. Kimura et al. found that patients developing severe neutropenia had significantly longer progression-free survival than those without (median 176 days vs 91 days, $p = 0.005$)[14]. However, such markers can only be assessed after treatment initiation. In contrast, PIV provides a pre-treatment, baseline biomarker, allowing stratification before therapy begins. Moreover, PIV is simple, reproducible, and cost-effective, derived from routine blood counts, unlike genomic assays.

Future research should focus on validating standardized cut-offs

across populations, assessing dynamic PIV changes during treatment. Incorporating PIV into prospective clinical trials may enable more precise treatment allocation and inform sequencing of CDK4/6 inhibitors with other targeted agents.

CONCLUSION

Baseline PIV is a clinically relevant predictor of radiological response in HR+/HER2− MBC patients treated with palbociclib. These findings are consistent with clinical trial and real-world data confirming the efficacy and safety of CDK4/6 inhibition, while offering novel insights into systemic inflammation as a determinant of outcome. Given its simplicity, reproducibility, and predictive accuracy, PIV represents a promising biomarker that could be incorporated into clinical practice to personalize management strategies in metastatic breast cancer.

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