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Predictive Value of Inflammatory Indexes as Biomarkers of Neoadjuvant Chemotherapy Response in Locally Advanced Breast Cancer

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ABSTRACT

Background: Breast cancer remains the most common cancer in women worldwide. Treatment has evolved into multimodal approaches, with pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) serving as a key prognostic marker. The aim of this study was to evaluate the value of inflammatory markers in predicting pCR to NAC in breast cancer.

Methods: This cross-sectional study of 74 patients with breast cancer who underwent NAC followed by surgery included demographic, tumor, and immune-inflammatory marker data. Receiver operating characteristic curve analysis and the Youden index were used to determine optimal cutoff values. Univariate and multivariate logistic regression assessed associations between markers and pCR, adjusting for tumor stage, human epidermal growth factor receptor 2 (HER2), and estrogen receptor (ER) status.

Results: Our multivariate analysis identified the pan-immune-inflammation value (PIV), HER2 status, and ER status as significant independent predictors of pCR. PIV (OR, 4.28; 95% CI, 1.59–16.88) remained significant among inflammatory markers, while the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) did not. HER2-positive (OR, 7.45; 95% CI, 2.30–24.15) and hormone receptor (HR)–negative (OR, 7.02; 95% CI, 2.63–18.70) statuses were also strongly associated with pCR.

Conclusion: PIV is a robust predictor of pCR in patients with breast cancer receiving NAC, offering a comprehensive reflection of the immune-inflammatory state. Incorporating PIV with tumor-specific markers (e.g., receptor status, Ki-67, grade) may enhance treatment stratification. Further validation in diverse cohorts is warranted.

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INTRODUCTION

Globally, breast cancer is the most common

cancer among women, with an estimated 2.3 million invasive cases diagnosed in 2020.¹ Over the past 3 decades, the age-standardized rate of invasive breast cancer in the United Kingdom has risen by nearly 25%.² Across the 27 European Union countries, breast cancer incidence and mortality rates vary

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widely, reaching up to 190 new cases and 45 deaths per 100 000 women annually.³

Over the past 50 years, breast cancer treatment has evolved from surgery-focused approaches to multimodal strategies integrating surgery, radiation, and systemic therapies, including targeted therapy. Neoadjuvant chemotherapy (NAC) trials have revealed that assessing tumor response *in vivo* is a critical prognostic indicator for long-term outcomes. Pathologic complete response (pCR), typically defined as the absence of residual invasive disease in the breast (ypT0 or ypT0/is) and axilla (ypN0) after NAC, has been associated with improved survival across various clinical trials and is frequently used as a surrogate endpoint for prognosis.^{4,5} Reported pCR rates in randomized trials assessing NAC and adjuvant chemotherapy range from 4% to 29.2%.^{6,7} Beyond pCR, the residual cancer burden (RCB) index offers further insight into NAC outcomes by evaluating primary tumor size, cellularity, nodal metastasis size, and the number of pathologically positive nodes. Higher RCB scores are linked to a greater risk of distant relapse at 5 years, ranging from 2.4% for RCB-I to 53.6% for RCB-III, with RCB-0 and RCB-I providing prognostic outcomes comparable to pCR.⁸

Inflammation is recognized as a critical hallmark of cancer and plays an important role in its progression.⁹ This relationship offers a promising target for novel therapies. Numerous studies have identified immune cells—including neutrophils, lymphocytes, and monocytes—and inflammation-based ratios, such as the monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR), as biomarkers influencing carcinogenesis and metastasis.^{10–13}

Recently, the relationship between the breast cancer immune microenvironment and response to NAC has been highlighted, with studies examining the role of the peripheral immune system in NAC response.¹⁴ While reduced immune and inflammatory activation might correlate with either improved or worse outcomes, results have varied across studies.^{15,16}

The aim of this study was to evaluate the predictive potential of the pan-immune-inflammation value (PIV) alongside MLR, PLR, and NLR in patients with breast cancer undergoing NAC. We explored whether baseline PIV predicts pCR in NAC-treated breast cancer, distinguishing its predictive power from other clinical factors.

Although recent studies have investigated PIV, our study specifically adds novelty by evaluating PIV's predictive capability against established inflammatory indexes (NLR, MLR, PLR) and by conducting detailed subgroup analyses based on

hormone receptor status and molecular subtype, thus clarifying its potential clinical utility.

METHODS

Patient population

Women older than 18 years with a pathohistologically confirmed diagnosis of locally advanced invasive breast cancer (BC) from core biopsy (B5b), who completed NAC followed by surgery at a single center between November 2022, and September 2024, and had no distant metastases at presentation were retrospectively included in the study. The sample size was not predetermined. We included patients diagnosed and treated consecutively in our institution during the defined period, resulting in a final cohort of 74 patients.

Exclusion criteria were as follows: (1) recurrent or *de novo* metastatic breast cancer; (2) concurrent diagnosis of another primary tumor; (3) ductal carcinoma *in situ*; (4) male breast cancer; and (5) incomplete laboratory data preventing calculation of the PIV. Adjuvant treatments, including radiotherapy, chemotherapy, biological therapy, and hormonal therapy, were administered according to standard care protocols.

Blood count and data collection

Clinical data, including medical history, tumor characteristics, and treatment details, were meticulously collected and recorded in Excel for all patients. Laboratory data on blood cell counts were retrieved from the hospital's electronic clinical repositories. Pretreatment blood counts, taken within 3 weeks prior to the initiation of NAC, were used for the analyses.

Inflammatory markers were calculated using the following formulas:

- $NLR = \text{neutrophil count (} 10^9/L) / \text{lymphocyte count (} 10^9/L)$
- $PLR = \text{platelet count (} 10^9/L) / \text{lymphocyte count (} 10^9/L)$
- $PIV = (\text{neutrophil count} \times \text{platelet count} \times \text{monocyte count}) / \text{lymphocyte count (all in } 10^9/L)$
- $MLR = \text{monocyte count (} 10^9/L) / \text{lymphocyte count (} 10^9/L)$

The patients were staged using the 8th edition of the American Joint Committee on Cancer (AJCC) *TNM Staging System*. Therapy response was evaluated using the MD Anderson Residual Cancer Burden (RCB) score.

Study design and endpoint

This retrospective study used a cross-sectional design, with data collected from November 2022 to September 2024. Pretreatment PIV, NLR, MLR, and PLR were calculated from laboratory parameters



before the start of chemotherapy, and data on therapy response were collected from the postsurgery pathohistology.

Data on predictors and pCR were collected concurrently from the existing medical records of patients, representing a cross-sectional dataset with approximately 2-year coverage. The primary endpoint of the study was the response to neoadjuvant therapy.

Patients were included via convenience sampling from a single-center clinical setting, potentially limiting generalizability and introducing selection bias. Those with incomplete records or who did not meet the inclusion criteria were excluded.

To minimize information bias, all data were extracted from standardized electronic medical records by independent reviewers using a predefined data collection form. Potential confounding variables (e.g., age, tumor stage, and receptor status) were accounted for in the statistical analysis using multivariate methods.

Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQRs) or means with standard deviations, while categorical variables were presented as frequencies and percentages. Associations between pCR and other clinicopathological characteristics were analyzed using the χ^2 test for categorical variables and the Student *t* test for continuous variables. In this research, $P < 0.05$ was considered to indicate statistical significance.

Receiver operating characteristic (ROC) curve analysis and the Youden index were used to determine the optimal cutoff of continuous variables. Internal validation procedures, such as bootstrapping or cross-validation, were not applied in this analysis due to the exploratory nature of the study and the limited sample size. All detailed data are available in the Supplementary Materials (Supplementary Figures 1,2,3 and 4) Consequently, the reproducibility of the ROC-derived cutoff values, including those determined by the Youden index, remain to be confirmed in independent cohorts. Univariate logistic regression was used to identify potential predictors, and those factors with $P < 0.20$ were then included in the multivariate logistic regression model.

Table 2. Receiver Operating Characteristic Curve Analyses for Pathologic Complete Response

Curve	Cutoff value	AUC	Sensitivity, %	Specificity, %	Youden index (max)
NLR	2.3	0.515	76.7	39.8	0.165
MLR	0.26	0.596	84.9	37.8	0.227
PLR	102	0.528	82.4	34.6	0.170
PIV	280	0.681	87.9	47.5	0.354
Ki-67 index	30%	0.667	81.8	60.7	0.425

AUC, area under the curve; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio.

RESULTS

The clinicopathological characteristics of the 74 patients included in the study are summarized in Table 1.

Table 1. Clinicopathological Characteristics of the Patients (N = 74)

Characteristic	Value
Age, mean (SD), y	56.7 (11.0)
Histological Type, No. (%)	
No specific type	68 (91.9)
Lobular	3 (4.1)
Ductal + lobular	3 (4.1)
Hormone Receptor Status, No. (%)	
Positive	51 (68.9)
Negative	23 (31.1)
HER2 Receptor Status, No. (%)	
Positive	18 (24.3)
Negative	56 (75.7)
Histopathological Grade, No. (%)	
G1	1 (1.4)
G2	36 (48.6)
G3	37 (50.0)
Ki-67, median (range), %	30 (5–90)
Pathologic Complete Response, No. (%)	
No	51 (68.9)
Yes	23 (31.1)
Molecular Subtype, No. (%)	
Luminal A	14 (18.9)
Luminal B	35 (47.3)
Triple-negative breast cancer	15 (20.3)
HER2-positive	10 (13.5)
Tumor Stage, No. (%)	
T1c	10 (13.5)
T2	48 (64.9)
T3	16 (21.6)

For the entire patient cohort, the optimal cutoff values were calculated based on the ROC curve analysis and Youden index. The optimal cutoff values for NLR, PLR, MLR, PIV, and Ki-67 were 2.3, 102, 0.26, 280, and 30%, respectively. The PIV cutoff point according to the ROC curve analysis allowed the identification of the following 2 categories: PIV low (≤ 280) in 51 patients (68.9%) and PIV high (> 280) in 23 patients (31.1%). Similarly, the ROC curve analysis for the PLR, MLR, NLR, and Ki-67 divided patients into high and low groups. Detailed data are shown in Table 2.



Regarding the association of patient characteristics with pCR, PIV ($P=0.005$), MLR ($P=0.04$), NLR ($P=0.009$), hormone receptor (HR) status ($P<0.001$), human epidermal growth factor receptor 2 (HER2) status ($P=0.002$), Ki-67 ($P=0.002$), histopathological grade ($P<0.001$), molecular type ($P<0.001$), and therapy regimens ($P<0.001$) were significantly associated with response to neoadjuvant therapy. In contrast, age ($P=0.70$), PLR ($P=0.44$), and histopathological type ($P=0.21$) did not show a statistically significant association. These data are presented in Table 3.

Univariate logistic regression was performed to see which of the factors are statistically significant predictors on their own. Patients in the low PIV group had an 8.2-fold higher probability of pCR than those in the high PIV group (OR, 8.20; 95% CI, 1.56–38.33; $P=0.007$). Similarly, low MLR (OR, 4.19; 95% CI, 1.11–15.77; $P=0.03$), low NLR (OR, 3.89; 95% CI, 1.33–11.34; $P=0.01$), negative HR status (OR, 8.29; 95% CI, 2.76–24.90; $P<0.001$), positive HER2 status (OR, 5.61; 95% CI, 1.85–17.01; $P=0.002$), high Ki-67 index (OR, 7.02; 95% CI, 2.11–23.33; $P<0.001$), higher-grade (G3) tumor (OR, 6.82; 95% CI, 2.19–21.24; $P<0.001$), and NAC type (OR, 3.75; 95% CI, 1.33–10.57; $P=0.01$) were all significantly associated with achieving pCR. On the other hand, age, PLR, and histological type showed no significant association with response to therapy.

Multivariate analysis confirmed that among systemic inflammatory markers, PIV was the only independent predictor of pCR in the study population (OR, 4.28; 95% CI, 1.59–16.88; $P=0.01$). Among other factors, HR status and HER2 receptor status kept their statistical significance as predictors of pCR. In contrast, Ki-67, histological grade, NLR, and MLR lost statistical significance in the multivariate analysis. These data are presented in Table 4.

Our results indicated that HR status and PIV independently predicted pCR in patients with breast cancer receiving NAC. To explore the relationship between PIV and HR status further, subgroup analyses were performed. In the HR-positive group ($n=51$), the pCR rate was 29.6% in the low-PIV group and 6.6% in the high-PIV group, with no significant difference in pCR likelihood between these PIV subgroups ($P=0.15$).

Conversely, in the HR-negative group ($n=23$), the pCR rate was 81.2% in the low-PIV group compared with 14.3% in the high-PIV group, showing a significant difference in pCR rates across PIV subgroups ($P=0.002$) (Figure 1).

When the analysis was stratified into triple-negative (ER-negative, PR-negative, and HER2-negative) and non-triple-negative groups, similar results were observed. The patients in the triple-

negative, low-PIV group demonstrated a significantly higher likelihood of achieving pCR ($P=0.004$).

Table 3. Association of Patient Characteristics with Pathologic Complete Response (pCR)

Characteristic	pCR, No. (%)		<i>P</i> value
	Yes (<i>n</i> = 23)	No (<i>n</i> = 51)	
Age, mean (SD), y	57.9 (10.6)	56.1 (11.2)	0.70 ^a
NLR			0.009 ^b
Low	17 (73.9)	21 (41.2)	
High	6 (26.1)	30 (58.8)	
MLR			0.04 ^b
Low	20 (87.0)	32 (62.7)	
High	3 (13.0)	19 (37.3)	
PLR			0.44 ^b
Low	4 (17.4)	13 (25.5)	
High	19 (82.6)	38 (74.5)	
PIV			0.005 ^b
Low	21 (91.3)	30 (58.8)	
High	2 (8.7)	21 (41.2)	
HR Status			<0.001 ^b
Negative	14 (60.9)	9 (17.6)	
Positive	9 (39.1)	42 (82.4)	
HER2 Status			0.002 ^b
Negative	12 (52.2)	44 (86.3)	
Positive	11 (47.8)	7 (13.7)	
Ki-67 Index			0.002 ^b
Low	4 (17.4)	29 (56.9)	
High	19 (82.6)	22 (43.1)	
Histopathology			0.21 ^b
Invasive ductal carcinoma	21 (91.3)	47 (92.2)	
Other histology types	2 (8.7)	4 (7.8)	
Histological Grading			0.001 ^b
G1/2	5 (21.7)	32 (62.7)	
G3	18 (78.3)	19 (37.3)	
Molecular Type			<0.001 ^b
Luminal A	0 (0)	14 (27.5)	
Luminal B	8 (34.8)	27 (52.9)	
HER2-positive	6 (26.1)	4 (7.8)	
Triple-negative	9 (39.1)	6 (11.8)	
NAC Regimen			<0.001 ^b
Anthracycline plus taxane	6 (26.1)	43 (84.3)	
Chemotherapy + pembrolizumab	4 (17.4)	2 (3.9)	
Chemotherapy + anti-HER2 (dual)	13 (56.5)	6 (11.8)	

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MLR, monocyte-to-lymphocyte ratio; NAC, neoadjuvant chemotherapy; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio.

NLR, MLR, PLR, and PIV categories (high vs low) are based on optimal ROC curve-derived Youden index cutoffs.

^aStudent *t* test.

^b χ^2 test.

**Table 4.** Univariate and Multivariate Logistic Regression Analysis for Predictors of pCR

Factor		Univariate analysis		Multivariate analysis	
		OR (95% CI)	P value	OR (95% CI)	P value
Age, y		1.01 (0.97–1.05)	0.62		
Histological grade	G3	6.82 (2.19–21.24)	<0.001	1.80 (0.38–8.56)	0.11
NLR	Low	3.89 (1.33–11.34)	0.01	3.30 (1.02–10.70)	0.12
MLR	Low	4.19 (1.11–15.77)	0.03	4.26 (0.76–28.23)	0.11
PLR	Low	1.62 (0.76–1.73)	0.44		
PIV	Low	8.20 (1.56–38.33)	0.007	4.28 (1.59–16.88)	0.01
HR status	Negative	8.29 (2.76–24.90)	<0.001	7.02 (2.63–18.70)	0.02
HER2 status	Positive	5.61 (1.85–17.00)	0.002	7.45 (2.30–24.15)	0.02
Ki-67 index	High	7.02 (2.11–23.33)	<0.001	3.86 (1.19–12.51)	0.10
Histopathology	IDC	0.59 (0.23–1.51)	0.27		
NAC regimen	Other vs anthracycline + taxane	3.75 (1.33–10.57)	0.01	1.60 (0.22–11.28)	0.13
Molecular type	Luminal B vs luminal A	0.57 (0.53–4.22)	0.44		
	HER2+ vs luminal A	0.19 (0.05–0.72)	0.21		
	TNBC vs luminal A	1.00 (0.19–5.12)	0.77		

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDC, invasive ductal carcinoma; MLR, monocyte-to-lymphocyte ratio; NAC, neoadjuvant chemotherapy; NLR, neutrophil-to-lymphocyte ratio; pCR, pathologic complete response; PIV, pan-immune-inflammation value; PLR, platelet-to-lymphocyte ratio; TNBC, triple-negative breast cancer.

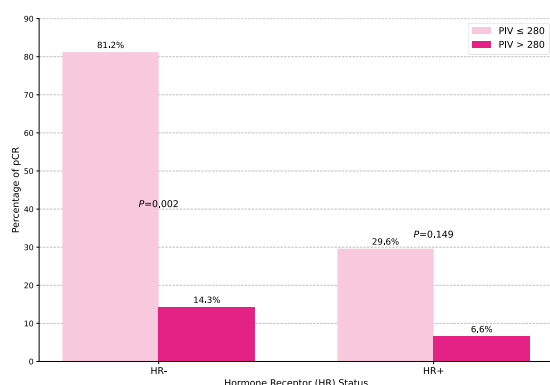


Figure 1. Comparison of pCR Rates in Low- vs High-PIV Groups Stratified by Hormone Receptor Status. pCR, pathologic complete response; PIV, pan-immune-inflammation value. Comparison between groups was done using the χ^2 test.

DISCUSSION

Our study explored the predictive value of inflammatory markers for pCR to NAC in breast cancer. Among the markers evaluated, PIV remained a statistically significant predictor of pCR in both univariate and multivariate analyses. Additionally, HER2 receptor status and HR receptor status confirmed their roles as significant independent predictors, emphasizing the interplay of immune-inflammatory status and tumor biology in chemotherapy response.

As a composite marker combining neutrophil, monocyte, lymphocyte, and platelet counts, PIV reflects the overall immune response in patients with cancer. The rationale behind this formulation lies in the distinct and often complementary roles these components play in tumor progression. Neutrophils, monocytes, and platelets are frequently elevated in cancer-related inflammation and are known to

support tumor proliferation and immune evasion. Conversely, lymphocytes play a key role in the antitumor immunity response. By placing lymphocyte count in the denominator, the PIV index captures the balance between tumor-promoting inflammation and antitumor immune response. Elevated PIV, linked to increased systemic inflammation and tumor-promoting immune states, has been associated with poor treatment outcomes. This aligns with several other studies, which have shown reduced chemotherapy efficacy with higher PIV levels, likely due to the immune-suppressive effects of its components.^{16,17} Conversely, a lower PIV, indicating a more favorable immune profile dominated by lymphocytes, may enhance chemotherapy response. Given its accessibility and cost-effectiveness, PIV could serve as a practical tool in clinical settings to identify patients less likely to achieve pCR. Patients with elevated PIV at baseline may benefit from closer clinical monitoring during neoadjuvant chemotherapy or consideration for treatment intensification strategies. This highlights PIV's potential as a biomarker for stratifying patients by NAC response likelihood.¹⁸

Multivariate analysis in our study revealed that NLR, MLR, and PLR were not significant predictors of pCR, a finding consistent with previous research reporting no association between NLR and pCR, despite its established relevance to overall survival (OS), and identifying MLR as the only marker significantly linked to disease-free survival (DFS).^{19,20} Changes in PLR during NAC cycles have been shown to influence chemotherapy response, while other studies have associated NLR, MLR, and PLR with OS across various subtypes and patient populations.^{21–24} These variations suggest that the



predictive power of these markers depends on cancer subtypes, NAC regimens, and patient genetics. The loss of significance for these factors may partially be attributed to collinearity between related inflammatory markers, particularly as PIV incorporates neutrophil, platelet, and monocyte counts that overlap with NLR, MLR, and PLR. Similarly, the loss of significance for Ki-67 and NAC regimen in the multivariate analysis is likely because HER2 and HR status account for much of the variability in treatment response, diminishing the independent contribution of other factors when adjusted for simultaneously. These findings highlight the importance of considering intervariable relationships when interpreting multivariable models, especially in studies with limited sample sizes. Our findings imply that PIV, reflecting a broader immune state, may provide more robust predictive capability than these narrower markers.

Our subgroup analysis revealed that the predictive value of PIV was pronounced in HR-negative patients but not in those with HR-positive tumors. This differential behavior may be explained by both biological and methodological factors. HR-negative breast cancers, particularly triple-negative subtypes, are known to be more immunogenic, with a higher infiltration of tumor-infiltrating lymphocytes and a more dynamic interaction with the host immune system. Consequently, systemic inflammatory markers such as PIV may better reflect tumor–host immune crosstalk and the likelihood of chemotherapy-induced tumor eradication in this context. In contrast, HR-positive tumors typically exhibit lower proliferative indices and reduced immune activation, potentially attenuating the association between systemic inflammation and treatment response. Moreover, it is possible that the smaller number of HR-negative patients achieving pCR in the high-PIV subgroup enhanced the statistical contrast in that group. For HR-positive patients, the lack of association may also be influenced by limited sample size, reducing the power to detect more modest effects.

In addition to the inflammatory markers assessed in our study, the systemic immune-inflammation index (SII)—calculated as (platelet count $\times$ neutrophil count) / lymphocyte count—has also emerged as a promising prognostic marker in several malignancies, including breast cancer. Recent studies have demonstrated its association with both treatment response and survival outcomes. For example, one study reported that higher SII levels were significantly associated with lower rates of pCR and worse DFS in young patients with breast cancer undergoing NAC.²⁵ Although SII was not included in our analysis, it shares several components with PIV

and may offer additional predictive value. Future research should explore SII in combination with PIV and other markers to refine immune-inflammatory profiling.

HER2-positive and estrogen receptor–negative statuses also emerged as significant predictors of pCR, consistent with prior research. HER2-positive tumors exhibit higher pCR rates with targeted therapies, and HR-negative tumors, due to higher proliferation rates, show greater chemotherapy sensitivity.²⁶

In line with our aim to evaluate the predictive significance of inflammatory markers for pCR, our findings demonstrate that PIV proved to be a significant and independent predictor of pCR in patients with breast cancer undergoing NAC, whereas NLR, MLR, and PLR did not maintain predictive value in the multivariate analysis.

CONCLUSION

In summary, this study identified the potential utility of PIV as an accessible, comprehensive marker of immune inflammation in predicting chemotherapy response. Integrating PIV with tumor-specific markers could enhance predictive models, improving patient stratification and potentially guiding therapeutic decision-making. The relatively small sample size in this study limits the generalizability of the findings. Further studies should aim to validate these findings in larger, multicenter cohorts and investigate dynamic changes in PIV during the course of therapy to further refine its clinical utility.

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CONFLICTS OF INTEREST

All the authors declare that there are no conflicts of interest, and that they have no relevant financial or non-financial interests to disclose.

ETHICAL CONSIDERATIONS

All patients provided written informed consent for treatment. This study was conducted retrospectively using de-identified clinical data collected during routine care. According to the institutional policy, formal ethical committee approval was not required. All procedures were carried out in accordance with the ethical standards of the institutional and national research committees, and with the 1964 Helsinki Declaration and its later amendments.

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DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical considerations, respecting patient confidentiality and institutional policies.

AI DISCLOSURE

The authors declare that generative AI was used

only to improve the language/grammar of the manuscript, and the authors take full responsibility for the content.

AUTHOR CONTRIBUTIONS

VD: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft; SP: Methodology, Writing – Review & Editing; NS: Formal Analysis, Data Curation; EB: Resources; NK: Resources, Visualization; MS: Data Curation, Visualization; TC: Writing – Review & Editing, Supervision.

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