



Unveiling the Diagnostic Potential of Platelet-to-Lymphocyte Ratio and HALP Score in Newly Diagnosed Breast Cancer: A Step Toward Early Detection

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ABSTRACT

Objective: Breast cancer (BC) is a global concern due to its high incidence worldwide. The alarming increase in BC cases highlights the need for careful management of the disease at multiple levels. This study investigated the diagnostic value of hemoglobin, albumin, lymphocyte and platelet counts (HALP score), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) in newly diagnosed BC patients.

Materials and Methods: A total of 84 individuals, including 42 healthy volunteers (group I) and 42 patients newly diagnosed with BC (group II), were included. Serum albumin levels were determined using spectrophotometry. The levels of tumor-markers carcinoembryonic antigen (CEA) and cancer antigen 15–3 (CA 15–3) in serum were analyzed by electrochemiluminescence immunoassay. Hemogram parameters were analyzed using fluorescence flow cytometry.

Results: The median PLR was significantly lower in group II than group I ($p = 0.014$). There were no statistical differences in HALP score, NLR, LMR, and prognostic nutrition index between the two groups ($p = 0.133$, $p = 0.993$, $p = 0.591$, and $p = 0.294$, respectively). The sensitivity and specificity of PLR in predicting BC were 61.90% and 64.29%, respectively, with an area under the curve of 0.665 ($p = 0.009$, 95% confidence interval: 0.5480 to 0.7819, cut-off value ≤ 124). PLR, CEA and CA 15–3 were independent risk factors for BC ($p < 0.05$).

Conclusion: The findings suggest that PLR may serve as a potential biomarker for the early diagnosis of BC; however, further validation is required. Conversely, the HALP score and other parameters did not demonstrate a significant association with early BC diagnosis. These results warrant corroboration through regional and community-based studies.

Keywords: HALP score; breast cancer; diagnosis

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Key Points

- Breast cancer has a high global incidence, necessitating improved diagnostic and management strategies.
- The research focused on evaluating the diagnostic utility of hematological biomarkers, including the hemoglobin, albumin, lymphocyte and platelet count score, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio, in newly diagnosed breast cancer patients.
- The PLR was significantly lower in breast cancer patients compared to healthy individuals ($p = 0.014$).
- PLR showed a sensitivity of 61.90% and specificity of 64.29% for predicting breast cancer.
- PLR may have potential as a diagnostic biomarker for breast cancer, but further validation through larger studies is necessary.

Introduction

Breast cancer (BC), which has a high global prevalence, continues to be a major health concern. The rising number of cases highlights the urgent need for effective management strategies across various levels. Understanding the underlying pathogenetic mechanisms is important for the rapid development and implementation of effective diagnostic and therapeutic approaches for BC (1). Carcinoembryonic antigen (CEA) and cancer antigen 15–3 (CA 15–3) as tumor markers are currently among the key biomarkers used for BC (2), primarily in diagnosis and for follow-up. However, their effectiveness in diagnosing early-stage BC remains questionable because of low sensitivity and specificity, leading to ongoing research efforts aimed at discovering more reliable biomarkers for early detection (3). Studies have also reported the use of these markers for monitoring recurrence and treatment rather than for early diagnosis (4, 5). Moreover, the limited sensitivity and specificity of tumor markers are compounded by analysis availability, as these tests may not directly be performed in all healthcare settings, such as public health laboratories and small county state hospitals. This underscores the need for accessible, minimally invasive, reliable, and cost-effective biomarkers in routine assessments (3, 6, 7).

While identifying new prognostic and predictive biomarkers is essential for early detection (8), recent studies indicate that inflammation significantly influences tumor development, progression, proliferation, invasion, and metastasis (9). Blood cells such as lymphocytes and monocytes contribute to these processes by releasing cytokines that drive inflammatory responses (10, 11). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and prognostic nutrition index (PNI) have been evaluated to predict prognostic outcomes, such as the risk of recurrence, poor disease-free survival, distant metastasis and cancer staging in different cancers (12–15).

Combining these indices often offers a more accurate prognosis than any single marker, and they can be derived from routine laboratory tests (10, 16). The hemoglobin, albumin, lymphocyte and platelet count (HALP score), combining hemoglobin, albumin, lymphocytes, and platelets, reflects nutritional status and systemic inflammation, serving as a significant prognostic biomarker in certain cancers (17, 18). The HALP score, which provides simple and rapid results, may be an important predictor of patients' pathological stages and indirectly predict disease survival (19). The evaluation of these hematological parameters in patients with BC appears to mainly focus on the prognosis of the disease in the current literature and the number of studies on their utility in diagnosis of BC was limited. Therefore, we investigated the diagnostic value of HALP score in newly diagnosed BC patients and aimed to support the results with analysis of other biomarkers including NLR, PLR, and PNI, which are hematological parameters frequently encountered in the literature.

Materials and Methods

Establishing Working Groups

This retrospective study included a total of 84 female participants aged between 18 and 75 years, comprising 42 patients with newly diagnosed BC (group II) who visited the Department of Medical Oncology at Nigde Omer Halisdemir University Training and Research Hospital, and 42 age-matched healthy volunteers (group I). The participants'

data, including albumin and hemogram test results, age, and any co-existing conditions, were gathered from the hospital's information system based on records from the time of initial BC diagnosis.

Inclusion and Exclusion Criteria

Patients were excluded if they had a history of surgery within the past six months, chronic diseases such as liver or kidney failure in addition to cancer, a concurrent diagnosis of another cancer in addition to BC, hematological comorbidities (e.g., anemia of chronic disease, thalassemia, thrombocytopenia), immunological diseases, or recent use of antibiotics. The control group consisted of healthy volunteers who met these criteria.

Blood Sample Protocol and Measurement Methods

Blood samples were collected using specific protocols to ensure consistent measurement methods:

- For albumin testing, blood was drawn into 5 mL biochemistry gel-separated tubes (BD, Becton Dickinson). The sera were obtained by centrifuging at 4.000 rpm for 10 minutes, and serum albumin levels were determined using a spectrophotometric approach on a Roche Cobas c701 spectrophotometer (Mannheim, Germany).
- The levels of CEA and CA 15–3 in serum were analyzed by electrochemiluminescence immunoassay using a Roche Cobas e801 analyzer (Mannheim, Germany). Blood for these tests was drawn into 5 mL tubes without anticoagulants and the serum was separated as described above (BD, Becton Dickinson).
- Hemogram parameters were analyzed using fluorescence flow cytometry on a Sysmex XN-1000 devices (Kobe, Japan) from blood samples taken into tubes containing ethylenediaminetetraacetic acid.

Calculation of Scores and Ratios

- The HALP score = $[\text{hemoglobin (g/L)} \times \text{albumin (g/L)} \times \text{lymphocytes (/L)}] / \text{platelets (/L)}$.
- NLR = neutrophil/lymphocyte count.
- PLR = platelet count/lymphocyte count.
- LMR = lymphocytes/monocytes.
- PNI was calculated using the formula: $\text{PNI} = 0.005 \times \text{lymphocytes/mm}^3 + 10 \times \text{albumin (g/L)}$.

Ethical Statement

Ethical approval was granted by the Nigde Omer Halisdemir University Faculty of Medicine Non-Interventional Ethics Committee (protocol number: 2023/81, date: 10.11.2023).

Statistical Analysis

SPSS, version 22.0 (IBM Inc., Armonk, NY, USA)) and GraphPad Prism 9.5.0 program (Boston, MA, USA) were used for statistical analysis. Descriptive statistics are given as mean, standard deviation, median and interquartile range. Normality was checked using the Shapiro-Wilk test, histograms, skewness, and kurtosis. Categorical variables were compared using the chi-square test. For comparing two group means, an independent samples t-test was used if parametric assumptions were met; otherwise, the Mann-Whitney U test was applied. Variance homogeneity was assessed using Levene's test; if

variances were unequal, the Welch test was applied, and if equal, the Student's t-test was performed. Correlation analysis was conducted using Spearman's test. GraphPad Prism was used to perform receiver operating characteristics (ROC) curve analysis to determine the sensitivity and specificity of HALP, NLR, PLR, LMR, and PNI. Logistic regression analysis was used to identify independent risk factors for BC.

Establishing Working Groups

G*Power version 3.1.9.4), the sample size was decided as 80 participants (patients + controls) to achieve 95% ($1 - \beta = 0.95$) power at $\alpha = 0.05$. According to reference article (20), the HALP score was taken as a reference parameter.

Results

Study Results

The study included age-matched groups, with both group I and group II having a mean age of 55.30 ± 12.5 years. Upon examination of the parameters, CEA, CA 15–3, C-reactive protein, mean corpuscular volum, and basophil count in group II were significantly higher

than in group I ($p = 0.016$, $p = 0.001$, $p = 0.001$, $p = 0.001$, and $p = 0.001$, respectively). Conversely, platelet and PLR values in group II were significantly lower than in group I ($p = 0.020$ and $p = 0.014$, respectively). No significant difference was observed between the groups with respect to other parameters ($p > 0.05$). Detailed analysis data for other tests are presented in Table 1.

Correlation results are shown in Table 2. In group I there was a weak negative correlation between HALP score and NLR ($r = -0.392$, $p < 0.001$) and a strong negative correlation between PLR and HALP score ($r = -0.851$, $p < 0.001$). A weak positive correlation was found between LMR *vs.* HALP score ($r = 0.440$, $p = 0.0041$). A strong negative correlation was found between NLR *vs.* PLR ($r = -0.632$, $p < 0.001$). There was no correlation between NLR *vs.* LMR, NLR *vs.* PNI and PLR *vs.* LMR ($r = 0.260$, $p = 0.453$, $r = -0.161$, $p = 0.382$, $r = -0.285$, $p = 0.661$, respectively).

In group II, a strong negative correlation was found between HALP score and NLR and HALP score and PLR ($r = -0.603$, $p < 0.001$, $r = -0.956$, $p < 0.001$, respectively), a weak positive correlation was found between LMR and HALP score ($r = 0.317$, $p = 0.041$). While there was a strong positive correlation between NLR and PLR ($r = 0.584$,

Table 1. Comparison of age and clinical variables between healthy controls (group I) and women with early diagnosed breast cancer (group II)

Parameters	Group I ($n = 42$) mean \pm SD or median (IQR)	Group II ($n = 42$) mean \pm SD or median (IQR)	<i>p</i> -value
Age, years	55.30 \pm 12.5	55.30 \pm 12.5	0.844
CEA, ng/mL	1.27 (0.96–1.70)	1.97 (1.29–3.12)	0.016
CA 15–3, ng/mL	12.20 (9.77–16.20)	19.5 (14.9–24.4)	0.001
Albumin, g/L	44.00 (42.75–45.25)	44.00 (40.97–45.00)	0.327
C-reactive protein, mg/L	1.60 (0.95–2.90)	3.35 (1.95–5.90)	0.001
Leukocyte count, ($10^3/\mu\text{L}$)	6.34 \pm 0.19	6.74 \pm 0.38	0.602
Hemoglobin (g/dL)	13.85 (12.90–14.42)	13.20 (12.4–14.05)	0.080
Erythrocyte count ($10^6/\mu\text{L}$)	4.70 (4.57–4.92)	4.72 (4.26–4.90)	0.230
MCV (fL)	83.00 (80.92–85.67)	87.7 (83.4–91.12)	0.001
MCH (pg)	29.90 (27.70–29.62)	29.00 (27.77–30.60)	0.597
MPV (fL)	10.13 \pm 1.11	10.40 \pm 0.86	0.728
Platelet count ($10^3/\mu\text{L}$)	292.45 \pm 60.74	247.50 \pm 69.31	0.020
Neutrophil count ($10^3/\mu\text{L}$)	3.47 (2.90–4.00)	3.78 (2.35–4.50)	0.486
Lymphocyte count ($10^3/\mu\text{L}$)	1.95 (1.77–2.42)	2.20 (1.74–2.60)	0.563
Basophil count ($10^3/\mu\text{L}$)	0.02 (0.01–0.03)	0.04 (0.02–0.06)	0.001
Eosinophil count ($10^3/\mu\text{L}$)	0.10 (0.07–0.18)	0.13 (0.08–0.20)	0.322
Monocyte count ($10^3/\mu\text{L}$)	0.45 (0.34–0.58)	0.48 (0.34–0.59)	0.855
HALP score	4.57 (3.25–5.84)	5.27 (4.10–6.06)	0.133
NLR	1.60 (1.26–2.18)	1.63 (1.22–2.20)	0.993
PLR	134.30 (113.55–169.50)	111.26 (93.21–141.98)	0.014
LMR	4.93 (4.04–5.98)	4.81 (3.70–6.00)	0.591
PNI	54.22 \pm 2.23	53.20 \pm 4.18	0.294

CEA: Carcinoembryonic antigen; CA 15–3: Cancer antigen 15–3; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PNI: Prognostic nutrition index; HALP score: Hemoglobin, albumin, lymphocyte and platelet count score; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MPV: Mean platelet volume; SD: Standard deviation; IQR: Interquartile range

$p < 0.001$), there was a strong negative correlation between NLR and LMR ($r = -0.490$, $p < 0.001$). There was also a weak negative correlation between NLR and PNI ($r = -0.357$, $p < 0.001$). There was a weak negative correlation between PLR and LMR ($r = -0.312$, $p = 0.045$) (Table 2).

In the ROC analysis PLR, CEA and CA 15–3 were significant predictors of early BC diagnosis ($p = 0.009$, $p = 0.017$, $p < 0.001$, respectively). HALP score, LMR, NLR, and PNI were not significant predictors of early BC diagnosis ($p > 0.05$) (Table 3 and Figure 1).

Logistics regression analysis was used to investigate whether CEA, CA 15–3 and PLR were independent risk factors for BC. CEA, CA 15–3 and PLR were shown to be independent risk factors for early BC in this study (Table 4).

There were no significant baseline differences between healthy participants in group I and group II in terms of NLR, LMR, PNI, and HALP score ($p > 0.05$). However, the PLR value significantly decreased in group II compared to group I ($p = 0.014$). Comparative data and p -values for the differences between other parameters are displayed in Figure 2.

Discussion and Conclusion

The present study set out to investigate the diagnostic potential of hematological markers of inflammation, including NLR, PLR, LMR, PNI, and HALP score with classical routine markers, CEA and CA 15–3, in patients with newly diagnosed with BC. The key finding was that PLR was significantly decreased in the newly diagnosed BC group, a result not previously reported. To the best of our knowledge, no other study has assessed the diagnostic value of NLR, PLR, LMR, PNI, and HALP scores together in newly diagnosed BC patients, making this the first study to evaluate these hematological parameters at the time of diagnosis.

Biomarkers may help in the early detection and earlier initiation of treatment in BC, but no current tumor marker can precisely predict the diagnosis or onset of the disease due to various factors that influence their levels, thereby affecting their sensitivity and specificity (21). Therefore, research has focused on finding easily accessible, minimally invasive, and reliable markers to complement existing diagnostic markers (7).

In the past years, the HALP score has been identified as a novel prognostic biomarker for predicting survival outcomes in various

Table 2. Correlation analysis results

Parameters	Group I (healthy participants)		Group II (breast cancer patients)	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
HALP score vs. NLR	-0.392	<0.001	-0.603	<0.001
HALP score vs. PLR	-0.851	<0.001	-0.956	<0.001
HALP score vs. LMR	0.440	0.004	0.317	0.041
NLR vs. PLR	-0.632	<0.001	0.584	<0.001
NLR vs. LMR	0.260	0.453	-0.490	<0.001
NLR vs. PNI	-0.161	0.382	-0.357	<0.001
PLR vs. LMR	-0.285	0.661	-0.312	0.045

HALP score: Hemoglobin, albumin, lymphocyte and platelet count score; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PNI: Prognostic nutrition index

Table 3. ROC analysis results for CEA, CA 15–3, PLR, NLR, HALP score, LMR and PNI

Parameters	AUC	Optimal cut-off point	<i>p</i> -value	95% confidence interval	Sensitivity (%)	Specificity (%)
CEA ng/mL	0.651	>1.38	0.017	0.5306 to 0.7710	66.67	64.29
CA 15–3 ng/mL	0.769	>15.60	<0.001	0.6673 to 0.8707	71.43	69.05
PLR	0.665	<124	0.009	0.5480 to 0.7819	61.90	64.29
NLR	0.510	>1.651	0.874	0.3853 to 0.6346	47.62	51.16
PNI	0.555	<54.12	0.381	0.4306 to 0.6805	50.00	52.38
HALP score	0.596	>5.079	0.131	0.4716 to 0.7200	59.52	61.90
LMR	0.545	<4.835	0.474	0.4208 to 0.6699	52.38	54.76

CEA: Carcinoembryonic antigen; CA 15–3: Cancer antigen 15–3; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PNI: Prognostic nutrition index; HALP score: Hemoglobin, albumin, lymphocyte and platelet count score; ROC: Receiver operating characteristic; AUC: Area under the curve

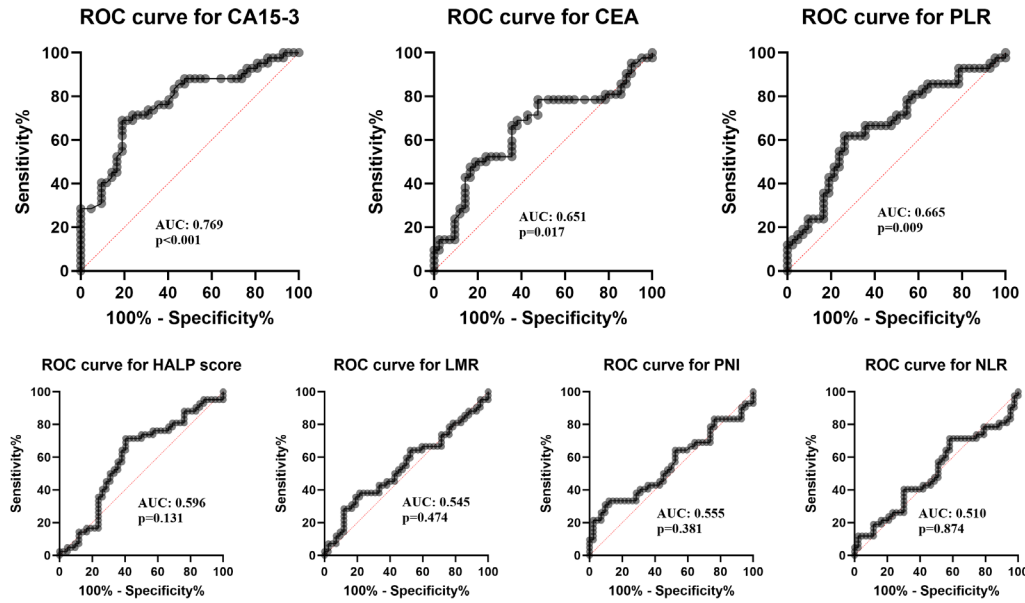


Figure 1. ROC curves of CEA, CA 15–3, PLR, NLR, HALP score LMR and PNI in detecting breast cancer

CEA: Carcinoembryonic antigen; CA 15–3: Cancer antigen 15–3; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PNI: Prognostic nutrition index; HALP score: Hemoglobin, albumin, lymphocyte and platelet count; ROC: Receiver operating characteristic curve

Table 4. Logistics regression analysis results for CEA, CA 15–3 and PLR

Parameters	Beta	OR	95% lower	95% upper	p-value
CEA ng/mL	0.424	1.529	1.090	2.137	0.006*
CA 15–3 ng/mL	0.160	1.174	1.085	1.290	<0.001*
PLR	-0.012	0.987	0.976	0.998	0.019*

CEA: Carcinoembryonic antigen; CA 15–3: Cancer antigen 15–3; PLR: Platelet-to-lymphocyte ratio; OR: Odds ratio

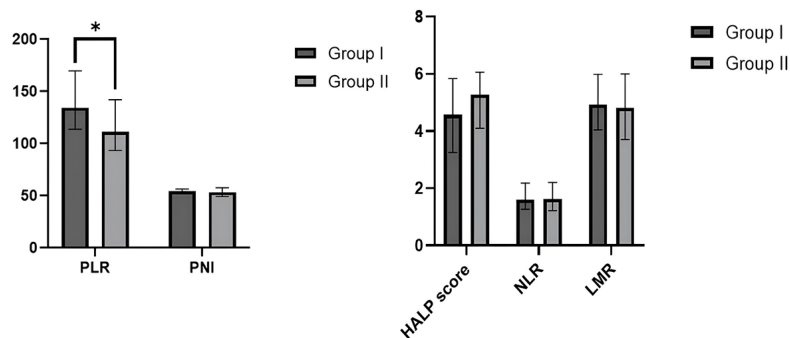


Figure 2. Comparative graphs of the results of all parameters ($p<0.05$)

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PNI: Prognostic nutrition index; HALP score: Hemoglobin, albumin, lymphocyte and platelet count; *: is represent $p<0.05$

cancers (22, 23). These parameters provide a comprehensive view of a patient's immuno-nutritional status, which is very important for cancer patients due to increased metabolic demands and risks of chronic conditions such as cachexia (10, 22). Although the HALP score has gained recognition in the scientific literature, it has not yet been widely implemented in clinical settings.

A large meta-analysis showed that lower pre-treatment HALP scores were linked to poorer outcomes in cancer patients, suggesting its potential as a prognostic tool (22). Another meta-analysis indicated that decreased HALP scores were associated with poor survival outcomes, supporting its role as a prognostic biomarker in some cancers (24). Studies in patients with metastatic bladder and kidney cancers have shown that higher HALP scores are linked to better

survival, further highlighting its prognostic value (23, 25). In gastric adenocarcinoma, higher HALP scores correlated with improved survival (26), and in tongue squamous cell carcinoma, it was an independent predictor of prognosis (27). Similarly, it has been used as a prognostic marker in lung cancer patients (10).

While prognostic findings for other cancers align with these outcomes, studies in BC patients show that the HALP score serves as an independent prognostic indicator for early-stage BC and is linked to a lower recurrence-free survival rate. It has been suggested that this score can predict tumor recurrence or metastasis before and after surgery (28). Further studies noted that late-stage BC patients had significantly lower HALP scores compared to those with early-stage disease (29). Nevertheless, the study conducted by Alandağ et al. (30) showed that HALP score had no prognostic value in early-stage triple-negative BC subtype. In a diagnostic study involving prostate cancer, although the HALP score was not found to be diagnostic, it was noted that further validation is needed through multicenter studies (31).

For BC diagnosis, low HALP scores were correlated with aggressive tumor characteristics, including advanced tumor stage and axillary lymph node positivity, though the score by itself was not sufficient to accurately predict axillary lymph node involvement (32). The present study found that HALP scores were higher in newly diagnosed BC patients than in healthy controls, but this increase was not significant. In addition, we observed a strong negative correlation between PLR and HALP scores within the BC group, suggesting a need for further diagnostic validation of the HALP score in newly diagnosed BC patients. Furthermore, we found that PLR values were lower in newly diagnosed BC patients compared to healthy participants in our study. The results of a study reported that low PLR values in BC patients receiving neoadjuvant treatment were associated with high chemotherapy sensitivity (33). Platelets are rich in growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta, and platelet-derived endothelial cell growth factor. Cancer cells often produce these PDGFs in abundance, playing a significant role in promoting tumor growth and influencing cancer histology. Lymphocytes play a crucial role in mounting the immune response against tumors (34). The decrease in PLR values in newly diagnosed BC patients in the present study is quite interesting because studies generally emphasize that there is thrombocytosis at the beginning of cancer. However, thrombocytosis occurs variably in 10% to 57% of cancer patients (34).

Existing studies on PNI, PLR, NLR, and LMR in BC patients have primarily focused on prognosis (24-36). Research on these parameters in BC has highlighted PLR as a significant marker of systemic inflammation, with preoperative PLR levels potentially outperforming other inflammatory markers in predicting clinical outcomes (36). A retrospective study also indicated that PLR and NLR may be linked to age at BC diagnosis, though more research is needed to fully understand their prognostic implications (35). Further findings suggest that NLR and PLR increase with advancing tumor stage, while LMR decreases, emphasizing their potential utility in staging BC (19). A low LMR has been associated with poor prognosis in BC, while NLR and PLR were not predictors of disease-free survival, though elevated levels were related to tumor size, recurrence and metastasis (37). From a diagnostic perspective, these markers have shown potential in bladder

cancer, where high NLR and PLR and low LMR and PNI were linked to invasive disease risk (38).

In the current study, the median values of HALP score, NLR, PNI, and LMR in group II did not differ significantly from those in group I, but PLR was significantly lower. ROC analysis showed significance for PLR and its sensitivity and specificity in detecting BC were moderate but better than the other biomarkers analyzed (except for CEA and CA15-3). At the same time, logistic regression analysis showed that PLR may be an independent risk factor for BC diagnosis. The significant difference between the groups and the fact that PLR has almost as good sensitivity and specificity as CEA and CA15-3 in the diagnosis of BC may suggest that PLR may be a potential biomarker in the diagnosis of BC. Despite the focus on prognostic evaluation in both BC and other cancers, the diagnostic relationship between the HALP score and systemic inflammatory markers, PNI, PLR, NLR, and LMR, remains unclear. This study is the first to assess these markers together in a diagnostic context, and we believe our findings may offer new insights not only for BC but also for other cancers.

Study Limitations

The current study has some limitations, including a small, region-specific population, which may limit the generalizability of our findings. Furthermore, as our study included newly diagnosed BC patients, we were unable to access certain pathological data (e.g., tumor size, grade, subtype), preventing a comprehensive evaluation of these prognostic markers.

HALP score may not be a viable diagnostic marker for BC, but decreased PLR levels may serve as a promising adjunct diagnostic marker for BC. Since PLR is derived from a simple, accessible, and inexpensive hemogram test, it offers significant advantages in BC diagnosis. However, PLR alone should not be used as a diagnostic tool for BC as changes in PLR and the cell numbers used to calculate may occur for many reasons, reducing its specificity. Therefore, further large-scale studies are needed to validate our findings.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Nigde Omer Halisdemir University Faculty of Medicine Non-Interventional Ethics Committee (protocol number: 2023/81, date: 10.11.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.S.; Concept: D.A., H.S., F.Y.; Design: D.A., E.B., U.K.; Data Collection or Processing: D.A., E.B., H.S., F.Y.; Analysis or Interpretation: D.A., H.S., U.K.; Literature Search: D.A., E.B., U.K., F.Y.; Writing: D.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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