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PROGNOSTIC SIGNIFICANT OF NEUTROPHIL: LYMPHOCYTE RATIO, PLATELET: LYMPHOCYTE RATIO, AND LYMPHOCYTE: MONOCYTE RATIO IN KURDISH PATIENTS WITH BREAST CANCER

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Abstract – *Objective:* *The purpose of this study was to investigate the prognostic impact of neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (dNLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR) on breast cancer given overall survival.*

Patients and Methods: *We retrospectively evaluated patients diagnosed with primary breast cancer from 2004 to 2020. The association between NLR, dNLR, LMR, and PLR and overall survival (OS) was analyzed.*

Results: *The one-year, three-year, five-year, and ten-year OS were 96%, 83%, 78%, 71%, and 63%, respectively. The parameters associated with patients with breast cancer included lymph node involvement, distant metastasis, and staging. We evaluated the baseline characteristics of the patients, according to the PLR, NLR, dNLR, and LMR, and found no significant differences.*

Conclusions: *Serum inflammatory indicators such as neutrophil, lymphocyte, as well as NLR dNLR, LMR, and PLR, were shown to have no significant influence on prognosis in patients with breast cancer. Prospective research with a larger population of patients will provide more reliable results.*

KEYWORDS: *Breast cancer, Prognosis, Neutrophil-to-lymphocyte ratio, NLR, Platelet to lymphocyte ratio, PLR, Lymphocyte-to-monocyte ratio, LMR.*

INTRODUCTION

Breast cancer is the most prevalent cancer among females, and its prevalence has risen dramatically in recent years. This is a heterogeneous disorder with different health effects and has specific genetic subtypes. One in eight women will have a breast cancer diagnosis in their lifetime[1]; 5-7% of women are diagnosed before 40 years; the incidence of the disease occurs mostly in the 25-39 age group[2,3]. Annually, there are about 1 million new breast cancer cases around the world, and the age of diagnosis appears to be high[4].

Due to the diagnosis variability and a wide range of treatments, a significant percentage of women still suffer from breast cancer. The factors that lead to breast cancer, invasion, and metastasis are prime; furthermore, identifying successful biomarkers that are helpful in diagnosis, prognosis, and treatment follow-up, is essential.

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The inflammatory response has been shown to play a significant role in the production and growth of different cancers, including breast cancer [5]. It is also generally accepted that results of cancer cases are only determined on their own by tumor features, but patient-related variables are often important factors. The inflammatory reaction includes systemic alterations induced by circulating cytokines and chemokines, such as an increase in neutrophil production or a small increase in platelet count[6]. The inflammatory response to cancer allows the growth and reproduction of malignant cells, angiogenesis, and breast cancer metastasis; moreover, subverts adaptive immune responses alter the reaction to chemotherapeutic agents [7]. According to recent epidemiological and clinical research, inflammatory reactions are correlated with breast tumors[8].

Serious inflammatory reactions lead to a weaker adaptive immune response, which along with immune deficiency and malignancy, contribute to the growth of cancer and impair overall survival. The existence of an elevated peripheral neutrophil-to-lymphocyte (NLR) ratio, an indicator of systemic inflammation in different cancers, was recognized as a poor prognostic factor[9]. In addition, inflammation also influences immune monitoring and therapy responses[10]. Many immunological and histological markers are directly linked to the prognosis of breast cancer, but achieving such indicators is time-consuming, laborious, and comparatively costly, greatly reducing their clinical use. Breast cancer's short- and long-term prognosis depends on patient age, tumor size, hormonal receptors, histological traits, human epidermal growth factor receptor 2 (HER2) status, and biological factors such as grade and receptor status.

The behavior of breast cancer is unpredictable so even in patients with the same classic prognostic factors, completely different clinical results are obtained [11]. However, many patients with a variety of features/markers may experience specific clinical outcomes. Biomarkers such as lymphocytes, neutrophils, neutrophil-lymphocyte ratio (NLR), red cell distribution distance, mean platelet distribution width (PDW), circulating tumor cells, and gamma-glutamyl transferase have been suggested as possible cancer prognostic factors[6, 12-14].

Evidence of NLR association with survival of patients with several forms of cancer, including breast cancer, is rising[15,16]. The published findings, however, are contradictory; some studies have documented significant associations of NLR with shorter DFS and OS in breast cancer patients[15,17]; nevertheless, other studies have demonstrated that NLR cannot be considered an independent prognosis factor for breast cancer[18,19]. An elevated PLR in breast cancer has been shown to adversely impact survival in a few studies[20,21]. In some cancers, such as head and neck tumors, bladder cancer, and soft tissue sarcoma, LMR has been confirmed as a prognostic marker[22,23]. This research aimed to assess the impact of peripheral blood NLR, dNLR, LMR, and PLR on OS and disease-free survival (DFS) in adult women with breast cancer.

PATIENTS AND METHODS

In a retrospective study that was conducted at Imam Reza Hospital, Kermanshah, Iran (2004-2020), 198 females with breast cancer were included. Clinical files were assessed; demographic records and pathological findings (including laboratory data, tumor size, lymph node status, HER2, and hormonal profile) were collected for each patient.

Estrogen receptor (ER), progesterone receptor (PR), and the amount of HER2 receptor protein were determined by immunohistochemistry (IHC). Levels of ER and PR expression were scored with the Allred method[24]; an Allred score ≥ 3 was regarded as positive. HER2 status was scored positive if the IHC result was 3+ and was scored negative if the result of staining was 0 or 1+. Cases with equivocal HER2 status 2+ for validation were candidates for fluorescence *in-situ* hybridization or silver *in-situ* hybridization. The status of the estrogen receptor (ER) and the progesterone receptor (PR) was characterized by IHC, and a value of $\geq$10% was considered positive. HER2 status was determined by *in situ* fluorescent hybridizations (FISH) or IHC.

The following parameters were used to determine the molecular subtype: luminal A, ER-positive and/or PR-positive and HER2-negative; luminal B, ER-positive and/or PR-positive and HER2-positive; enhanced HER2, ER- and PR-negative with positive HER2; and triple-negative, ER-negative, PR negative, and HER2-negative.

Complete blood count (CBC) tests data were collected a week before surgery. The NLR was defined as the absolute count of neutrophils divided by the absolute count of lymphocytes. The ratio of derived neutrophils to lymphocytes (dNLR) was determined as the absolute count of neutrophils divided by the derived count of lymphocytes. PLR was considered the absolute count of platelets divided by the absolute count of lymphocytes.

The LMR was defined as the absolute count of lymphocytes divided by the absolute count of the monocytes.

Exclusion

Patients with hematologic disorders, cerebrovascular disease, heart failure, any inflammatory signs or conditions, coronary artery disease, end-stage renal disease, peripheral arterial disease, or a lack of information about pathologic or laboratory data were excluded.

Follow up

Women underwent follow-up investigations for 12-156 months following breast cancer surgery.

Statistical analysis

The statistical analysis was performed using the SPSS software (IBM Corporation, Armonk, NY, USA). Overall survival (OS) was calculated from the operation date to the date of death. The 25th, 50th, and 75th percentiles were used to divide patients into equal quartiles (i.e., the 4th or highest NLR quartile contained patients with the uppermost 25% NLR values). Means and standard deviations, as well as frequencies and percentages, were used to represent the continuous and categorical variable distributions, respectively. The chi-square test was used to analyze the relationship between each categorical variable and quartiles. The association between each variable (including NLR quartiles) and survival was investigated by the Kaplan Meier test. To analyze the combined effects of those factors, a Cox proportional hazards model was used to incorporate those variables that were associated with survival. A *p*-value of less than 0.05 was considered significant.

RESULTS

The age range of the 198 women was 20 to 83 years, with a mean age of 47.29±46 years. The follow-up time ranged from 12 to156 months, and the median follow-up time was 108 months. Baseline characteristics of the breast cancer patients according to their overall survival are given in Table 1.

Lymphoma node metastasis was detected in 41.3% of the patients. The median levels of NLR, PLR, LMR, and dNLR were 1.92 (0.1–11.86), 136.91 (1.20-958.02), 4.08 (0.5– 42.17), and 1.5 (0.04–7.20), respectively.

At the initial diagnosis, 37.7% of the patients presented with stage 0-1 breast cancer, followed by 5% with stage 2a, and 57.9% with stage 2b-4. The 1-year, 3-year, 5-year, and 10-year OS were 96%, 83%, 78%, 71% and 63%, respectively.

The inflammatory markers and clinicopathologic characteristics were evaluated for univariate survival analysis. The parameters associated with the OS of patients with breast cancer included lymph node involvement, distant metastasis, and staging (Table 1, Figure 1). None of the inflammatory markers were associated with prognosis (Table 1). Also, there was no significant relationship between PLR quartiles (Table 2), NLR quartiles (Table 3), dNLR quartiles (Table 4), LMR quartiles (Table 5), and clinicopathological characteristics.

In the Cox model, due to the alignment between the staging and distant metastasis, only the distant metastasis and lymph node involvement were entered. In this model, variables of distant metastasis (HR = 39.245, 95% CI; 12.508-123.131) and lymph node involvement (HR =4.146 95% CI; 1.372-12.52) were significant (Table 6).

DISCUSSION

The findings of this study revealed that distant metastasis, lymph node involvement, and staging, were the most critical variables affecting the survival of breast cancer patients. A previous study reported that breast cancer patients with a 5-year overall survival rate were based on menopausal status, tumor size, and axillary lymph node metastases[16].

According to some studies in Iran, the median age at the time of diagnosis is 45 to 50 years old which is in agreement with the results of the current study[25]. However, these findings contradict the results reported in Western Europe and North America[26, 27]. One of the reasons for the discrepancy in these results is probably the late diagnosis of cancer in Iran[25, 28].

This research showed that a greater percentage of positive axillary lymph nodes raised the risk of death associated with breast cancer. According to Kim et al [29] axillary lymph node metastasis is the most important prognostic factor determining local regulation, disease-free survival, and overall survival. Similar to Macià et al[30] and Moraes et al [31] findings, our study confirmed that one of the most important determinants of survival in breast cancer patients is the stage of cancer, and late-stage diagnosis is associated with reduced overall survival.

TABLE 1. Baseline characteristics of the breast cancer patients according to their overall survival.

Variable	N (%)	Mean±SE OS (Month)	p
Age			
≤50	133 (67.2%)	120. 35±5.67	0.177
>50	65 (32.8%)	106..15±9.06	
Menopause			
Premenopause	132 (67%)	119.98± 5.72	0.190
Postmenopause	65 (33%)	106.15± 9.60	
Lymph node involvement			
Yes	94 (58.8%)	107.42± 7.89	0.001
No	66 (41.3%)	145.13± 4.29	
Distant metastasis			
Yes	56 (28.7%)	50.86± 5.61	0.000
No	139 (71.3%)	150.36± 2.8	
OCP before menopause			
Yes	134 (68.4%)	119.20± 5.90	0.674
No	62 (31.6%)	113.63± 8.89	
FH Family History			
Yes	105 (53.8%)	119.25± 6.77	0.529
No	90 (45.5%)	113.90± 7.24	
Size of tumor			
2 or less than 2	40 (23.5%)	121.09± 12.17	0.385
More than 2	130 (76.5%)	114.47± 6.22	
Stage			
0-1	59 (37.1%)	148.54± 4.18	0.000
2a	8 (5%)	129± 2.59	
2b-4	92 (57.9%)	92.09± 7.96	
Histology			
Ductal in situ	4 (2%)	120± 19.59	0.669
Ductal invasive	190 (96.4%)	115.92± 5.14	
Other types		80± 14.23	
Type of breast			
Luminar A	58 (29.6%)	122± 8.79	0.666
Luminar B	95 (48.5%)	106.304± 6.81	
Her2overexpressed	23 (11.7%)	104± 14.17	
Platelet ($x10^3\ \mu l^{-1}$)			
Platelet ≤275	114 (57.6%)	121±6.09	0.263
Platelet >275	84 (42.4%)	107.76±8.25	
Neutrophil ($x10^3\ \mu l^{-1}$)			
Neutrophil≤ 4.54	110 (55.8%)	120.35±6.4	
Neutrophil>4.54	87 (44.2%)	110.48±7.72	
NLR			
NLR<1.44	48 (24.4%)	106.75± 11.13	0.696
1.44 ≤NLR≥1.92	49 (24.9%)	115.85± 9.02	
1.92≤NLR≥2.55	51 (25.8%)	117.37± 7.93	
NLR >2.55	49 (24.9%)	113.09± 10.59	
dNLR			
dNLR<1.19	48 (24.4%)	109.28± 11.24	0.834
1.19 ≤dNLR≥1.50	50 (25.4%)	112.24± 9.30	
1.50 ≤dNLR≥1.95	49 (24.9%)	122.91± 9.00	
dNLR >1.95	50 (25.4%)	117.52± 10.26	
PLR			
PLR<97	47 (23.9%)	114.36± 9.36	0.327
97 ≤PLR<121	51 (25.9%)	123.12± 9.60	
121≤PLR<155	47 (23.9%)	126± 9.89	
PLR≥155	52 (26.4)%	95.21± 9.33	
LMR			
LMR <3.3	47 (24.2%)	108.98± 10.87	0.942
3.3 ≤LMR <4.08	50 (25.8%)	109.33± 8.494	
4.08≤LMR <5.43	49 (25.3%)	115.88± 9.92	
LMR ≥ 5.43	48 (24.7%)	117.93± 10.035	

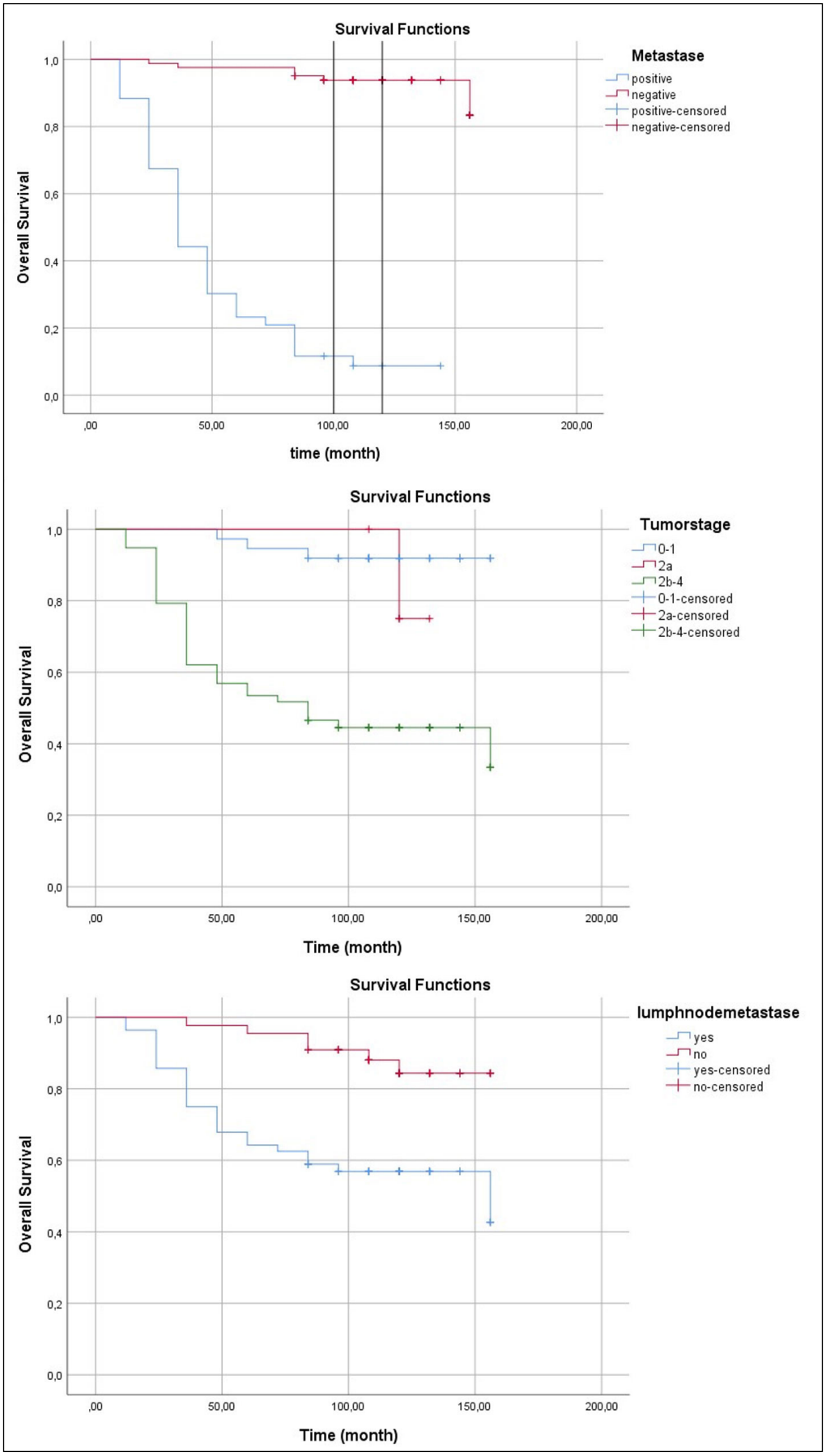

Fig. 1. Kaplan–Meier survival curves stratified by distant metastasis, lymph node involvement and staging.

TABLE 2. Baseline characteristics of the breast cancer patients according to their PLR quartile.

Characteristics	*Overall*	*PLR quatile 2 PLR<97*	*PLR quartile 2 97 ≤PLR<121*	*PLR quartile 3 121≤PLR<155*	*PLR quartile 4 PLR≥155*	*p*
Total						
Number of deaths		20 (24.7%)	21 (25.9%)	21 (25.9%)	19 (23.5%)	0.491
Age in years						
<50	133	23 (17.3%)	37 (27.8%)	33 (24.8%)	40 (30.1%)	0.178
>50	64	24 (37.5%)	14 (21.9%)	14 (21.9%)	12 (18.8%)	0.139
Lymph node involvement						
Yes	94	23 (24.5%)	22 (23.4%)	23 (24.5%)	26 (27.7%)	0.961
No	65	15 (23.1%)	19 (29.2%)	16 (24.6%)	15 (23.1%)	0.892
Lymph node number						
≤4	51	9 (17.6%)	9 (17.6%)	13 (25.5%)	20 (39.2%)	0.09
5-9	22	9 (40.9%)	5 (22.7%)	4 (18.2%)	4 (18.2%)	0.453
≥10	15	4 (26.7%)	7 (46.7%)	3 (20%)	1 (6.7%)	0.191
Organ metastasis						
Yes	56	11 (19.6%)	18 (32.1%)	9 (16.1%)	18 (32.1%)	0.208
No	138	34 (24.6%)	33 (23.9%)	38 (27.5%)	33 (23.9%)	0.936
OCP before menopause						
Yes	133	29 (21.8%)	38 (28.6%)	32 (24.1%)	34 (25.6%)	0.748
No	62	18 (29%)	12 (19.4%)	15 (24.2%)	17 (27.4%)	0.734
Family History	105	26 (24.8%)	32 (30.5%)	24 (22.9%)	23 (21.9%)	0.614
Side of tumor						
Left	89	18 (20.2%)	28 (31.5%)	25 (28.1%)	18 (20.2%)	0.33
Right	97	26 (26.8%)	19 (19.6%)	19 (19.6%)	33 (34%)	0.137
Size of tumor						
2 or less than 2	40	11 (27.5%)	12 (30%)	6 (15%)	11 (27.5%)	0.556
More than 2	129	32 (24.8%)	29 (22.5%)	37 (28.7%)	31 (24%)	0.787
Stage						
0-1	59	14 (23.7%)	15 (25.4%)	15 (25.4%)	15 (25.4%)	0.9
2a	8	4 (50%)	2 (25%)	2 (25%)	0 ()%)	0.74
2b-4	91	21 (23.1%)	21 (23.1%)	21 (23.1%)	28 (30.8%)	0.664
Histology						
Ductal *in situ*	4	1 (25%)	1 (25%)	1 (25%)	1 (25%)	0.9
Ductal invasive	189	45 (23.8%)	50 (26.5%)	45 (23.8%)	49 (25.9%)	0.93
Type of cancer						
Luminal A	58	17 (29.3%)	18 (31%)	13 (22.4%)	10 (17.2%)	0.456
Luminal B	94	21 (22.3%)	23 (24.5%)	23 (24.5%)	27 (28.7%)	0.856
Her 2 over expressed	23	4 (17.4%)	8 (34.8%)	4 (17.4%)	7 (30.4%)	0.586
Triple negative	20	5 (25%)	2 (10%)	7 (35%)	6 (30%)	0.5
Menopause						
Pre menopause		22 (16.7%)	37 (28%)	33 (25%)	40 (30%)	0.131
Post menopause		24 (37.5%)	14 (21.9%)	14 (21.9%)	12 (18.8%)	0.139

Our findings established that in breast cancer patients NLR, dNLR, PLR, and LMR parameters are not associated with overall survival, instead, the inflammation has a role in the progression of tumorigenesis [34]. Peripheral blood tests performed before therapy or at the time of diagnosis may reveal inflammatory conditions in the tumor. Absolute white blood cell count, C-reactive protein (CRP), cytokines, platelet-to-lymphocyte ratio (PLR), and NLR are associated with distinct outcomes in cancer patients [7,32]. Previous research found a relationship between inflammatory markers (including peripheral neutrophil, lymphocyte, and platelet numbers) and poor outcomes in breast cancer and other malignancies. With an unknown mechanism, pretreatment to increase peripheral blood neutrophil and platelet counts has been related to low survival in patients with a variety of malignancies [33-35]. Circulating platelets and serum vascular endothelial growth factor (VGEF) levels have been found to have a direct relationship, and platelets can promote tumor development by stimulating angiogenesis through the VGEF [33, 36]. Also, in our research, patients with greater neutrophil and platelet counts had a worse survival rate, although the difference was not statistically significant.

NLR is a biomarker for inflammation that may be evaluated more quickly and simply than traditional markers at a reasonable cost. High preoperative NLR has been related to a poor prog-

TABLE 3. Baseline characteristics of the breast cancer patients according to their NLR quartile.

Characteristics	*Overall*	*NLR quartile 1 (NLR<1.44)*	*NLR quartile 2 1.44 ≤NLR≥1.92*	*NLR quartile 3 1.92≤NLR≥2.55*	*NLR quartile 4 NLR >2.55*	*p*
Number of deaths		12 (25%)	13 (27%)	9 (19%)	13 (27%)	0.836
Age in years						
Lymph node involvement						
Yes	94	22 (23%)	19 (20%)	26 (27%)	27 (28%)	0.657
No	65	18 (27%)	21 (32%)	16 (24%)	10 (25%)	0.264
Lymph node number						
≤4	51	8 (15%)	10 (19%)	16 (31%)	17 (33%)	0.206
5-9	22	8 (36%)	5 (22%)	3 (13%)	6 (27%)	0.526
≥10	15	5 (33%)	4 (26%)	4 (26%)	2 (13%)	0.800
Organ metastasis						
Yes	56	15 (26%)	11 (19%)	13 (23%)	17 (30%)	0.69
No	138	33 (23%)	36 (26.1%)	38 (27%)	31 (22%)	0.85
OCP before menopause						
Yes	133	15 (26.8%)	11 (19.6%)	13 (23.2%)	17 (30.4%)	0.714
No	62	33 (23.9%)	36 (26.1%)	38 (27.5%)	31 (22.5%)	0.853
Family History	105	25 (23.8%)	26 (24.8%)	35 (33.3%)	19 (18.1%)	0.177
Side of tumor						
Left	90	20 (22.5%)	22 (24.7%)	26 (29.2%)	21 (23.6%)	0.833
Right	97	22 (22.7%)	25 (25.8%)	23 (23.7%)	27 (27.8%)	0.907
Size of tumor						
2 or less than 2	40	10 (25%)	12 (30%)	9 (22.5%)	9 (22.5%)	0.934
More than 2	129	29 (22.5%)	30 (23.3%)	36 (27.9%)	34 (26.4%)	0.812
Stage						
0-1	59	15 (25.4%)	19 (32.2%)	16 (27.1%)	9 (15.3%)	0.319
2a	8	2 (25%)	3 (37.5%)	3 (37.5%)	0	0.882
2b-4	91	21 (23%)	18 (19.8%)	23 (25.3%)	29 (31.9%)	0.418
Histology						
Ductal in situ	4	0 (0%)	1 (25%)	2 (50%)	1 (25%)	p>0.005
Ductal invasive	189	48 (25.4%)	47 (24.9%)	47 (24.9%)	47 (24.9%)	p>0.005
Type of cancer						
Luminal A	58	17 (29.3%)	15 (25.9%)	14 (24.1%)	12 (20.7%)	0.83
Luminal B	94	20 (21.3%)	25 (26.6%)	22 (23. 4%)	27 (28.7%)	0.765
Her 2 over expressed	23	8 (34.8%)	4 (17.4%)	7 (30.4%)	4 (17.4%)	0.586
Triple negative	20	3 (15%)	5 (25%)	8 (40%)	4 (20%)	0.5
Menopause						
Pre menopause	132	25 (18.9%)	30 (22.7%)	40 (30.3%)	37 (28%)	0.245
Post menopause	64	23 (35.9%)	19 (29.7%)	11 (17.2%)	11 (17.2%)	0.08

nosis in breast cancer patients[19]. The cutoff value of NLR is a variety among ethnic origins. Azab et al [37] reported that the NLR cutoff value of 3.3 has a predictive significance in breast cancer. Our NLR cutoff value was lower than this result (2.22) which may be due to the fewer neutrophil counts in the Asian race, so the number of lymphocytes considers a prognostic factor [38]. In a study on 1527 breast cancer patients by Dirican et al [17] high NLR (NLR 4) was taken as an independent predictor factor of both DFS and OS. They reported that lymph node involvement, tumor size, HER2 positivity, distant metastasis, and high staging are related to high NLR, whereas ER and PR positivity are associated with low NLR. Templeton et al [35] published a meta-analysis comprising three original papers and reported no significant link between NLR and breast cancer survival; this result was according to our findings in this regard [32]. Ulas et al[39] also demonstrated that for NLR and PLR no significant effect.

The lymphocytes, as one of the most essential components of the immune system, affect the growth of tumors. Tumor-infiltrating lymphocytes in various malignancies (such as melanoma, colorectal cancer, and ovarian cancer) infiltrate tumor mass, reduce tumor recurrence, and improve prognosis [40, 41]. Platelets play an important role in cancer development, promoting tumor growth through cytokine-mediated angiogenesis [42]. White blood cells and platelets travel to the affected area via the venous system when tissue damage occurs. Platelet-derived growth factors (PDGF), Platelet factor 4 (PF4), TGF- (Trans-

TABLE 4. Baseline characteristics of the breast cancer patients according to their dNLR quartile.

Characteristics	*Overall*	*dNLR quartile 1 (NLR<1.19)*	*dNLR quartile 2 1.19 ≤NLR≥1.50*	*dNLR quartile 3 1.50 ≤NLR≥1.95*	*dNLR quartile 4 NLR >1.95*	*p*
Number of deaths		12 (25%)	13 (27%)	9 (19%)	13 (27%)	0.836
Age in years						
<50	133	26 (19.5%)	32 (24.1%)	36 (27.1%)	39 (29.3%)	0.418
>50	64	22 (34.4%)	18 (28.1%)	13 (20.3%)	11 (17.2%)	0.210
Lymph node involvement						
Yes	94	21 (22.3%)	25 (26.6%)	20 (21.3%)	28 (29.8%)	0.657
No	65	18 (27.7%)	18 (27.7%)	17 (26.2%)	12 (18.5%)	0.696
Side of tumor						
Left	90	19 (21.3%)	23 (25.8%)	26 (29.2%)	21 (23.6%)	0.763
Right	97	23 (23.7%)	26 (26.8%)	20 (20.6%)	28 (28.9%)	0.686
Organ metastasis						
Yes	56	13 (23.2%)	15 (26.8%)	12 (21.4%)	16 (28.6%)	0.891
No	138	35 (25.4%)	33 (23.9%)	37 (26.8%)	33 (23.9%)	0.961
OCP before menopause						
Yes	133	31 (23.3%)	36 (21.7%)	33 (24.8%)	33 (24.8%)	0.952
No	62	17 (27.4%)	14 (22.6%)	15 (24.2%)	16 (25.8%)	0.973
Family History	105	26 (24.8%)	29 (27.6%)	28 (26.7%)	22 (21%)	0.786
Size of tumor						
2 or less than 2	40	10 (25%)	11 (27.5%)	11 (27.5%)	8 (20%)	0.934
More than 2	120	30 (23.3%)	33 (25.6%)	30 (23.3%)	36 (27.9%)	0.867
Stage						
0-1	59	15 (25.4%)	16 (27.1%)	17 (28.8%)	11 (18.6%)	0.727
2a	8	2 (25%)	3 (37.5%)	3 (37.5%)	0 (0%)	0.9
2b-4	90	20 (22%)	23 (25.3%)	18 (19.8%)	30 (33%)	0.3
Histology						
Ductal *in situ*	4	0 (0%)	1 (25%)	3 (75%)	0 (0%)	0.625
Ductal invasive	189	48 (25.4%)	49 (25.9%)	43 (22. 8%)	49 (25.9%)	0.919
Type of cancer						
Luminal A	58	17 (29.3%)	17 (29.3%)	10 (17.2%)	14 (24.1%)	0.540
Luminal B	94	19 (20.2%)	27 (28.7%)	23 (24.5%)	25 (26..6%)	0.695
Her 2 over expressed	23	9 (39.1%)	2 (8.7%)	6 (26.1%)	6 (26.1%)	0.253
Triple negative	20	3 (15%)	4 (20%)	10 (50%)	3 (15%)	0.08
Menopause						
Pre menopause	132	26 (19.7%)	32 (24.2%)	36 (27.3%)	38 (28.8%)	0.479
Post menopause	64	22 (34.4%)	18 (28.1%)	13 (20.3%)	11 (17.2%)	0.210

forming growth factor), and vascular endothelial growth factor (VEGF), are all secreted by thrombocytes [43, 44]. The VEGF can help platelets enhance tumor growth by helping to promote angiogenesis [45].

Proinflammatory cytokines such as IL-1 and IL-6 promote megakaryocyte proliferation, which results in thrombocytosis [46,47]. Thrombocytosis has been identified as an unfavorable prognostic marker in several malignancies[48,49]. In line with the results of this study, a meta-analysis review estimated the one-, two-, three-, five-, and ten-year breast cancer survival to be 95.8, 82.4, 69.5, and 58.1, respectively[50]. Furthermore, the impact of factors such as nutritional factors and blood sugar, cholesterol, and other factors on inflammation and cancer should not be neglected. Hyperglycemia, for example, has a direct influence on cancer cell proliferation, death, and metastasis. In addition, hyperglycemia has an indirect effect on cancer cells by increasing the levels of insulin/IGF-1 and inflammatory cytokines in the blood [51, 52]. High glucose levels stimulate several signaling pathways that work together to influence cancer cell activity, proliferation, migration, invasion, and recurrence [53]. Furthermore, nutraceuticals like quercetin can influence the regulation of other inflammatory mediators involved in breast cancer[54]. Generally, due to not using a national or provincial cancer registration program, determining whether the observed survival rate rose or decreased in our study is very likely. Among the limitations of the current study are its retrospective nature, a limited sample size, and a short period of follow-up in certain patients. Also, like all retrospective studies, the selection bias is not unlikely. Furthermore, patients were not evenly distributed based on clinicopathological variables, and there was little information on the relationship between these characteristics and NLR.

TABLE 5. Baseline characteristics of the breast cancer patients according to their LMR quartiles.

Characteristics	*Overall*	*LMR quartile 1 LMR <3.3*	*LMR quartile 2 3.3 ≤LMR <4.08*	*LMR quartile 3 4.08≤LMR <5.43*	*LMRquartile 4 LMR ≥ 5.43*	*p*
Number of deaths		12 (25%)	13 (27%)	9 (19%)	13 (27%)	0.836
Age in years						
<50		33 (25.8%)	36 (28.1%)	35 (27.3%)	24 (18.7%)	0.43
>50		9 (22%)	8 (19.5%)	8 (19.5%)	16 (39%)	0.237
Lymph node involvement						
Yes	93	30 (32.3%)	19 (20..4%)	26 (28%)	18 (19.4%)	0.657
No	63	6 (9.5%)	18 (28.6%)	16 (25.4%)	23 (36.5%)	0.696
Organ metastasis						
Yes	56	16 (28.6%)	14 (25%)	14 (25%)	12 (21.4%)	0.891
No	135	30 (22.2%)	35 (25.9%)	35 (25.9%)	35 (25.9%)	0.961
OCP before menopause						
Yes	130	30 (23.1%)	42 (32.3%)	30 (23.1%)	28 (21.5%)	0.952
No	62	17 (27.4%)	8 (12.9%)	17 (27.4%)	20 (32.3%)	0.973
Family History	105	26 (24.8%)	22 (21%)	33 (31.4%)	24 (22.9%)	0.786
Size of tumor						
2 or less than 2	39	4 (15.4%)	11 (28.2%)	11 (28.2%)	11 (28.2%)	0.934
More than 2	127	34 (26.8%)	33 (26%)	31 (24.4%)	29 (22.8%)	0.867
Stage						
0-1	57	6 (10.5%)	16 (28.1%)	17 (29.8%)	18 (31.6%)	0.727
2a	8	0 (0%)	2 (25%)	5 (62.5%)	1 (12.5%)	0.9
2b-4	90	31 (31.4%)	18 (20%)	22 (24.4%)	19 (21.1%)	0.3
Histology						
Ductal *in situ*	4	1 (25%)	1 (25%)	1 (25%)	1 (25%)	0.625
Ductal invasive	186	45 (24.2%)	48 (25.8%)	46 (24.7%)	47 (25.3%)	0.919
Type of cancer						
Luminal A	57	15 (26.3%)	13 (22.8%)	15 (26.3%)	14 (24.6%)	0.540
Luminal B	94	23 (24.5%)	24 (25.5%)	22 (23.4%)	25 (26..6%)	0.695
Her 2 over expressed	21	4 (19.0%)	8 (38.1%)	4 (19.0%)	5 (23.8%)	0.253
Triple negative	20	3 (15%)	5 (25%)	8 (40%)	4 (20%)	0.08
Menopause						
Pre menopause	130	34 (26.2%)	34 (26.2%)	35 (26.9%)	27 (20.8%)	0.479
Post menopause	63	13 (20.6%)	15 (23.8%)	14 (22.2%)	21 (33.3%)	0.210

TABLE 6. Multivariate Cox Regression Analysis.

Variable	*B (standard error)*	*(WALD)*	*p-value*	*HRa*	*95% CI*
Lump node involvement					
no*				1	
yes	1.422 (0.564)	6.353	0.012	4.146	(1.372- 12.52)
Distant Metastasis					
No*				1	
yes	3.670 (0.583)	39.569	0.000	39.245	12.508-123.131

CONCLUSIONS

The findings of this study demonstrate that women diagnosed with breast cancer in Iran have a lower overall survival rate of 5 and 10 years than women in other countries. The results of an analysis of factors reported in this paper show that delay in diagnosis and diagnosis in the end-stage lead to reductions in breast cancer survival in Iran. We believe this is related to a lack of information, cultural differences, and limited possible treatments.

Finally, we discovered that NLR, PLR, and LMR did not influence prognosis. It is suggested that extensive studies be conducted with a prospective approach to achieve definitive results. Also, systematic studies that include the findings of such studies can confirm the results.

Ethical approval:

The experiments used in this study were approved by the Ethics Committee of Islamic Azad University (IR.KUMs.REC.1400.702).

Informed consent:

Once the current investigation focused on retrospective data collection, no informed permission was required. Nonetheless, we acquired legal authorization from the Hospital Majors, laboratories, local, and state Health Secretariats to access databases, laboratory, and medical records.

Availability of data and material:

No additional data are available

Conflict of interests:

The authors declare no conflict of interest

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Author contribution:

The authors confirm contribution to the paper as follows: study conception and design: SH.M; data collection M.T; analysis and interpretation of results: S.KH and SH.M; draft manuscript preparation: M.T. All authors reviewed the results and approved the final version of the manuscript.

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