ORIGINAL RESEARCH

Prognostic Significance of Inflammatory Biomarkers in Patients with Breast Cancer Skeletal Metastases

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Purpose: Skeletal metastases are a common problem in breast cancer patients. Identifying new prognostic factors can improve survival estimations and guide healthcare professionals in therapeutic decision-making. Our study aimed to determine the prognostic value of inflammatory biomarkers such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and C-reactive protein/albumin ratio (CAR) in patients with breast cancer skeletal metastases.

Patients and Methods: Clinical data from 212 patients with breast cancer skeletal metastases were retrospectively analyzed. The optimal cut-off values of each inflammatory biomarker were extracted from the receiver operating characteristic (ROC) curves. Patients were divided into high-value and low-value groups according to the cut-off values of NLR, LMR, and CAR. We investigated the relationship between inflammatory biomarkers and clinicopathological characteristics. The Kaplan–Meier method was used to measure progression-free survival (PFS) and overall survival (OS). The survival difference was compared by the univariate analysis. Cox multivariate regression analysis was performed to identify independent prognostic factors.

Results: The median age of the patients was 55 years, and the median follow-up was 45 months. LMR<3.43 (P<0.0001), NLR≥2.48 (P<0.0001), and CAR≥0.34 (P=0.035) were found to be associated with worse PFS in the univariate analysis. Meanwhile, LMR<3.43 (P<0.0001), NLR≥2.48 (P<0.0001), and CAR≥0.34 (P=0.025) were linked to the poor OS. The multivariate analysis revealed that NLR≥2.48 (HR 2.044, P=0.007) and LMR<3.43 (HR 0.532, P=0.012) were independent prognostic factors for OS; LMR<3.43 (HR 0.501; P=0.006) and NLR≥2.48 (HR 1.971, P=0.011) were similarly prognosticating worse PFS. Radiotherapy to the affected bone and ER (+) was favorable for the prognosis of breast cancer skeletal metastases. The number of involved sites of bone metastases>3 was adverse for PFS.

Conclusion: LMR<3.43 and NLR≥2.48 were independently associated with worse prognosis of patients of breast cancer skeletal metastases.

Keywords: breast cancer skeletal metastases, inflammatory biomarkers, overall survival, progression-free survival, prognostic factor

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Introduction

Breast cancer is the primary cause of death in feminine malignancies.[1] Bone is the most common site of metastasis from breast cancer, and 75% of patients with late-stage breast cancer will develop bone metastasis.[2] Patients with bone metastasis generally experience skeletal-related events (SREs), such as spinal cord

compression, serious ostalgia, as well as hypercalcemia and even pathological fracture,[3] which result in reduced mobility and have a dramatic impact on the patient's quality of life inevitably.

Cancer patients present local and systemic modifications of the inflammatory response.[4] The relationship between the components of the inflammatory response and the prognosis is a research topic that has gained great attention.[5] Several inflammatory parameters have been extensively confirmed and employed by healthcare providers as prognostic indicators in various types of diseases in recent years. Duan et al[6] summarized that preoperative elevated NLR was associated with poor prognosis in breast cancer. Mandaliya et al[7] suggested that LMR was a prognostic biomarker in stage IV non-small cell lung cancer, and the prognostic role of CAR in esophageal cancer was demonstrated by Liu et al.[8]

Thio et al[9] have investigated inflammatory biomarkers in patients with skeletal metastases from several malignancies and found that NLR can serve as an independent prognostic factor. However, on account of breast cancer patients with skeletal metastases, the prognostic significance of inflammatory biomarkers has not been entirely clear. As easy and cost-effective biomarkers, NLR, LMR, and CAR may reflect the level of inflammation in the body, with the trait of non-invasive, could be measured in peripheral blood. Therefore, our study aimed to determine whether NLR, LMR, and CAR are associated with prognosis in patients with breast cancer skeletal metastases, and to carry out a novel investigation into the utility of inflammatory these biomarkers as indicators in such patients.

Patients and Methods
Patient Enrollment
This study was based on the Helsinki Declaration and approved by the Ethics Committee of the First Affiliated Hospital of Medical College of Shihezi University. The written forms of informed consent for individual patients were not required since the study was retrospective, and all data analyzed is anonymous.

The analysis consists of a large cohort of consecutive breast cancer patients with skeletal metastases at the First Affiliated Hospital of Medical College of Shihezi University who had a measurement of NLR, LMR, and CAR before starting a new systemic therapy between January 2009 and June 2020. We enrolled patients with histological confirmation

of breast cancer and they were diagnosed skeletal metastases by clinical manifestations, imaging examinations, or bone biopsies after the radical operation (mastectomy or breast-conserving surgery, and axillary lymph node dissection or sentinel lymph node biopsy); they underwent systemic treatment subsequently. Data for differential blood counts were collected prior to a new systemic therapy (chemotherapy; endocrine therapy; targeted therapy; bisphosphonate treatment; surgery, or radiotherapy to the affected bone; analgesia, or other supportive treatments).

The exclusion criteria were as follows: 1) Patients with hematological, immune, inflammatory diseases, and inflammatory breast cancer; 2) Patients who used anti-inflammatory drugs or immunosuppressants before enrollment;3) Patients who refused systemic treatment according to the NCCN guidelines;[10] 4) Patients with incomplete data for hematology or follow-up materials.

Data Collection
The data extracted from the medical record included: 1) Data for breast cancer: age, primary site, primary tumor size, histological pathology, histological grade, molecular subtype, type of breast cancer surgery, T stage, N stage, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status, and Ki-67 label index. 2) Data for skeletal metastases: the first site of the affected bone, visceral metastasis during follow-up, the number of involved sites of bone metastases, and systemic therapy information were collected from the medical records. Differential blood counts were collected within one week before a new systemic therapy, and the counts of neutrophils, lymphocytes, monocytes, albumin, and C-reactive protein were extracted from blood counts and used to calculate the corresponding values of NLR, LMR, and CAR. Chemotherapy, targeted therapy, endocrine therapy, surgery and radiotherapy to the involved bone were administered in appropriate patients according to available clinical practice guidelines.

Follow-Up
Patients were followed-up regularly after the diagnosis of breast cancer skeletal metastases. The follow-up was scheduled three months, six months, twelve months after diagnosis, and then every year. The dates and causes of death were recorded if the patients were dead. The follow-up included assessing disease progression and confirming the patient's death or loss to follow-up.

In our study, we set June 2020 as the deadline for follow-up. OS represented the stretch from the time of the diagnosis

until death for any reason. PFS is defined as the time elapsed between diagnosis and tumor progression.

Statistical Analysis

SPSS22.0 (SPSS Inc, Chicago, IL) was used to perform statistical analysis. Fisher's exact test or chi-squared test was adopted for categorical variables. The OS and PFS were evaluated by the Kaplan–Meier method, and the Log rank test was used to assess the survival differences between patients divided into two groups according to the optimal cut-off values of NLR, LMR, and CAR, which were obtained from time-dependent ROC curves. The Cox proportional hazard model was used for univariate and multivariate analyses to analyze the factors affecting the prognosis and to test for factors' independence. The hazard ratio (HR) and corresponding 95% confidence intervals (CIs) were also calculated. Statistical tests were two-sided, and a P value<0.05 was considered to have statistical significance.

Results

Patients Baseline Characteristics

A total of 212 patients with breast cancer with skeletal metastases were included in this study (Figure 1), and the baseline characteristics were displayed in Table 1. The mean age of the population was 54.76 (median 55; range 25–85) years. Of the firstly affected bone, the thoracic spine was the most common location (n=78), followed by the rib (n=51), and the lumbar spine (n=39). A little more than half of the patients (52.4%) had multiple skeletal metastases (n=111). Concerning systemic therapy, patients all have received chemotherapy and surgical treatment of breast cancer, 66.5% have undergone radiotherapy to the primary site (n=141), 18.9% have received endocrine therapy (n=40), 54.2% have experienced targeted therapy (n=115), 75% patients have received bisphosphonate treatment (n=159), and those who have experienced radiotherapy to the affected bone account for 34.4% (n=73), undergone surgery to the affected bone take up 22.2% (n=47).

The Cut-Off Values of Inflammatory Biomarkers

Determined by the ROC curves, the optimal cut-off values of NLR, LMR and CAR were 2.48, 3.43, and 0.34, and the corresponding areas under the curves (AUCs) were 0.648, 0.625, and 0.534, respectively (Table 2, Figure 2). Patients were divided into low and high ratio groups according to cut-off values. 42.5% of the patients (90) had a low NLR (<2.48), and 57.5% (122) had a high NLR (≥2.48). 50.9% of patients
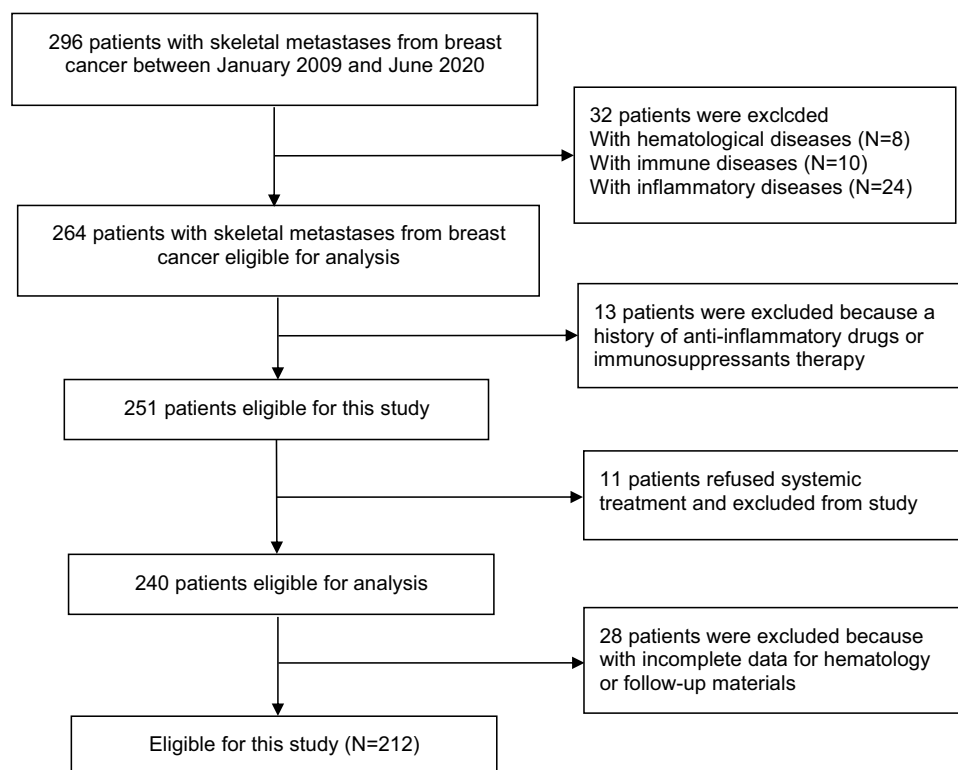

Figure 1 Study flow chart.

Table 1 Clinicopathologic Characteristics of 212 Breast Cancer with Skeletal Metastases Patients

Variables	Number	%
Age (years)		
<55	96	45.3
≥55	116	54.7
Pathology		
Invasive ductal carcinoma	195	92.0
Invasive lobular carcinoma	13	6.1
Other	4	1.89
Histological Grade		
I–II	76	35.8
III–IV	136	64.2
T stage		
T1	18	8.5
T2	92	43.4
T3	42	19.8
T4	60	28.3
N stage		
N0	7	3.3
N1	71	33.50
N2	97	45.7
N3	37	17.5
HER2 status		
(-)	87	41.0
(+)	125	59.0
ER status		
(-)	92	43.4
(+)	120	56.6
PR status		
(-)	146	68.9
(+)	66	31.1
Ki-67		
<14%	71	33.5
≥14%	141	66.5
The number of involved sites of visceral metastases		
0	106	50.0
1	20	9.43
>1	86	40.6
The number of involved sites of bone metastases		
1	101	47.6
2–3	90	42.5
>3	21	9.9
Site of affected bone		
Femur	15	7.1
Rib	51	24.1

(*Continued*)

Table 1 (Continued).

Variables	Number	%
Lumbar spine	39	18.4
Thoracic spine	78	36.8
Humerus	16	7.5
Other	13	6.1
Type of breast cancer surgery		
Breast-conserving surgery	86	40.6
Radical mastectomy	126	59.4
Number of chemotherapeutic line		
First-line	100	47.2
Second-line	95	44.8
Third-line or more	17	8.0
Primary site radiotherapy		
No	71	33.5
Yes	141	66.5
Endocrine therapy		
No	172	81.1
Yes	40	18.9
Targeted therapy		
No	97	45.8
Yes	115	54.2
Bisphosphonate treatment		
No	53	25.0
Yes	159	75.0
Surgery to the affected bone		
No	165	77.8
Yes	47	22.2
Radiotherapy to the affected bone		
No	139	65.6
Yes	73	34.4
NLR		
<2.48	90	42.5
≥2.48	122	57.5
LMR		
<3.43	108	50.9
≥3.43	104	49.1
CAR		
<0.34	168	79.2
≥0.34	44	20.8

Abbreviations: HER2, human epidermal growth factor receptor 2; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein/albumin ratio.

(108) were classified as low LMR (<3.43) and 49.1% (104) as high LMR (≥3.43). 79.2% of patients (168) were categorized as low CAR (<0.34) and 20.8% (44) as high CAR (≥0.34).

Table 2 Receiver Operating Characteristics (ROC) Analyses of NLR, LMR, and CAR in Patients with Breast Cancer Skeletal Metastases

Variables	Cut-Off Value	AUC (95% CI)	Sensitivity	Specificity
NLR	2.48	0.648(0.573–0.722)	0.738	0.523
LMR	3.43	0.625(0.549–0.701)	0.591	0.675
CAR	0.34	0.534(0.452–0.616)	0.300	0.848

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein/albumin ratio.

Associations Between Inflammatory Biomarkers and Clinicopathological Characteristics

Our analysis revealed that NLR was significantly associated with the N stage (P=0.018), and LMR was linked to the T stage (P=0.002) and N stage (P=0.045); However, there was no apparent association between CAR and the clinicopathological characteristics (Table 3).

Survival

The median duration of follow-up was 45.0 months (range 2.0 to 88.0). During follow-up, 72 patients (34.0%) experienced the progression of the disease, and 80 patients (37.7%) died. The Kaplan–Meier analyses of PFS and OS according to the cut-off values of NLR, LMR, and CAR were shown in Figure 3.

The rate of progression-free survival in patients with breast cancer skeletal metastases was 66%, with a mean PFS of 28.82 (range 2–88) months. The PFS was worse in the group of NLR≥2.48 than NLR<2.48 (estimated 3-year PFS: 50.5% vs. 73.8%, P<0.0001), in the group of LMR<3.43 than LMR≥3.43 (estimated 3-year PFS: 45.6% vs. 75.6%, P<0.0001) as well as in the group of CAR≥0.34 than CAR<0.34 (estimated 3-year PFS: 46.3% vs. 64.6%, P=0.031).
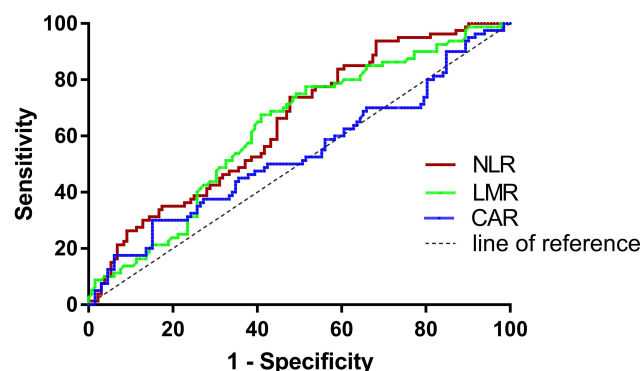
A total of 80 patients (37.7%) died during the follow-up period (mean 31.95 months; range 2–88 months), either directly related to breast cancer skeletal metastases or systemic therapy complications. The OS was significantly lower in the group of NLR≥2.48 (estimated 3-year OS: 51.2% vs. 76.7%, P<0.0001), the group of LMR<3.43 (estimated 3-year OS: 47.8% vs. 80.3%, P<0.0001), and the group of CAR≥0.34 (estimated 3-year OS: 48.9% vs. 67.7%, P=0.022).

Univariate and Multivariate Analyses of Prognostic Factors for PFS

In univariate analysis, histological grade (P=0.016), ER status (P=0.027), the number of involved sites of bone metastases (P=0.003), radiotherapy to the affected bone (P=0.009), NLR (P<0.0001), LMR (P<0.0001), and CAR (P=0.035) were significantly linked with PFS. All potential prognostic factors extracted from the univariate analysis were submitted for Cox proportional hazards analysis. Multivariate analysis indicated that patients with the number of involved sites of bone metastases>3 (HR 2.047; P=0.049) and NLR≥2.48 (HR 1.971; P=0.011) were linked to worse PFS. The risk of progression was relatively decreased in patients who have received radiotherapy to the affected bone (HR 0.458; P=0.005). Patients with ER (+) had longer PFS (HR 0.601; P=0.026), and a similar association was observed for LMR≥3.43 (HR 0.501; P=0.006) (Table 4).

Univariate and Multivariate Analyses of Prognostic Factors for OS

Univariate analysis revealed a significant impact of histological grade (P=0.020), ER status (P=0.031), the number of involved sites of bone metastases>3 (P=0.005), radiotherapy to the affected bone (P=0.009), NLR (P<0.0001), LMR (P<0.0001), and CAR (P=0.025) on OS. All potential prognostic factors were submitted for multivariate analysis. The results exhibited that the ER status,

Figure 2 The receiver operating characteristic (ROC) curves of NLR, LMR and CAR.

Table 3 Associations Between Inflammatory Biomarkers and Clinicopathological Characteristics

Variables	NLR			LMR			CAR		
	Low	High	P value	Low	High	P value	Low	High	P value
Age (years)									
<55	36	60		51	45		62	34	
≥55	54	62	0.184	57	59	0.563	84	32	0.220
Primary site									
Upper inner	11	11		11	11		18	4	
Lower inner	19	15		14	20		27	7	
Upper outer	35	48		40	43		57	26	
Lower outer	14	24		22	16		22	16	
Other sites	11	24	0.262	21	14	0.487	22	13	0.184
Tumor size									
<2cm	28	39		29	38		46	21	
≥2cm,<5cm	40	42		44	38		57	25	
>5cm	22	41	0.244	35	28	0.309	43	20	0.986
Histological type									
Ductal	84	111		96	99		136	59	
Lobular	5	8		9	4		7	6	
Other	1	3	0.735	3	1	0.235	3	1	0.470
Histological grade									
I–II	35	41		35	41		54	22	
III–IV	55	81	0.428	73	63	0.287	92	44	0.608
T stage									
T1	7	11		8	10		14	4	
T2	44	48		58	34		64	28	
T3	14	28		23	19		25	17	
T4	25	35	0.453	19	41	**0.002**	43	17	0.455
N stage									
N0	6	1		2	5		4	3	
N1	22	49		45	26		46	25	
N2	44	53		42	55		65	32	
N3	18	19	**0.018**	19	18	**0.045**	31	6	0.172
Molecular subtype									
Luminal B HER2-	19	30		28	21		34	15	
Luminal B HER2+	35	36		33	38		58	13	
HER2 enriched	17	37		29	25		44	10	
Triple negative	19	19	0.159	18	20	0.642	32	6	0.274
ER status									
(-)	54	66		61	59		92	28	
(+)	36	56	0.391	47	45	0.971	76	16	0.290
PR status									
(-)	56	90		78	68		115	31	
(+)	34	32	0.073	30	36	0.282	53	13	0.798
HER2 status									
(-)	38	49		46	41		66	21	
(+)	52	73	0.763	62	63	0.639	102	23	0.311

(*Continued*)

Table 3 (Continued).

Variables	NLR			LMR			CAR		
	Low	High	P value	Low	High	P value	Low	High	P value
Ki-67									
<14%	32	39		37	34		51	20	
≥14%	58	83	0.584	71	70	0.809	95	46	0.509
The number of involved sites of visceral metastases									
0	47	59		54	52		80	26	
1	7	13		12	8		16	4	
>1	36	50	0.733	42	44	0.793	72	14	0.161
The number of involved sites of bone metastases									
1	45	56		49	52		84	17	
2–3	38	52		44	46		67	23	
>3	7	14	0.638	15	6	0.141	17	4	0.326

Note: Bold text, P value < 0.05.
Abbreviations: OS, overall survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; CI, confidence interval; T, tumor; N, lymph node involvement; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein/albumin ratio.

radiotherapy to the affected bone, NLR, and LMR were all essentially associated with OS. (ER+: HR 0.599, P=0.025; undergone the radiotherapy to the affected bone: HR 0.452, P=0.005; NLR≥2.48: HR 2.044, P=0.007; LMR≥3.43: HR 0.532, P=0.012) (Table 5).

Discussion

Skeleton is the most common metastatic site for breast cancer, and skeleton metastases seriously reduced life quality and expectancy following diagnosis.[11,12] The highly heterogeneous in clinicopathological characteristics poses a considerable challenge in the systemic therapy of breast cancer skeletal metastases. Prolonging survival and preventing progression remain complicated issues. It is increasingly recognized that the systematic inflammatory response plays an essential role in the survival of malignancies.[13] The prognostic value of several inflammatory parameters such as NLR, LMR and CAR has been reported to be associated with the outcome of various types of disease.[14–17] However, there are no published studies regarding the prognostic significance of inflammatory biomarkers in breast cancer skeletal metastases. So our study aimed to identify possible prognostic factors for OS and PFS of breast cancer skeletal metastases patients through the combination of univariate and multivariate analyses with NLR, LMR,

and CAR, to conduct a novel investigation into the utility of these inflammatory biomarkers as indicators in such patients.

Our research revealed that for patients with breast cancer skeletal metastases, LMR<3.43 and NLR≥2.48 were independently associated with PFS and OS. LMR and NLR are composite inflammatory biomarkers based on peripheral blood cells. LMR is calculated according to the formula: lymphocyte/monocyte; NLR means the ratio of neutrophil/lymphocyte. Therefore, a reasonable explanation for the underlying mechanism tended to be that lower LMR represents a lower count of lymphocytes, as well as a larger count of monocytes. An increase in NLR means growth in neutrophils, a reduction in lymphocytes, or both.

Lymphocytes are the main component involved in tumor immune response, which inhibits the proliferation of tumor cells through lymphocyte-mediated cytotoxicity and cytokines released.[18,19] The lack of lymphocytes will lead to a decrease in CD4+ helper lymphocytes and an increase in CD8+ inhibitory cells to deteriorate the anti-tumor ability.[20,21] Monocytes are considered pro-tumor cells as they promote the dissemination and progression of neoplasms.[22] Tumor-associated macrophage is relevant to the aggregation and differentiation of excessive monocytes in the
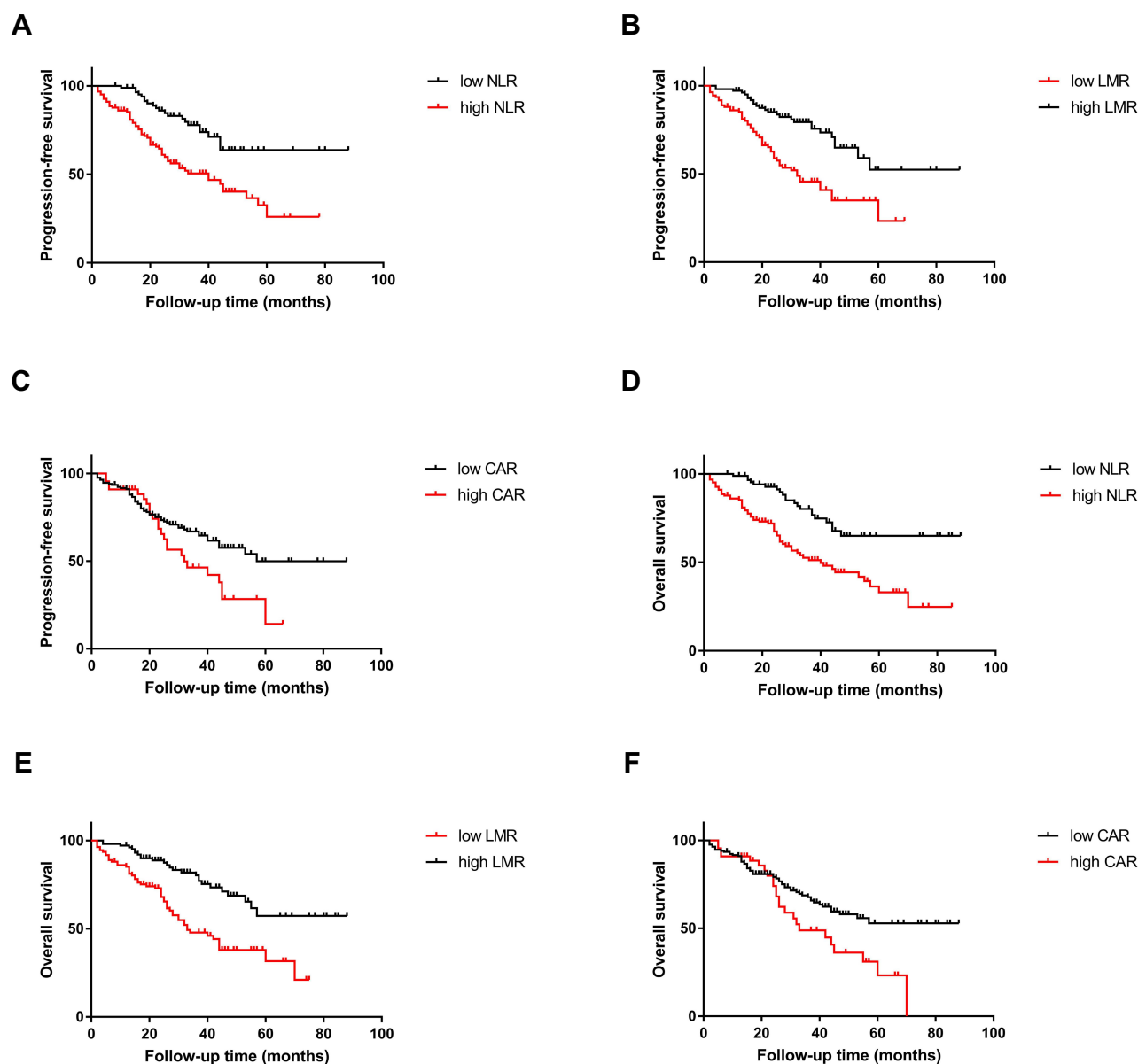
Figure 3 The Kaplan–Meier curves of PFS for (**A**) NLR, (**B**) LMR, (**C**) CAR, and the Kaplan–Meier curves of OS for (**D**) NLR, (**E**) LMR, (**F**) CAR.

tumor stroma, which not only advances tumor invasion but also lessens the aggressive ability of anti-tumor immune cells.[23] Therefore, elevated monocytes in peripheral blood reflect the hard tumor burden of the body, and even the state of immunosuppression.[24] Neutrophils support the proliferation, invasion, angiogenesis of tumor cells, and restrain the secretion of cytokines, which can exert direct or indirect killing effects.[25] Current studies have proved that the neutrophils destroy tumors nonspecifically by generating reactive oxygen species, and the process is similar to the bactericidal mechanism.[26,27] Whether neutrophils prevent the

immune response of protection or promote the process of malignant skeletal metastases.[28] Elevated NLR and reduced LMR may be related to inadequate immunocompetence in breast cancer patients with skeletal metastases. These theoretical foundations of inflammation may support the application of inflammatory symbols as prognostic indicators of bone metastases from breast cancer.

The main objectives of comprehensive treatment for breast cancer with bone metastasis are: 1) To relieve pain, rebuild function, and improve quality of life; 2) To treat and prevent SREs; 3) To control tumor progression

Table 4 Associations Between Clinicopathologic Characteristics and PFS in Breast Cancer Skeletal Metastases Patients

Variables	Number of Patients	Number of Events	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	P value	HR (95% CI)	P value
Age (years)						
<55	96	30	I		/	
≥55	116	50	1.344(0.853–2.117)	0.202	/	/
Histological grade						
I–II	76	19	I		I	
III–IV	136	61	1.883(1.125–3.153)	**0.016**	1.328(0.738–2.389)	0.344
ER status						
(-)	92	44	I		I	
(+)	120	36	0.609(0.392–0.946)	**0.027**	0.601(0.384–0.941)	**0.026**
PR status						
(-)	146	59	I		/	
(+)	66	21	0.766(0.465–1.261)	0.295	/	/
HER2 status						
(-)	146	59	I		/	
(+)	66	21	0.981(0.626–1.535)	0.931	/	/
Ki-67						
<14%	71	32	I		/	
≥14%	141	48	0.865(0.552–1.356)	0.527	/	/
The number of involved sites of visceral metastases						
0	106	39	I		/	
I	20	12	1.748(0.915–3.342)	0.091	/	
>I	86	29	0.818(0.503–1.330)	0.418	/	/
The number of involved sites of bone metastases						
I	101	30	I		I	
2–3	90	37	1.433(0.885–2.321)	0.143	1.570(0.902–2.731)	0.110
>3	21	13	2.659(1.383–5.110)	**0.003**	2.047(1.003–4.179)	**0.049**
Type of surgery						
Breast-conserving surgery	86	30	I		/	
Radical mastectomy	126	50	1.402(0.890–2.206)	0.145	/	/
Radiotherapy to the primary site						
No	71	23	I		/	
Yes	141	57	1.079(0.664–1.752)	0.759	/	/
Endocrine therapy						
No	172	67	I		/	
Yes	40	13	0.712(0.393–1.291)	0.264	/	/
Targeted therapy						
No	97	40	I		/	
Yes	115	40	0.674(0.434–1.046)	0.079	/	/
Bisphosphonate treatment						
No	53	21	I		/	
Yes	159	59	0.896(0.544–1.475)	0.666	/	/

(*Continued*)

Table 4 (Continued).

Variables	Number of Patients	Number of Events	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	P value	HR (95% CI)	P value
Surgery to the affected bone						
No	165	63	1		/	
Yes	47	17	1.009(0.590–1.726)	0.972	/	/
Radiotherapy to the affected bone						
No	139	62	1		1	
Yes	73	18	0.498(0.294–0.842)	**0.009**	0.458(0.264–0.794)	**0.005**
NLR						
<2.48	90	21	1		1	
≥2.48	122	59	2.667(1.619–4.394)	**<0.0001**	1.971(1.169–3.321)	**0.011**
LMR						
<3.43	120	36	1		1	
≥3.43	92	44	0.376(0.235–0.601)	**<0.0001**	0.501(0.305–0.823)	**0.006**
CAR						
<0.34	168	56	1		1	
≥0.34	44	24	1.675(1.038–2.702)	**0.035**	1.297(0.791–2.127)	0.302

Note: Bold text: P value < 0.05.
Abbreviations: PFS, progression-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; CI, confidence interval; T, tumor; N, lymph node involvement; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein/albumin ratio.

and prolong patient survival. Systemic therapy is the dominant strategy, among which chemotherapy, endocrine therapy, and targeted therapy are fundamental, and bisphosphonates can prevent and deal with SREs. Reasonable local therapy controlled the symptoms of bone metastasis, surgery and radiotherapy are positive and effective methods to manipulate single bone metastasis.[29] Our result suggests that the number of involved sites of bone metastases>3 predicted worse PFS in patients. The multiple skeletal metastases posed a noticeable challenge in therapy, which is comparable to the result reported by Parkes et al.[30] The radiotherapy to the affected bone can significantly reduce the progression rate and improve OS, which is necessary for breast cancer patients with skeletal metastases.

ER represents a primary transcription factor that promotes the formation of neoplasms in HR-positive breast cancer.[31,32] The biological effects of estrogen are mediated principally by ER-alpha, which acts as a ligand-inducible transcription agent.[33] Endocrine therapy is the first choice for patients with hormone-responsive breast cancer whose condition progresses slowly. Our findings explicated that ER (+) as a potent favorable prognostic factor in the subset of patients with breast cancer bone

metastasis, which is similar to the decision announced by Ren et al.[34]

To the best of our knowledge, this is the first study concerned the relationship between inflammatory biomarkers and the prognosis of breast cancer skeletal metastases. Still, there are limitations. 1) Patients included in the study only from one center, so international multi-center studies with larger sample sizes are required to verify our findings; 2) Our results are susceptible to some biases due to the retrospective nature. Therefore, prospective studies and extended follow-up duration are needed; 3) Patients who have not undergone the breast cancer surgical treatment were excluded so that the conclusion may not apply to them; 4) We adopted the ROC curves to determine the optimal critical values with both sensitivity and specificity, and the determination of the uniform cut-off values of inflammatory biomarkers may significantly advance the final consensus. Breast cancer skeletal metastasis is a complicated process, which involves plentiful factors. Prospective studies are required to further explore the potential mechanism, to prognosticate and screen the high-risk population with a worse prognosis and provide targeted intervention timely.

Table 5 Associations Between Clinicopathologic Characteristics and OS in Breast Cancer Skeletal Metastases Patients

Variables	Number of Patients	Number of Events	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	P value	HR (95% CI)	P value
Age (years)						
<55	96	30	I		/	
≥55	116	50	1.306(0.829–2.058)	0.250	/	/
Histological grade						
I–II	76	19	I		I	
III–IV	136	61	1.847(1.103–3.093)	**0.020**	1.314(0.731–2.365)	0.362
ER status						
(-)	92	44	I		I	
(+)	120	36	0.614(0.395–0.955)	**0.031**	0.599(0.382–0.939)	**0.025**
PR status						
(-)	146	59	I		/	
(+)	66	21	0.768(0.466–1.264)	0.298	/	/
HER2 status						
(-)	146	59	I		/	
(+)	66	21	0.993(0.634–1.555)	0.975	/	/
Ki-67						
<14%	71	32	I		/	
≥14%	141	48	0.806(0.515–1.264)	0.348	/	/
The number of involved sites of visceral metastases						
0	106	39	I		/	
I	20	12	1.489(0.779–2.845)	0.229	/	/
>I	86	29	0.631(0.384–1.038)	0.070	/	/
The number of involved sites of bone metastases						
I	101	30	I		I	
2–3	90	37	1.427(0.881–2.311)	0.148	1.475(0.852–2.554)	0.165
>3	21	13	2.553(1.331–4.900)	**0.005**	1.925(0.946–3.918)	0.071
Type of surgery						
Breast-conserving surgery	86	30	I		/	
Radical mastectomy	126	50	1.429(0.908–2.250)	0.123	/	/
Radiotherapy to the primary site						
No	71	23	I		/	
Yes	141	57	1.118(0.689–1.815)	0.651	/	/
Endocrine therapy						
No	172	67	I		/	
Yes	40	13	0.710(0.392–1.287)	0.259	/	/
Targeted therapy						
No	97	40	I		/	
Yes	115	40	0.682(0.440–1.059)	0.089	/	/
Bisphosphonate treatment						
No	53	21	I		/	
Yes	159	59	0.903(0.549–1.487)	0.688	/	/

(*Continued*)

Table 5 (Continued).

Variables	Number of Patients	Number of Events	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	P value	HR (95% CI)	P value
Surgery to the affected bone						
No	165	63	1		/	
Yes	47	17	1.031(0.603–1.763)	0.912	/	/
Radiotherapy to the affected bone						
No	139	62	1		1	
Yes	73	18	0.495(0.293–0.837)	**0.009**	0.452(0.261–0.783)	**0.005**
NLR						
<2.48	90	21			1	
≥2.48	122	59	2.732(1.658–4.503)	**<0.0001**	2.044(1.211–3.451)	**0.007**
LMR						
<3.43	120	36	1		1	
≥3.43	92	44	0.381(0.238–0.609)	**<0.0001**	0.532(0.324–0.872)	**0.012**
CAR						
<0.34	168	56	1		1	
≥0.34	44	24	1.730(1.071–2.793)	**0.025**	1.340(0.817–2.198)	0.246

Note: Bold text: P value < 0.05.
Abbreviations: OS, overall survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; CI, confidence interval; T, tumor; N, lymph node involvement; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein/albumin ratio.

Conclusion

Our study demonstrated that the number of involved sites of bone metastases>3 predicted worse PFS, and the radiotherapy to the affected bone and ER (+) were favorable prognostic factors for breast cancer bone metastases. LMR<3.43 and NLR≥2.48 were both significantly and independently associated with worse survival. With the feature of convenience and accessibility, LMR and NLR could be helpful in predicting the outcome of patients of breast cancer skeletal metastasis.

Abbreviations

NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein/albumin ratio; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; SREs, skeletal-related events.

Data Sharing Statement

The underlying de-identified data used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent

The study complied with the Declaration of Helsinki. All procedures involving human participants in this study approved by the ethics committee of the First Affiliated Hospital of Medical College of Shihezi University. Written forms of informed consent for individual patients were not required since the study was retrospective. All data analyzed is anonymous. Patients or their legal guardians know of and approved the publication.

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Disclosure

The authors report no conflicts of interest in this work.

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