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Prognostic value of pro-inflammatory markers at the preoperative stage in Algerian women with breast cancer

Research Article

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Abstract:

Background: Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI) are widely used to assess patient's outcome in many types of neoplasms including breast cancer. The aim of this study was to select the best parameter with a high prognostic value by defining the optimal cutoff value for each parameter in patients undergoing mastectomy.

Patients and Methods: This is a retrospective monocentric study enrolling 59 patients. The receiver operating characteristic (ROC) curve was used for the obtention of the optimal cutoff values of NLR, PLR, MLR, SII, and SIRI. The Kaplan–Meier curve and log-rank test were used to assess recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS).

Results: Among the five parameters, we obtained the optimal cutoff values for NLR, MLR, SII, and NLR but not for PLR (AUC $\leq$0.5). To assess the RFS, the optimal cutoff values for NLR, MLR, SII, and SIRI were defined as 2.11, 0.16, 472, and 0.6888, respectively. High MLR ($p = 0.0165$), SII ($p = 0.0368$), and SIRI ($p = 0.012$) were associated to shorter RFS. For DMFS, the optimal cutoff values for NLR, MLR, SII, and SIRI were 1.60, 0.28, 472, and 0.6888, respectively. Interestingly, the Kaplan–Meier curve showed that patients with high MLR ($p < 0.0001$), SII ($p = 0.0345$), and SIRI ($p = 0.0255$) exhibited shorter DMFS.

Conclusions: The MLR, SII, and SIRI indices would be the best indicators. They could constitute a promising predictive tool in the detection of locoregional and distant metastasis.

Keywords: *breast cancer • SII • MLR • SIRI • prognostic factor • survival*

1. Introduction

Breast cancer (BC) is still at the top list among cancers with high incidence and mortality in Algeria[1]. Indeed, the recent data show that BC takes the first place representing 40% of new cases registered in 2020 among women cancers. Moreover, this neoplasm ranked as the second place in term of mortality in both sexes[1]. Chronic inflammation, whether occurring before or after cancer, can promote the occurrence, development, and metastasis of cancer[2]. The systemic inflammation is one of the key hallmarks investigated during the study of the interaction between the tumor cells and the host[3]. Also, inflammatory proteins, immune cells, and cytokines are all present and readily observable in systemic circulation conducing to dynamic and systemic immune response[4]. Among them, neutrophils and monocytes (which will differentiate into macrophages) are first immune cells infiltrating the tumor microenvironment site and have a major contribution during the immunoediting process with

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dual function acting as pro- or anti-tumoral activity in a context-dependent manner[5]. Thus, their inflammatory mediators like proinflammatory cytokines/chemokines and angiogenic factors in addition to components of the extracellular matrix will thereby influence the systemic inflammatory response in BC patients[6]. In addition, platelets have been shown to be associated with the tumor growth and angiogenesis through the secretion of plethora of molecules including transforming growth factor β and vascular endothelial growth factor leading to more inflammatory cells migration[7]. In contrast, it is well reported that the most anti-tumor activity is mediated by cytotoxic T cells, and solid tumors with high tumor infiltrating lymphocytes (TIL) were associated with good prognosis in breast cancer[8]. This could lead to speculate that the low lymphocyte number could be associated with the poor outcome[9]. In the same way, a study conducted on breast cancer indicates that patients show different times to disease progression according to their molecular subtype[10]. For that, biomarkers are required to enhance the prognosis of patients. Thus, various blood markers of inflammation have been evaluated in patients with different malignant tumors. These indicators include neutrophil, monocyte, platelet, and lymphocyte numbers allowing a calculation of several ratios and indexes like neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI).

Cumulating evidence shows that systemic inflammation markers are associated with an immune response that promotes cancer and are a worse prognostic factor for cancer patients[11, 12]. However, to date, no publications shed the light on their role in Algerian patients with breast cancer. Accordingly, we set two major aims: (i) the selection of the optimal cutoff point of these biomarkers for each endpoint (i.e., RFS, DMFS, OS) and (ii) the evaluation of their relationships with clinical parameters and patient's survival.

2. Methods

2.1. Patients

We retrospectively analyzed the cases of 59 patients with breast cancer who underwent radical mastectomy during November 2012 to January 2014 at Pierre and Marie Curie Center, Mustapha Pacha Hospital in Algiers, Algeria. The local ethics committee "Agence Thématique de Recherche Scientifique de la Santé et de la Vie, ATRSSV" has approved our study. The study was in accordance with Declaration of Helsinki and its later amendments. The need for informed consent was waived due to the retrospective nature of the study.

All the patients were subjected to radical mastectomy. Chemotherapy regimens included cyclophosphamide (500 mg/m^2), doxorubicin (50 mg/m^2), and 5-fluorouracil (5-FU) (500 mg/m^2) during a treatment period spanning between 4 and 8 cycles (a median value of 6 cycles). Targeted therapy was used with trastuzumab during a 2-year treatment period. For most patients, the post-operative radiotherapy was performed with 34 Gy/10 fractions (14/51 patients; 27.45%) or 46–50 Gy/23–25 fractions (30/51 patients; 58.82%). ER+/PR+ patients received hormonotherapy within 5 years using tamoxifen and anti-aromatase "letrozole" and "anastrozole."

The exclusion criteria were as follows: (1) the presence of hematologic illness, acute or chronic infection, and other diseases that may impact hematologic indexes; (2) no history of other malignant tumors; (3) patients treated with neoadjuvant chemotherapy; and (4) patients with distant metastasis at diagnosis.

2.2. Data collection

Patients' clinicopathologic characteristics and routine blood results were obtained from medical records. The clinicopathologic variables such as age, tumor size, lymph node stage, stage disease, tumor location, histological classification, SBR classification, molecular classification, and treatment type were collected.

The inflammatory indexes were calculated with the following formulas: NLR = neutrophil counts/lymphocyte counts; MLR = monocyte counts/lymphocyte counts; and PLR = platelet counts/lymphocyte counts; SII (systemic immune-inflammation index) = neutrophil counts x platelet counts/lymphocyte counts; SIRI (systemic inflammatory response index) = neutrophil counts x monocyte counts/lymphocyte counts.

We determined the optimal cutoff points for these continuity factors by obtaining receiver operating characteristic (ROC) curves, which were used to divide the patients into 2 subgroups for further analysis.

2.3. Follow-up strategy

All the patients were followed up every three months in the first three years after operation, every six months in the next five years, and once a year thereafter. Follow-up information was obtained retrospectively through medical records and telephone interviews. Follow-up

included assessing disease progression, confirming patient death, and lost follow-up.

The recurrence-free survival (RFS) was defined as the time from the first day of surgery to the date of relapse, metastasis, lost follow-up, or death. Distant metastasis-free survival (DMFS) was defined as the time from surgery to the first distant metastasis, lost follow-up, or death. The overall survival (OS) was calculated from the date of the patient's first surgery to the death (or the last follow-up).

2.4. Pathology Methods and Molecular Subtypes

Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) statuses and Ki67expression were determined by immunohistochemical staining. The cutoff value of positive ER or PR was ≥1% for stained cell, and the cutoff value of high Ki-67 was ≥14% for immunoreactive tumor cell nuclei. Additionally, a value of 0 or 1+ was reported as HER2 negative, and a value of 3+ was considered HER2 positive. For the molecular subtypes, all the patients were classified as luminal A (ER+ and/or PR+, HER2-, Ki-67 <14), luminal B (ER+ and/or PR+, HER2-, Ki-67 ≥14%), luminal B-like (ER+ and/or PR+, HER2+, any Ki-67), HER2-enriched (ER-, PR-, HER2+, any Ki-67), or triple-negative (ER-, PR-, HER2-, any Ki-67) breast cancer (TNBC).

2.5. Statistical analysis

Statistical analyses were conducted by XLSTAT software (version 16.0) and GraphPad Prism ver. 6.0.1 (GraphPad Software, San Diego, CA, USA). ROC analysis was used to determine the optimal cutoff value for patient dichotomization thresholds. We used the Kaplan–Meier method to evaluate the RFS, DMFS, and OS, and the log-rank test was used to evaluate survival differences between patients partitioned into two groups according to the cutoff obtained. Chi-square or Fisher exact test was used, when necessary, to assess the association between inflammatory and clinicopathological parameters. Univariate analyses were performed using the Cox proportional hazards model, and the hazard ratios (HRs) and corresponding 95% confidence intervals (Cis) of each factor were reported. The backward selection was applied to keep only significant variables in the model for multivariate analysis. A two-tailed *P* value <0.05 was considered statistically significant.

3. Results

3.1. Patient's characteristics

A total of 59 patients were enrolled in this study. The median age of patients were 46 years old. Most of patients were at a T1–T2 tumor stage (64.39%) (**Table 1**).

The baseline hematological values are shown in **Table 2**. There were 34 patients with nodal metastasis (57.62%) and 49 (83.05%) with ductal localization. Most of patients were at early stage of BC with 40 (67.79%) patients at clinical stages I–II and 15 (25.42%) patients at clinical stage III.

Table 1: Clinical characteristics of breast cancer patients.

Characteristic		Untreated BC
Age Median (range)		46 (30–75)
T stage	T1	8 (13.55%)
	T2	30 (50.84%)
	T3	8 (13.55%)
	T4	8 (13.55%)
	ND	5 (8.47%)
N stage	N0	20 (33.89%)
	N1	28 (47.45%)
	N2	5 (8.47%)
	N3	1 (1.69%)
	ND	5 (8.47%)
Stage disease	IA	2 (3.39%)
	IIA	21 (35.59%)
	IIB	17 (28.81%)
	IIIA	6 (10.17%)
	IIIB	8 (13.55%)
	IIIC	1 (1.69%)
	ND	4 (6.78%)
Laterality of tumor	Right breast	24 (40.67%)
	Left breast	35 (59.32%)
Histological classification	CCI	49 (83.05%)
	CLI	4 (6.78%)
	Mixte	5 (8.47%)
	colloid	1 (1.69%)
SBR classification	I	1 (1.69%)
	II	35 (59.32%)
	II/III	2 (3.39%)
	III	20 (33.89%)
	ND	1 (1.69%)
Molecular classification	Lum A	6 (10.17%)
	Lum B	24 (40.67%)
	Lum B-like	7 (11.86%)
	HER2+	9 (15.25%)
	TNBC	8 (13.55%)
	Lum A or B	5 (8.47%)
Treatment	Chemotherapy	58/59
	Radiotherapy	51/59
	Hormonotherapy	36/42
	Anti-HER2	16/16

3.2. ROC curves and optimal cutoff value selection for biomarkers

Different approaches were used to define the best optimal cutoff for biomarkers using either ROC or median value as threshold. In this study, the optimal cutoff values for NLR, PLR, SII, MLR, and SIRI were evaluated using the receiver operating characteristic (ROC) curve. When considering RFS as endpoint, the results showed that NLR = 2.11, PLR = 291.81, SII = 472, MLR = 0.16, and SIRI = 0.6888 were the optimal cutoff values (**Table 3**). The area under the ROC curves (AUCs) of NLR, PLR, SII, MLR, and SIRI were 0.568, 0.440, 0.578, 0.693, and 0.741, respectively. When DMFS was taken as endpoint, the results showed that the optimal cutoff values for NLR, PLR, SII, MLR, and SIRI were 1.6, 128.33, 472, 0.28, and 0.6888, respectively. The AUCs were 0.59, 0.497, 0.634, 0.657, and 0.722, respectively. When OS was selected as endpoint, the cutoff values for NLR, PLR, SII, MLR, and SIRI were 2.85, = 119.52, = 712, = 0.11, and = 1.3823. The AUCs were 0.508, 0.404, 0.544, 0.559, and 0.605, respectively. Due to the low AUC value for PLR, this marker was waived for later analysis for the three endpoints.

Table 2: Baseline hematological values. Note: Values represent mean ± standard deviations (SD). Abbreviations: MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SIRI, systemic inflammation response index; SII, systemic immune-inflammatory index; (‡): n=42; (†): (10^9 cells/L).

Blood values	Population
Mean white blood cell† (± SD)	6.926 (± 1.720)
Mean neutrophils† (± SD)	4.152 (± 1.307)
Mean lymphocytes† (± SD)	2.180 (± 0.6109)
Mean monocytes†‡ (± SD)	0.4483 (± 0.2294)
Mean platelets† (± SD)	264.553 (± 63.215)
Mean MLR‡ (± SD)	0.2256 (± 0.1675)
Mean NLR (± SD)	2.021 (± 0.7890)
Mean PLR (± SD)	130.8 (± 59.11)
Mean SIRI‡ (± SD)	0.8649 (±0.4827)
Mean SII (± SD)	530.5 (±209.3)

3.3. Correlation between the clinicopathological characteristics and inflammatory biomarkers

There was no significant association between all inflammatory markers and clinicopathological factors, including age, lymph node metastasis, tumor grade, clinical staging, and laterality of tumor with both RFS and DMFS as endpoint (**Table 4**).

Table 3: Optimal cutoff values of preoperative NLR, PLR, SII, MLR, SIRI for predicting RFS, DMFS, and OS in breast cancers. Abbreviations: AUC, area under curve; CI, confidence interval; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; SIRI, systemic inflammatory response index; RFS, relapse-free survival; DMFS, distant metastasis-free survival; OS, overall survival; (‡): n=42.

Subgroups	Cutoff value	AUC	Sensitivity (%)	Specificity (%)	Youden index	95% CI of AUC	P-value
Recurrence-free survival							
NLR	2.11	0.568	41.4	76.7	0.181	0.425-0.712	0.35
PLR	291.81	0.440	6.9	100	0.069	0.295-0.585	0.419
SII	472	0.578	69	53.3	0.223	0.434-0.722	0.287
MLR‡	0.16	0.693	85.7	57.1	0.428	0.538-0.847	**0.014**
SIRI‡	0.6888	0.741	85.7	57.1	0.428	0.598-0.885	**0.001**
Distant metastasis-free survival							
NLR	1.6	0.59	88.9	34.1	0.23	0.434-0.746	0.258
PLR	128.33	0.497	50	63.4	0.134	0.334-0.660	0.974
SII	472	0.634	77.8	51.2	0.29	0.49-0.779	0.069
MLR‡	0.28	0.657	41.7	86.7	0.284	0.485-0.829	0.074
SIRI‡	0.6888	0.722	91.7	46.7	0.384	0.569-0.875	**0.004**
Overall survival							
NLR	2.85	0.508	42.9	90.4	0.333	0.208-0.808	0.957
PLR	119.52	0.404	57.1	50	0.071	0.174-0.633	0.412
SII	712	0.544	42.9	80.8	0.237	0.295-0.793	0.730
MLR‡	0.11	0.559	100	18.9	0.189	0.3-0.819	0.653
SIRI‡	1.3823	0.605	40	86.5	0.265	0.346-0.865	0.426

Table 4: Clinicopathological characteristics of breast cancers according to inflammatory markers for RFS and DMFS.

Subgroups	N	SII		P value	N	NLR		P value	N	MLR		P value	N	SIRI		P value
		Low	High			Low	High			Low	High			Low	High	
Recurrence-free survival																
Age	59			0.601	59			0.7787	42			0.3357	42			0.3357
≤ 46		14	16			20	10			6	16			6	16	
> 46		11	18			21	8			9	11			9	11	
T staging	55			0.5648	55			0.2127	39			1	39			0.7281
T1+T2		16	23			29	10			10	16			11	15	
T3+T4		8	8			9	7			5	8			4	9	
N staging	55			1	55			0.7630	39			1	39			1
N0		9	11			13	7			4	7			4	7	
N+		15	20			25	10			11	17			10	18	
Clinical staging	55			1	55			0.1892	39			1	39			0.7281
I+II		17	23			30	10			10	16			11	15	
III+IV		7	8			8	7			5	8			4	9	
SBR classification	58			0.2661	58			1	41			1	41			0.1703
I+II		18	20			26	12			9	18			7	20	
III		6	14			13	7			5	9			7	7	
Laterality of tumor	59			0.7897	59			1	42			0.2072	42			1
Right breast		11	13			16	8			4	13			6	11	
Left breast		14	21			24	11			11	14			9	16	
Distant metastasis-free survival																
Age	59			0.601	59			1	42			1	42			0.3357
≤ 46		14	16			8	22			17	5			6	16	
> 46		11	18			8	21			16	4			9	11	
T staging	55			0.5648	55			0.3263	39			0.1938	39			0.7281
T1+T2		16	23			9	30			23	3			11	15	
T3+T4		8	8			6	10			9	4			4	9	
N staging	55			1	55			0.5308	39			1	39			1
N0		9	11			4	16			9	2			4	7	
N+		15	20			11	24			23	5			10	18	
Clinical staging	55			1	55			0.7348	39			0.1938	39			0.7281
I+II		17	23			10	30			23	3			11	15	
III+IV		7	8			5	10			9	4			4	9	
SBR classification	58			0.2661	58			0.5413	41			0.6925	41			0.1703
I+II		18	20			11	27			20	7			7	20	
III		6	14			4	16			12	2			7	7	
Laterality of tumor	59			0.7897	59			0.1518	42			0.2708	42			1
Right breast		11	13			9	15			15	2			6	11	
Left breast		14	21			7	28			18	7			9	16	

3.4. Kaplan–Meier curve and survival analysis

Next, we set up the survival curves for each inflammatory index by dividing patients into two groups based on cutoff points obtained by ROC curves. For RFS as endpoint, results showed that high MLR, high SII, and high SIRI were significantly associated with poor RFS (**Figure 1A**). We observed that after 111 months of follow-up, more than 81% of patients with high SII met recurrence or death versus 48% of patients with low SII (p = 0.0368). We observed that when 85% of enrolled patients with low MLR survived after 50 months of surgery, 50% of those with high MLR showed signs of recurrence or death (p = 0.0165) (**Figure 1A**). Similarly, when 86% of enrolled patients with low SIRI survived after 50 months of surgery, 50% of those with high SIRI succumbed to death or showed signs of recurrence (p = 0.012) (**Figure 1A**). However, NLR showed no significant statistical difference (p=0.2501) (**Figure 1A**).

For DMFS as endpoint, we obtained the same results, as high MLR, SII, and SIRI were associated

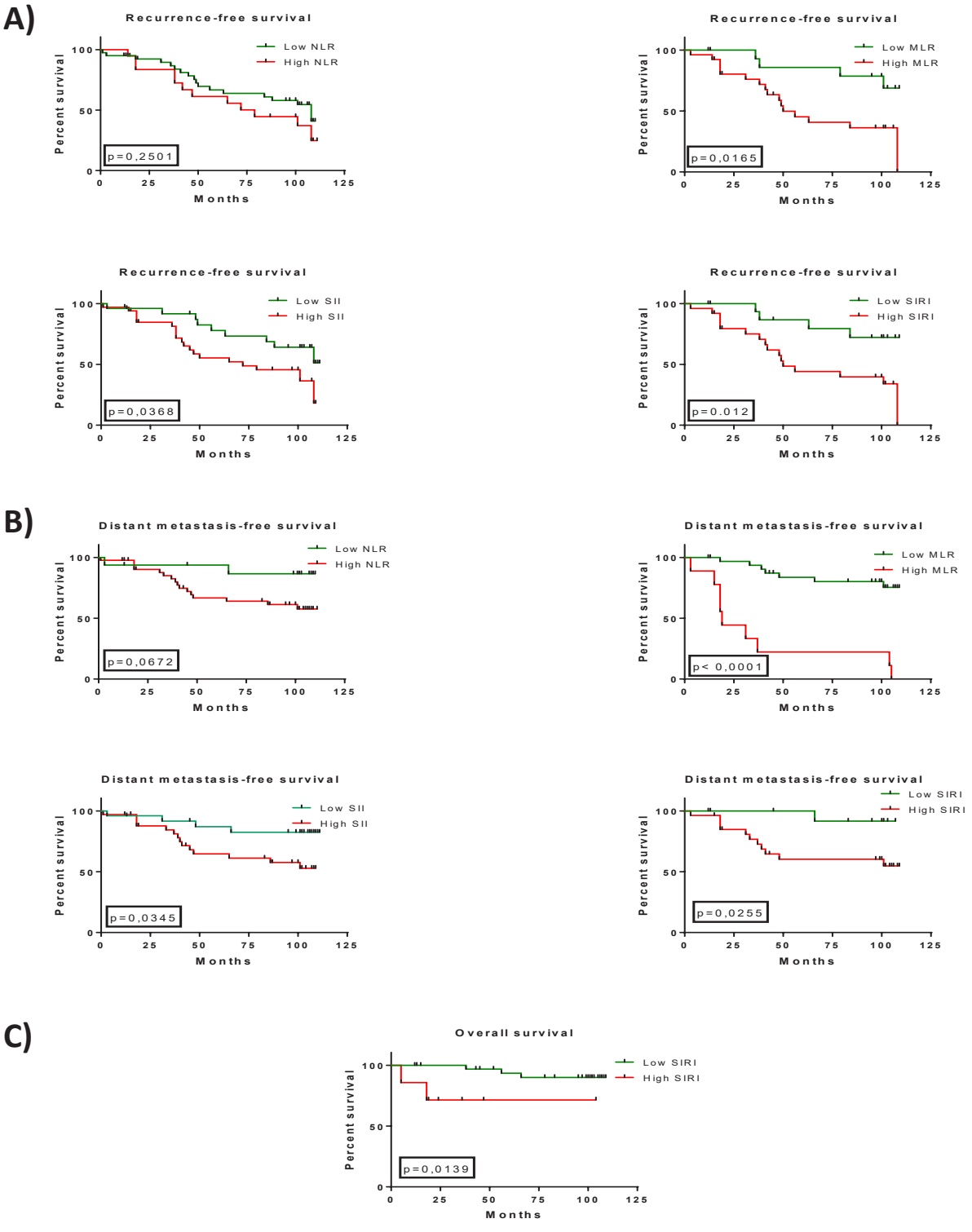


Figure 1: Prognostic value of inflammatory markers for breast cancer patients. (A) Kaplan-Meier curves of RFS for NLR, MLR, SII and SIRI. (B) Kaplan-Meier curves of DMFS for NLR, MLR, SII and SIRI. (C) Kaplan-Meier curves of OS for SIRI.

with shorter DMFS. Interestingly, 50% of patients with high MLR showed a distant metastasis or death only after 19 months after surgery compared to those with low MLR showing 96% of survival (p < 0.0001) (**Figure 1B**). Also, after 111 months of follow-up, 82% of patients with low SII survived compared to 52% with high SII (p = 0.0345) (**Figure 1B**). At the same line, patients with low SIRI had longer DMFS than patients with high SIRI with 91% vs 54% of survival (p = 0.0255), respectively (**Figure 1B**). Although high NLR group showed a more distant metastasis rate than the group with low NLR, the difference was at the borderline of significance (p=0.0672) (**Figure 1B**).

When taking OS as endpoint, a Kaplan–Meier curve analysis showed that only SIRI was a statistically significant marker linked to overall survival (p=0.0139) (**Figure 1C**). Thus, patients with low SIRI had a longer survival rate versus those with high SIRI at the end of follow-up with 90% vs 71% of survival, respectively.

3.5. Univariate and multivariate analyses

Furthermore, we sought to know if these current inflammatory parameters were independent prognostic factors at different endpoints. First, the univariate analysis showed that for RFS as endpoint, at the exception of NLR, all other markers showed significant difference with high levels associated to poorer RFS (**Table 5**). Indeed, MLR (HR=4.311, p=0.02) was the most marker linked to worst outcome followed by SIRI (HR=3.845, p=0.033) and SII (HR=2.263, p=0.044), respectively.

For DMFS as endpoint, both SII (HR=3.118, p=0.045) and MLR (HR=5.556, p=0.004) showed statistically significant difference with high levels associated with worst outcome (**Table 6**), while SIRI was at borderline of significance (HR=7.261, p=0.058).

The multivariate analysis was not established since the model was not validated by multiple regression with backward elimination (**data not shown**).

Table 5: Univariate Cox regression analysis for RFS. Abbreviations: HR, hazard ratio; CI, confidence interval.

	HR	95% CI	*P*
Age	1.237	0.596-2.568	0.569
T staging	1.318	0.611-2.845	0.482
N staging	1.265	0.56-2.858	0.572
SBR classification	1.055	0.478-2.328	0.894
NLR	1.532	0.73-3.217	0.26
SII	2.263	1.022-5.014	**0.044**
MLR‡	4.311	1.262-14.729	**0.020**
SIRI‡	3.845	1.116-13.246	**0.033**

Table 6: Univariate Cox regression analysis for DMFS. Abbreviations: HR, hazard ratio; CI, confidence interval.

	HR	95% CI	*P*
Age	0.820	0.323-2.079	0.676
T staging	1.380	0.518-3.680	0.519
N staging	0.751	0.291-1.942	0.555
SBR classification	0.834	0.297-2.342	0.730
NLR	1.822	0.718-4.625	0.207
SII	3.118	1.023-9.501	**0.045**
MLR‡	5.556	1.707-18.085	**0.004**
SIRI‡	7.261	0.935-56.366	0.058

4. Discussion

Despite the easy way to obtain them and the affordable cost of these markers, to the best of our knowledge, no study has been performed in Algerian patients, and only one research study reported North African patients with inflammatory breast cancer, which is considered as a rare subtype[13]. Analyzing systemic inflammatory markers in the blood may be one way to comprehend a role of inflammation in breast cancer risk[6]. There are more evidence suggesting that the systemic inflammatory response promotes tumor progression by modifying the interactions between neoplastic and non-neoplastic cells. Hematopoiesis is aberrant in individuals with solid tumors, resulting in altered hematopoietic progenitor cell composition and myeloid-biased differentiation[4]. Thus, the imbalance in neutrophil, monocyte, and platelet counts relative to lymphocytes is observed. Remarkably, most of cutoffs used in publications are issued from Asian, European, or American populations[14]. Also, several studies showed discrepancy in cutoff selection for inflammatory markers selected at the different endpoints. Moreover, most of studies reported their optimal cutoff based on OS/RFS/DFS instead of DMFS. For that, we aimed to set up our optimal cutoff point selection for these markers at different selected endpoints such as RFS, DMFS, and OS for better relapse-risk stratification. As first observation, these cutoffs were slightly different with respect to those found in literature. Hence, defined cutoff values for these inflammatory markers in our population are crucial for further investigations especially since studies showed disparities in the NLR ratio depending on racial differences[15, 16]. When RFS was selected as

endpoint, the NLR cutoff value was 2.11. Various NLR cutoffs were identified in previous reports ranging from 1.34 to 4[14, 17]. Our NLR cutoff is close to those reported by Truffi et al. with 2.21 as NLR optimal cutoff for DFS as endpoint in study including 1806 patients with breast cancer meeting our inclusion and exclusion criteria[18]. When DMFS was selected as endpoint, the NLR cutoff value was 1.6, which is relatively low compared to that of Orditura's study with NLR value of 1.97[19]. Also, a few studies used this endpoint for the estimation of their cutoff values for all five markers.

Respective to the molecular subtype, non-metastatic breast cancer, and DFS/RFS as endpoint, data extracted from meta-analysis showed that the MLR cutoff value ranged from 0.19 to 0.22 in Asian population[20], whereas our MLR optimal cutoff value was lower defined at 0.16. The decrease observed in this ratio may be attributed to disturbance in monocyte and/or lymphocyte counts where their numbers could be affected by inherited (e.g., age, ethnicity) and environmental factors rather than pathological condition[21, 22]. Thereby, larger studies in the same population are required to minimize these fluctuations. Our data showed that the MLR value of 0.28 was the optimal cutoff value selected for DMFS as endpoint, which is similar to results of Truffi et al. and He J et al. where they reported 0.28 and 0.2632 as the MLR values, respectively[18, 23].

For SII, a meta-analysis based on seven articles from Asian patients highlighted that SII cutoffs varied from 442 to 624[24]. In our cohort, the optimal cutoff value of SII was 472 for both RFS and DMFS. In another publication, Li et al determined a best cutoff for SII at 514 and a high value was associated to worse prognosis in breast cancer patients undergoing surgery with 6 years of follow-up[25].

SIRI is the less investigated index among other markers in breast cancer. Instead, some studies reported the optimal cutoff values of 0.65 for OS[26] and 0.54 for OS in another study[27], but no publication has set a SIRI cutoff with RFS and DMFS as endpoint in BC even those including patients receiving NACT[28]. In our cohort, the cutoff was set at 1.38 for OS which is higher compared to that in literature. Nevertheless, we should be careful in drawing assumptions since the AUC and *p* value were far from the significance threshold. Overall, in our cohort, for both SII (cutoff value = 472) and SIRI (cutoff value = 0.688), the optimal cutoff value was identical for both RFS and DMFS as endpoints which could be considered as advantageous for further prospective studies compared to other markers.

After that, we sought to determine any correlations between the above-mentioned markers and the clinical parameters. Although many studies associated high values of these indexes with clinical features such as tumor stage, histological and molecular types in breast cancer and other malignancies[29, 30]. In our cohort, we failed to demonstrate any relationships between clinical parameters with above-cited indexes. This result is in line with meta-analysis data showing no significant association between LMR (inverse of MLR) and clinical parameters[20].

Patient survival can be predicted using systemic inflammatory indexes, which may be connected to a variety of underlying mechanisms. Tumor-induced inflammation and alterations in immune function play a significant role in the link between NLR/MLR and the prognosis of the tumor. NLR is the most inflammatory parameter investigated in multiple diseases including breast cancer. High level of this ratio was associated in most studies to poor prognosis[14]. However, in our study, we did not observe a statistically significant difference between group with high NLR versus low NLR when assessing patients' survivals. The prognostic value of NLR could be inconsistent among breast cancer subtypes. Indeed, some studies linked poor prognosis of high NLR to ER+/PR+ subtypes, whereas others linked it to ER-/HER2- or TNBC subtype[14, 17, 31-33]. Unfortunately, we did not run this analysis in our cohort due to the small number of patients in each subgroup. In the same way and in a study conducted on non-small-cell lung cancer (NSCLC), it was reported that high NLR is related to cytokines/chemokines production increase such as TNF-α, IL-6, and IL-8. These cytokines were linked to poor prognosis and lower response to immune checkpoint inhibitors[34]. Considering these data, further investigation combining NLR to cytokines/chemokines profile would strength our understanding of breast cancer pathophysiology.

Even though PLR was reported to play a pivotal role as poor prognosis in different malignancies, it did not have a prognostic role in our cohort. In fact, its prognostic impact had been a subject to controversies in breast cancer. In one hand, many studies reported that PLR was implicated in prognosis, while high values were associated to worst one[18, 35, 36]. In the other hand, PLR was reported to be not associated to poor prognosis in TNBC[37].

Interestingly, when combining neutrophils with platelets (SII), the prognostic effect was more prominent. Moreover, there was a positive correlation between neutrophils and platelets with *p* value at the border of significance (*P*= 0.05; data not shown). Many studies revealed a crosstalk between platelets and neutrophils associated to cancer promotion in part via the induction of NETosis[38]. Also, platelet–neutrophil network participated in metastatic niche formation

through interaction with tumor cells via CXCL-5/CXCL-8/CXCR-2 axis[39, 40]. Together, these complex interactions highlight a potential role of tumor-induced NETosis as a poor prognosis in cancer patients[41]. Likewise, SII was significantly associated to poor prognosis regardless of the molecular subtypes[25]. Moreover, a meta-analysis confirmed that SII was a predictive marker of relapses and patient's survival in breast cancer[24]. Accordingly, these findings allow us to suggest the great potential of this index as a prognostic parameter instead of calculating NLR and PLR separately.

Importantly, the association of MLR with high degree of distant metastasis in our cohort evokes its contribution to this process. Likely, Gerratana et al. found that high MLR was associated with number of sites at the onset of metastatic disease[42]. In the same line, Liu et al. reported a significant inverse correlation between LMR in NSCLC patients and brain metastasis especially linked to female gender[43]. Thus, studying the link between breast cancer and monocytes' interactions with female hormones could constitute a promising perspective. Moreover, CCL-2 a potent monocyte chemoattractant is involved in various malignancies and is associated to nodal and distant metastasis[44-46]. Thus, mechanisms behind CCL-2-induced metastasis are multiple, in part, via the induction of epithelial–mesenchymal transition, recruitment and/or polarization of immunosuppressive cells like neutrophils, regulatory T cells, and type 2 macrophages[47]. In a previous study, Wangchinda et al. evoked that different breast cancer subtypes were associated with different times to disease progression with liver and brain as common sites of metastasis associated with early relapse among patients[10]. Taken together, further studies are crucial to dig the association of MLR values with different molecular subtypes and organs linked to distant metastasis.

SIRI was calculated based on neutrophil, monocyte, and lymphocyte counts. In this study, only SIRI had a significant association with patients' survivals for three endpoints (RFS, DMFS, and OS). At the cellular and molecular levels, many studies reported interactions between monocytes/macrophages and neutrophils through the release of cytokines mainly IL-17 by γδT cells which in turn regulates G-CSF production enhancing neutrophil recruitment. Thus, IL-17 production is under IL-1β expressed by tumor-associated macrophages (TAM)[48]. In addition, neutrophils that are releasing IL-8 and TNF-α lead to recruitment and activation of macrophages[49]. Remarkably, a positive correlation was found between monocytes and neutrophils in glioblastoma rising the importance of these innate cells in maintaining immunosuppressive microenvironment[50] reflecting the poorer prognosis at the clinical level.

Given this context, we suggest that SII and SIRI depict the equilibrium between the host's immunological status and the rate of tumor progression, and it may be able to forecast a patient's prognosis for BC. However, larger investigations are required to validate these suggestions. Additionally, more studies combining these indexes (SII and SIRI) will be the suitable perspectives for better patient's stratification for treatment options. Also, it appears important to assess these biomarkers with the cellular infiltration into the tumor microenvironment with the aim to see any correlation between the local immune response and the systemic inflammation especially in HER2+-enriched and triple-negative subtypes[37, 51]. Indeed, in a recent paper, Onagi et al. demonstrated that TIL and more strongly regulatory T cells correlated positively with both NLR and PLR in TNBC accompanied with high PDL-1 expression[37]. This could suggest the existence of local immunosuppressive environment in this subtype.

In our study, the survival curves were more relevant for these markers based on their respective cutoffs at RFS and DMFS but not OS endpoint. This could be explained by the fact that breast cancer management has improved these recent years allowing to more delays regarding relapse and survival among patients which suggest to extend the time of follow-up at least to 20 years.

However, the present study presented several limitations due to the small number of the cohort which limited our analysis with conclusive remarks regarding the association of these inflammatory markers with BC subtypes especially inflammatory breast cancer (IBC) and treatment strategies. Also, multivariate analysis represents another limitation to the study as we could not demonstrate the independent prognostic value of these markers regardless of other co-variables such as molecular subtypes. For example, Wangchinda et al. demonstrated that molecular subtypes were behind early or late recurrence appearance (beyond 5 years of follow-up); with ER+/PR+ and HER2- patients associated to later recurrence than other subtypes[10]. Moreover, in a meta-analysis, the authors showed that the poor prognosis of NLR was strongly associated with ER-/HER2- subtype[32].

5. Conclusions

In summary, our study identified the optimal cutoff point for each inflammatory marker based on three endpoints (RFS, DMFS, and OS) and highlighted the important role of MLR, SII, and SIRI as prognostic tools in monitoring breast cancer patients in our population.

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Declarations of interest

None.

Data statement

The data that support the findings of this study are available from the corresponding author [AAZ] upon reasonable request.

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