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Local and systemic inflammatory markers as prognostic and predictive markers in locally advanced triple negative breast cancer

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SUMMARY

Introduction: Local inflammatory markers have been defined as prognostic and predictive markers in triple negative markers as proved by many studies. The prognostic and predictive value of systemic inflammatory markers such as Neutrophil Lymphocyte Ratio (NLR) and lymphocyte monocyte ratio (LMR) remain to be elucidated.

Aim of study: To evaluate Pathological Complete Response (PCR) to neoadjuvant chemotherapy in locally advanced cancer breast in relation to Tumor Infiltrating Lymphocytes (TILs), neutrophil lymphocyte ratio and lymphocyte monocyte ratio as well as overall survival and disease free survival.

Patients and methods: In Tanta university Hospital, oncology department form January 2012 to December 2013, 67 patients with locally advanced TNBC stage IIB, IIIB 0r IIIC using TNM 8th edition . All patients received neoadjuvant chemotherapy in the form of dose dense AC followed by paclitaxel (adriamycin and cyclophosphamide 60 mgm/m^2 and 600 mgm/m^2 respectively the cycle is repeated every 2 weeks for 4 cycles followed by paclitaxel 175mgm/m^2 every 2 weeks for 4 cycles). All cycles with G-CSF support. Pre treatment TILs, NLR and LMR were evaluated with PCR and as prognostic factor of survival.

Results: Low NLR has been detected in 74.6% of cases and has been associated with high TILs and this was statistically significant (p value=0.03). High LMR was observed in 80.6% of cases and correlated significantly with TILs (p-value=0.003).

Pathological CR was found to be associated with high TILs, low NLR and high LMR.

In our study we evaluated the pre neoadjuvant systemic and local inflammatory markers as prognostic marker we found that in multivariate analysis, the lymphocyte monocyte ratio maintained their statistical significance with overall survival. While tumor infiltrating lymphocyte maintained their statistical significance as prognostic factors with overall survival and disease free survival.

Conclusion: Systemic inflammatory markers can be used as marker of pathological complete response in locally advanced triple negative breast6 cancer with neoadjuvant chemotherapy.

Key words: radiation-induced negative breast cancer, lymphocyte monocyte ratio, chemotherapy

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INTRODUCTION

In women, breast cancer is the most common cause of death [1]. Among breast cancer subtypes, high recurrence and prognosis was higher in hormone receptor negative and triple negative breast cancer subtypes [2]. So it is very important to search for new predictive biomarkers.

In Surrounding tumor environment, systemic inflammatory response including, lymphocytes, and platelets cause tumor progression [3]. High Neutrophil- Lymphocyte Ratio (NLR) and Low Lymphocyte Ratio (LMR) are associated with bad prognosis and tumor progression in different types of cancers [4-7]. Also, in tumor microenvironment, antitumor immune response is shown in the form of Tumor-Infiltrating Lymphocytes (TILs). It is associated with prognosis in different malignancies including breast cancer [8-10].

The relation between systemic and local inflammatory markers such as NLR or LMR and TILs respectively has not widely studied [11-13]. In all malignancies especially breast cancer immune response tumor is getting great interest.

In this study, we primarily analyzed the relation between TILs andboth NLR and LMR expression. Also we studied pathological complete response in patients with locally advanced triple negative cancer breast with NLR, LMR and TILs and their effect on survival both Overall Survival (OS) and disease Free Survival (DFS).

Patients

In Tanta university Hospital oncology department form January 2012 to December 2013, 67 patients with locally advanced TNBC stage IIB (T2, N1, M0 or T3, N0, M0), IIIA (T1-2, N2, M0 or T3, N1-2, M0), IIIB (T4 N0-3M0) or IIIC (any T N3 M0) using TNM 8th edition [14]. All patients received neoadjuvant chemotherapy in the form of dose dense AC followed by paclitaxel (adriamycin and cyclophosphamide 60 mgm/m^2 and 600 mgm/m^2 respectively the cycle is repeated every 2 weeks for 4 cycles followed by paclitaxel 175 mgm/m^2 every 2 weeks for 4 cycles). All cycles with G-CSF support. Ethical approval was obtained before study start.

American Society of Clinical Oncology-College of American Pathologists guidelines defined triple negative breast cancer as estrogen receptor (ER), progesterone receptor (PR), and HER2

negative [15, 16]. Nuclear staining less than 1% of tumor cells is considered as ER and PR negative. HER2 negativity by immunohistochemistry (IHC) is defined as 0/1 (no staining, or weak incomplete membrane staining in <10% of invasive tumor cells) or by silver *in situ* hybridization (SISH) negative (Dual-probe HER2/CEP17<2.0 with an average HER2 copy number<4.0 signals/cell).

Baseline complete blood picture, and core biopsy obtained before neoadjuvant treatment were collected. By dividing absolute neutrophil by absolute lymphocyte was used to calculate Neutrophil Lymphocyte Ratio (NLR). The Lymphocyte Monocyte Ratio (LMR) was calculated by dividing the absolute lymphocyte count by the absolute monocyte count. CD15, CD3 and CD 68 immunostaining was used for more identification of neutrophils, lymphocytes and monocytes respectively (Figure 1).

We used Receiver operating characteristic curve were used to calculate both NLR andLMR. NLR of 1.7 was used as the cutoff value to differentiate between high-NLR (≥1.7) and low-NLR (<1.7). LMR of 5.3 was used as cut off value to differentiate between high LMR (>5.3) and LMR (<5.3).

The cut of value of ki67 were considered to be 14%. Ki 67 above 14 was considered high.

The pretreatment tru cut biopsy was used for evaluation of TILs. Fixation with done with formalin 10% andparaffin embedded.

Evaluation of stromal TILs was done using recommended maneuver by TILs working group 2014 [17]. The cut value was 20%. Cases less than or equal 20% were considered low while cases >20% were considered high.

Objectives

Response evaluation criteria version 1.1 was used to assess response [18]. Pathological complete response (pCR/) was the primary endpoint which is defined as the absence of tumor (invasive and/or in situ) both in the breast and axilla (ypT0 ypN0) and correlation between TILs and both NLR and LMR. Secondary andobjectives were overall survival (OS) and disease-free survival (DFS).

Statistical analysis

Spss version 21 was used for analysis. Fisher's exact test or Mann-Whitney U test used to show associations between pathological CR and NLR. LMR, TILs, and different clinicopathological parameters. OS and DFS were estimated using the Kaplan-Meier method and compared using the log-rank test. For multivariate analysis we used cox proportional hazard model (hazard ratios with 95% confidence intervals. A p value <0.05 was considered significant.

RESULTS

Clinicopathological characteristics of 67 patients' triple negative breast cancer were shown in (Table 1).

All cases were female and median age was 47 years old at study start. Cut point of tumor infiltrating lymphocytes, neutrophil lymphocyte ratio and lymphocyte monocyte ratio depend on

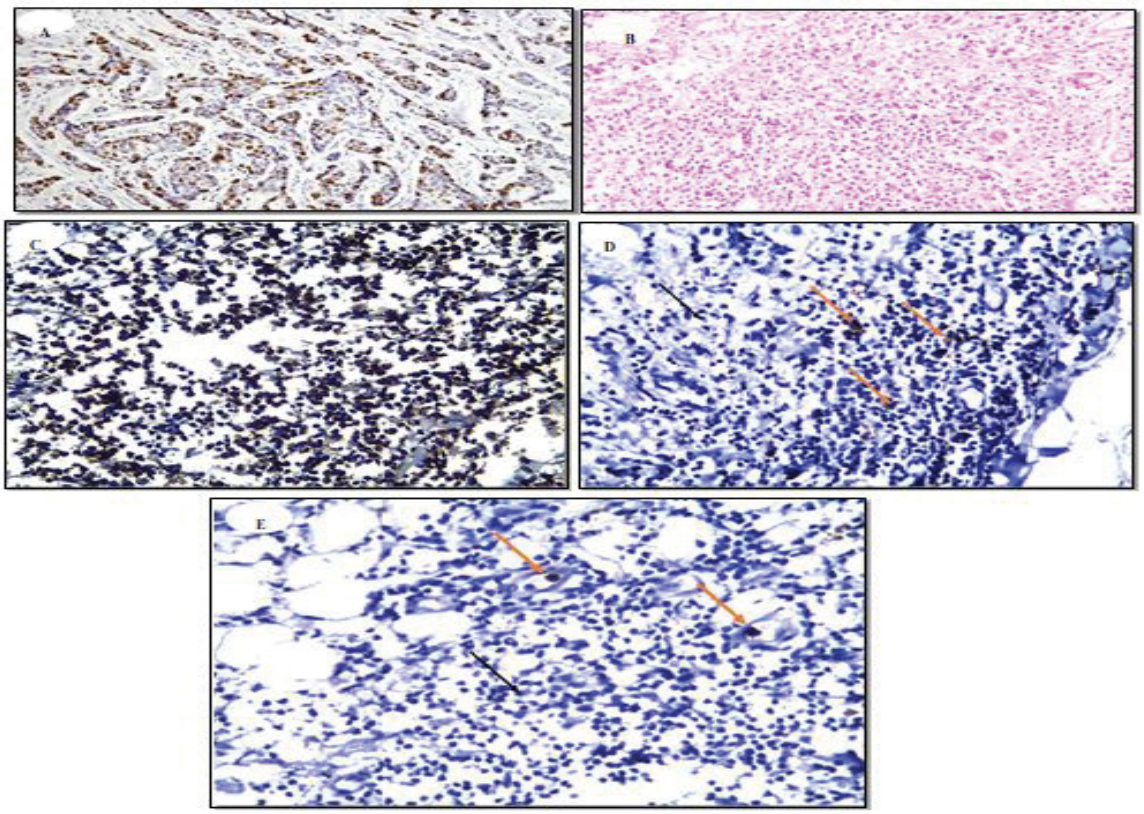

Fig. 1. Case of triple negative breast carcinoma with, (A) Positive ki67 immunostaining more than 14% (X200), (B) Focal area of polymorphic inflammatory cellular infiltrate containing lymphocytes, neutrophils and monocytes (H and E X400), (C) TIL more than 20% with positive CD3 immunostaining (X400), (D) NLR less than 1.7 (0.8), neutrophils with positive CD15 immunostaining (orange arrows) surrounded by negative stained lymphocytes (black arrow) (X400), (E) LMR more than 5.3 (7.1), monocytes with positive CD68 immunostaining (orange arrows) surrounded by negative stained lymphocytes (black arrow) (X400)

Tab. 1. Patient characteristics of 67 patients with TNBC

Clincopathological characteristics	N	%
Age		
<47	34	50.70%
>47	33	49.30%
Menopausal		
premenopausal	40	59.70%
postmenopausal	27	40.30%
Performance status		
0-1	43	64.20%
2	24	35.80%
T stage		
T2	51	76.10%
T3	14	20.90%
T4	2	3%
N stage		
N1	45	62.50%
N2	21	29.20%
N3	1	1.40%
Histology		
IDC	64	95.50%
ILC	3	4.50%
Grade		
01-Feb	47	70.10%
03-Jan	20	29.90%
Her2 neu		
1	15	22.40%
2	62	77.60%
Stage		
IIb	42	62.70%
IIIa	20	29.90%
IIIB	2	3%
IIIc	3	4.50%
Type of surgery		
MRM	27	40.30%
BCS	40	59.70%
Ki 67		
≤ 14%	14	20.90%
>14%	53	79.10%
LVSI		
Present	58	86.60%
absent	9	13.40%
TIL		
≤ 20%	12	17.90%
>20%	55	92.10%
NLR		
>1.7%	17	25.40%
<1.7%	50	74.60%
LMR		
<5.3%	12	19.40%
≥ 5.3%	55	80.60%

receiver operating characteristic curve. It was 20%, 1.7, and 5.3 for TILs, NLR and LMR respectively. TILs were more than 20% in 55 patients (82.1%). NLR was <1.7 in 50 patients (74.6%) and LMR was >5.3 in 55 patients (82.1%).

High TILs were significantly correlated with low NLR (0.03*) and high LMR (0.0001*) (Table 2 and Figure 2).

Pathological CR was correlated was N stage, grade, HER2 (P=0.000), stage, LVSI, TILs, NLR and LMR. Pathological CR was associated with high TILs, low NLR and high LMR. As shown in (Table 3).

As regard overall survival (OS), in univariate analysis the factors with statistical significance were N stage, NLR, TILs and LMR

Tab. 2. Correlation between TIL and both NLR and LLMR

			NLR		Total	p-value
			>1.7	< or equal 1.7		
TILs	< or equal 20%	Count	6	6	12	0.03*
		% within TIL	50.00%	50.00%	100.00%	
		% within NLR	35.30%	12.00%	17.90%	
	>20%	Count	11	44	55%	
		% within TIL	20.00%	80.00%	100.00%	
		% within NLR	64.70%	88.00%	82.10%	
			LMR		Total	p-value
			<5.3	>or equal 5.3		
TILs	< or equal 20%	Count	6	6	12	0.003*
		% within TIL	50.00%	50.00%	100.00%	
		% within LMR	46.20%	11.10%	17.90%	
	>20%	Count	7	48	55	
		% within TIL	12.70%	87.30%	100.00%	
		% within LMR	53.80%	88.90%	82.10%	

* p value less than 0.05

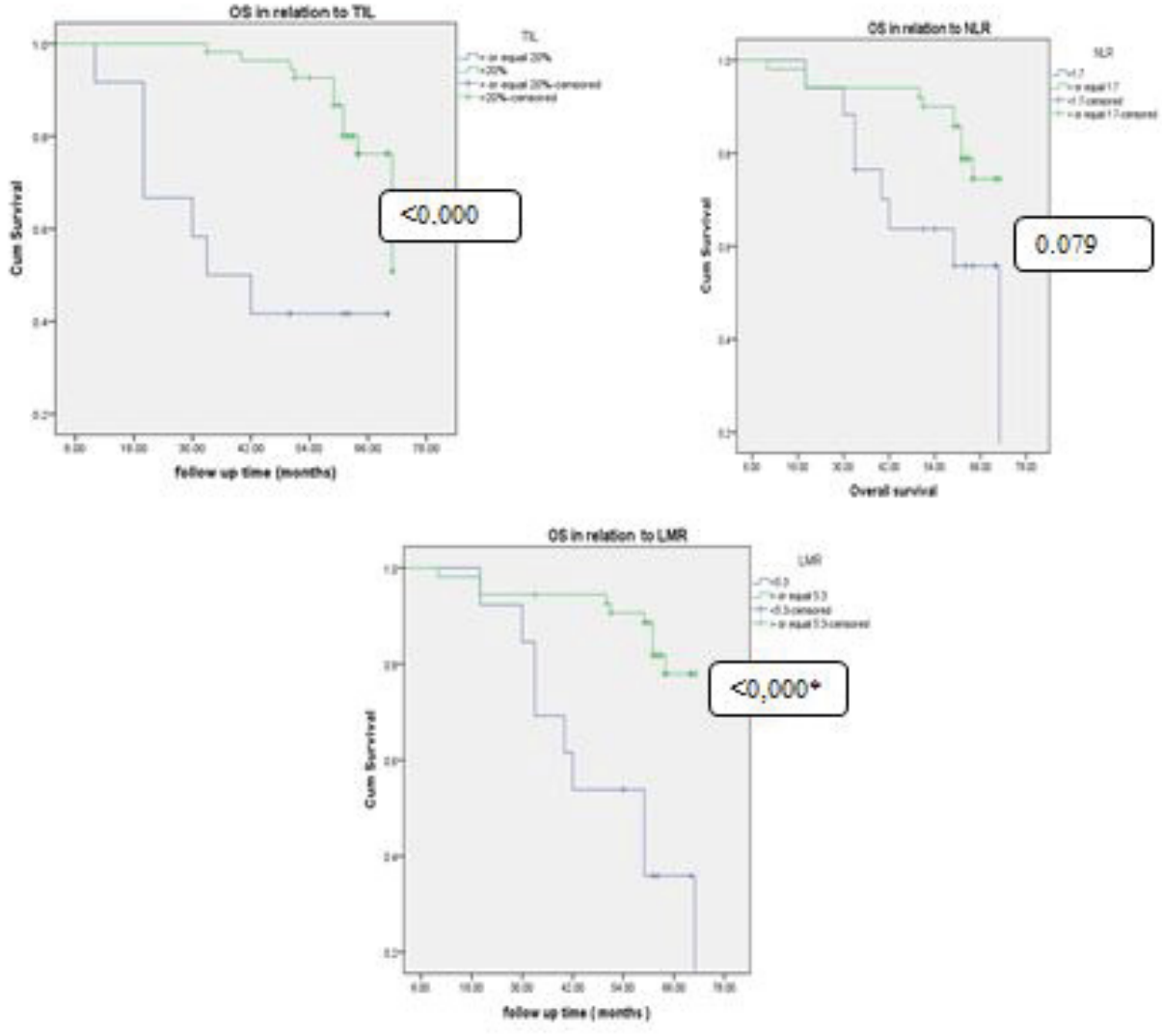

Fig. 2. OS in relation to TIL, NLR and LMR

(Figure 1). While in multivariate analysis, only TILs and LMR maintained their statistical significance (Table 4).

As regard Disease Free Survival (DFS), in univariate analysis the factors with statistical significance were N stage, TILs and LMR (Figure 3). While in multivariate analysis, only TILs maintained their statistical significance (Table 5).

DISCUSSION

Characteristic cancer features depends on tumor microenvironment [19]. Among local inflammatory markers, TILs has been reported to play an important role in immune response [20, 21]. High TILs are associated with response to neoadjuvant chemotherapy in TNBC [22-24]. Systemic

Tab. 3. correlation between response and different clinicopathological factors

Patients characteristics	Response						p-value
	Pathological CR		Partial Response		No Response		
	n	%	n	%	n	%	
Age							
<47	19	51.40%	10	41.70%	5	83.30%	0.188
>47	18	48.6%	14	58.30%	1	17.60%	
Menopausal							
premenopausal	20	54.1%	15	72.50%	5	83.30%	0.375
postmenopausal	17	45.9%	9	36.50%	1	17.60%	
Performance status							
0-1	27	77%	14	58.30%	2	33.30%	0.13
2	10	27%	10	41.70%	4	66.70%	
T stage							
T2	32	86.5%	16	66.70%	3	50%	0.074
T3	5	13.5%	6	25%	3	50%	
T4	0	0%	2	8.30%	0	0%	
N stage							
N1	29	78.4%	12	50%	4	66.70%	0.003*
N2	8	21.6%	12	50%	1	16.70%	
N3	0	0%	0	0%	1	16.70%	
Histology							
IDC	34	91.9%	24	100	6	100	0.28
ILC	3	8.1%	0	0%	0	0%	
Grade							
1-2	30	81.1%	15	62.50%	2	33.60%	0.036*
3	7	18.9%	9	37.50%	4	66.70%	
Her2 neu							
1	7	18.9%	3	12.50%	5	83.30%	0.001*
2	30	91.1%	21	87.50%	1	16.70%	
Stage							
IIb	27	73%	12	50%	3	50%	
IIIa	10	27%	8	33.30%	2	33.30%	0.141
IIIb	0	0%	2	8.30%	0	0%	
IIIc	0	0	2	8.30%	1	16.70%	
Type of surgery							
MRM	12	32.4%	13	54.20%	2	33.30%	0.224
BCS	25	67.6%	11	45.80%	4	66.70%	
Ki 67							
<14%	7	18.9%	24	16.70%	3	50%	0.181
>14%	30	81.1%	0	83.30%	3	50%	
LVSI							
Present	28	75.7%	24	100%	6	100%	0.015*
absent	9	24.4%	0	0%	0	0%	
TIL							
<20%	4	10.8%	3	12.50%	5	100%	0.000*
>20%	3	89.2%	21	87.50%	1	0%	
NLR							
>1.7%	5	13.50%	6	25%	6	100%	0.000*
<1.7%	32	86.5%	18	75%	0	0%	
LMR							
<5.3%	2	5.4%	4	16.70%	6	100%	0.000*
>5.3%	35	94.6%	20	83.30%	0	0%	

* p value less than 0.05

inflammatory markers such as LMR and NLR have been associated with prognosis of breast cancer [25-27]. Correlation between local and systemic inflammatory markers in triple negative breast cancer in neoadjuvant setting has not been evaluated.

The neutrophil lymphocyte ratio and lymphocyte monocyte ratio can be easily derived from peripheral blood count providing easily reproducible method of evaluation of triple negative breast cancer patients in neoadjuvant setting.

Low NLR has been detected in 74.6% of cases and has been associated with high

TILs and this was statistically significant (p value=0.03) [27-29]. High LMR was observed in 80.6% of cases and correlated

Tab. 4. Univariate and multivariate analysis of different clinicopathological with OS

Parameter	Univariate Analysis Sig	Multivariate Analysis Sig
Age ≤ 47 versus > 47	0.799	
Menopause (premenopausal versus postmenopausal)	0.256	
PS (0-1 vs 2)	0.821	
Pathology (IDC vs ILC)	0.712	
T stage (T2 vs T3)	0.001*	0.037*
N stage (N1 vs N2 vs N3)	0.004*	0.188
Stage (IIb vs IIIa vs IIIC)	0.004*	0.428
Grade (00-1 vs 2)	0.807	
LVSI (present vs absent)	0.371	
Ki 67 (≤ 14 vs >14)	0.918	
Surgery (MRM vs breast conservative)	0.682	
TIL (≤ 20% vs >20%)	0.000*	0.011*
NLR (≤ 1.7 vs ≥ 1.7)	0.079	
LMR (<5.3 VS ≥ 5.3)	0.000*	0.193

* p value less than 0.05

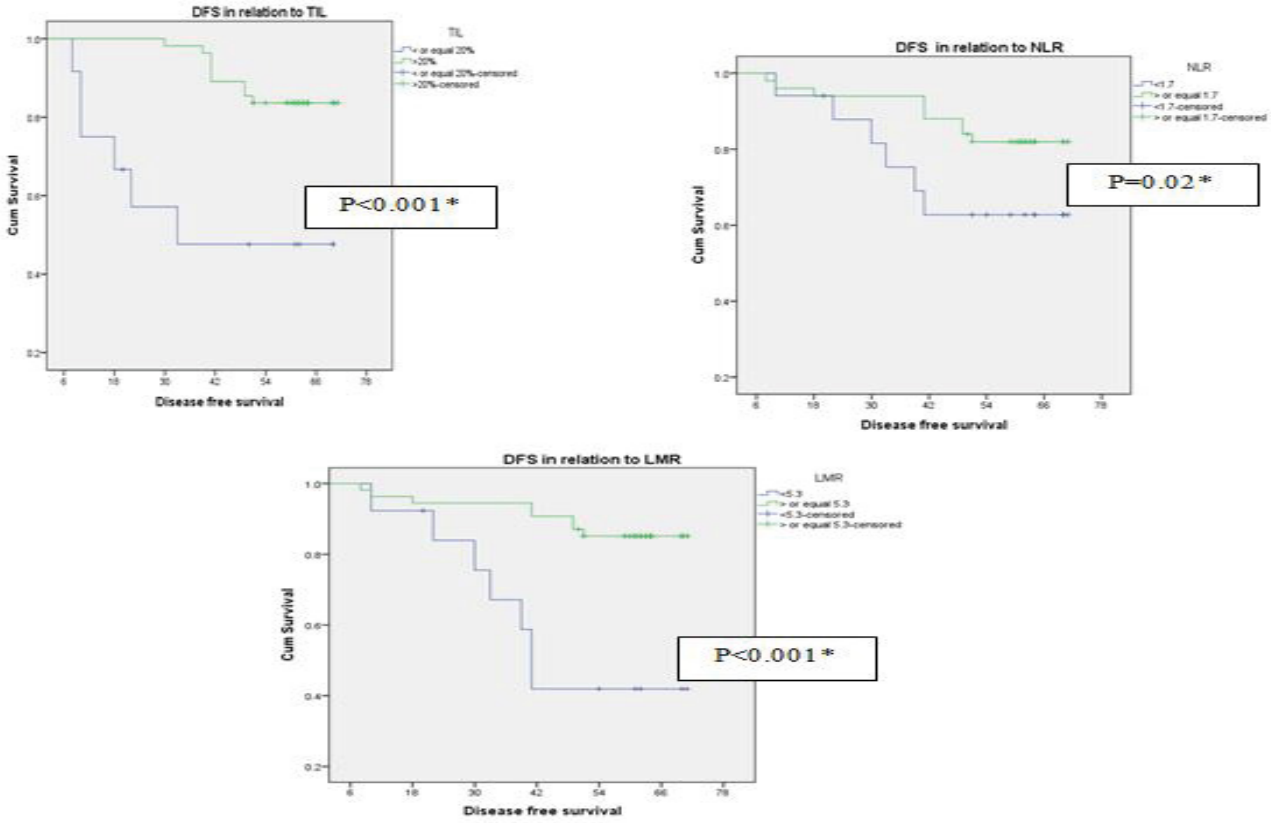

Fig. 3. DFS in relation to TIL, NLR and LMR

significantly with TILs (p value=0.003) [28, 30]. On evaluation of response to neoadjuvant chemotherapy, we found that pathological CR has been statistically significant with low N stage as detected by other authors [31, 32]. Low grade, score of her 2 and low Lymphovascular Space Invasion (LVSI) were statistically significant with pathological CR [33-35]. Pathological CR was found to be associated with high TILs , low NLR and high LMR as reported by many authors [27-30].

Low lymphocyte count is associated with inadequate immunologic response to tumor with resultant progressive tumor and metastases. Inside the tumor the monocytes infiltrate it and are converted to macrophages result also in tumor progression, recurrence, and metastases [36, 37]. Low LMR indicated low lymphocyte count and high monocyte count and so associated with bad prognosis [26, 28]. On evaluation of overall survival (OS), in univariate analysis the factors with statistical significance were N stage, NLR, TILs and LMR. While in multivariate analysis, only TILs and LMR maintained their statistical significance [9].

As regard Disease Free Survival (DFS), in univariate analysis the factors with statistical significance were N stage, TILs and LMR [9, 27]. While in multivariate analysis, only TILs maintained their statistical significance [9].

Tab. 5. Univariate and multivariate analysis of different clinicopathological with DFS

Parameter	Univariate Analysis Sig	Multivariate Analysis Sig
Age ≤ 47 versus >47	0.812	
Menopause (premenopausal versus postmenopausal)	0.491	
PS (0-1 vs 2)	0.751	
Pathology (IDC vs ILC)	0.513	
T stage (T2 vs T3)	0.010*	0.011*
N stage (N1 vs N2 vs N3)	0.031*	0.462
Stage (IIb vs IIIa vs IIIC)	0.058	
Grade (00-1 vs 2)	0.863	
LVSI (present vs absent)	0.33	
Ki 67 (≤ 14 vs >14)	0.871	
Surgery (MRM vs breast conservative)	0.941	
TIL (≤ 20% vs > 20%)	<0.001*	0.008*
NLR (<1.7 vs ≥ 1.7)	0.020*	0.234
LMR (<5.3 VS ≥ 5.3)	<0.001*	0.031*
* p value less than 0.05		

CONCLUSION

In our study we evaluated the pre neoadjuvant systemic and local inflammatory markers as prognostic marker we found that in multivariate analysis, the lymphocyte monocyte ratio maintained their statistical significance with overall survival. While tumor infiltrating lymphocyte maintained their statistical significance as prognostic factors with overall survival and disease free survival.

LIMITATION

The limitation of our study is small sample size, multicenter studies are more warranted to confirm our findings.

CONFLICT OF INTEREST

Authors declares there is no any conflict of interest.

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