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Original Research Article

Nodal Metastasis in Endometrial Cancer Anticipated by Simple Pretreatment NLR and PLR Serum Marker

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Abstract: ***Background:*** Endometrial cancer is the sixth most common malignancy in females according to Globocon data 2020 and has been increasing in recent years. Advanced stage, type II sub type, deep myometrial invasion and lymph node (LN) metastasis are Prognostic factors. Radiological imaging such as MRI quite useful for the detection of disease extent, still MR had a 10% false positive rate and a 35% false negative rate. So Surgical staging becomes mandatory to stage the disease for apparently uterine confined endometrial cancer includes TAH + BSO + LN Assessment either with minimally invasive or open technique along with peritoneal fluid cytology. ***Material And Methods:*** This study was a prospective observational study which was conducted under Department of Surgical Oncology, Government Rajaji Hospital and Madurai Medical College, Madurai. Non metastatic endometrial cancer FIGO stage IA-III who underwent surgical staging were studied. Thus, total 50 patients were studied. The study was carried out for a period of November 2022 to September 2023. The collected data was compiled in Microsoft Excel 2010. Data describing quantitative measures was expressed as mean, median, mean + SD, standard deviation. Qualitative type of data was expressed as percentage or proportion. Data was analyzed using SPSS (Statistical Programme for Social Sciences) software 21 version, Open Epi Software Version 2.3. ***Results:*** A total of 50 patients were enrolled in this study (median age was 58 years, ranging from 30 to 75 years). Mean NLR was 3.5 $\pm$ 0.8 and 2.1$\pm$0.3 in positive and negative cases of lymph node metastasis respectively. And mean PLR was 226.1 $\pm$ 33.4 and 107.9$\pm$41.1 in positive and negative cases of lymph node metastasis respectively. Present study showed that LN metastasis was more frequently observed in patients with Type II tumor ($p < 0.001$), Deep myometrial invasion ($p = 0.01$), Cervical stromal invasion ($p = 0.007$), lymphovascular invasion ($p<0.001$), positive washing cytology, or malignant ascites ($p = 0.003$). It was also seen that the cutoff value of NLR was 2.8 and that of PLR was 201. In the high NLR group using the cutoff value advanced stage, type II cancer, deep myometrial invasion, and cervical stromal invasion were significant. The patients with higher PLR had advanced stage, ovarian metastasis were significant. ***Conclusion:*** The presence of lympho vascular invasion and higher NLR and PLR can predict LN metastasis in endometrial cancer.

Keywords: Inflammatory Markers, NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), Lymph Node metastsis, Endometrial cancer, LVI.

INTRODUCTION

Endometrial cancer (EC) is the most common malignancy of the female reproductive system in developed countries [1]. For early stages [International Federation of Gynecology and Obstetrics (FIGO) stages I or II] of endometrial cancer ,5-year survival accounts for 74–91%. However, for patients diagnosed with stage III or IV disease, 5-year survival rate decreased to 57–66% and 20–26%, respectively [2]. Radiological imaging in form of MRI is useful to stage the disease, still it had 10% false positive rate and a 35% false negative rate [3]. Systemic immune and coagulation responses, as well as alterations in the tumor microenvironment play an important role in the initiation, progression, and control of cancer [4]. Recently, studies have begun exploring prognostic values of inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), as biomarkers of systemic

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inflammatory responses associated with cancer development and progression [5]. Inflammation evidently plays an important role in development of cancer and its progression [6]. Systemic inflammatory markers have been reported to be prognostic and predictive markers in various kinds of cancers [7]. The Neutrophil To Lymphocyte Ratio (NLR) is another marker of systemic inflammatory response and some studies have shown elevated NLR to be a significant prognostic factor in patients with various malignancies.

The Platelet to Lymphocyte Ratio (PLR) is reportedly a significant prognostic indicator in resected pancreatic cancer. Few studies has shown correlation of prognosis of gynecological cancer and NLR and PLR values [8-11]. Therefore, the development of a non-invasive preoperative test with better performance is needed to identify patients with diseased pelvic and/or para-aortic LNs to guide for further adjuvant therapy.

Aim:

To investigate whether lymph node metastasis can be predicted by these inflammatory markers NLR, and PLR independently.

MATERIAL AND METHODS

Present study was a prospective observational study which was conducted under Department of Surgical Oncology, Government Rajaji Hospital and Madurai Medical College, Madurai. Non metastatic endometrial cancer FIGO stage IA-III who underwent surgical staging that including peritoneal wash cytology, total abdominal hysterectomy, bilateral salphingoophorectomy, pelvic lymph node dissection with or without para-aortic node dissection were studied. Thus, total 50 patients were studied. The study was carried out for a period of November 2022 to September 2023.

INCLUSION CRITERIA

Women diagnosed with FIGO stage I to III endometrial cancer {diagnosis was made on biopsy, and staging was done based on the extent of disease on imaging} who candidate for surgical staging.

EXCLUSION CRITERIA

- Metastatic Disease
- Recurrent Disease
- Previous Cancer
- Smoker
- Refused Primary Surgery
- Known Case of Chronic Inflammatory Disease
- Surgically Unfit

All selected cases were studied after taking informed consent. Demographic details were taken and data regarding age at diagnosis, FIGO staging, tumor histology, myometrial infiltration, cervical stromal invasion, LVSI, LN metastasis including pelvic and paraaortic lymph nodes, pretreatment Complete blood count etc. were collected. The collected data was compiled in Microsoft Excel 2010. Data describing quantitative measures was expressed as mean, median, mean + SD, standard deviation. Qualitative type of data was expressed as percentage or proportion. Data was analyzed using SPSS (Statistical Programme for Social Sciences) software 21 version, Open Epi Software Version 2.3. p value <0.05 was considered significant. For quantitative type of data test of significance applied was student t test and for Qualitative data Chi square test was applied.

- NLR was defined as absolute neutrophil count divided by absolute lymphocyte count
- PLR was defined as absolute platelet count divided by absolute lymphocyte count

RESULTS

A total of 50 patients were enrolled in this study (median age was 58 years, ranging from 30 to 75 years). All patients underwent total abdominal hysterectomy or modified radical hysterectomy, with bilateral salpingo-oophorectomy and peritoneal washing cytology and pelvic lymph node dissection and/or para-aortic lynph node dissection. Para-aortic lynph node dissection done in selected cases where intraoperative multiple enlarged suspicious pelvic nodes or intraoperative assement of paraaortic area for enlaged nodes.

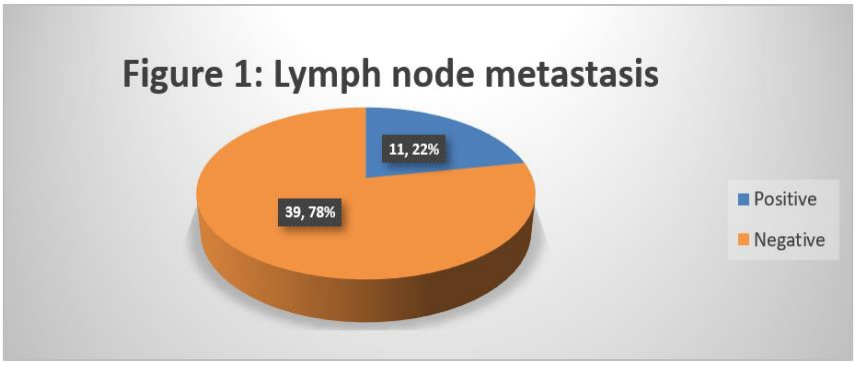

Figure 1: Shows the patient's characteristics according to the LN metastasis status where it was seen that only 11 that is 22 % cases had positive LN metastasis

Mean NLR was 3.5 ± 0.8 and 2.1±0.3 in positive and negative cases of lymph node metastasis respectively. And mean PLR was 226.1 ± 33.4 and 107.9±41.1 in positive and negative cases of lymph node metastasis respectively.

Table 1: Lymphnode metastasis (n=11)

Lymphnode	Frequency	Percentage
Pelvic lymphnode	9	81.8
Para aortic lymphnode +pelvic lymphnode	2	18.2
Total	11	100

Out of 11 patients, para aortic dissection was also done in 2 cases. Both were histologically positive for metastasis and both had higher NLR and PLR.

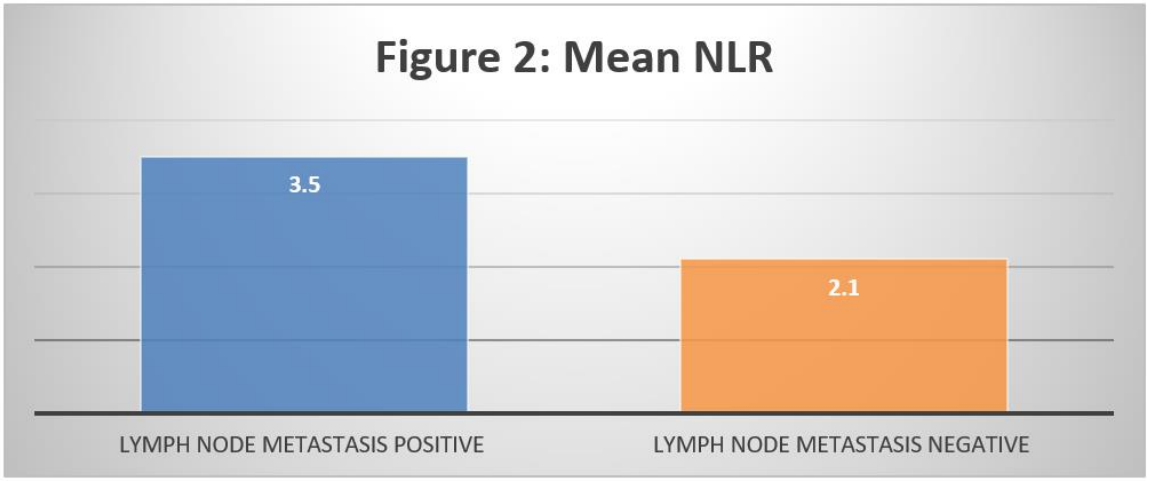

Figure 2: shows that Mean NLR values seen to be higher among lymph node metastatic cases

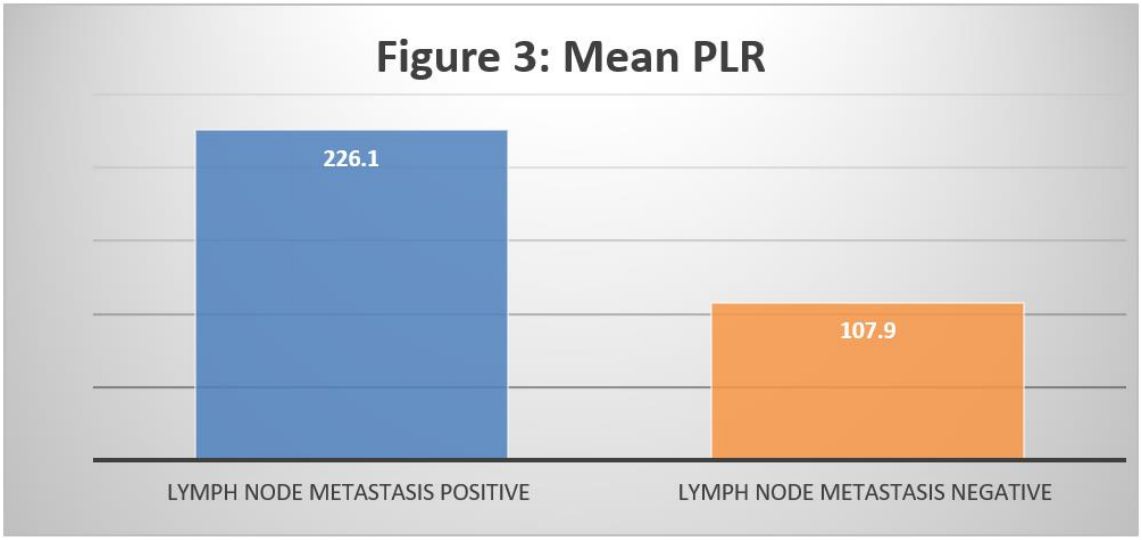

Figure 3: shows that Mean PLR values are higher among lymph node metastatic cases.

Table 2: Characteristics of the patients according to NLR values

Patients	Total	NLR values		P value
		High >2.8 (n=11)	Low <2.8 (n=39)	
Age at Diagnosis in years	50	65.4±10.6	62.3±7.3	0.2
FIGO STAGE				
I	16	0	16	<0.001*
II	17	1	16	
III	17	10	7	

HISTOLOGICAL TYPE				
I	39	4	35	<0.001*
II	11	7	4	
MYOMETRIAL INVASION				
Inner half	23	2	21	<0.001*
Outer half	27	9	18	
CERVICAL STROMA INVASION				
Absent	43	7	36	0.007*
Present	7	4	3	
LVSI				
Absent	44	5	39	<0.001*
Present	6	6	0	
OVARIAN METASTASIS				
Negative	48	9	39	0.003*
Positive	2	2	0	
WASH CYTOLOGY				
Negative	48	9	39	0.003*
Positive	2	2	0	

Table 3: Characteristics of the patients according to PLR values

Patients	**Total**	**PLR values**		**P value**
		High >201 (n=12)	**Low <201 (n=38)**	
Age at Diagnosis in years	50	65.8±10.2	62.5±7.3	0.26
FIGO STAGE				
I	16	0	16	<0.001*
II	17	1	16	
III	17	11	6	
HISTOLOGICAL TYPE				
I	39	4	35	<0.001*
II	11	8	3	
MYOMETRIAL INVASION				
Inner half	23	3	20	0.04*
Outer half	27	9	18	
CERVICAL STROMA INVASION				
Absent	43	8	35	0.01*
Present	7	4	3	
LVSI				
Absent	44	6	38	<0.001*
Present	6	6	0	
OVARIAN METASTASIS				
Negative	48	10	38	0.005*
Positive	2	2	0	
WASH CYTOLOGY				
Negative	48	10	38	0.005*
Positive	2	2	0	

On correlation between NLR and LN metastasis it was seen that Sensitivity-90.9%, specificity 97.4%, Positive predictive value -90.9%, negative predictive value 97.4% and diagnostic accuracy 96%.

Table 4: Correlation between NLR and LN metastasis

NLR level	**LN metastasis**		**Total**	**Univariate analysis Odds ratio**
	Yes	**No**		
High	10	1	11	380 (21.8-6622)
Low	1	38	39	
Total	11	39	50	

On correlation between PLR and LN metastasis it was seen that Sensitivity-100%, specificity 97.44%, Positive predictive value -91.6%, negative predictive value 100% and diagnostic accuracy 98%.

Table 5: Correlation between PLR and LN metastasis

PLR level	LN metastasis		Total	Univariate analysis Odds ratio
	Yes	No		
High	11	1	12	0.94 (0.6668-1.22)
Low	0	38	38	
Total	11	39	50	

Present study showed that LN metastasis was more frequently observed in patients with Type II tumor (p <0.001), Deep myometrial invasion (p =0.01), Cervical stromal invasion (p = 0.007), lymphovascular invasion (p<0.001), positive washing cytology (p =0.003).

Additionally, significantly higher NLR (p<0.001) and higher PLR (p < 0.001) were detected in the patients with LN metastasis.

It was also seen that the cutoff value of NLR was 2.8 and that of PLR was 201. In the high NLR group using the cutoff value advanced stage, type II cancer, deep myometrial invasion, and cervical stromal invasion were significant. The patients with higher PLR had advanced stage, ovarian metastasis as well as positive wash cytology were significant.

DISCUSSION

Our study results concluded that higher NLR and PLR pretreatment value can predict lymph node metastasis in in patients with radiologically negative nodes. As we have enough evidence that support frequent activation of systemic immune response in cancer patient and numerous inflammatory cells have been found in tumor tissue. Elevation of immune response is associated with poor survival in multiple cancer [12]. Carcinoma of endometrium also showing correlation with higher NLR and prognosis [13]. LN dissection has not given any therapeutic survival advantages in early stage endometrial cancers. So selective LN dissection might be an option for treatment of early stages due to paucity of reliable LN assement for metastasis preoperatively [14]. Still prognostic factors of pathological lymph node metastasis were evident only after surgical staging [2].

Present study showed that median age was 58 years, ranging from 30 to 75 years and mean age was 60.8 years. Study by Isa Temur *et al.,* [4] showed that mean age was 57.2 and median was 58 (27-91) years.

Higher NLR and PLR can be surrogate marker for para aortic LN metastasis.

Mean NLR was 3.5 $\pm$ 0.8 and 2.1$\pm$0.3 in positive and negative cases of lymphnode metastasis respectively. And mean PLR was 226.1 $\pm$ 33.4 and 107.9$\pm$41.1 in positive and negative cases of lymph node metastasis respectively. Till now there is no consensus regarding optimal cutoff value of NLR or PLR used to predict LN metastasis in endometrial cancer.

In the study by Suh *et al.,* [15], the cutoff value of NLR was 1.97.

Study by Isa Temur *et al.,* [4] showed that mean NLR was 2.8 and 2.3 and mean PLR was 146.3 and 133 in positive and negative cases of lymphnode metastasis respectively, whereas study by Cong, R *et al.,* [6] showed that mean NLR was 2.01 and PLR was 121.11 in positive cases.

And in our present study the cutoff value of NLR and PLR was 2.8 and 201 respectively.

Figure 1 shows the patient's characteristics according to the LN metastasis status where it was seen that only 11 I.e 22% cases had positive LN metastasis.

Figure 2 shows that Mean NLR values seen to be higher among metastatic cases.

Figure 3 shows that Mean PLR values are higher among metastatic cases.

Present study showed that on correlation between NLR and LN metastasis it was seen that Sensitivity-90.9%, specificity 97.4%, Positive predictive value -90.9%, negative predictive value 97.4% and diagnostic accuracy 96% and on correlation between PLR and LN metastasis it was seen that Sensitivity-100%, specificity 97.44%, Positive predictive value -91.6%, negative predictive value 100% and diagnostic accuracy 98%. Study by Isa Temur *et al.,* [4] found sensitivity of 63% and a specificity of 72% for NLR.

Present study showed that Significance was seen for Type II tumor (p <0.001), Deep myometrial invasion (p =0.01), Cervical stromal invasion (p = 0.007), lymphovascular invasion (p<0.001), positive washing cytology (p =0.003). Higher NLR(p<0.001) and higher PLR (p < 0.001) were detected in the patients with LN metastasis.

Study by Isa Temur *et al.,* [4] showed significant parameters for deep myometrial invasion, cervical invasion, and LVSI (p = 0.033, 0.001; p = 0.01,

0.026; and 0.01, 0.01, respectively). NLR, and PLR were revealed to be statistically significant with regard to lymph node involvement ($p = 0.001$, $p = 0.006$, and $p = 0.001$, respectively).

As per our study report, NLR and PLR can be used suurogate marker to predict lymph node metastasis and avoid surgical complication associated with pelvic or paraaortic lymph dissection.

All our these 50 patients are under follow up as per guidelines to evaluate outcome which correlates with NLR and PLR ratio.

We concede that our study has certain shortcomings. It was a performed in a single institution with limited number of cases. More distant analyses is required using a large number of cases from different institutions to confirm the results and to discover appropriate cutoff values.

CONCLUSION

The presence of lympho vascular invasion and higher NLR and PLR can predict LN metastasis in endometrial cancer. They are easy-to-use, inexpensive and accessible markers in each health care center. Further studies are required to determine thresholds for eliciting their predictive values.

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