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Predictive value of preoperative neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in predicting lymph node metastasis in endometrial cancer

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ABSTRACT

Background: Predicting lymph node metastasis in endometrial cancer patients is one of the most critical elements in assessing disease prognosis and selecting whether to undertake lymphadenectomy. There is limited and contradictory information about the predictive efficacy of neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratio in predicting lymph node metastasis.The purpose of the present study was to evaluate the predictive efficacy of preoperative neutrophil and platelet-to-lymphocyte ratios for predicting lymph node metastases in endometrial cancer patients.

Materials and methods: This retrospective study was conducted on the medical records of endometrial carcinoma patients treated at Al-Zahra Hospital in Tabriz with gynecological cancers in between 2016 -2020. Demographic data including age, initial symptoms, history of cancer, chemotherapy, serum Cancer Antigen 125 (CA125) level, pre-operative level of complete blood count (CBC), white blood cells (WBCs), neutrophils, lymphocytes, monocytes, hemoglobin, curettage result, and cancer surgery stage were extracted from patient's files. We utilized the receiver operating characteristic curve (ROC) to calculate the optimal value of the cut-off point for NLR and PLR. All analyses were conducted using Statistical Package for the Social Sciences (SPSS) 26.

Results: From the total of 131 participants, More than two third histopathological subtype was endometrioid endometrial carcinoma [73.0%]. The ROC curve revealed that the cut-off for NLR and PLR was 2.47 and 62.67, respectively. The rising trend of NLR is a prognostic marker for lymphatic metastasis, according to a logistic regression analysis [hazard ratio = 1.20; 95% [CI], 1.5-2.3; P = 0.001]. Although the rising trend of PLR was associated with an increased risk of lymph node metastasis, it has no significant predictive value in the present model P= 0.1]

Conclusion: The rising trend of NLR can be utilized as an independent predictor of lymphatic metastasis in women with endometrial cancer and can aid clinicians in pre-operative risk stratification and treatment strategy.

Keywords: *Endometrial carcinoma, metastasis to lymph nodes, neutrophil to lymphocyte, platelet to lymphocyte ratio*

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INTRODUCTION

Endometrial carcinoma is the fourth most prevalent cancer following breast, lung, and colon cancers, and the third highest cause of cancer-related death among women [1]. This cancer accounts for 6.0% of all female cancers worldwide and 2.35% of female cancers in Iran [2, 3]. However, 70-75% of patients are diagnosed with cancer in stage I, which has a positive prognosis. As a result, 80.0% of all cancer cases identified in stage I survive for 5 years [4]. The prevalence of endometrial cancer has grown recently all over the world. Obesity has been proposed as one of the primary causes of this malignancy, along with aging and a drop in the rate of hysterectomy for benign uterine tumors [5].

Endometrial carcinoma is classified into two categories based on etiology, molecular features, and clinical behavior [6]. Type I endometrial cancer is the most frequent, accounting for about 80% of all occurrences. Endometrioid endometrial carcinoma (EEC) is the most frequent type of cancer in this group; it arises in premenopausal women as part of premalignant hyperplasia and is usually estrogen-progesterone positive. Type II of this malignancy, which typically develops in the postmenopausal atrophic condition, is receptor negative and has a poor prognosis; serous or clear cell carcinomas are common kinds in this group. [7]. The other type is endometrial carcinosarcoma, which was previously known as Müllerian mixed malignant tumors but is now classified as metaplastic cancer with an extremely poor prognosis [8] and is classed as type II.

In most cases, surgery is the only way to achieve complete recovery [9-11], which includes hysterectomy, adnexal residual removal, and pelvic and para-aortic lymphadenectomy [12]. Despite many efforts over the years to improve diagnostic criteria and surgery, radiotherapy, and chemotherapy treatments, endometrial cancer management faces a significant risk of recurrence, and discussing the use of lymphadenectomy in treatment can be difficult and challenging due to changes in histological classification [12-13]. Yet the therapeutic effectiveness of lymphadenectomy is debatable, as it may increase postoperative complications, and even two randomized studies have called into doubt the usefulness of routine lymphadenectomy on patients' survival [14-15]. On the other hand, other studies suggest that individuals who have not been diagnosed with lymphatic metastases and just undergo hysterectomy without lymphadenectomy or postoperative radiation have a very poor prognosis [16, 8]. As a result, identifying characteristics that can predict lymph node metastasis prior to surgery or even after hysterectomy without lymphadenectomy is extremely valuable [17].

The combined use of magnetic resonance imaging (MRI) and serum Cancer Antigen 125 (CA125) imaging, estimation of tumor size, myometrial invasion, the histological type and tumor grade, lymphovascular space invasion (LVSI), and immunological staining of estrogen and progesterone receptors in endometrial tissue have been cited as predictors of lymph node metastasis [18-23]. However, their usefulness is limited by the expense and time required to investigate such aspects. Therefore, research in the field of predictive biomarkers, from genomic to molecular, is constantly required for this topic, so that not only is prediction accurate but also that it is cost-effective. The significance of this prediction is especially essential before surgery; therefore, a simple preoperative blood test is very important for predicting the prognosis of patients with endometrial carcinoma (EC), which has piqued physicians' interest recently [22-23]. The ratios of inflammatory markers neutrophil-to-lymphocyte ratio(NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) have been extensively used to forecast the prognosis of colorectal cancer [26], lung cancer [27], esophageal cancer [28], and breast cancer [29]. This is because the host's response to malignant tumors is associated with a process of systemic inflammation that causes thrombocytopenia, increased neutrophils, and lymphocytopenia [23–24].

Limited studies have been undertaken and contradicting outcomes have been reported in connection to the prediction of lymphatic metastasis and the decision for lymphadenectomy in patients with endometrial cancer in the early stages of the disease [30-31]. Furthermore, the necessity of performing lymphadenectomy in the treatment of these patients is suspected due to the lack of likelihood of impact on the disease's prognosis [33, 32]. As a result, selective lymph node dissection should be considered as a therapy option in the early

stages of endometrial cancer. These signs can be measured and examined as part of routine patient testing, but they are still classified as new biomarkers. As a result, we can now evaluate the significance of lymph node dissection and easily gather peripheral blood markers to evaluate at-risk patients and reduce the costs of treatment. Therefore, the purpose of the present study was to evaluate the predictive value of preoperative NLR and PLR in lymph node metastasis in endometrial cancer.

MATERIALS AND METHODS

Study population

The present retrospective cross-sectional analysis was conducted on the medical records of 165 endometrial cancer patients treated at Al-Zahra Hospital in Tabriz between 2016 and 2020, after receiving the required permissions and ethical code [IR.TBZMED.REC.1400.034]. The patients' informed consent was also obtained via the phone and verbally.

Patients with a definite diagnosis of endometrial cancer who had therapy and surgery at Al-Zahra Hospital in Tabriz and had a complete blood count (CBC) the day before the surgery were included in the research.

Patients without full blood count data before surgery were excluded. Patients with incomplete clinico-pathological data, with simple hyperplasia, sarcoma diagnosis in histopathology result, with other simultaneous malignancies or hematologic disorders, or those that received radiotherapy or chemotherapy before surgery were also excluded.

Finally, 165 medical records of endometrial cancer patients were reviewed in terms of inclusion criteria, and data from 131 cases qualified to participate in the research were collected and analyzed.

Data collection

Demographic, clinical and pathological data of the patients including age, number of pregnancies and deliveries, initial symptoms at the time of visit, disease records, Pap smear results, history of cancer, history of chemotherapy, serum CA125 level, pre-operative CBC, WBC, neutrophil , lymphocyte, monocyte, hemoglobin, Pipelle biopsy result or endometrial curettage, and stage of the disease based on the criteria of the Federation of Gynecology and Obstetrics (FIGO) and the status of disease recurrence in the last follow-up were extracted from the hospital records. It should be noted that the decision to manage the treatment was made based on the FIGO protocol in this hospital. The NLR and PLR were the independent variables in this research. This study's dependent variable was lymph node metastasis, whereas the background factors were age, number of pregnancies and deliveries, diabetes, hypertension, or other chronic conditions. The data was then imported into SPSS 26.0 and evaluated. The dispersion and frequency indices of demographic and clinical data were determined using descriptive tests. The cut point of both ratios was determined using the ROC curve. The predictive value of NLR and PLR to predict lymph node metastasis was investigated using univariate and multivariate regressions.

Statistical analysis

Statistical analysis was performed using IBM SPSS 26.0 (SPSS, Inc., Chicago, Illinois, USA). All included participants were stratified according to the preoperative NLR and PLR cutoffs, which were generated by a receiver operating characteristic (ROC) curve. Survival analysis of the ratios was performed using Kaplan-Meier analysis, and the P value was used to identify significant differences between groups. The Cox proportional hazard models and the Schoenfeld residuals test were conducted to respectively evaluate the hazard ratios and proportional hazard assumptions of the variables. Associations between continuous and categorical variables were analyzed using the independent t-test and the chi-square test. A logistic regression analysis was conducted on the following NLR and PLR and lymphovascular invasion (absent, present). All tests were two-sided, and a P value < 0.05 was considered statistically significant. R software was used to establish the nomogram to indicate the relationship between possible prognostic factors and actual OS, and Harrell’s concordance index (C-index) and a calibration curve were used to measure discriminative capacity. If the C-index is over 0.7 and the calibration curve is approximately matching with the basic curve, the nomogram will be of good prognostic significance.

RESULTS

Finally, information on 131 patients with endometrial cancer who were sent to Al-Zahra Hospital for treatment was examined, and the average age of the patients was 57.16±9.40, according to the data.

From the total of 131 participants, [90.9%] patients were diagnosed at stage I or II, while [9.1%] were diagnosed at stage III or IV. The majority of the patients underwent hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy [88.0%]. More than two third histopathological subtype was endometrioid endometrial carcinoma [73.0%] [Table1]. The mean NLR and PLR were 2.10 [range 0.73–56.14] and 156.84 [range 72.06–738.45] respectively. ROC curves were generated to identify the optimal cutoffs for the NLR and PLR [Fig. 2]. A cutoff of 2.74 [area under the curve, AUC = 0.723] for the NLR had the highest Youden index. Similarly, cutoffs of 62.66 [AUC = 0.632] was identified for the PLR. For further analysis, we dichotomized patients into low and high groups by the cutoffs. Chi-square tests [$P < 0.05$] showed that the NLR and PLR were significantly associated with patient age and clinical stage. Table 2 shows that a high NLR and PLR were not associated with in the univariate lymph node metastases analysis and the multivariate analysis [$P > 0.05$] [Table2]. But in the subgroup analysis, the HRs of an increasing values of NLR, PLR [trend NLR and PLR] were1.32[0.76 to 1.97] and 1.4[0.78 to 1.75]; $P<0.0001$ and showed good prognostic value in multivariate analyses. Some clinical characteristics, including patients older than 50 years and patients with Stage III to IV were also significantly associated with lymph node metastases in both the univariate and multivariate analyses [Table3]. As the multicollinearity was detected as low level, all the variables were retained in the model. Besides, no violations of proportional hazards or other model assumptions were found by testing Schoenfeld residuals. Kaplan-Meier analysis. the results indicated that patients with high preoperative NLR and PLR had significantly higher risk for lymph node metastases.

TABLE 1: Demographic and clinical profile of patients

Variable		N=131 Quantity [%]	Variable		N=131 Quantity [%]
Age		*[9.54]57.6	Pipelle-biopsy	Endometrioid carcinoma	[47.32]62
				Adenocarcinoma	[32.06]42
Number of deliveries	No records of delivery	[23.74]28		Serous carcinoma	[6.87]9
	1	[4.13]5		Sarcoma	[3.81]5
	≥2	[72.06]98		Atypical hyperplasia	[9.92]13
First symptoms	AUB	[31.29]41			
	PCB	[2.29]3			
	PMB	[66.41]87	MRI	Normal	[40.45]53
PMH	Normal	[34.35]45		Endometrial mass <10mm	[58.01]76
	HTN	[58.34]77		Endometrial mass > 10mm	[1.70]2
	Diabet	[6.87]9	Ultrasound	Normal	[34.35]45
Cancer History	No	[90.83]119		Endometrial mass	[65.64]86
	Yes	[9.16]12	Hysto-pathology	Endometrioid carcinoma	[84.73]111
Lymph node metastasis	No	[90.83]119		Serous carcinoma	[11.45]15
	Yes	[9.16]12		Clear cell	[3.05]4
				Normal	[0.76]1
Lab values		Mean [S.D]	Lab values		Mean [S.D]

[Blood analysis]		[Blood analysis]	
CA125	[69.20]36.79	Neutrophil	[1977.00]3765.30
Hb	[1.80]12.55	Platelet	[6449.16]280121.73
Lymphocyte	[976.69]1786.14	White blood cell [WBC]	[2838.09]6087.32
Monocyte	[3.87]5.36		

AUB: Abnormal Uterine bleeding, PCB: post coital bleeding, PMB: Post Menopause Bleeding,

HTN: Hypertension

*Mean [standard deviation]

TABLE 2: Univariate and multivariate regression analysis in evaluating the variables of clinicopathology, NLR and PLR in predicting lymph node metastasis

Variable		Univariate		Multivariate	P value
		HR[CI95%]	P value	HR[CI95%]	
Age	<50	1[Reference]		1[Reference]	
	≥50	1.02[0.41 to 1.50]	0.03	0.40[0.33 to 0.71]	0.04
Stage	I-II	1[Reference]		1[Reference]	
	III-IV	1.30[0.93 to 1.61]	0.01	0.75[0.44 to 1.10]	0.05
Grade	1	1[Reference]		1[Reference]	
	≥2	1.01 [0.77 to 1.93]		0.91 [0.54 to 1.89]	
Diabetes	No	1[Reference]		1[Reference]	
	Yes	1.21 [-0.90 to 2.82]		0.71 [-0.40 to 1.92]	0.30
Lymph node metastasis	No	1[Reference]		1[Reference]	
	Yes	1.52[1.02 to 2.19]	0.02	0.74[0.53 to 1.16]	0.04
Histopathological Sub type	Endometrioid carcinoma	1[Reference]		1[Reference]	
	Serous carcinoma	0.65 [-0.21 to 1.42]	0.4	0.37 [-0.13 to 0.84]	0.2
	clear carcinoma	0.64 [-0.24 to 1.39]	0.1	0.27 [-0.23 to 0.76]	0.2
NLR	Low<2.47	1[Reference]		1[Reference]	
	High≥2.47	0.3[-0.1 to 0.8]	0.8	0.02[0.2 to -0.07]	0.9
PLR	Low<62.66	1[Reference]		1[Reference]	
	High≥62.66	0.1[-1.4 to 2.2]	0.5	0.02[0.1 to -0.06]	0.7

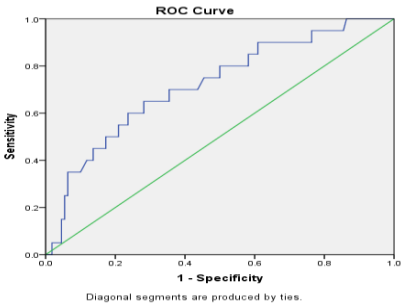

FIG 1: ROC curve of the predictive value of neutrophil-lymphocyte in diagnosing lymph node metastasis in endometrial cancer patients

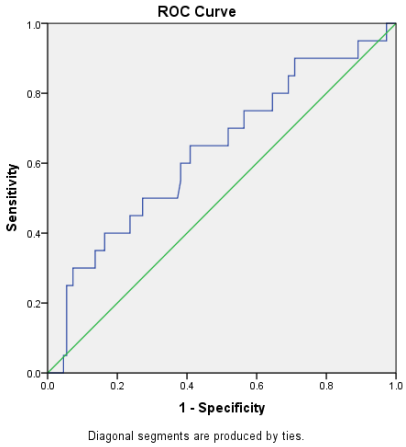

FIG 2: ROC curve of platelet-lymphocyte predictive value in diagnosing lymph node metastasis in endometrial cancer patients

TABLE 3: Univariate and multivariate regression analysis in evaluating NLR and PLR variables in predicting lymph node metastasis in trend and normal states

Variable		Univariate		multivariate	
		HR[CI95%]	P value	HR[CI95%]	P value
Lymph node metastasis	No	1[Reference]		1[Reference]	
	Yes	1.18[1.13 to 2.54]	0.01	0.91[0.64 to 1.25]	0.01
NLR	Low	1[Reference]		1[Reference]	
	High	0.93[-0.44 to 1.68]	0.3	0.03[0.10 to -0.04]	0.8
Trend NLR	Low	1[Reference]		1[Reference]	
	High	1.90[1.15 to 3.27]	0.01	1.32[0.76 to 1.97]	0.0001
PLR	Low	1[Reference]		1[Reference]	
	High	0.18[-1.47 to 2.61]	0.7	0.02[-0.12 to 0.06]	0.9
Trend PLR	Low	1[Reference]		1[Reference]	
	High	1.65[1.04 to 2.72]	0.03	1.4[0.78 to 1.75]	0.0001

DISCUSSION

This was the first research to look at the prognostic efficacy of NLR and PLR in predicting lymphatic metastasis in endometrial cancer patients. In our study, higher cut off for NLR and PLR were not prognostic factors for lymph node metastasis prediction. But the elevated trend of the above ratios was an independent predictor for lymph node metastasis. The findings are consistent with some previous studies [34, 35] discussing the prognostic value of the NLR and PLR for lymph node metastasis, but none of them focused on predictive values of the increasing trend of these ratios for lymph node metastasis.

Prior research has focused mostly on survival, and since no comparable studies were located, we relied instead on studies that looked at the predictive value of ratios in predicting cancer survival. In line with our study, Illgen et al. found that the NLR was higher in individuals with endometrial cancer than in those with hyperplasia with or without atypia. However, there was no significant difference in PLR between the two groups. Perhaps the divergent findings might be explained by the fact that one study focused on pathology and the other on the capacity to predict lymph node metastasis. Other variables, such as the frequency of type and grade of cancer in two studies, may also contribute to this disparity [34]. Unal et al. discovered that the prognostic influence of PLR and NLR on lung cancer survival was closely associated with the overall survival index and the disease-free survival index. They also found that

lymphatic metastasis is related to the prognosis of lung cancer, which is consistent with our findings indicating the prognostic efficacy of high ratio values in lymphatic metastasis [35]. In another study, Ural et al., [2014], investigated the potential association between NLR and PLR and the pathology outcomes of individuals with abnormal vaginal bleeding. Their findings revealed a significant correlation between NLR and endometrial cancer pathology reports. The reports on NLR were comparable to those of the current investigation, but those of PLR were different. The purpose of the current research was to assess the ability of NLR and PLR in predicting lymph node metastasis, or the ability to predict tumor spread, which makes the comparison rather challenging. Perhaps the difference in the significance of PLR in the present study is because tumors of this nature tend to spread and invade lymph nodes, affecting the amount of NLR and PLR, whereas in the previous study, the frequency of this type of tumor was low, which explains why the relationship between PLR and cancer pathology was not significant [36]. Dong et al., investigated the values of NLR and PLR to predict the survival index of endometrial cancer. They discovered that an NLR greater than 2.47 is an independent index for predicting all survival indices of cancer patients, including overall survival, specific survival, and cancer-free survival, which contradicts the findings of the current investigation. The reason for the discrepancy between the two studies is the different nature of the objectives, so that the findings of the regression model in the previous study indicated the suitability of NLR for predicting survival, whereas the findings of the current study indicate that this ratio is not appropriate for decision-making and action during or after the operation for determining lymph node metastasis [37]. Consistent with our findings, Cong et al and Illgen et al found a significant effect of NLR in predicting survival rates due to endometrial cancer, using an NLR cut-off point of 2.43; however, neither of these studies used regression analysis to investigate the effect of potential factors affecting the prognosis of endometrial cancer [38, 34]. CummHaruma et al. investigated the prognostic effect of NLR and PLR on endometrial cancer patients' survival. The regression study revealed that NLR, PLR, and a combination of other inflammatory indices and ratios may accurately predict cancer survival [39].

Significance and limitations

Given that there are few studies in this field and that identifying predictive factors of lymphatic metastasis is effective in adopting a suitable and timely treatment approach in patient survival and disease prognosis, the findings of the current study demonstrate the value and importance of the study in evidence-based practice. Because the data were retrospective, it was not feasible to obtain some information that required real-time investigations, which is one of the current study's drawbacks, as it does not allow for the testing of some hypotheses. On the other hand, the variety of carcinomas introduced may limit practical conclusions in the field of endometrial malignancies. However, it is hoped that the findings of this study would serve as a foundation for future applied research.

CONCLUSION

According to the results of this study, NLR and PLR did not predict lymphatic metastasis in patients with endometrial carcinoma. However, the results of the regression model showed that the increasing trend of NLR and PLR is a predictor of lymphatic metastasis in patients with endometrial carcinoma. So, it is suggested that future studies investigate each of the subtypes of endometrial cancer with a certain frequency and inflammatory indicators, so that regression analysis can give us more specific answers for predicting how cancer will behave.

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