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Positive correlation between NLR and PLR in 10,458 patients with endometriosis in reproductive age in China

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Abstract. – OBJECTIVE: The platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR), which can be easily measured from whole blood counts, are composite reflections of significant inflammatory response pathways. However, the relationship between PLR and NLR in patients with ovarian endometriosis is only partially supported by clinical evidence. This study aimed at identifying useful markers for early diagnosis by examining the relationship between PLR and NLR in patients with ovarian endometriosis.

PATIENTS AND METHODS: Between June 2015 and December 2022, we gathered clinical data of 10,458 endometriosis patients who visited the Gynecology Division of the Affiliated Hospital of Jining Medical University. All statistical analyses were performed using the R statistical package.

RESULTS: The results of the univariate analysis, smoothed curve fitting, multiple regression analysis, and subgroup analysis revealed that NLR was always positively correlated with PLR. Further analysis based on the curve fitting threshold effect revealed a significant positive correlation between NLR and PLR when NLR < 2.07 (β: 34.49). Furthermore, when NLR > 2.07, there was a significant positive correlation between NLR and PLR (β: 16.93).

CONCLUSIONS: The finding that NLR and PLR have a positive correlation confirms that inflammation plays a role in the pathogenesis of ovarian endometriosis. Therefore, PLR and NLR could be used as new biomarkers for the diagnosis of endometriosis.

Key Words:
Endometriosis, Diagnosis, Inflammatory response, Platelet-lymphocyte ratio, Neutrophil-lymphocyte ratio.

Abbreviations
Ems: endometriosis; PLR: platelet-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; OE: ovarian endometriosis; BMI: body mass index; LRT: likelihood ratio test; COVID-19: coronavirus disease 2019.

Introduction

Endometriosis (Ems) is a chronic, systemic disease marked by the implantation and expansion of endometrial tissue outside the uterus, most frequently in the ovaries. It affects 10% of women in reproductive age and results in a range of symptoms, including chronic pelvic pain, dysmenorrhea, and infertility, lowering patients' quality of life and causing serious economic and social issues for families and patients[1-3]. It is therefore particularly important to find an effective monitoring indicator to guide the early diagnosis of Ems. In-depth research[4-6] has demonstrated that the inflammatory response is crucial to the pathogenesis of endometriosis. Additionally, earlier research[7,8] has demonstrated that endometrial cells influence the onset of Ems by expressing related inflammatory factors. Nevertheless, there are few studies[9] examining the connection between the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) in endometriosis patients.

The biomarkers of inflammation, NLR and PLR, are widely available and reproducible[10,11], and numerous studies[12-16] on the connection between PLR and NLR in cancer, cardiovascular disease, rheumatoid arthritis, acute rheumatic fever, and other illnesses have been conducted. It has been demonstrated[17] that PLR and NLR can predict the onset of pre-eclampsia and eclampsia in pregnant women. The prognosis of gynecological tumors, like sarcomas and endometrial cancer, has also been linked to PLR and NLR[18,19]. In recent literature[9,20], the significance of PLR and NLR in the differential diagnosis of Ems and other diseases has been emphasized.

In order to better understand the role of inflammation in Ems, this study set out to compare PLR and NLR in patients with the disease. It also aims at providing a newly discovered marker of inflammation for the diagnosis of Ems.

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Patients and Methods

Study Design and Population

The Jining Medical University Hospital Ethics Committee approved this single-center cross-sectional study (approval number: 2022C064). Furthermore, since the study was conducted retrospectively, informed consent was not required.

Data were initially collected from 10,458 participants. The participants' entry and inclusion deadlines were June 2015 and December 2022, respectively.

Inclusion criteria: (1) preoperative clinical presentation and ancillary tests for diagnosing Ems, (2) post-operative pathological diagnosis of Ems, and (3) women in childbearing age.

Exclusion criteria: (1) antibiotic or antithrombotic therapy administered within 3 months pre-operatively, (2) hematological disorders, cachexia, autoimmune diseases, metabolic disorders, hypersplenism or current infections, (3) permanent immunomodulatory medicines, glucocorticoids or anti-inflammatory drugs, (4) patients over the age of 18, (5) pregnant or breastfeeding females, and (6) previous medication or surgical therapy for endometriosis.

To protect patients' privacy, data from the electronic patient record systems in hospitals that did not include identifiable information were obtained. In the final analysis, 9,524 patients were enrolled. The study population was divided into the Low-Body mass index (BMI) group (BMI < 24.00 kg/m^2) and the High-BMI group (BMI ≥ 24.00 kg/m^2), based on BMI values.

Variables

Patients' age and BMI, as well as routine blood indices, were all collected retrospectively. During the hospitalization, routine blood indices were recorded. After an 8-hour fast, peripheral venous blood was collected and processed in the laboratory. Using the same blood sample, PLR was calculated by dividing the platelet count by the lymphocyte count, and NLR was calculated by dividing the neutrophil count by the lymphocyte count. All measurements were taken by our hospital's laboratory technicians and inspectors.

Statistical Analysis

Continuous variables normally distributed were represented by the average standard deviation, whereas non-normally distributed continuous variables were represented by medians. Categorical variables were also expressed as frequencies or percentages. To compare differences in categorical, normally distributed, and non-normally distributed variables among NLR quartile groups, the Chi-square test, one-way analysis of variance, and Kruskal-Wallis' test were used. The data analysis was carried out in two stages. Step one involved developing multivariate linear regression models that were adjusted according to patient characteristics and significant variables in the univariate analysis. To address the nonlinear issues of NLR and PLR, the generalized additive model and smooth curve fitting (punitive spline method) were used in step two. If nonlinearity was found, the recursive algorithm was used to determine the inflection point first. After that, it was used to build a two-piece linear regression on both sides of the inflection point. The *p*-value obtained from the logarithmic likelihood ratio test was used to determine the best fitting model (LRT). To ensure data robustness, a sensitivity analysis was also performed. Moreover, we converted NLR to a categorical variable and calculated the *p*-value of the trend to confirm NLR results as a continuous variable and look for nonlinearity. All statistical analyses were carried out using the R statistical package (available at: http://www.r-project.org; The R Foundation for Statistical Computing, Vienna, Austria). The statistical significance level was set at 0.05 on both sides.

Results

Baseline Patient Characteristics

The 9,254 participants in the final data analysis were selected using stringent screening criteria (Figure 1). Table I shows the NLR quartile-based baseline characteristics of the chosen participants. 9,254 participants were enrolled, with a mean age of 41.35±8.31 years and a mean BMI of 25.49±42.04 kg/m^2. Age and BMI showed statistically significant differences (all p=0.05). Neutrophil counts and PLR were higher among participants in the highest NLR (Q4) group than among participants in the other groups. Low lymphocyte and platelet counts were present.

Univariate Analysis of PLR

The findings of the univariate analysis are presented in Table II. In the univariate linear regression, BMI had no relationship with PLR. On the other hand, univariate analysis showed that platelet count (β: 0.50, 95% CI: 0.48, 0.51), neutrophil count (β: 4.37, 95% CI: 3.59, 5.14) and NLR (β: 18.35, 95% CI: 17.74, 18.96) were positively associated with PLR. Interestingly, BMI in the

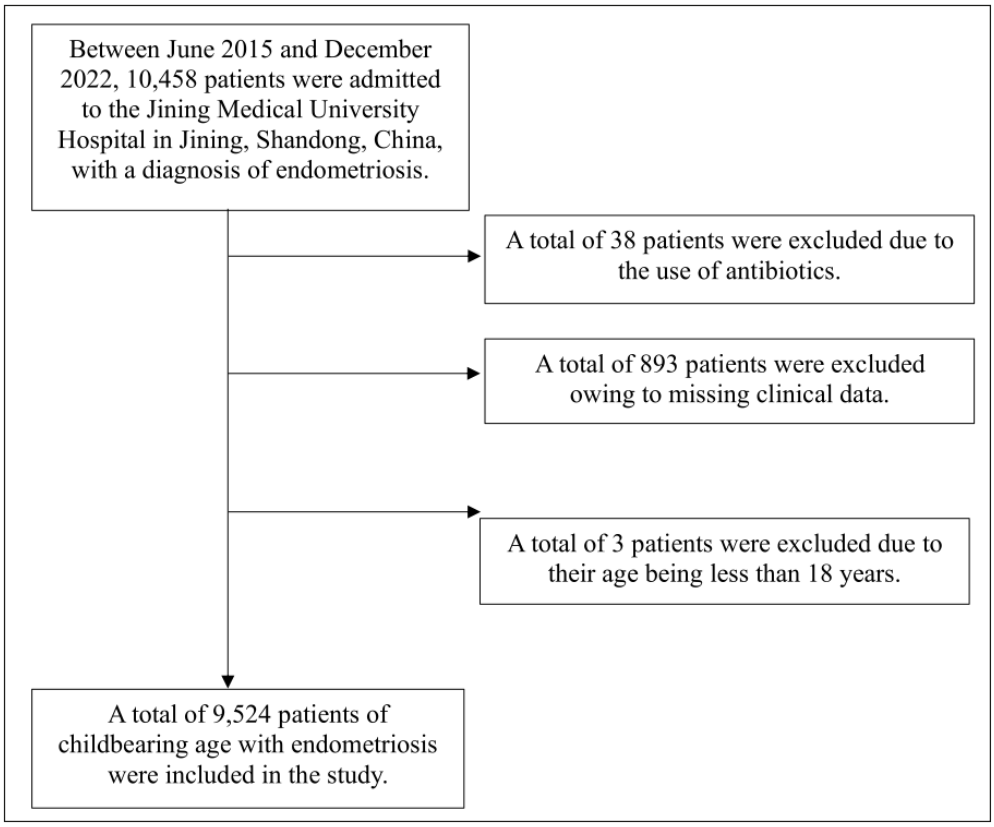

Figure 1. Patient inclusion flowchart.

Table I. Baseline characteristics of patients based on the NLR quartiles.

	NLR (min-max)				
Characteristic	**Q1 (0.34-1.45)**	**Q2 (1.45-1.95)**	**Q3 (1.95-2.80)**	**Q4(2.80-47.63)**	***p*-value**
N	2,314	2,313	2,313	2,314	
Age (years, mean ± SD) BMI	41.04 ± 8.67	41.72 ± 8.21	41.95 ± 8.16	40.67 ± 8.13	<0.001
(kg/m^2, mean ± SD) BMI	23.98 ± 4.85	24.51 ± 4.53	27.95 ± 83.64	25.50 ± 4.86	0.007
< 24.00 kg/m^2	1,273 (55.01%)	1,118 (48.34%)	1,041 (45.01%)	898 (38.81%)	<0.001
≥ 24.00 kg/m^2	1,041 (44.99%)	1,195 (51.66%)	1,272 (54.99%)	1,416 (61.19%)	
Platelet count (109/L, mean ± SD)	277.99 ± 77.24	286.51 ± 77.38	287.63 ± 81.84	273.49 ± 86.95	<0.001
Neutrophil count (109/L, mean ± SD)	2.46 ± 0.76	3.24 ± 0.84	3.99 ± 1.10	6.24 ± 2.46	<0.001
Lymphocyte count (109/L, mean ± SD)	2.17 ± 0.60	1.91 ± 0.49	1.73 ± 0.46	1.43 ± 0.45	<0.001
NLR (mean ± SD)	1.15 ± 0.22	1.70 ± 0.15	2.31 ± 0.24	4.84 ± 3.34	<0.001
PLR (mean ± SD)	135.49 ± 47.63	157.28 ± 53.26	175.21 ± 61.60	212.16 ± 108.21	<0.001

Ems: endometriosis; PLR: platelet-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; OE: ovarian endometriosis; BMI: body mass index; LRT: likelihood ratio test; COVID-19: coronavirus disease 2019.

Low-BMI group was significantly and positively correlated with PLR, while BMI in the Low-BMI group was not significantly correlated with PLR.

Results of Adjusted Linear Regression

After adjusting for confounders, we developed models to investigate the independent effects of

Table II. Univariate analysis of PLR.

	Low-BMI group		High-BMI group		Total	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Age (years, mean ± SD)	1.80 (1.54, 2.07)	<0.0001	1.99 (1.72, 2.25)	<0.0001	1.89 (1.71, 2.08)	<0.0001
BMI (kg/m^2, mean ± SD)	2.75 (1.39, 4.11)	<0.0001	0.01 (-0.03, 0.04) 0.7164		0.01 (-0.03, 0.05) 0.6378	
Platelet count ($10^9/L$, mean ± SD)	0.53 (0.50, 0.55)	<0.0001	0.47 (0.45, 0.50)	<0.0001	0.50 (0.48, 0.51)	<0.0001
Neutrophil count (109/L, mean ± SD)	7.67 (6.46, 8.87)	<0.0001	2.03 (1.02, 3.04)	<0.0001	4.37 (3.59, 5.14)	<0.0001
Lymphocyte count ($10^9/L$, mean ± SD)	-84.21 (-87.51, -80.90)	<0.0001	-78.24 (-81.19, -75.29)	<0.0001	-80.91 (-83.12, -78.71)	<0.0001
NLR (mean ± SD)	21.45 (20.55, 22.34)	<0.0001	15.96 (15.12, 16.79)	<0.0001	18.35 (17.74, 18.96)	<0.0001
NLR quartile						
Q1 (0.34-1.45)	Reference	Reference	Reference			
Q2 (1.45-1.95)	23.58 (17.90, 29.25)	<0.0001	19.59 (13.58, 25.60)	<0.0001	21.99 (17.85, 26.13)	<0.0001
Q3 (1.95-2.80)	38.74 (32.95, 44.53)	<0.0001	39.77 (33.84, 45.69)	<0.0001	40.01 (35.87, 44.16)	<0.0001
Q4 (2.80-47.63)	91.99 (85.96, 98.03)	<0.0001	65.86 (60.07, 71.65)	<0.0001	77.15 (72.98, 81.31)	<0.0001

Ems: endometriosis; PLR: platelet-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; OE: ovarian endometriosis; BMI: body mass index; LRT: likelihood ratio test; COVID-19: coronavirus disease 2019.

NLR on PLR (multivariate linear regression). The effect sizes (β) and 95% confidence intervals are shown in Table III. The model-based effect size in the unadjusted model (Model I) corresponds to a one-unit rise in NLR in comparison to PLR. For example, in the adjusted Model II, when NLR increased by one unit, PLR increased by 18.54 units (β: 18.54, 95% CI: 17.94, 19.13), while in the adjusted Model III, when NLR increased by one unit, PLR increased by 18.54 units (β: 18.54, 95% CI: 17.94, 19.13). NLR was changed from a continuous variable to a categorical variable for the sensitivity analysis (NLR quartiles). The *p*-values for the NLR trend were consistent with the outcomes when NLR was a continuous variable in both the minimally and fully adjusted models. Results from BMI-based subgroup analyses of the study population generally confirm those from the entire study population.

Relationship Between NLR and PLR

After considering potential confounders, smoothed curve fits were carried out, as seen in Figures 2 and 3 (including age and body mass index). PLR and NLR had a non-linear relationship; as NLR rose, so did PLR. NLR and PLR were found to significantly positively correlate when NLR was lower than 2.07 (β: 34.49, 95% CI: 31.07, 37.90; $p<0.0001$), as shown in Table IV. Additionally, a significant positive connection between NLR and PLR was discovered when

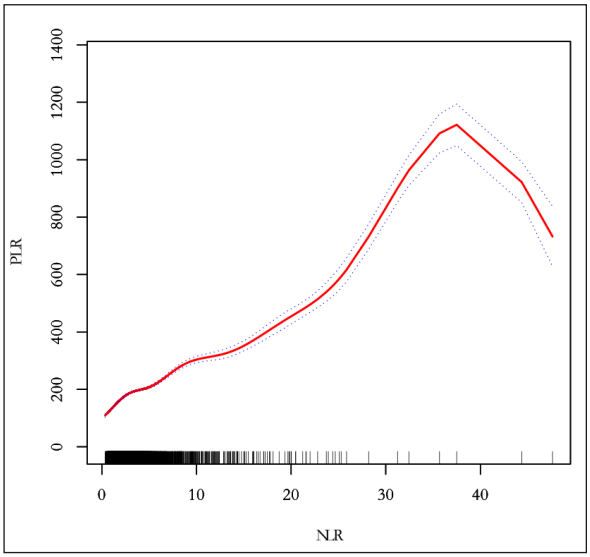

Figure 2. Relationship between NLR and PLR. Smooth fitting curves of NLR and PLR. The solid red line denotes a smooth curve fitting between the variables. The blue line denotes the 95% confidence interval for fitting. The model was adjusted for age and BMI.

Table III. Relationship between NLR and PLR in different models.

	Crude Model		Model I		Model II	
Variable	**β (95% CI)**	***p*-value**	**β (95% CI)**	***p*-value**	**β (95% CI)**	***p*-value**
Total-NLR	18.35 (17.74, 18.96)	<0.0001	18.54 (17.94, 19.13)	<0.0001	18.54 (17.94, 19.13)	<0.0001
Total-NLR quartile						
Q1 (0.34-1.45)	Reference	Reference	Reference			
Q2 (1.45-1.95)	21.99 (17.85, 26.13)	<0.0001	21.04 (17.02, 25.07)	<0.0001	21.04 (17.02, 25.07)	<0.0001
Q3 (1.95-2.80)	40.01 (35.87, 44.16)	<0.0001	38.82 (34.79, 42.86)	<0.0001	38.82 (34.79, 42.86)	<0.0001
Q4 (2.80–47.63)	77.15 (72.98, 81.31)	<0.0001	79.03 (74.98, 83.08)	<0.0001	79.03 (74.98, 83.08)	<0.0001
Low-BMI-NLR	21.45 (20.55, 22.34)	<0.0001	21.22 (20.35, 22.10)	<0.0001	21.23 (20.35, 22.10)	<0.0001
Low-BMI-NLR quartile						
Q1 (0.34-1.45)	0	0	0			
Q2 (1.45-1.95)	23.58 (17.90, 29.25)	<0.0001	22.27 (16.69, 27.85)	<0.0001	22.27 (16.69, 27.85)	<0.0001
Q3 (1.95-2.80)	38.74 (32.95, 44.53)	<0.0001	36.81 (31.12, 42.51)	<0.0001	36.80 (31.10, 42.49)	<0.0001
Q4 (2.80–47.63)	91.99 (85.96, 98.03)	<0.0001	89.50 (83.56, 95.44)	<0.0001	89.50 (83.55, 95.44)	<0.0001
High-BMI-NLR	15.96 (15.12, 16.79)	<0.0001	16.60 (15.79, 17.40)	<0.0001	16.60 (15.79, 17.40)	<0.0001
High-BMI-NLR quartile						
Q1 (0.34-1.45)	0	0	0			
Q2 (1.45-1.95)	19.59 (13.58, 25.60)	<0.0001	19.88 (14.08, 25.68)	<0.0001	19.88 (14.08, 25.68)	<0.0001
Q3 (1.95-2.80)	39.77 (33.84, 45.69)	<0.0001	40.44 (34.73, 46.16)	<0.0001	40.46 (34.74, 46.18)	<0.0001
Q4 (2.80-47.63)	65.86 (60.07, 71.65)	<0.0001	73.25 (67.62, 78.88)	<0.0001	73.26 (67.62, 78.89)	<0.0001

Model II was adjusted for age. Model III was adjusted for age (smooth) and BMI (smooth). Ems: endometriosis; PLR: platelet-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; OE: ovarian endometriosis; BMI: body mass index; LRT: likelihood ratio test; COVID-19: coronavirus disease 2019.

NLR was higher than 2.07 (β: 34.49, 95% CI: 31.07, 37.90; $p<0.0001$).

Discussion

In this study, patients with Ems showed a non-linear positive connection between NLR and PLR. In the entire analysis, PLR showed an upward tendency as NLR rose. Furthermore, we discovered a strong positive connection between NLR and PLR when NLR <2.07 after doing subgroup analysis, sensitivity analysis, and threshold effect analysis. There was a strong positive connection between NLR and PLR when NLR > 2.07.

Table IV. Threshold effect analysis of the relationship between NLR and PLR.

	PLR	
	Adjusted β value (95% CI)	***p*-value**
Model I		
One linear effect	18.40 (17.81, 18.99)	<0.0001
Model II		
Breakpoint (k)	2.07	
<2.38 Segment effect 1	34.49 (31.07, 37.90)	<0.0001
>2.38 Segment effect 2	16.93 (16.26, 17.59)	<0.0001
Effect difference between II and I	-17.56 (-21.24, -13.89)	<0.0001
Predicted value of equation at the breakpoint	168.88 (166.95, 170.81)	
LRT test		<0.001

Model I: Linear analysis. Model II: Nonlinear analysis. LRT and logarithmic likelihood ratio tests ($p<0.05$ means that model II is significantly different from model I, representing a nonlinear relationship). Adjusted variables: age and BMI. Statistical significance was set at $p<0.05$. Ems: endometriosis; PLR: platelet-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; OE: ovarian endometriosis; BMI: body mass index; LRT: likelihood ratio test; COVID-19: coronavirus disease 2019.

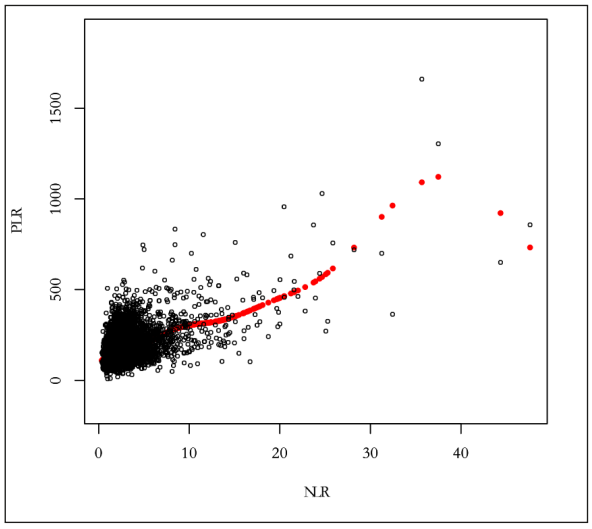

Figure 3. Relationship between NLR and PLR. The scatter diagram for NLR and PLR distributions. The solid red line denotes a smooth curve fitting between the variables. The blue line denotes the 95% confidence interval for fitting. The model was adjusted for age and BMI.

Endometriosis is most commonly found in the ovaries and can lead to a range of symptoms, including infertility[1,2]. Usually, in case of endometriosis or early diagnosis of malignancies, a fertility-sparing treatment is needed. Before surgical treatments, patients are suggested to preserve fertility through ovarian stimulation by an antagonist protocol and freeze all their gametes through a vitrification system for future pregnancies[21-23]. It is also important to highlight the role played by a good lifestyle and psychological support[24,25]. Inflammation is crucial in the development of Ems[4]. Therefore, it is essential to look for markers of inflammation as effective monitoring indicators for the early diagnosis of Ems. PLR is more predicative than platelet or lymphocyte count alone, since it can indicate a combination of several inflammatory pathways that whole blood cells have acquired[26]. PLR has been mentioned in several articles[27,28] as a potential biomarker for inflammation. According to research[29,30], PLR is an independent risk factor that also affects the prognosis of coronavirus disease 2019 (COVID-19): a higher PLR is in fact strongly linked to mortality in COVID-19 patients. A clinical investigation by Chen et al[31] also found that PLR is a separate risk factor for post-operative metastasis in cases of malignancy, with a high PLR predicting a greater probability of post-operative recurrence and metastasis. Several differential diagnostic investigations[32,33] have shown that PLR is a critical marker for developing a predictive model for the diagnosis of endometriosis.

NLR is also a well-established inflammatory marker, as well as a highly relevant prognostic indicator for patients suffering from multiple diseases[34,35]. A retrospective study by Jing et al[36] found that NLR could be used to diagnose infertility in endometriosis patients. Furthermore, the combination of NLR and CA125 was found[1,2] to be more sensitive in diagnosing endometriosis than CA125 alone.

Obesity is a high-risk factor for endometriosis. Therefore, we analyzed the groups according to BMI and the results showed a positive correlation between NLR and PLR in both normal weight and overweight patients with endometriosis.

Previous research[37] has shown that inflammatory cytokines, chemokines, other inflammatory mediators, and pain-related substances act sequentially on inflammatory cells during the development of endometriosis. These reversal results in the recruitment of more inflammatory cells to the lesion, alter the original environment of the peritoneal and pelvic cavity and create a new inflammatory microenvironment. Inflammatory cells and factors play a significant role in the growth, implantation, infiltration, and migration of endometriosis, creating a vicious cycle in the disease's development.

To our knowledge, this is the first study in which a correlation between NLR and PLR has been proposed in patients with endometriosis and the simplicity and accessibility of our monitoring indexes has allowed our study to have the following advantages: 1) it helps us to elucidate the role of the inflammatory response in the development of endometriosis; 2) it can also better guide clinical efforts to diagnose endometriosis early and slow down the progression of the disease; 3) it helps monitoring health in potential and current patients.

Limitations

The current study shows some limitations. First, since the participants in this study were all diagnosed as Ems patients, the generalizability of the findings was difficult. Second, due to the unavoidable selection and assessment biases, NLR and PLR dynamics were not investigated. Third, we excluded: (1) those with hematological disorders, malignancies, autoimmune diseases, metabolic disorders, or pre-existing infections; (2) patients taking glucocorticoids, long-term immunomodulatory medications, or anti-inflammatory medications; and (3) patients under the age of 18. As a result, the findings of this study could not be generalized to individuals in these categories. We will include these two components in a subsequent study.

Conclusions

NLR and PLR, as new validated markers, can help exploring the potential risk factors of Ems and providing new ideas for studying the pathogenesis of Ems. At the same time, they can better guide clinical work as biomarkers for early diagnosis of Ems and slow down the progression of the disease. Moreover, NLR and PLR, as inexpensive and simple biomarkers, can be more widely used in community screening for Ems.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The Jining Medical University Hospital Ethics Committee approved this single-center cross-sectional study (approval number: 2022C064).

Informed Consent

Because the study was conducted retrospectively, informed consent was not required.

Availability of Data and Materials

The data used to support the findings of this study have been included in this article.

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Authors' Contributions

CP interpreted the patient data on UL. YD collected the data and was the main contributor to writing the manuscript. YP and XX conducted the survey and wrote the manuscript. XS and YD analyzed the patient data on UL. All authors read and approved the final manuscript.

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