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ORIGINAL RESEARCH

Inflammatory Markers in Women with Infertility: A Cross-Sectional Study

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Purpose: Infertility is highly correlated with inflammation. We sought to evaluate the independent relationships between each inflammatory marker in women with infertility.

Patients and Methods: This cross-sectional study included 1028 infertile patients who were hospitalized at Jining Medical University between January 2016 and December 2022. NLR and PLR were the independent and dependent variables measured at baseline, respectively. Age, body mass index (BMI), and menstrual status were covariates. Based on BMI, the study population was split into two groups: Low-BMI and High-BMI.

Results: A stratified analysis revealed that the overweight group had significantly higher levels of WBC, platelet count, lymphocyte count, neutrophil count and NLR. Comparing the overweight group to the normal weight group, the levels were noticeably higher in the overweight group. Significantly positive correlations between NLR and PLR were found in both univariate and multiple regression analyses.

Conclusion: There was a significant positive correlation between NLR and PLR in infertility patients. These results will help in the search for biomarkers of infertility and in the development of infertility prediction models.

Keywords: infertility, inflammation marker, PLR, NLR, lymphocyte count

Introduction

Infertility has been on the rise in recent years, impacting between 8–12% of couples globally who are of reproductive age on an annual basis.[1,2] According to the World Health Organization (WHO), infertility is the inability of a sexually active couple to conceive even after a year of trying and no use of contraception.[3] It is crucial to understand the etiology of infertility since it has a substantial impact not only on women's reproductive health but also on couples' psychological wellbeing and family connections. There is mounting evidence that certain infertility-related illnesses are linked to long-term inflammatory illnesses.[4] The inflammatory response is simultaneously influenced by a number of reproductive events, including ovulation, menstrual production, placenta production and implantation, and pregnancy.[5–8] It is vital to investigate how the inflammatory response contributes to the etiology of infertility.

The platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) are emerging inflammatory markers. And they are easily assessed from whole blood counts and are an important composite reflection of opposing inflammatory pathways. PLR and NLR may be helpful markers of the body's systemic immunological and inflammatory condition, according to accumulating evidence.[9,10] There are associations between PLR and NLR, and solid tumors and metabolic disorders, respectively, according to a number of earlier research.[11–14] On the link between the numerous inflammatory signs in patients with infertility, there is, however, little research. In order to better understand how inflammation contributes to the onset and progression of infertility, the primary goal of this study was to define the relationships between PLR and NLR in women with infertility.

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Materials and Methods

Study Design

This cross-sectional study used baseline levels of NLR as independent factors and PLR levels as dependent variables to assess the inflammatory response in infertile patients.

Study Participants

Patients with infertility participated in this study, and information was gathered from the Department of Gynecology at the Affiliated Hospital of Jining Medical University. No identifying information about the participants was accessible, thus data were taken from the hospital's electronic medical record system in order to maintain patient privacy. Due of the ability to track the study cohort, informed permission was not required. The hospital's Institutional Review Board gave its approval to the study (approval number: 2022C030). Our research is in line with the Declaration of Helsinki.

Between January 2016 and December 2022, 1028 female patients of reproductive age who were diagnosed with infertility at the Department of Gynecology, Affiliated Hospital of Jining Medical University. The pursuing inclusion standards were applied: (1) infertility as determined by auxiliary tests and preoperative clinical presentation; (2) inability to conceive following a year of regular, unprotected sexual activity. With these criteria, people who: (1) used antibiotics within three months of the procedure; (2) had haematological disorders, malignancies, autoimmune diseases, metabolic diseases, hypersplenism, or active infections; (3) used glucocorticoids, long-term immunomodulatory drugs, or anti-inflammatory drugs; (4) were younger than 18 years old; and (5) were pregnant or nursing were excluded from the study. Last but not least, 320 instances in all were included in the study. The study population was divided into the Low-BMI group (BMI < 24.00 kg/m^2) and the High-BMI group (BMI ≥ 24.00 kg/m^2) based on BMI values.

Variables

Retrospective data collection was done on patient information such as age, BMI, menstrual status, and regular blood indicators. BMI is calculated by dividing weight (kg) by the square of height (m). The regularity of menstruation, the amount of menstruation and the absence of dysmenorrhoea are obtained by asking the patient during history taking. The criteria for regular menstruation are a menstrual cycle of 21 to 35 days and a period of 4 to 6 days. Those who meet the criteria are considered regular and those who do not are considered irregular. Menstrual flow is judged to be less than 20mL, 20–80mL is normal and over 80mL is too much. During hospitalization, the following routine blood indices were obtained. After an 8-hour fast, peripheral venous blood was collected and processed in the laboratory. Blood indicators were usually obtained 2 days before the procedure. All measurements were taken in our hospital by laboratory technicians and inspectors. Platelet counts, lymphocyte count and neutrophil count were measured using the Sysmex XN2000 blood cell analyzer. In order to calculate PLR, the lymphocyte count was divided by the platelet count, NLR by the neutrophil count respectively. All data were collected using the same blood sample.

The study included the following kinds of covariates: (1) demographic information; (2) previously reported factors affecting the study's variables; and (3) variables chosen based on clinical knowledge. Consequently, a fully adjusted model was produced using the following variables: Menstrual status (at baseline) is an example of a categorical variable. Continuous variables include age, body mass index (BMI), and standard blood indicators are examples of continuous variables (obtained at baseline).

Statistical Analyses

There are two ways to portray continuous variables: those with a normal distribution are shown as the average standard deviation (SD). Frequencies or percentages are used to express categorical variables. To examine group differences, we utilized the 2 test (for categorical variables) and one-way analysis of variance (for a normal distribution) (quartiles). There were two stages to the data analysis. Three models were created in Step 1 using univariate and multivariate linear regression analyses: Model I (no covariates were adjusted) and Model II (social

demographics were the only covariates modified). In Step 2, the nonlinearities of NLR and PLR were resolved using a generalized additive model and smooth curve fitting (punitive spline approach). All analyses were performed using the R statistical package (http://www.R-project.org R Foundation). Statistical significance was set at P values <0.05 (double-sided).

Results

Baseline Characteristics of the Study Participants

The quantitative data collection includes 320 people who met the inclusion criteria (Figure 1). Table 1 displays the baseline characteristics of the patients chosen. Based on BMI values, the study population was separated into two groups: Low-BMI (BMI 24.00 kg/m^2) and High-BMI (BMI 24.00 kg/m^2). The average age of all participants was 35.76±4.69 years, with roughly 50.63% having multiple UL. Mean white blood cell count, platelet count, lymphocyte count, neutrophil count, PLR and NLR were 5.44±1.65*10^9/L, 271.27±62.97*10^9/L, 1.96±0.54*10^9/L, 3.84±1.60*10^9/L, 147.49±49.13 and 2.12±1.19. Meanwhile, the mean white blood cell count, platelet count, lymphocyte count and neutrophil count were all higher in the high BMI group than in the low BMI group. In addition, there were statistical differences in BMI, WBC, platelet count, lymphocyte count and neutrophil count between the high BMI and low BMI groups. However, there were no statistically significant differences in PLR and NLR between the two groups.

Univariate Analysis of PLR

Table 2 shows the results of the univariate analysis. Age, BMI, menstrual status and WBC were not correlated with PLR in the study population. Secondly, Platelet Count (β=0.43, 95% *CI*=0.36, 0.50), Neutrophil Count (β=4.09, 95% *CI*=0.65, 7.52), NLR (β=19.49, 95% *CI*=15.46, 23.53) was positively correlated with PLR in the whole study population. Lymphocyte Count (β=−62.83, 95% *CI*=−70.39, −55.28) was significantly negatively correlated with PLR. Separate analyses of the study population by BMI yielded similar results to the total study population.

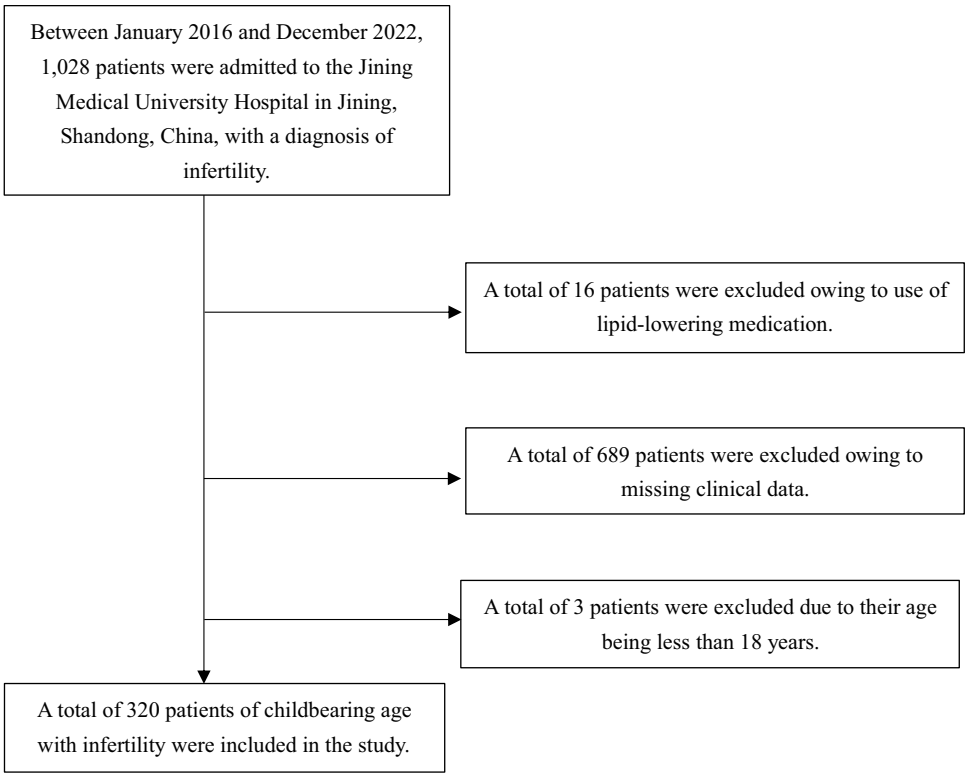

Figure 1 Inclusion and exclusion criteria process.

Table 1 Baseline Characteristics of the Study Population

Characteristics	Total	Low-BMI Group	High-BMI Group	*P*-value
Quantity, n	320	158	162	
Age (years, mean ± SD)	35.76 ± 4.69	35.66 ± 4.73	35.86 ± 4.67	0.704
BMI (kg/m^2, mean ± SD)	24.54 ± 3.85	21.59 ± 1.73	27.41 ± 3.11	<0.001
Menstrual pattern n (%)				0.161
Regularly	318 (99.38%)	158 (100.00%)	160 (98.77%)	
Irregularly	2 (0.62%)	0 (0.00%)	2 (1.23%)	
Menstrual flow volume n (%)				0.694
Light	3 (0.94%)	2 (1.27%)	1 (0.62%)	
Moderate	314 (98.12%)	154 (97.47%)	160 (98.77%)	
Heavy	3 (0.94%)	2 (1.27%)	1 (0.62%)	
Dysmenorrhea n (%)				0.380
No	309 (96.56%)	154 (97.47%)	155 (95.68%)	
Yes	11 (3.44%)	4 (2.53%)	7 (4.32%)	
WBC (10^9/L, mean ± SD)	5.44 ± 1.65	5.16 ± 1.43	5.70 ± 1.80	0.003
Platelet Count (10^9/L, mean ± SD)	271.27 ± 62.97	258.96 ± 61.54	283.28 ± 62.20	<0.001
Lymphocyte Count (10^9/L, mean ± SD)	1.96 ± 0.54	1.86 ± 0.46	2.05 ± 0.58	0.002
Neutrophil Count (10^9/L, mean ± SD)	3.84 ± 1.60	3.48 ± 1.67	4.19 ± 1.46	<0.001
PLR	147.49 ± 49.13	148.25 ± 53.48	146.75 ± 44.64	0.786
NLR	2.12 ± 1.19	2.01 ± 1.18	2.22 ± 1.19	0.109

Abbreviations: BMI, body mass index; CI, confidence interval; WBC, white blood cell count; PLR, Platelet-Lymphocyte Ratio; NLR, Neutrophil-Lymphocyte Ratio; PCOS, polycystic ovary syndrome; TNF, tumor necrosis factor; CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; NOX, NADPH oxidases; SOD, superoxide dismutase.

Table 2 Univariate Analysis of PLR

Variable	Total *β* (95% CI) *P*-value	Low-BMI Group *β* (95% CI) *P*-value	High-BMI Group *β* (95% CI) *P*-value
Age (years, mean ± SD)	−0.34 (−1.49, 0.82) 0.5676	−1.18 (−2.94, 0.59) 0.1926	0.51 (−0.97, 1.99) 0.5020
BMI (kg/m^2, mean ± SD)	1.34 (−0.80, 3.48) 0.2198	−1.05 (−5.90, 3.80) 0.6719	2.06 (−0.14, 4.26) 0.0679
Menstrual pattern n (%)			
Regularly	Reference		Reference
Irregularly	−30.99 (−99.63, 37.65) 0.3769		−30.99 (−93.25, 31.27) 0.3307
Menstrual flow volume n (%)			
Light	Reference	Reference	Reference
Moderate	68.30 (12.67, 123.94) 0.0167	72.33 (−1.83, 146.50) 0.0578	60.41 (−27.40, 148.21) 0.1794
Heavy	60.44 (−17.82, 138.71) 0.1311	56.10 (−48.12, 160.31) 0.2930	69.13 (−54.65, 192.92) 0.2753
Dysmenorrhea n (%)			
No	Reference	Reference	Reference
Yes	12.30 (−17.34, 41.94) 0.4166	7.12 (−46.12, 60.37) 0.7935	15.32 (−18.51, 49.15) 0.3762
WBC (10^9/L, mean ± SD)	−1.37 (−4.69, 1.96) 0.4206	−0.56 (−6.42, 5.30) 0.8517	−1.87 (−5.71, 1.97) 0.3413
Platelet Count (10^9/L, mean ± SD)	0.43 (0.36, 0.50) <0.0001	0.56 (0.45, 0.66) <0.0001	0.31 (0.21, 0.41) <0.0001
Lymphocyte Count (10^9/L, mean ± SD)	−62.83 (−70.39, −55.28) <0.0001	−81.12 (−93.94, −68.30) <0.0001	−51.59 (−60.30, −42.87) <0.0001
Neutrophil Count (10^9/L, mean ± SD)	4.09 (0.65, 7.52) 0.0203	6.99 (2.08, 11.90) 0.0059	0.36 (−4.39, 5.11) 0.8819
NLR	19.49 (15.46, 23.53) <0.0001	23.46 (17.36, 29.56) <0.0001	15.72 (10.45, 20.99) <0.0001

Abbreviations: BMI, body mass index; CI, confidence interval; WBC, white blood cell count; PLR, Platelet-Lymphocyte Ratio; NLR, Neutrophil-Lymphocyte Ratio; PCOS, polycystic ovary syndrome; TNF, tumor necrosis factor; CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; NOX, NADPH oxidases; SOD, superoxide dismutase.

Results of Unadjusted and Adjusted Linear Regression

In this work, two models were developed to examine the separate effects of NLR and PLR (Table 3). In the unadjusted model, NLR was positively associated with PLR (β = 19.49, 95% *CI* = 15.46, 23.53). After correction for age (model I), NLR remained positively associated with PLR (β=19.24, 95% *CI*=15.18, 23.30). Subsequently, independent BMI subgroup

Table 3 Relationship Between NLR and PLR in Different Models

Variable	Crude Model *β* (95% CI) *P*-value	Model I *β* (95% CI) *P*-value
Total	19.49 (15.46, 23.53) <0.0001	19.48 (15.43, 23.53) <0.0001
Low-BMI group	23.46 (17.36, 29.56) <0.0001	23.24 (17.11, 29.36) <0.0001
High-BMI group	15.72 (10.45, 20.99) <0.0001	15.83 (10.56, 21.11) <0.0001

Note: Model I adjusted for age.

Abbreviations: BMI, body mass index; CI, confidence interval; WBC, white blood cell count; PLR, Platelet-Lymphocyte Ratio; NLR, Neutrophil-Lymphocyte Ratio; PCOS, polycystic ovary syndrome; TNF, tumor necrosis factor; CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; NOX, NADPH oxidases; SOD, superoxide dismutase.

analyses were performed on the study population, with results for the low BMI group (β=23.24, 95% *CI*=17.11, 29.36) and the high BMI group (β=15.83, 95% *CI*=10.56, 21.11) largely similar to those for the whole study population.

Relationship Between NLR and PLR

In this study, we investigated the relationship between PLR and NLR (Figure 2). After adjusting for potential confounders such as age, the results of the smoothed fitted curves and generalised additive models showed that PLR increased as NLR increased. Based on the techniques described above, separate smoothed-fit curves were created for low and high BMI patients with infertility, and there was no significant difference in the relationship between NLR and PLR compared to the overall population studied. (Figures 3 and 4) Threshold effects were further investigated based on the curve fits, as shown in Table 4. Curiously, NLR was significantly positively correlated with PLR when NLR < 2.69 (β = 33.38, 95% *CI* = 23.93, 42.82), whereas NLR was positively correlated with PLR when NLR > 2.69 (β = 9.89, 95% *CI* = 2.95, 16.83).

Discussion

In this work, saturation threshold analysis, multiple regression analysis and univariate analysis were all used to thoroughly analyse the relationship between PLR and NLR. The results of the study showed that PLR was positively associated with NLR. The relationship was fairly consistent with the entire study population based on BMI-based subgroup analyses. Notably, NLR was significantly positively correlated with PLR when NLR was less than 2.69, but

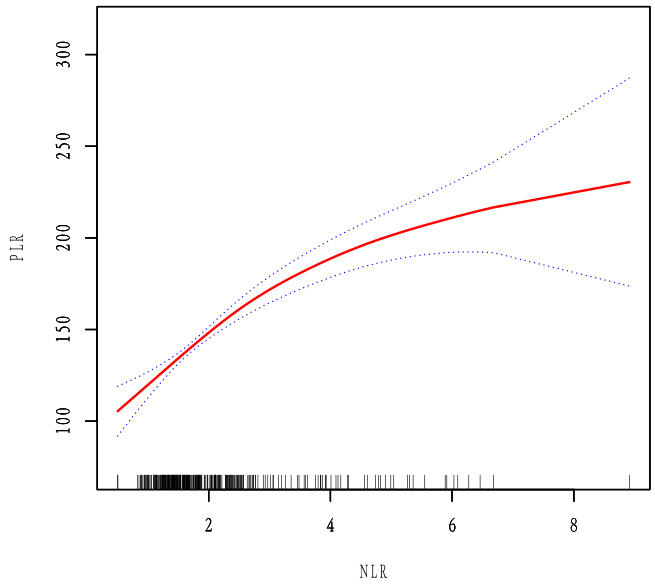

Figure 2 Association between NLR and PLR in the total study population (mmol/L). Figure 2 shows the smooth fitting curve of NLR and PLR. The solid red line represents the smooth curve fit between the variables. Blue bands represent the 95% confidence interval of the fit. The model was adjusted for age.

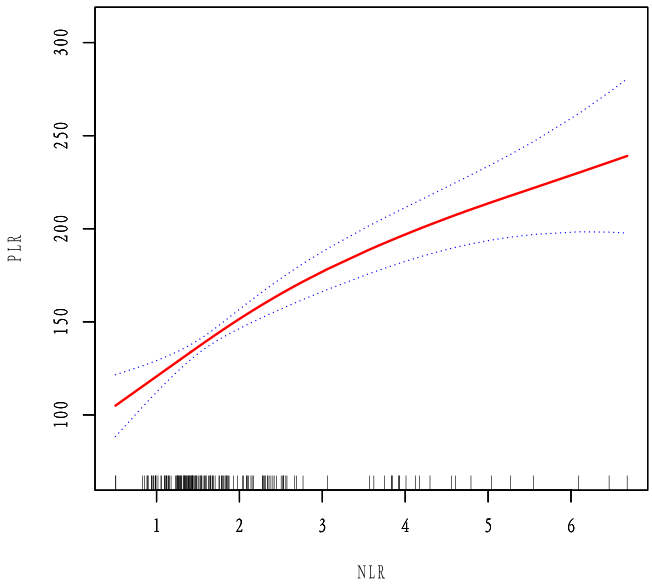

Figure 3 Association between NLR and PLR in the Low-BMI group study population (mmol/L). Figure 3 shows the smooth fitting curve of NLR and PLR. The solid red line represents the smooth curve fit between the variables. Blue bands represent the 95% confidence interval of the fit. The model was adjusted for age.

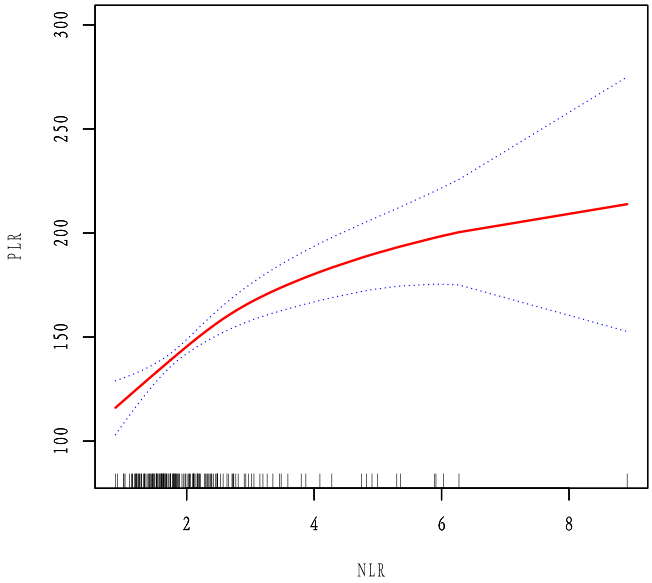

Figure 4 Association between NLR and PLR in the High-BMI group study population (mmol/L). Figure 4 shows the smooth fitting curve of NLR and PLR. The solid red line represents the smooth curve fit between the variables. Blue bands represent the 95% confidence interval of the fit. The model was adjusted for age.

positively correlated with PLR when NLR was greater than 2.69. Therefore, we consider the positive correlation between PLR and NLR to be stable.

The third major disease affecting human life and health today, after cancer and cardiovascular disease, infertility has emerged as a major medical and social issue affecting the reproductive health and development of all humans.[2] Tubal factors, ovulation issues, endometriosis, and unexplained infertility are typical reasons of female infertility.[3] Of these, polycystic ovarian syndrome (PCOS) is linked to the majority of ovulatory diseases of infertility.[15] C-reactive protein (CRP), IL-18, TNF-α, IL-6, white blood cell count (WBC), monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1α (MIP-1α) are all noticeably elevated, according to a prior review.[16] Numerous studies[17,18] have demonstrated that inflammation is linked to PCOS progression and is favorably correlated with markers such PLR, NLR, and SII. The severity of

Table 4 Threshold Effect Analysis of the Relationship Between NLR and PLR

Adjusted Indicators	NLR *β* (95% CI) *P*-value
Model I	
One linear effect	19.26 (15.23, 23.30) <0.0001
Model II	
Break point (k)	2.69
<k segment effect 1	33.38 (23.93, 42.82) <0.0001
>k segment effect 2	9.89 (2.95, 16.83) 0.0056
Effect difference between 2 and 1	−23.49 (−37.75, −9.23) 0.0014
Predicted value of equation at break point	173.02 (162.82, 183.22)
LRT test	0.001

Notes: (P < 0.05 denotes that Model II significantly differs from Model I, revealing a nonlinear relationship) Adjusted variables: age. P<0.05 is significant.
Abbreviations: Model I, linear analysis; Model II, nonlinear analysis; LRT test, logarithmic likelihood ratio test.

endometriosis adhesions was shown to favorably correlate with PLR, CA125, and co-markers by Guo C et al[19] PLR and NLR may be employed as possible blood indicators for endometriosis, according to a number of studies.[20–22] Patients who have been given the diagnosis of unexplained infertility or premature ovarian failure also display an imbalanced adaptive immune system and continue to experience chronic inflammation.[23] This generally agrees with what we discovered. The increased risk of infertility and subfertility is caused by obesity.[3,24,25] As a result, we separated the study population into two groups based on BMI: Low-BMI group and High-BMI group. The results of the subgroup analysis revealed that the overweight group had significantly higher levels of WBC, platelet count, lymphocyte count, neutrophil count and NLR. The connection between PLR and NLR did not exhibit any notable abnormalities in the univariate or multivariate analysis of the two groups.

The mechanism might work like this. Through enhanced NF-kB -p65 phosphorylation, increased expression of the redox family of NADPH oxidases (NOX), and the formation of superoxide (O_2), which is then reduced to hydrogen peroxide (H_2O_2) by the superoxide dismutase, inflammation causes oxidative stress (SOD). Following free movement from the organelle to the cytoplasm, ROS species (O^{2-} and H_2O_2) stimulate NF-kB -p65 phosphorylation, which raises the release of proinflammatory cytokines like TNF-α and IL-6 and spreads inflammation.

A significant risk factor for the emergence of infertility is inflammation. After correcting for other factors, our results demonstrate that PLR is favorably linked with NLR in infertile patients. Interestingly, the super-rearranged group had significantly greater levels of WBC, platelet count, lymphocyte count, neutrophil count and NLR than the regular group. This implies that the inflammatory response may be crucial to the development and spread of disease. Dynamic monitoring of PLR and NLR may help to determine the progression of infertility and provide a feasible direction for clinical treatment.[26]

This study's advantage is that non-linearity is examined in an observational study. Additionally, it has undergone statistical adjustment to significantly lessen impacting influences. Additionally, this study's extensive data set was successful in minimizing population selection bias.

This study does have certain restrictions, though. First, patients with infertility who had been identified in southwest Shandong, China, made up the study's participants. Therefore, additional multicenter investigations are required to enhance this study's generalizability and extrapolation. Second, obesity is a significant factor that affects infertility; however, we just grouped obesity and did not thoroughly examine the connection between obesity and the inflammatory response. Finally, due to distinct pathophysiology, women under the age of 18 were excluded from this investigation.

Conclusion

To our knowledge, this is the first clinical study to examine the relationship between PLR, an indicator of inflammation, and NLR in infertility patients. In addition, this study grouped infertility patients by different BMIs. In women with infertility, this study found a stable positive correlation between PLR and NLR. The results of this study will contribute to the development of future infertility prediction models and provide a new possible attempt to diagnose infertility.

Abbreviations

BMI, body mass index; CI, confidence interval; WBC, white blood cell count; PLR, Platelet-Lymphocyte Ratio; NLR, Neutrophil-Lymphocyte Ratio; PCOS, polycystic ovary syndrome; TNF, tumor necrosis factor; CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; NOX, NADPH oxidases; SOD, superoxide dismutase.

Data Sharing Statement

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

Ethics Approval

This study was approved by the Jining Medical University's Affiliated Hospital institutional review board (approval number: 2022C030).

Consent to Participate

The requirement for informed consent was waived given the retrospective nature of this study.

Consent to Publish

Identifying information was removed to protect patient confidentiality.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflict of interests to report.

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