Retrospective analysis of prognostic value of the neutrophil-to-lymphocyte ratio in early miscarriages
A 8-year survey

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Abstract

This study aims to identify prognostic value of neutrophil-to-lymphocyte ratio (NLR) in early miscarriages. A total of 260 pregnant women with vaginal spotting were recruited from the Department of Obstetrics and Gynecology of the Kyung Hee Medical Center from January 1, 2011, and December 31, 2018. Venous samples were obtained from the women for measurements of platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and NLR. All the patients were in < 14 gestational weeks of their pregnancy. Eighty-four patients were excluded because of incomplete data, loss of follow-up, and serious medical diseases. We enrolled 176 women for analysis and divided them into two groups. Group 1 included 104 women with threatened abortion; and group 2, 72 women with missed abortion. A significant difference in NLR was found between the groups ($p = 0.001$; $P < .01$). The multivariate analysis also revealed that NLR was the only prognostic factor of early miscarriage (odd ratio [OR], 0.732; 95% confidence interval [CI], 0.612–0.881, $P = .001$). The area under the Receiver-operating characteristic of NLR for distinguishing between the missed and threatened abortion groups was 0.792, and the best cutoff value was 5.72 ($P < .05$).

Abbreviations: CA125 = cancer antigen 125, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, ROC = receiver-operating characteristic.

Keywords: lymphocyte, miscarriage, neutrophil

1. Introduction

Neutrophils and lymphocytes constitute the first line of defense of the body against foreign invaders.[1] They are the first inflammatory and regulatory markers found in injured areas, respectively. They activate major cell types involved in acute and chronic inflammation. neutrophil-to-lymphocyte ratio (NLR) is a simple parameter to easily assess the inflammatory status patients.[2] A recent study showed that NLR is a strong prognostic indicator in various diseases.[1] Furthermore, NLR has also been associated with poor clinical outcomes in various diseases, including myocardial infarction, coronary artery disease, atherosclerosis, chronic obstructive pulmonary disease, and high nuclear grade renal cell carcinoma in obese individuals.[1]

Threatened abortion is a common complication of pregnancy. It is reported to occur in approximately 1-fifth of pregnancies, of which an estimated 3% to 16% are subsequently miscarried.[3] Various biochemical markers have been studied to establish their predictive abilities of the outcome of threatened abortion. Some of the commonly studied biochemical markers are serum human chorionic gonadotropin, progesterone, estradiol, pregnancy-associated plasma protein A, cancer antigen 125 (CA125), human placental lactoge, alpha fetoprotein, inhibin A, follistatin, and activin A levels.[4]

However, predicting a threatened or missed abortion is difficult because predictive methods are unreliable and the underlying mechanisms are complicated. Previous meta-analyses showed that progesterone therapy may reduce the risk of miscarriage in pregnant women with a threatened abortion. The costs of surgery and hospitalization and the complications associated with surgery and anesthesia are major unresolved concerns. Besides infection and bleeding, decreased fertility caused by intrauterine adhesions may be unacceptable for women with missed abortion who have not yet fulfilled their motherhood desires.[5] Thus, we evaluated whether the NLR value significantly differed between the patients with threatened and missed abortions and whether NLR is useful for determining the prognostic factor of early miscarriage.

2. Materials and methods

2.1. Design, sample, and setting

This study was approved by the Research Ethics Committee of the Kyung Hee University Hospital (KHUH 2019-12-053). Review Board and the investigation conformed with the principles outlined in the Declaration of Helsinki.

NLR has proven its usefulness in the stratification of mortality in major cardiac events as a strong prognostic factor in several types of cancers, or as a predictor and marker of inflammatory or infectious pathologies and postoperative complications. Threatened abortion is defined as vaginal bleeding, a closed cervix, and the presence of a fetal heartbeat. It is 1 of the most common complications of pregnancy, with an incidence of 20% to 25%, and can severely affect women's physical and emotional health. Missed abortion is defined as unrecognized intrauterine death of the embryo or fetus without expulsion of the products of conception. It constitutes approximately 15% of clinically diagnosed pregnancies. Women experiencing a missed abortion may be unaware due to the lack of obvious symptoms. However, predicting threatened or missed abortion is difficult because predictive methods are unreliable and its underlying mechanisms are complicated.

We retrospectively reviewed patients diagnosed with abortion at Kyung Hee Medical Center from January 1, 2011, and December 31, 2018. All the patients were in < 14 gestational weeks of their pregnancy. Patients were excluded from the study if,

(1) the diagnosis of abortion was not clear,
(2) the patient had severe medical disease,
(3) the patient was lost to follow-up.

2.2. Data collection

A total of 260 pregnant women with vaginal spotting were recruited from the Department of Obstetrics and Gynecology of the Kyung Hee Medical Center from January 1, 2011, and December 31, 2018. All the patients were in < 14 gestational weeks of their pregnancy. Eighty-four patients were excluded because of incomplete data, loss of follow-up, and serious medical diseases. We enrolled 176 women for analysis and divided them into two groups. Group 1 included 104 women with threatened abortion; and group 2, 72 women with missed abortion (Fig. 1).

Venous samples were obtained from the women for measurements of platelet-to-lymphocyte ratio (PLR), LMR, and NLR.
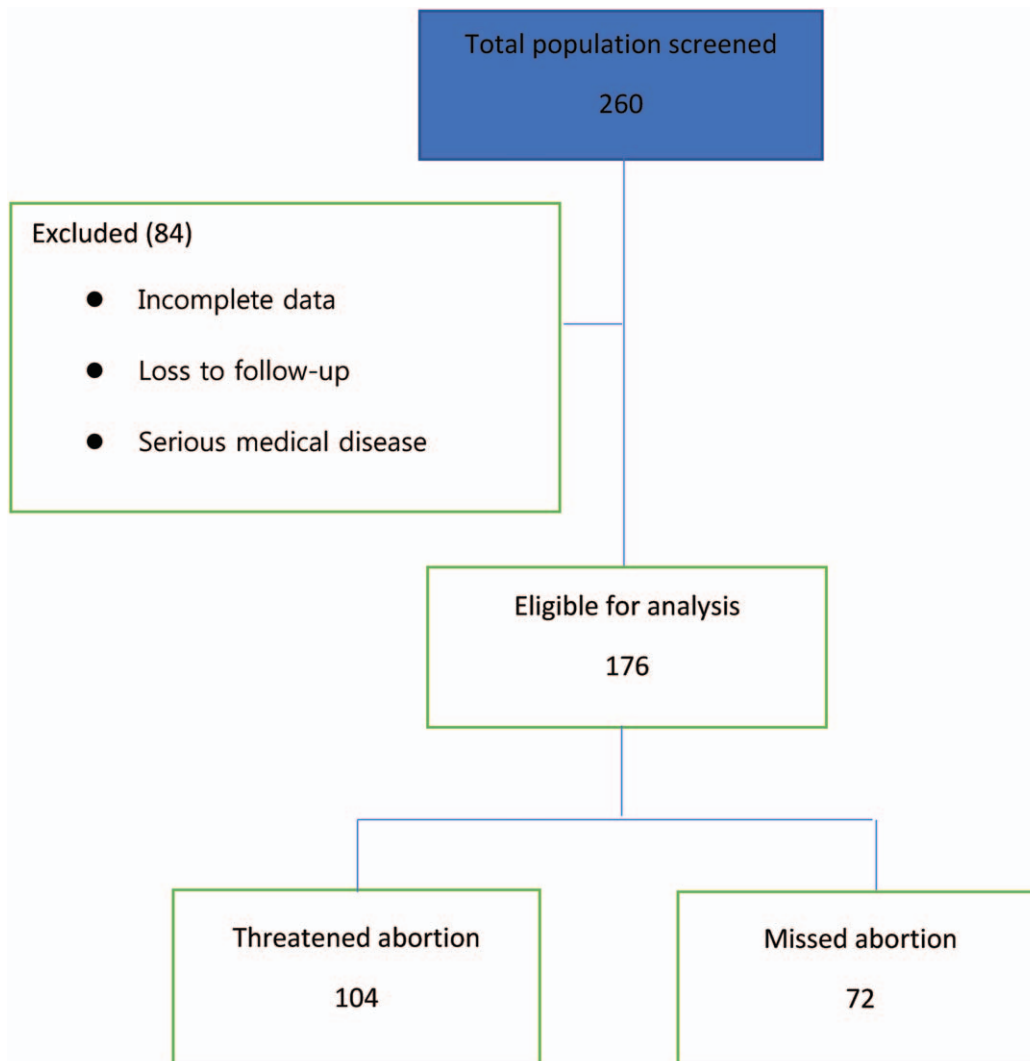

Figure 1. Study flowchart.

PLR was defined as absolute platelet count divided by the absolute lymphocyte count, and LMR was defined as the ratio of absolute lymphocyte to absolute monocyte. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

2.3. Statiscal analysis

Statistical analyses were performed using the SPSS version 20.0 software (IBM-SPSS, Chicago, IL). Data are presented as mean ± standard deviation (SD) for continuous variables. We assessed the normality of the data with the Shapiro-Wilk test. For all the variables, the test had a P value of < .05, indicating that all the data significantly deviated from the normal distribution. The Mann-Whitney U test was used in the two-group comparisons and to determine the groups that caused the significant differences. Furthermore, logistic regression analyses were performed to identify the relationship between NLR and threatened or missed abortion. Two-sided P values of < .05 were considered statistically significant. A receiver-operating characteristic (ROC) analysis was performed to assess the best cutoff value for predicting threatened and missed abortions.

3. Results

During the 8-year period, 176 patients who met the standard were included in this study.

3.1. Patients' characteristics

The patients' baseline characteristics are shown in Table 1. A significant difference in NLR was found between the groups ($P=.001$; $P<.01$).

Table 1

Baseline characteristics of the pregnant women.

Characteristics	Threatened abortion group	Missed abortion group	p Value
Maternal age, years, mean ± SD	32.53 ± 6.08	33.08 ± 4.23	0.806
Gestational days, mean ± SD	63.30 ± 18.61	62.97 ± 19.66	0.911
PLR	13.00 ± 8.15	12.64 ± 8.01	0.565
LMR	5.25 ± 3.84	4.77 ± 1.52	0.324
NLR	5.25 ± 3.84	3.59 ± 3.13	0.003

LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.
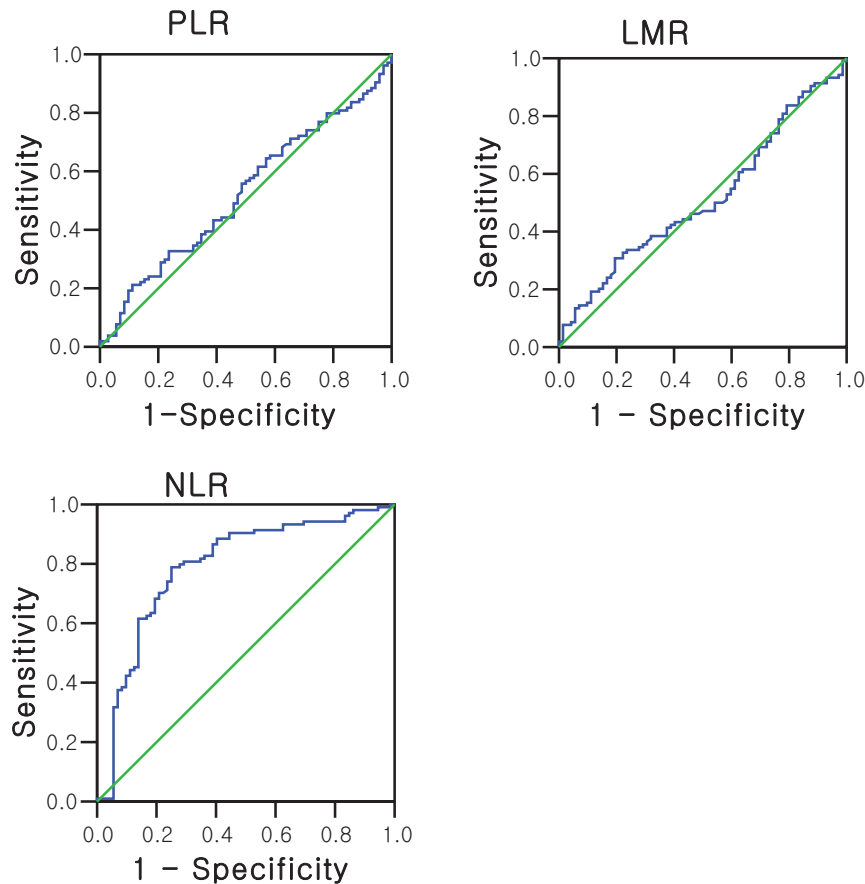
3.2. Predictive factors

Table 2 shows the results of the logistic regression analyses. Maternal age, gestational day, PLR, LMR, and NLR were included in the univariate analyses. No significant differences in PLR and LMR (all P values > .05) and no significant relationships with NLR were found between the groups ($P=.001$). The multivariate analysis also revealed that NLR was the only prognostic factor of early miscarriage (odd ratio, 0.732; 95% confidence interval, 0.612–0.881, $P=.001$). The results of the ROC analyses for PLR, LMR, and NLR are shown in Fig. 2. The area under the ROC of NLR for distinguishing between the missed and threatened abortion groups was 0.792, and the best cutoff value was 5.72 ($P<.05$).

4. Discussion

The findings from this study show that NLR has an eligible prognostic value in early miscarriages. According to the literature search using related keywords in relevant topics, this is the first study to compare to PLR, LMR, and NLR in patients with a threatened or missed abortion. In addition, this is the first study to show the relationship between NLR and early miscarriages. NLR has proven its usefulness in the stratification of mortality in major cardiac events as a strong prognostic factor in several types of cancers, or as a predictor and marker of inflammatory or infectious pathologies and postoperative complications. Threatened abortion is defined as vaginal bleeding, a closed cervix, and the presence of a fetal heartbeat. It is 1 of the most common complications of pregnancy, with an incidence of 20% to 25%, and can severely affect women's physical and emotional health. Missed abortion is defined as unrecognized intrauterine death of the embryo or fetus without expulsion of the products of conception. It constitutes approximately 15% of clinically diagnosed pregnancies. Women experiencing a missed abortion may be unaware due to the lack of obvious symptoms. However, predicting threatened or missed abortion is difficult because predictive methods are unreliable and its underlying mechanisms are complicated. In a previous study, biochemical markers, including serum progesterone, human chorionic gonadotropin, pregnancy-associated plasma protein A, estradiol, and CA125 levels, have been studied in the prediction of the outcome in women with a threatened miscarriage.[6] Serum CA125 level is the most reliable marker for predicting the outcome of threatened miscarriage.[6] However, results have been conflicting.

Women presenting with a threatened miscarriage are often extremely distressed, and providing care can be challenging to health-care professionals, more so because of the difficulty to provide reasonable information on the potential outcome. These

Table 2

Logistic regression analyses.

	Univariable logistic regression			Multivariable logistic regression[*]		
	OR	95% CI	p Value	OR	95% CI	p Value
Maternal Age	1.017	0.962–1.076	0.555	–	–	–
Gestational Days	0.999	0.983–1.015	0.910	–	–	–
PLR	0.990	0.955–1.026	0.564	0.989	0.953–1.026	0.543
LMR	0.935	0.811–1.078	0.353	0.936	0.808–1.084	0.376
NLR	0.734	0.609–0.880	0.001	0.732	0.612–0.881	0.001

[*] Adjusted by age (days).
CI = confidence interval, LMR = lymphocyte-to-monocyte ratio, NNR = neutrophil-to-lymphocyte ratio, OR = odds ratio, PLR = platelet-to-lymphocyte ratio.

Figure 2. The ROC curve analysis for PLR, LMR, and NLR. The areas under curve for the PLR, LMR, and NLR were 0.524 (95% confidence interval [CI], 0.438–0.610; $p > 0.05$), 0.515 (95% CI, 0.429–0.601; $p > 0.05$), and 0.792 (95% CI, 0.721–0.864; $p < 0.05$), respectively. ROC = receiver-operating characteristic.

women end up undergoing repeated scans during their early pregnancy to allay their anxieties, which in turn adds to the increase in waiting times and costs. In the presence of reliable predictive biomarkers, the above-mentioned challenges can be mitigated and potentially new therapeutics can be directed to patients identified as having an increased risk of miscarriage.

Missed abortion is a specific type of miscarriage and refers to embryonic or fetal death with failure of the retained intrauterine products of conception to discharge naturally.[7] Missed abortion may have no obvious symptoms, but it occurs in approximately 8% to 20% of clinically diagnosed pregnancies.[8] It may cause maternal morbidity, including endometrial injury, coagulative dysfunction, depression, and anxiety. Currently, multiple etiologic factors, including parental chromosomal abnormalities, immunological factors, endocrine disorders, uterine abnormalities, hereditary thrombophilia, infections, and environmental factors, have been identified in missed abortion and may occur in up to 50% of all women with miscarriages.[9]

Several inflammatory-related prognostic factors such as PLR, NLR, and LMR have been recently evaluated for their ability to predict the outcomes of patients with various diseases. The literature provides many examples where the NLR was used as an independent prognostic factor of morbidity and mortality in several conditions such as cancers and cardiovascular diseases.[2] NLR is also useful in the prediction and detection of inflammatory and infectious conditions, and their postoperative complications.[10]

5. Conclusions

We were concerned of the causative factors of infection that lead to early miscarriage, thus we examined infection markers such as PLR, LMR, and NLR. In statiscally, the NLR was the only prognostic value of this study and cutoff value of NLR was 5.72. This means that the higher level of 5.72 is on maintaining the pregnancy and the lower level of 5.72 is increased the early miscarriages, so obsessive treatment is needed for pregnancy. Owing to the convenience of detecting results from venous samples, these markers are useful tools for predicting early miscarriage, and thus the pregnancy outcomes, and for preventing early miscarriage.

Author contributions

Youngsun Kim was the sole contributor to this research.

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