Experimental & Clinical Article

Obstetrics; *Maternal Fetal Medicine and Perinatology*

The Utility of Systemic Inflammatory Markers to Predict Emergent Cerclage

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ABSTRACT

OBJECTIVE: The inflammatory markers examined in this study have been previously associated with adverse neonatal outcomes in numerous studies, raising the question of whether cervical insufficiency is also linked to these markers. To address this issue, the present study was designed to identify a simple, cost-effective biochemical predictor of unpredictable cervical insufficiency.

STUDY DESIGN: This retrospective study included a total of 34 patients who underwent emergency cerclage procedures at the clinic between 2018 and 2024. The control group consisted of pregnant women randomly selected from the patient population who sought care at the outpatient clinic for routine pregnancy check-ups. They were followed throughout their pregnancies at our hospital and delivered at term without complications. The systemic immune-inflammation index, systemic inflammation response index, neutrophil-lymphocyte ratio, lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio were calculated from the complete blood counts of both groups during the first and second trimesters. Group comparisons and receiver operating characteristic analyses were performed.

RESULTS: The lymphocyte-to-monocyte ratio in patients who underwent emergency cerclage was significantly higher than that observed in healthy pregnant women during both the first and second trimester complete blood counts.

CONCLUSION: Lymphocyte-to-monocyte ratio may be a promising and cost-effective marker for predicting CI requiring EC. Further prospective studies with larger cohorts are warranted.

Keywords: Cervical cerclage; Inflammation; Complete blood count; Antenatal care

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Introduction

Cervical insufficiency (CI) is an obstetric challenge, marked by the cervix opening too soon, often without pain, and placing the pregnancy at risk of second-trimester loss or early delivery. The prevalence of CI is estimated to be less than 1% of pregnancies, yet it remains one of the leading causes of spontaneous second-trimester pregnancy loss (1). Nevertheless, the mechanisms underlying CI remain poorly understood. Many potential causes have been suggested, spanning from congenital abnormalities to acquired complications (2).

The management of CI has evolved over the years, with cervical cerclage being the primary intervention. Traditionally, this procedure has been performed either prophylactically in women with a history of cervical incompetence or as an emergency intervention in cases of acute cervical dilation (3). Emergency cerclage (EC) is indicated when a woman presents with cervical shortening, dilation, or bulging membranes in the second trimester. The success rates of EC vary (4), and the presence of intra-amniotic infection or inflammation is a critical factor influencing the outcomes of EC, as these conditions can significantly diminish the likelihood of a successful pregnancy (5).

Elevated maternal inflammatory markers like interleukin-6, interleukin-8, and systemic immune-inflammation index (SII) have been linked to poor pregnancy outcomes after cervical cerclage (6,7). The systemic inflammation response

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index (SIRI) has also emerged as a significant biochemical marker for predicting maternal-neonatal outcomes after cervical cerclage (6,7). These markers reflect the systemic inflammatory response and may indicate the risk of complications such as preterm labor or infection, which are critical considerations in managing pregnancies complicated with CI (8). Additionally, the neutrophil-lymphocyte ratio (NLR) has been proposed as a practical and efficient parameter for assessing systemic inflammation, with studies indicating its potential utility in predicting early delivery in high-risk populations (9,10). The lymphocyte to monocyte ratio (LMR) has also been studied as a promising inflammatory marker in various clinical settings, such as gestational diabetes mellitus (11), where it serves as an indicator of systemic inflammation and immune dysregulation. The platelet-to-lymphocyte ratio (PLR) is another critical inflammatory marker that reflects both inflammatory and coagulation pathways.

Nevertheless, all earlier studies were designed to predict the outcome of pregnancies complicated by CI with these inflammatory markers. The results of these studies consistently indicate that pregnancy outcomes are adversely affected by increasing levels of inflammatory markers (12-14). This study aims to evaluate the potential predictive value of inflammatory markers measured at the time of EC for the development of CI. For this purpose, SII, SIRI, NLR, PLR, and LMR values obtained from first and second trimester complete blood counts (CBC) were compared between patients who underwent EC and healthy pregnant controls.

Material and Method

All procedures of this study were performed in accordance with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Selcuk University Rectorate Local Ethics Committee reviewed this study on 21.11.2024 and approved it with the decision number E-70632468-050.04-880232. Consent was obtained from all participants for data use.

Our cross-sectional study focused on patients who underwent the cerclage procedure at Selcuk University Faculty of Medicine, Department of Obstetrics and Gynecology, between 2018 and 2024. A total of 61 cerclage cases performed at our clinic between 2018 and 2024 were reviewed. Eighteen cases were excluded from the study because they had been administered prophylactically. Four of the remaining cases were excluded due to twin pregnancy. Additionally, the first-trimester blood counts of two patients were not available, and three patients had comorbidities, which resulted in their exclusion from the study. Consequently, 34 patients were included in the study as an EC group. None of them had a history of CI or preterm labor. This exclusion was done to obtain a more homogeneous group of patients and to include only cases of sudden cervical insufficiency that were unpredictable and had no risk factors. The control group comprised pregnant women who were randomly chosen from the patient population who had applied to the outpatient clinic for routine pregnancy control. These patients ranged in age from 18 to 45 years, had no comorbidities, and were all followed throughout pregnancy in our hospital, delivering at term without complications.

The SII, SIRI, LMR, PLR, and NLR values were calculated independently for the first and second trimesters based on the CBC data obtained for both the control group and the EC group. The SIRI was calculated using the following formula: (neutrophil count × monocyte count)/lymphocyte count, and the SII was calculated using the following formula: (platelet count × neutrophil count)/lymphocyte count. LMR, PLR, and NLR were computed using the formulas for lymphocyte count/monocyte count, platelet count/lymphocyte count, and neutrophil count/lymphocyte count, respectively.

Statistical analysis

The analyses were evaluated using the SPSS (Statistical Package for the Social Sciences) version 22 software. Descriptive data were presented as absolute and relative frequencies for categorical variables and as mean ± standard deviation (SD) and median with interquartile range (25th–75th percentile) for continuous variables. Pearson's chi-square test was used to compare categorical variables between groups. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. For comparisons between two groups, the Student's t-test was employed for normally distributed variables, while the Mann-Whitney U test was used for variables that were not normally distributed. Receiver Operating Characteristic (ROC) curves were constructed, and the area under the curve (AUC), sensitivity, and specificity were determined to evaluate the diagnostic performance of first-trimester LMR (LMR-1) and second-trimester LMR (LMR-2) values. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was set at $p<0.05$.

Results

As seen in Table I, 74 patients were enrolled in the study, of whom 34 had received emergent cerclage, while 40 served as healthy controls. No significant differences were observed in terms of age, obstetric history, body mass index, or anthropometric measurements between the two groups (Table I).

Comparisons of first-trimester CBC parameters and inflammatory markers are shown in Table II. As seen, the mean MPV and monocyte count values of the cerclage group were significantly lower than those of the control group, and the LMR ratio was found to be significantly higher. SII, SIRI, NLR, and PLR values were higher in the cerclage group, although the differences were not statistically significant.

Table III presents a comparison of second-trimester CBC parameters and inflammatory marker levels between the cerclage and control groups. The PDW and LMR values of the cerclage group were found to be significantly higher, while eosinophil and basophil values were significantly lower than those in the control group. The SII, SIRI, NLR, and PLR values of the cerclage group were higher than those of the control group, although these differences were not statistically significant.

The utility of the first-trimester LMR value in predicting CI was investigated using ROC analysis, and cut-off values were determined. When a cut-off value of 3.209 was used, AUC=0.706, a sensitivity of 88.2%, specificity of 52.5%, positive predictive value of 61.2%, negative predictive value of 84%, and a p-value of 0.001 were determined, indicating that it is a good predictor, as shown in Figure 1.

Using a cut-off value of 2.904 for second-trimester LMR levels, AUC=0.673, the sensitivity was found to be 79.4%, the specificity was 52.5%, the positive predictive value was 58.7%, the negative predictive value was 75.0%, and the p-value was 0.007. It was also shown to be a good predictor, as illustrated in Figure 2.

Table I: *Comparison of demographic and clinic parameters according to the presence of cerclage*

	Emergency Cerclage Group (n=34)	Control Group (n=40)	p
Cervical length (mm)	11.20±6.12	29.8 ± 4.56	0.001
Gestational week at the time of cerclage	22 weeks (20 weeks 1/7 day- 23 weeks 6 days)	-	-
Age	28.12 ± 6.19	27.93 ± 4.5	0.878
Gravida	2.00 (1.00-3.00)	2.00 (1.00-3.00)	0.825
Parity	0.00 (0.00-1.00)	1.00 (0.00-1.50)	0.142
Height (cm)	162.21 ± 5.82	161.14 ± 6.53	0.478
Weight (kg)	73.41 ± 17.11	69.20 ± 11.54	0.234
BMI (kg/m^2)	27.80 ± 5.91	26.68 ± 4.44	0.378

BMI, body mass index

Table II: *Comparison of first-trimester blood count parameters between groups*

First Trimester Blood Count Parameters	Emergency Cerclage Group (n=34) Mean± SD Mean (25p-75p)	Control Group (n=40) Mean ±SD Mean (25p-75p)	p*
WBC (103/uL)	10.00 ± 2.2	9.60 ± 2.26	0.441
HGB (g/DL)	12.95 ± 1.15	12.50 ± 1.35	0.127
HTC (%)	39.06 ± 2.91	37.98 ± 3.24	0.137
PLT (10^3/uL)	295.26 ± 66.39	292.15 ± 68.54	0.844
RBC (10^6/uL)	4.57 ± 0.43	4.53 ± 0.41	0.682
MCV (fL)	85.90 ± 4.41	84.06 ± 6.17	0.151
MCH (pG)	28.46 ± 1.79	27.66 ± 2.79	0.155
MCHC (g/L)	33.14 ± 1.06	32,85 ± 1.44	0.341
RDW (%)	13.60 (13.20-14.20)	13.70 (13.10-14.60)	0.696
PDW (%)	11.65 (10.60-16.10)	12.10 (10.70-12.80)	0.307
MPV (fL)	9.70 (9.20-10.10)	10.50 (9.90-10.90)	**0.003**
PCT (%)	0.30 (0.23-0.34)	0.30 (0.26-0.35)	0.488
NEUTROPHIL (10^6/uL)	6.95 ± 1.9	6.38 ± 2.09	0.227
LYMPHOCYTE (10^6/uL)	2.35 ± 0.93	2.20 ± 0.56	0.397
MONOCYTE (10^6/uL)	0.54 (0.42-0.67)	0.63 (0.54-0.79)	**0.033**
EOZONOPHYL (10^6/uL)	0.08 (0.03-0.16)	0.10 (0.06-0.19)	0.328
BAZOPHYL (10^6/uL)	0.03 (0.02-0.05)	0.04 (0.03-0.05)	0.358
NEUTROPHIL %	67.90 ± 9.07	67.58 ± 5.81	0.856
SII	977.90 ± 461.4	863.45 ± 362.08	0.236
SIRI	1.88 (1.34-2.50)	1.71 (1.17-2.30)	0.246
LMR	4.36 ± 1.81	3.42 ± 1.28	0.011
PLR	138.92 ± 43.5	136.92 ± 35.69	0.828
NLR	2.95 (2.22-4.06)	2.91 (2.29-3.46)	0.745

SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, LMR: Lym-phocytes-to-monocytes ratio, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-lymphocyte ratio. Bold indicates significant

Table III: *Comparison of second-trimester blood parameters between groups*

Second trimester blood count parameters	Emergency Cerclage Group (n=34) Mean± SD Mean (25p-75p)	Control Group (n=40) Mean± SD Mean (25p-75p)	p*
WBC (10^3/uL)	10.85 ± 2.79	10.55 ± 2.46	0.616
HGB (g/DL)	11.99 ± 1.23	11.79 ± 1.27	0.499
HTC (%)	35.65 ± 3.85	35.33 ± 3.08	0.692
PLT (10^3/uL)	260.47 ± 51.15	239.52 ± 62.72	0.124
RBC (10^6/uL)	4.09 ± 0.5	4.05 ± 0.31	0.666
MCV (fL)	87.40 ± 5.61	87.33 ± 6.3	0.957
MCH (pG)	29.41 ± 2.07	29.15 ± 2.97	0.680
MCHC (g/L)	33.63 ± 0.74	33.31 ± 1.36	0.222
RDW (%)	13.80 (13.40-14.60)	14.35 (13.55-15.10)	0.176
PDW (%)	13.85 (11.20-16.30)	12.00 (10.65-13.15)	**0.040**
MPV (fL)	10.18 ± 1.18	12.47 ± 12.11	0.277
PCT (%)	0.26 ± 0.05	0.26 ± 0.05	0.526
NEUTROPHIL (10^6/uL)	8.12 ± 2.55	7.70 ± 2.12	0.446
LYMPHOCYTE (10^6/uL)	2.02 ± 0.72	1.99 ± 0.52	0.823
MONOCYTE (10^6/uL)	0.57 (0.40-0.78)	0.65 (0.56-0.85)	0,079
EOZONOPHYL (10^6/uL)	0.08 (0.04-0.12)	0.10 (0.06-0.19)	**0.027**
BAZOPHYL (10^6/uL)	0.02 (0.01-0.03)	0.03 (0.02-0.05)	**0.009**
NEUTROPHIL %	73.91 ± 8.75	72.46±5.75	0.396
SII	993.38 (680.06-1231.01)	893.33 (734.40-1465.00)	0.398
SIRI	2.53 (1.96-3.89)	2.05 (1.57-3.14)	0.101
LMR	4.06 (2.96-5.42)	3.83 (3.10-5.14)	**0.011**
PLR	3.76 (2.95-4.50)	2.87 (2.17-3.72)	0.737
NLR	132.43 (104.21-163.22)	124.86 (94.14-148.07)	0.334

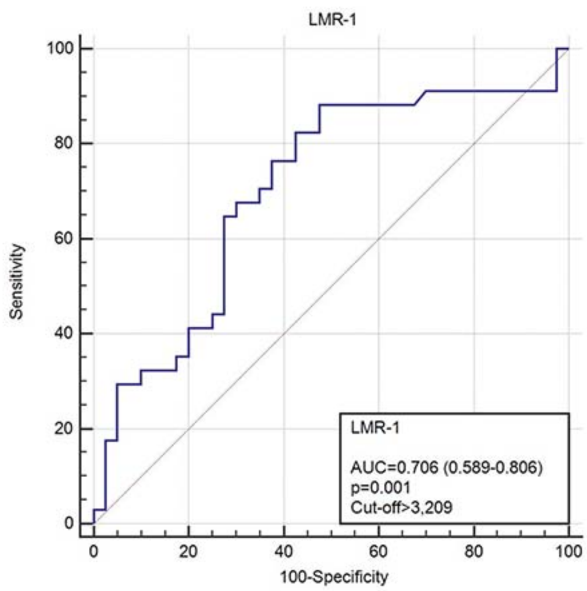

Figure 1: *ROC curve analysis of the first-trimester LMR levels to predict cervical cerclage*

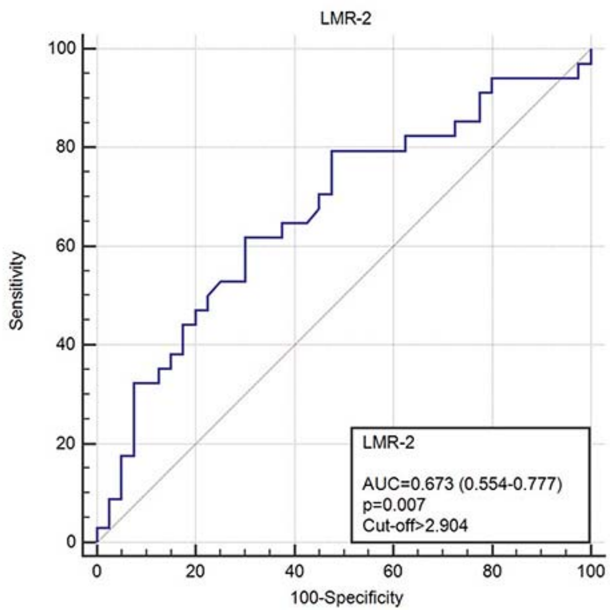

Figure 2: *ROC curve analysis of the second-trimester LMR levels to predict the cervical cerclage*

Discussion

CBC parameters are routinely used worldwide to monitor health status during pregnancy because they are reliable, simple, rapid, and cost-effective. During pregnancy, physiological changes occur and can be observed in the CBC. Some parameters decrease, such as HGB, RBC, and PLT, while others increase, including WBC, neutrophils, and monocytes (15). The fact that SII, SIRI, LMR, NLR, and PLR can also be easily calculated using CBC and their ability to interpret inflammatory processes in a large number of diseases (16) has encouraged us to evaluate these inflammatory markers for CI prediction. Our findings demonstrate that elevated LMR values in both the first and second trimesters are associated with CI in pregnancies requiring EC (p=0.011 and p=0.011, respectively). This finding suggests that LMR may have a role in predicting CI.

Evidence suggests that inflammatory markers are significant predictors of maternal-neonatal outcomes in patients undergoing cervical cerclage. For instance, a study by Fang et al. highlighted the significance of monitoring maternal inflammation markers, including SII and SIRI, during the perioperative period to predict outcomes after cervical cerclage (13). This aligns with findings from Lin, who emphasized that elevated levels of these indices may indicate adverse neonatal outcomes in pregnant patients who underwent cerclage (7). However, none of these studies has shed light on predicting cervical insufficiency. Therefore, we aimed to identify a biochemical marker that could predict CI and to better evaluate the significance of these values in CI. We conducted our study in patients who presented with sudden cervical shortening and underwent EC without a history of previous cerclage, preterm labor, or other comorbidities.

During a normal pregnancy, lymphocyte counts remain stable throughout pregnancy, and monocytes increase marginally with gestational age (17). Consequently, PLR and LMR show a clear downward trend, while SII and NLR tend to increase with advancing gestational weeks (18). The results of this study also show that SII and NLR values increased with advancing gestational age in both groups, while LMR and PLR values decreased concomitantly. Also, there was no statistically significant difference between the EC group and the control group in terms of SII, SIRI, NLR, and PLR values in both the first and second trimesters. Still, it is noteworthy that these values were higher in the EC group in both trimesters. However, there was a significant difference in LMR values between the groups in the first and second trimesters. The observation that LMR values differed significantly not only at the time of EC but also during the first trimester enhances the reliability of this marker as a potential predictor of CI.

Pregnancy is associated with a well-known shift from Th1 to Th2 immune responses, as well as a general activation of the nonspecific immune response (19). Changes in the proportions of different monocyte subsets accompany this (20). The changes in monocyte subsets and the decrease in LMR during pregnancy are thought to contribute to the maternal immune tolerance necessary for fetal development (21,22). Monocytes and macrophages play essential roles in implantation, placentation, and maintaining a healthy pregnancy. Alterations in these processes have been linked to pregnancy-related complications, such as preeclampsia, fetal growth restriction, and pregnancy loss (21,22). In light of the existing literature, the finding that LMR levels in the cerclage group in our study were higher than those obtained in the control group may be interpreted as evidence that immune regulation was not achieved and fetal rejection occurred in these pregnant women. Therefore, it must be acknowledged that our understanding of these inflammatory markers is limited.

Our study presents several strengths. Most prominently, it investigates the predictive utility of routinely available, cost-effective systemic inflammatory markers in identifying cases of CI requiring emergent cerclage. By focusing on a homogeneous patient population without prior risk factors such as preterm birth or history of cerclage, the study minimizes variables and increases the validity of its findings. Additionally, using blood samples from both the first and second trimesters allows for temporal analysis, reinforcing the potential utility of LMR as an early predictive biomarker. However, the present study is subject to several limitations, including its retrospective nature, single-center design, and the relatively small number of patients included.

In summary, the findings indicate that the LMR holds promise as a prognostic biomarker, offering potential utility in distinguishing patient risk and guiding evidence-based clinical management. LMR can be easily calculated and incorporated into CBC, making it a part of routine pregnancy follow-up. While further research in this area is undoubtedly necessary, we believe that our study will contribute to the existing literature on this subject, as it is the first to explore the role of inflammatory markers in predicting CI.

Declarations
Ethics approval and consent to participate: All participants signed a consent form for data use. The study was reviewed and approved by the ethics committee of Selcuk University Rectorate (Ethics approval reference number: E-70632468-050.04-880232, date 21.11.2024). All procedures were performed according to the Declaration of Helsinki.
Availability of data and materials: The data supporting this study are available through the corre-sponding author upon reasonable request.
Competing interests: The authors declare that they have no competing interests.
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Authors' contributions: ACD, and NB: Raised the presented idea. ACD, NB, and GO: Designed the study. NB, and LA: conducted the analyses. ACD: Developed the first draft of the manuscript. AP, and GO: Critically revised the manuscript. All authors read and approved the final manuscript.
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