The Role of Preoperative Inflammatory Markers in Cervical Cerclage Success

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ABSTRACT

Objective: To compare the inflammatory markers between therapeutic and emergency cerclage and assess the predictive role of inflammatory markers for the latency period.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Obstetrics and Gynaecology, Bursa Yuksek Ihtisas Training and Research Hospital, Turkiye, from January 2016 to September 2022.

Methodology: The therapeutic cerclage group (n = 64) included patients with a history of cervical insufficiency, normal prenatal screening test results, and who underwent cerclage based on history indications. The emergency cerclage group (n = 14) included patients with painless cervical dilation in the second trimester or a history of preterm and a short cervix on ultrasonography. Exclusion criteria composed of multiple pregnancies, active uterine contractions, vaginal bleeding, chorioamnionitis, membrane rupture, foetal anomalies, history of conization or abdominal cerclage, and having inflammatory diseases. Sociodemographic features, perinatal outcomes, and inflammatory markers such as neutrophil-to-lymphocyte ratio, C-reactive protein, and systemic immune-inflammation index were compared. Systemic immune-inflammation index was calculated by formulating the multiplication value of the neutrophil and platelet count divided by the lymphocyte count.

Results: The latency period was shorter (5.5 (0-29) *vs.* 20 (1-31) weeks, p <0.001) in the emergency cerclage group. Neutrophil-to-lymphocyte ratio and systemic immune-inflammation index, which are representatives of increased inflammatory state, were significantly higher in the emergency cerclage group (p = 0.007 for both). Systemic immune-inflammation index was correlated with cerclage to delivery interval for all patients (r = -0.307, p = 0.006). Also, it predicted neonatal mortality with a cut-off value of 1078.08, 90% sensitivity and 70.59% specificity (AUC = 0.776, p <0.001) and low Apgar scores with 57.1% sensitivity and 74% specificity (AUC = 0.641, p = 0.038).

Conclusion: Systemic immune-inflammation index, correlated with cerclage to delivery interval, could be a marker for predicting neonatal mortality and morbidity in cerclage patients.

Key Words: *Cervical cerclage, Inflammatory markers, Perinatal outcomes, Systemic immune-inflammation index.*

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INTRODUCTION

Cervical cerclage is a surgical procedure used for prophylactic obstetric intervention in women with weakened cervical integrity.[1] The procedure is applied for the history of cervical insufficiency, indications based on ultrasonography, and physical examination findings.[2] The procedure could be performed therapeutically or emergently. Therapeutic cerclage is performed around the 11-14th weeks of pregnancy in asymptomatic women with risk factors in their history, where cervical length is measured.[3]

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Women with a history of spontaneous second-trimester loss or preterm birth and who have not undergone history-based cerclage can benefit from ultrasound-indicated cerclage if they experience cervical shortening through serial sonographic monitoring. The success of these procedures may be influenced by various clinical factors including age, body mass index, history of preterm birth, inflammatory markers such as high C-reactive protein (CRP) levels and cervical dilatation.[4]

The inflammatory factors predicting the latency period after cerclage have not been completely studied. There is a debate about the beneficial role of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) values in predicting the latency period after the cerclage procedure. In the literature, increased cervical mucus interleukin-8 was found to be related to preterm birth after ultrasound indicated cerclage.[5] Another inflammatory marker predicting the outcome of cerclage is CRP. CRP was found to predict the outcome of emergency cerclage in patients who have dilated cervix and bulging membranes.[6] Another study demonstrated

that CRP was useful in predicting preterm birth in ultrasound-indicated cerclage in patients with a short cervix and prior preterm birth.[7] The newly used marker, named as systemic immune-inflammation index (SII) is an economical and easily available predictor of some inflammatory diseases. The SII value was calculated by formulating the multiplication value of the neutrophil and platelet count divided by the lymphocyte count. In the literature, high SII levels were reported to be associated with coronary artery diseases and poor outcomes of cancer patients.[8] There are only a few studies in the literature searching the role of SII in cerclage success.[8-10] Only two of these studies have considered the predictive role of SII for neonatal outcomes.[8,9]

The present study hypothesises that emergency conditions lead to more inflammatory responses. Thus, inflammatory markers should be higher in emergent conditions than elective circumferences. Moreover, a high inflammatory response shortens the latency period. A marker, reflecting the inflammation, must be higher in emergency cerclage than a therapeutic one and could correlate with the length of the latency period. Therefore, this study aimed to assess the role of inflammatory markers including SII in therapeutic or emergency cerclage, to evaluate the correlation with latency period, and to determine the role of these markers in the prediction of neonatal mortality.

METHODOLOGY

This study was conducted retrospectively at Bursa Yuksek Ihtisas Training and Research Hospital, Turkiye, from January 2016 to September 2022. This study was approved by the local Ethics Committee. Written informed consent was taken from all patients for using their medical data for research. The study was conducted in accordance with the rules of the Declaration of Helsinki.

A total of 78 pregnant patients were divided into two subgroups based on the indication for cerclage: Therapeutic cerclage (n = 64) and emergency cerclage (n = 14). The inclusion criteria for the therapeutic cerclage group were having a history of cervical insufficiency, normal prenatal screening test results during the first trimester, and underwent cerclage based on history indications. The inclusion criteria for the emergency cerclage group were having painless cervical dilation in the second trimester or a history of preterm and a short cervix on ultrasonography measured below 25 milimetres.

Exclusion criteria composed of multiple pregnancies, active uterine contractions, vaginal bleeding, chorioamnionitis, membrane rupture, foetal anomalies, history of conization or abdominal cerclage, and having inflammatory diseases. All patients underwent transvaginal cerclage of the McDonald type using povidone-iodine under spinal or general anaesthesia for sterilisation.[10] A Mersilene suture is used to apply cervical suturing as close as possible to the internal OS. All cerclage procedures were performed by the same surgeon. Preoperative cefazolin 1 to 2 mg based on weight is routinely administered for cerclage procedures.

The patients' preoperative complete blood count was measured using a Beckman Coulter LH 780 Analyzer (blood analyser). Biochemical tests were also recorded, including CRP, fibrinogen, and albumin levels. The SII value was calculated by formulating the multiplication value of the neutrophil and platelet count dividing by the lymphocyte count.

The primary outcome of the study was to compare the SII levels between two cerclage groups. Secondary outcomes were determining the correlation of this marker with cerclage to delivery interval and evaluating the predictive role of SII for neonatal outcomes.

Shapiro-Wilk's test was used to determine the normality of distribution of all variables. The normally distributed continuous variables were described using mean ± standard deviation and the non-normally distributed variables were expressed as median. Categorical variables were presented as frequency and percentages. Student's t-test and Mann-Whitney U test were used for comparing continuous variables, Chi-square or Fisher's exact tests for categorical variables. Spearman correlation coefficient was used to analyse the correlation between inflammatory markers and cerclage to delivery interval for each group. Receiver operating curve was performed to determine the predictive role of SII for neonatal outcomes. The analysis was performed using the SPSS version 22.0 programme and a value of $p < 0.05$ was considered statistically significant.

RESULTS

Demographic characteristics, examination findings, and neonatal features of therapeutic cerclage and emergency cerclage groups were presented in Table I and II. There was no significant difference between the two groups in terms of age, the ratio of preterm delivery, the presence of chorioamnionitis, comorbid disease, cerclage history, and neonatal mortality. The therapeutic cerclage group had significantly higher gravidity, parity, abortions, history of preterm birth rate, delivery week, first and fifth minutes Apgar scores, and birth weight whereas hospitalisation time after cerclage was shorter. In the emergency cerclage group, cervical length and cerclage to delivery interval were shorter than the therapeutic cerclage group while cervical dilatation and cerclage weeks were higher in the emergency group.

Inflammatory markers examined before cerclage were presented in Table III. Neutrophils, NLR, and fibrinogen levels were higher in the emergency cerclage group. Moreover, SII was significantly higher in the emergency cerclage group as compared to the therapeutic cerclage group [1397 (485 - 4059) *vs.* 814 (92.6 - 4165), p = 0.007].

The correlation between inflammatory markers and cerclage to the delivery interval was evaluated by Spearman correlation coefficient. SII was found to be negatively correlated with cerclage to delivery interval for all study groups (r = -0.307, p = 0.006) while other inflammatory markers were not correlated with latent period.

Table I: Comparison of demographic characteristics between groups.

Parameters	Emergency cerclage (n = 14)	Therapeutic cerclage (n = 64)	p-value
Age (years)	31.79 ± 5.2	33.47 ± 6.2	0.348
Gravida (n)	2 (1-3)	3 (1-7)	**<0.001**
Parity (n)	0 (0-1)	1 (0-3)	**0.002**
Abort (n)	0 (0-2)	1 (0-5)	**0.005**
Preterm birth history (n,%)	1 (7.1%)	40 (62.5%)	**<0.001**
Comorbid disease (n,%)	1 (7.1%)	3 (4.7%)	0.555
Cerclage history (n,%)	1 (7.1%)	23 (35.9%)	0.052

Table II: Comparison of examination findings and neonatal results between groups.

Parameters	Emergency cerclage (n = 14)	Therapeutic cerclage (n = 64)	p-value
Cervical length (mm)	14.5 (10-37)	35 (10-40)	**0.037**
Cervical dilatation	10 (71.4%)	3 (4.7%)	**<0.001**
GA at cerclage (weeks)	19 (17-27)	14 (12-24)	**<0.001**
Hospitalisation after cerclage (day)	4 (1-10)	2 (1-16)	**0.023**
Cerclage to delivery interval (week)	5.5 (0-29)	20 (1-31)	**<0.001**
Preterm delivery (n,%)	2 (16.7%)	16 (26.2%)	0.718
Chorioamnionitis	3 (21.4%)	9 (14.1%)	0.443
GA at delivery (weeks)	28.5 (22-37)	35 (22-40)	**0.019**
Foetal weight (g)	1097 (400-3160)	2650 (350-3950)	**0.003**
Apgar score (1 min)	6 (0-9)	9 (0-9)	**0.012**
Apgar score (5 min)	7.5 (0-10)	10 (0-10)	**0.005**
Neonatal mortality	3 (21.4%)	7 (10.9%)	0.373

Notes: Descriptive analyses are presented using (X ± SD), median (min-max), and categorical variables as n (%). Abbreviations: GA, Gestational age. Statistically significant value is indicated in bold.

Table III: Comparison of inflammatory markers between groups.

Parameters	Emergency cerclage (n = 14)	Therapeutic cerclage (n = 64)	p-value
CRP (mg/dL)	11.8 (3.1 - 148)	9.6 (3.3 - 86)	0.252
WBC (x10^3/mL)	11.3 (2.2 - 21.9)	10.1 (5.4 - 18.2)	0.338
Neutrophils (x10^3/mL)	9.4 (5.2 - 19.9)	7.3 (3.7 - 15.2)	**0.016**
Lymphocyte (x10^3/mL)	1.7 (0.63 - 3.21)	2.1 (0.39 - 17.4)	0.180
Platelet (x10^3/mL)	253.5 (169 - 336)	253 (140 - 504)	0.598
NLR	5.5 (2 - 17.27)	3.6 (0.3 - 20)	**0.007**
PLR	178.8 (67.9 - 393.7)	109 (15.7 - 533)	0.120
PCT (%)	0.25 (0.18 - 0.36)	0.25 (0.13 - 0.56)	0.906
RDW (%)	13.8 (12 - 22.6)	13.8 (12.1 - 25.4)	0.974
Albumin (g/L)	37.6 (29 - 41)	36.5 (24.1 - 44.8)	0.840
Fibrinogen (mg)	507.2 ± 67.4	449.1 ± 91.9	**0.028**
CRP/Fibrinogen	0.020 (0.007 - 0.331)	0.023 (0.005 - 0.2)	0.696
CRP/Albumin	0.35 (0.08-5.1)	0.25 (0.08 - 3.6)	0.322
Platelet/Albumin	6.71 (4.5 - 10.6)	6.91 (3.9 - 14)	0.917
SII (x10^3/mL)	1397.9 (485 - 4059.6)	814.7 (92.6 - 4165.3)	**0.007**

Note: Descriptive analyses are presented using (X ± SD), median (min-max). CRP, C-reactive protein; WBC, White blood cell; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte Ratio; PCT, Platecrit; RDW, Red cell distribution width; SII, Systemic immune inflammation index. Statistically significant value is indicated in bold.

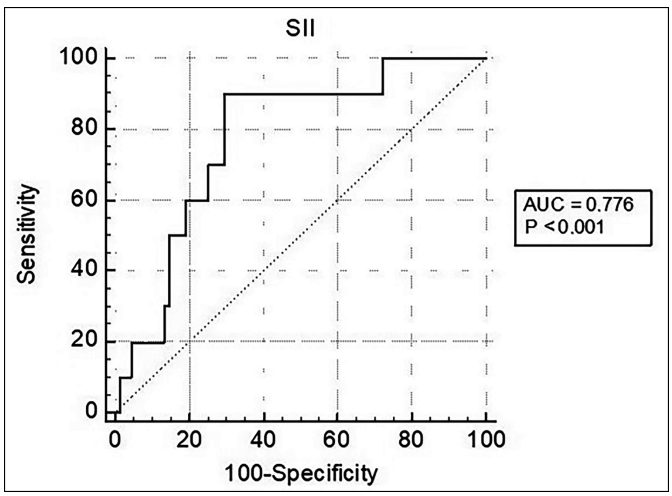

Figure 1: The receiver operating curve evaluating the role of SII in predicting neonatal mortality.

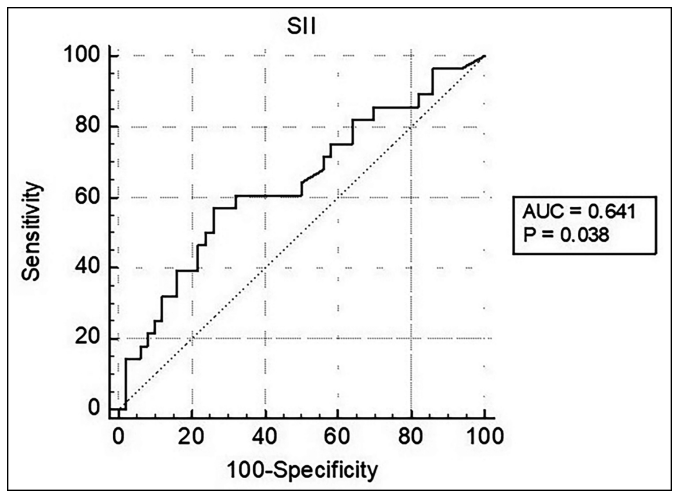

Figure 2: The receiver operating curve evaluating the role of SII in predicting low Apgar scores.

The predictive role of SII for neonatal mortality and low Apgar scores after cerclage was evaluated using ROC (receiver operating characteristics) curve analysis and demonstrated in Figure 1 and 2. SII had a predictive role for neonatal mortality with a cut-off value of 1078.08 with 90% sensitivity and 70.59% specificity (AUC = 0.776, p <0.001) and had a predictive role for low Apgar scores with 57.1% sensitivity and 74% specificity (AUC = 0.641, p = 0.038).

DISCUSSION

Preterm labour is an important cause of neonatal mortality among worldwide.[11,12] Cervical insufficiency is one of the contributing factors of preterm birth.[13,14]

Cervical cerclage is particularly effective in extending gestation duration and reducing mid-trimester pregnancy loss related to cervical insufficiency.[15,16] However, reliable indicators to predict the outcome of cervical cerclage are currently limited. Predicting disease prognosis through easily available and cost-effective blood count markers has facilitated their implementation in clinical practice.[5,17]

Elective cerclage is associated with a reduced risk of inflammation and chorioamnionitis compared to emergency cerclage. NLR is one of the inflammatory markers. Since labour is an inflammatory process, previous studies reported that NLR could predict preterm birth.[18] Although the cut-off value is controversial, there are two studies that accept 4.7 and 6.2 as cut-off values for the prediction of preterm labour.[10,19] There are only a few studies searching the NLR between therapeutic and emergency cerclage groups. Gulucu *et al.* reported that there was no difference between emergency and therapeutic cerclage groups for NLR.[10] Similar to that study, Akdemir *et al.* found no difference between prophylactic and emergency cerclage groups.[20] Contrary to these studies, the present study demonstrated that NLR was found to be higher in the emergency cerclage group. This inconsistency could be related to the gestational week at cerclage.

Another inflammatory marker for cerclage patients is SII. It is a combination of platelet count and neutrophil-to-lymphocyte ratio that reflects the balance of immune status and inflammatory processes. There is only one study comparing SII between emergency and therapeutic cerclage groups. Gulucu *et al.* claimed that the SII showed no difference between the emergency and therapeutic cerclage groups.[10] As NLR, higher SII values in the emergency cerclage group were detected. This could be related to higher NLR levels in the emergency cerclage group.

Studies have shown that certain markers are associated with the success rate of cervical cerclage.[5,8,10] For instance, inflammatory markers in maternal peripheral blood are significantly linked to the success rate of cervical cerclage. However, not all markers have prognostic significance in predicting the success of cerclage procedures.[19] Fang *et al.* reported inflammatory markers, such as the neutrophil count, type II aritson, and the systemic inflammation response index (SIRI), in the maternal peripheral blood were significantly associated with the success rate of cervical cerclage.[8] In another study by the same authors, both higher pre- and post- cerclage SII levels were claimed to be related to shorter cerclage to the delivery interval.[9] In a study from Turkiye, SII was negatively correlated with the delivery week which suggested that SII is related to a shorter latency period.[10] Similarly, this current research revealed a strong correlation between SII and the cerclage to the delivery interval in cerclage patients. Thus, the present study suggested that as the inflammation decreases, the interval between the cerclage procedure and birth may lengthen.

The data searching the role of inflammatory markers, especially SII in neonatal outcomes is limited.[21,22] In a study by Lin *et al.,* higher pre- and post-cerclage SII levels were reported to be related to longer hospitalisation time for neonatal indications, lower Apgar scores of first, fifth, and tenth minutes, higher neonatal mortality and neonatal intensive care unit.[9] Similarly, Fang *et al.* showed that higher SII was associated with earlier delivery week, low-birth weight, and Apgar scores.[8] In the present study, SII had a predictive role for neonatal mortality with a cut-off value of 1078.08 with 90% sensitivity and 70.59% specificity and had a predictive role for low Apgar scores with 57.1% sensitivity and 74% specificity.

The present study has some limitations. First of all, each study group had a small sample size and this is a retrospective single-centred study. Second, follow-up laboratory parameters were not considered and the analysis was performed for only precerclage levels.

CONCLUSION

SII, which is an economical and easily available inflammatory marker, can be used to predict neonatal mortality and low Apgar scores. Thus, using inflammatory markers separate or together may be crucial for a more comprehensive understanding and monitoring of inflammation levels.

ETHICAL APPROVAL:
This study was approved by the local ethics committee (Date: 17.06.2021/ Project No: 21-KAEK-161).

PATIENTS' CONSENT:
Written informed consent was taken from all patients for using their medical data for research.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
GO: Data curation and writing of the original draft.
LO: Conceptualisation and design.

BD: Design, methodology, supervision, and statistical analysis.
BO: Formal analysis and data curation.
All authors approved the final version of the manuscript to be published.

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