

# The Association of Inflammatory Markers with Maternal-Neonatal Outcome After Cervical Cerclage

Jiaoning Fang<sup>1,\*</sup>, Yingying Lin<sup>2,\*</sup>, Zhiwei Chen<sup>3,\*</sup>, Yan Lin<sup>1</sup>, Mian Pan<sup>1</sup> 

<sup>1</sup>Department of Obstetrics, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, People's Republic of China; <sup>2</sup>Department of Healthcare, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, People's Republic of China; <sup>3</sup>Department of Gynecologic, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Mian Pan; Yan Lin, Department of Obstetrics, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Medical University, Fuzhou, People's Republic of China, Tel +86-13178031273; +86-591-86329321; +86-13665051036, Email panmian1973@126.com; 571313649@qq.com

**Objective:** Cervical cerclage is effective in prolonging the number of weeks gestation in patients with cervical insufficiency(CI). However, valuable predictors with successful cervical cerclage remain limited. It aimed to evaluate the value of the systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) to predict the outcomes of cervical cerclage.

**Methods:** This study analyzed 374 participants. Inflammatory markers were calculated using maternal peripheral blood. The association of inflammatory markers and the outcome of cervical cerclage were analyzed. And the optimal cut-off values of inflammatory markers were calculated. Also, the Chi-square test and logistic and linear regression analyses were performed to evaluate inflammatory markers with the maternal outcome and neonatal outcomes.

**Results:** 374 pregnancies were included in this study. Finally, 268 (71.7%) participants suffered successful cervical cerclage. This study demonstrated that the baseline BMI (cm<sup>2</sup>/kg), the bulging membrane, cervical dilation (≥2cm), the amniotic sac herniation, the neutrophils counts, the systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) were significant difference between the successful and unsuccessful groups (all P<0.05). Additionally, maternal blood inflammatory markers, such as WBC, lymphocyte, neutrophils, monocyte, platelet counts, SII, and SIRI, were significantly associated with maternal-neonatal outcomes. Furthermore, the results demonstrated that the SII level had the highest OR (OR=4.626; 95% CI (2.500–8.560)), as well as the following: SIRI level (OR = 3.795; 95% CI (1.989–7.242)), cervical dilation (≥2cm) (OR =3.477; 95% CI (1.458–10.844)), and amniotic sac herniation (OR = 1.796; 95% (0.473–4.975)).

**Conclusion:** This study demonstrated that the baseline SII level and SIRI level are important biochemical markers for predicting the outcome of cervical cerclage and maternal-neonatal outcomes with non-invasive procedures. They can help to provide personalized treatment before surgery and enhance postoperative surveillance.

**Keywords:** cervical cerclage, maternal-neonatal, outcome, inflammatory markers, peripheral blood

## Introduction

Globally, approximately 15 million pregnancies are born yearly, indicating a global preterm birth rate of about 11%.<sup>1</sup> It is reported that nearly 1 million babies die because of preterm birth under 5 years,<sup>1</sup> causing problems for families and society. Although cervical insufficiency is relatively rare, accounting for less than 0.5% of all pregnancies,<sup>2</sup> it remains the leading risk factor for preterm birth (PTB), and the incidence could be up to 2.0%.<sup>3</sup> Cervical cerclage is the only effective way to treat cervical insufficiency. It is reported that cervical cerclage is effective in prolonging the number of weeks gestation in patients with cervical insufficiency compared with traditional treatments such as bed rest and oral fetal



preservation drugs.<sup>4</sup> Cervical cerclage strengthens the cervix by providing mechanical support for the cervix, which prevents the extension of the lower part of the uterus in the second trimester to achieve the purpose of fetal preservation and reduce the risk of PTB by about 20% in pregnant women with cervical insufficiency.<sup>5–8</sup> Unfortunately, despite the importance of this surgery, valuable predictors with successful cervical cerclage remain limited, especially using non-invasive methods.

Cervical cerclage is widely used in clinical practice. However, postoperative abortion and preterm birth still occur, and the mechanism remains unclear. Richard Brown et al<sup>9</sup> demonstrated that it might be related to inflammation and preconception BMI. It is reported that 80% of acute cervical insufficiency may be related to intranet-amniotic infection.<sup>9</sup> Similarly, another study<sup>10</sup> proposed that the interleukin-10, interleukin-6, mannose-2, and gene promoter representing the inflammatory gene increase in patients with cervical insufficiency, which increases the incidence of preterm birth. Recently, some studies revealed that intrauterine infection and inflammation are important risk factors for postoperative prognosis after cervical cerclage.<sup>11–13</sup> More importantly, they may increase the risk of long-term disability in preterm infants.<sup>14</sup> Therefore, numerous studies have found that the levels of interleukin (IL)-1, IL-6, and IL-8 in the amniotic fluid can be used to evaluate the success of cervical cerclage.<sup>11–13</sup> However, these studies have been limited to small samples and invasive methods.

Importantly, recent studies have revealed that the blood neutrophil-lymphocyte ratio (NLR) is an independent diagnostic and prognostic factor of clinical inflammatory diseases, including preterm labor and gestational diabetes (GDM).<sup>15,16</sup> Fortunately, the systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI), derived from blood cell counts, are novel and comprehensive inflammatory predictors that can affect suitably the local immune status and systemic inflammation throughout the human body.<sup>17–19</sup> What is more, current studies have confirmed that SII and SIRI can better reflect the chronic inflammatory state in the body than NLR and other inflammatory indicators.<sup>20,21</sup> Therefore, they can serve as valuable predictors of systemic inflammation with more diagnostic effectiveness and stability. Furthermore, easy access to blood samples provides convenience for investigating the peripheral inflammation in disease. Nevertheless, the relationships of SII and SIRI with the outcome after cervical cerclage remain unknown.

In the present study, we analyze the associations between the inflammatory markers, including SII and SIRI, and the clinical outcomes with maternal-neonatal outcomes after cervical cerclage. We aimed to evaluate whether the inflammatory markers in maternal blood are valuable biomarkers to predict the outcomes of cervical cerclage with a non-invasive method.

## Materials and Methods

### Participants

This study analyzed 374 participants from Fujian Provincial Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University (FMCH) from January 1, 2018, to May 31, 2022. According to the guidelines, women were recruited to the study if they had cervical cerclage and indications for cervical cerclage.<sup>22</sup> Pregnant women were excluded due to the following criteria: (1) multifetal pregnancies, (2) severe medical and surgical complications; (3) fetal anomalies; (4) patients with incomplete clinical data. This study was approved by the Hospital Ethics Committee (2021KLR601). Detailed data on maternal-neonatal outcomes were collected from computerized obstetric records, neonatal databases, and handwritten records.

### The Procedure of Cervical Cerclage

Our previous article elaborated on the specific surgical steps and preoperative management of cervical cerclage surgery.<sup>23</sup> Prophylactic antibiotics (intravenous Cefmetazole 1g) were given, and spinal anesthesia was performed before cerclage. The type of cerclage is McDonald for all participants. All cerclages were inserted by the same operating team using a standard technique. According to the American College of Obstetricians, antibiotics were given. And Gynecologists were changed by the maternal blood or endocervical culture results.<sup>24</sup> Also, a single course of antenatal betamethasone



was used for women between 23 and 34 weeks of pregnancy to reduce neonatal RDS. Delivery was suggested if chorioamnionitis, fetal distress, ongoing preterm labor, or other criteria for an emergent delivery were met.

## Definition

Successful cervical cerclage was defined as the birth of a neonate discharged from the hospital without identifiable morbidity. Unsuccessful cervical cerclage resulted in miscarriage, intrauterine death, neonatal death, or neonatal morbidity. And significant neonatal morbidity was defined as the presence of any of the following: intra-ventricular hemorrhage (VIH), necrotic enterocolitis (NEC), patent ductus arteriosus (PDA), retinopathy of prematurity, RDS, or sepsis.

## Blood Cell Count Assay

The blood samples were collected before the cervical cerclage procedure during the face-to-face interviews and were sent to the laboratory. White blood cell (WBC) counts, neutrophil, lymphocyte, monocyte, and platelet counts were detected with flow cytometry (XE-3000, SYSMES, Kobe, Japan). The SII (platelet count $\times$ neutrophil count/lymphocyte count) and SIRI (monocyte count $\times$ neutrophil count/lymphocyte count) were calculated with absolute neutrophil count ( $\times 10^9$  /L), monocyte count ( $\times 10^9$  /L), lymphocyte count ( $\times 10^9$  /L) and platelet count ( $\times 10^9$  /L).<sup>25,26</sup>

## Statistical Analysis

The measurement data were calculated with chi-square tests, and the counting data were *t*-tests using SPSS version 26.0 (IBM, Armonk, NY, USA). The area under the receiver operating characteristic (ROC) curve (AUC) was used to assess the predictive efficiency of inflammatory markers (SII and SIRI) with successful cervical cerclage. Also, the Spearman rank correlation coefficient was used to determine relationships between inflammatory markers (SII and SIRI) and maternal-neonatal outcomes. Multiples logistic regression analysis was performed to evaluate risk factors associated with the prognosis of the cervical cerclage. The results were presented as odds ratio (OR) and 95% confidence interval (CI). In all statistical tests, the differences were considered statistically significant at P-values<0.05.

## Results

### The Clinical Characteristic of Maternal-Neonatal Outcomes

374 pregnancies were included in this study. The maternal data and neonatal characteristics are presented in Table 1. The mean age of the participants was  $31.1\pm0.2$  years, and the mean body mass index (BMI) was  $22.8\pm0.2$  (cm<sup>2</sup>/kg). And then, the mean gestational age at the time of cerclage, PPRM, and delivery was  $23^{+5}(15^{+1}-27^{+2})$  weeks,  $36^{+2}(22^{+3}-41^{+1})$  weeks, and  $34^{+5}(17^{+3}-41^{+3})$  weeks, respectively. Moreover, the mean interval between cerclage and delivery was  $88.1\pm2.3$  days. Of the patients, 13 (3.5%) had a postpartum hemorrhage, 20 (5.3%) had gestational hypertension and 50 (13.4%) had gestational diabetes (GDM). As for neonatal outcomes, 41 (11.0%) newborns died. Besides, most newborns have a good outcome delivered in the appreciable period ( $\geq 28$  weeks). The mean birth weight was  $2688.9\pm46.8$ g. There were some severe neonatal complications such as RDS (63/333, 4.1%), IVH (18/333, 5.5%), NEC (14/333, 4.2%), retinopathy of prematurity (19/333, 5.7%), PDA (23/333, 6.9%) and sepsis (15/333, 4.5%) in this study.

### The Inflammatory Markers are Predictive Risk Factors for Unsuccessful Cervical Cerclage

Finally, 268 (71.7%) participants suffered successful cervical cerclage. This study demonstrated that the baseline BMI (cm<sup>2</sup>/kg), the bulging membrane, cervical length (<1.5cm), cervical dilation ( $\geq 2$ cm), the amniotic sac herniation, the neutrophils counts, the SII and the SIRI were significantly different between the successful and unsuccessful groups (all P<0.05). As shown in Table 2, the maternal age, recurrent abortion, times of gravitas, times of parity, WBC, lymphocyte, monocyte, and platelet counts were not significantly different.



**Table 1** Clinical Characteristics of the Study Population

Characteristics		Number of Cases (%)
Mother	Maternal age (years)	31.1±0.2(20–50)
	BMI (cm <sup>2</sup> /kg)	22.8±0.2
	Gravida	3 (0–7)
	Parity	0(0–3)
	Bulging membrane	77 (20.6)
	Cervical length(cm)	
	≤1.5	318 (85.0)
	>1.5	56 (15.0)
	Cervical dilation(cm)	
	≥2	65 (17.4)
	<2	309 (82.6)
	Recurrent Abortion	35 (9.4)
	GA at cerclage (weeks)	23 <sup>+5</sup> (15 <sup>+1</sup> –27 <sup>+2</sup> )
	GA at PPRM (weeks)	36 <sup>+2</sup> (22 <sup>+3</sup> –41 <sup>+1</sup> )
	GA at delivery (weeks)	34 <sup>+5</sup> (17 <sup>+3</sup> –41 <sup>+3</sup> )
	Cerclage to delivery interval (days)	88.1±2.3 (0–189)
	Cesarean delivery	142(38.0)
	GDM	50 (13.4%)
	Gestational hypertension	20(5.3%)
	Herniation of the amniotic sac	105(28.1)
	Postpartum hemorrhage	13(3.5)
	WBC(×10 <sup>9</sup> /L)	10.3±0.1
	Neutrophils(×10 <sup>9</sup> /L)	7.8±0.1
	Lymphocyte (×10 <sup>9</sup> /L)	1.8±0.1
	Monocyte (×10 <sup>9</sup> /L)	0.6±0.1
	Platelet (×10 <sup>9</sup> /L)	239.0±3.1
	SI(×10 <sup>9</sup> /L)	1058.1±24.3
	SIRI(×10 <sup>9</sup> /L)	2.9±0.1
Newborn	GA at delivery (week)	
	<24 wk	19(5.1)
	≥24 to <28 wk	36(9.6)
	≥28 to <32 wk	48(12.8)
	≥32 to <34 wk	23(6.1)

(Continued)



Table 1 (Continued).

Characteristics	Number of Cases (%)
≥34 to <37 wk	66(17.6)
37≥wk	182(48.7)
Birth weight (g)	2688.9±46.8 (690–4675)
Apgar score (1 min)	9.6±0.1 (3–10)
Apgar score (5 min)	9.9±0.1 (8–10)
Apgar score (10 min)	10.0±0.0 (8–10)
Mortality	41(11.0)
NICU admission	16(21.9)
Time in hospital (days)	12.7±1.1 (0–97)
RDS	63(18.9)
IVH	18(5.4)
Sepsis	15(4.5)
NEC	14(4.2)
Retinopathy of prematurity,	19(5.7)
PDA	23(6.9)

**Notes:** Continuous variables are presented as mean ± SD (range) and categorical variables as n (%). Recurrent abortion was defined as at least three spontaneous abortions.

**Abbreviations:** BMI, body mass index; GA, gestational age; PPROM, preterm premature rupture of membranes; GDM, gestational diabetes; WBC, white blood cell; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus.

## The Relationships Between the Inflammatory Markers and Maternal-Neonatal Outcomes

According to Table 3, we found that maternal blood inflammatory markers, such as WBC, lymphocyte, neutrophils, monocyte, platelet counts, SII, and SIRI, were significantly associated with maternal outcomes. It suggested that a longer cerclage to delivery interval times with a lower WBC counts, a lower neutrophils counts, a lower monocyte counts, lower SII and lower SIRI levels ( $r = -0.307$ ,  $P < 0.001$ ;  $r = -0.343$ ,  $P < 0.001$ ;  $r = -0.138$ ,  $P = 0.008$ ;  $r = -0.332$ ,  $P < 0.001$ ;  $r = -0.351$ ,  $P < 0.001$ ).

The associations between maternal blood inflammatory markers and neonatal outcomes are shown in Table 3. Significant relationships were revealed between mothers with a lower WBC counts, a higher neutrophils counts, a lower lymphocyte counts, a higher monocyte counts, a higher platelet counts, a higher SII and higher SIRI levels with an earlier delivery age ( $r = -0.176$ ,  $P = 0.001$ ;  $r = -0.224$ ,  $P < 0.001$ ;  $r = -0.329$ ,  $P < 0.001$ ;  $r = -0.278$ ,  $P < 0.001$ ), lower birth weight ( $r = -0.163$ ,  $P = 0.002$ ;  $r = -0.174$ ,  $P < 0.001$ ;  $r = -0.114$ ,  $P = 0.030$ ;  $r = -0.319$ ,  $P < 0.001$ ;  $r = -0.208$ ,  $P < 0.001$ ), a lower neonatal Apgar score (5 min) ( $r = -0.113$ ,  $P = 0.038$ ), a lower neonatal Apgar score (10 min) ( $r = -0.115$ ,  $P = 0.035$ ;  $r = -0.119$ ,  $P = 0.029$ ), a lower rate of NICU admission ( $r = 0.129$ ,  $P = 0.016$ ;  $r = 0.137$ ,  $P = 0.011$ ), and a lower mortality rate ( $r = -0.166$ ,  $P = 0.001$ ;  $r = -0.170$ ,  $P = 0.001$ ;  $r = 0.102$ ,  $P = 0.049$ ;  $r = -0.319$ ,  $P < 0.001$ ;  $r = -0.259$ ,  $P < 0.001$ ).

## Predictive Value of Inflammatory Markers for Outcomes After Cervical Cerclage

ROC analyses of SII and SIRI were performed to predict the outcomes after cervical cerclage. The SII and SIRI level were evaluated individually (Figure 1A and B). We revealed that AUC for the SII level (0.783) was higher than that for



**Table 2** The Association Between Clinical Factors and Cervical Cerclage Outcomes

Variable	Successful (N=268) n (%)	Unsuccessful (N=106) n (%)	P-value
Maternal age (years)	30.7±4.3	31.8±5.0	0.074
BMI(cm <sup>2</sup> /kg)	22.5±3.3	23.5±3.6	0.023
Gravida	2(0–8)	3(1–7)	0.105
Parity	0(0–3)	1(0–3)	0.515
Recurrent Abortion	21(7.8%)	14(13.2%)	0.108
Bulging membrane	51(19.0%)	26(24.5%)	0.031
Cervical length(cm)			0.001
<1.5	133(49.6%)	72(67.9%)	
≥1.5	135(50.4%)	34(32.1%)	
Cervical dilation(cm)			<0.001
≥2	24(9.0%)	41(38.7%)	
<2	244(91.0%)	65(61.3%)	
Amniotic sac herniation	56(20.9%)	49(46.2%)	<0.001
WBC(×10 <sup>9</sup> /L)	10.0±2.1	10.8±2.5	0.253
Neutrophils (×10 <sup>9</sup> /L)	7.5±1.7	8.4±2.2	<0.001
Lymphocyte (×10 <sup>9</sup> /L)	1.8±0.5	1.8±1.2	0.413
Monocyte (×10 <sup>9</sup> /L)	0.6±0.2	0.6±0.2	0.782
Platelet (×10 <sup>9</sup> /L)	235.8±57.2	243.560.7	0.253
SII (×10 <sup>9</sup> /L)	915.5±298.0	1400.4±567.0	<0.001
SIRI (×10 <sup>9</sup> /L)	2.4±1.0	3.8±1.8	<0.001

**Note:** Categorical data were analysed using chi-squared tests, and continuous data with t-tests.

**Abbreviations:** BMI, body mass index; WBC, white blood cell; SII, systemic immune inflammation index; SIRI, systemic inflammation response index.

the SIRI level (0.739). Also, the optimal cut-off of the SII level was 1226.797, and the optimal cut-off of the SIRI level was 3.201. The logistic regression analysis parameters for detecting successful and unsuccessful cervical cerclage were calculated based on the combinations of SII and SIRI. The model =  $-4.9234 + 0.0025 \times \text{SII} + 0.3874 \times \text{SIRI}$ . In particular, we found the combination of SII and SIRI had a higher AUC (0.797), and the optimal cut-off was  $-0.822$  (Figure 1C).

The independent risk factors associated with outcome after cervical cerclage in multivariable logistic regression analysis are shown in Table 4. The results demonstrated that the SII level had the highest OR (OR=4.626; 95% CI (2.500–8.560)), as well as the following: SIRI level (OR = 3.795; 95% CI (1.989–7.242)), cervical dilation (≥2cm) (OR = 3.477; 95% CI (1.458–10.844)), and amniotic sac herniation (OR = 1.796; 95% (0.473–4.975)).

## Discussion

Recently, cervical insufficiency has increased yearly,<sup>27</sup> and the perinatal mortality rate has also increased, bringing severe economic burden and serious psychological harm to individuals and families. Cervical cerclage is a valuable method to prolong gestational age and prevent mid-trimester pregnancy loss with CI. However, some adverse outcomes, such as preterm premature rupture of membranes and chorioamnionitis, may fail cervical cerclage.<sup>28,29</sup> Unfortunately, there is no clinically effective indicator to predict the efficacy of cervical cerclage. Therefore, there is an urgent need to study some



**Table 3** Relationships Between the Inflammatory Markers and Maternal-Neonatal Outcomes

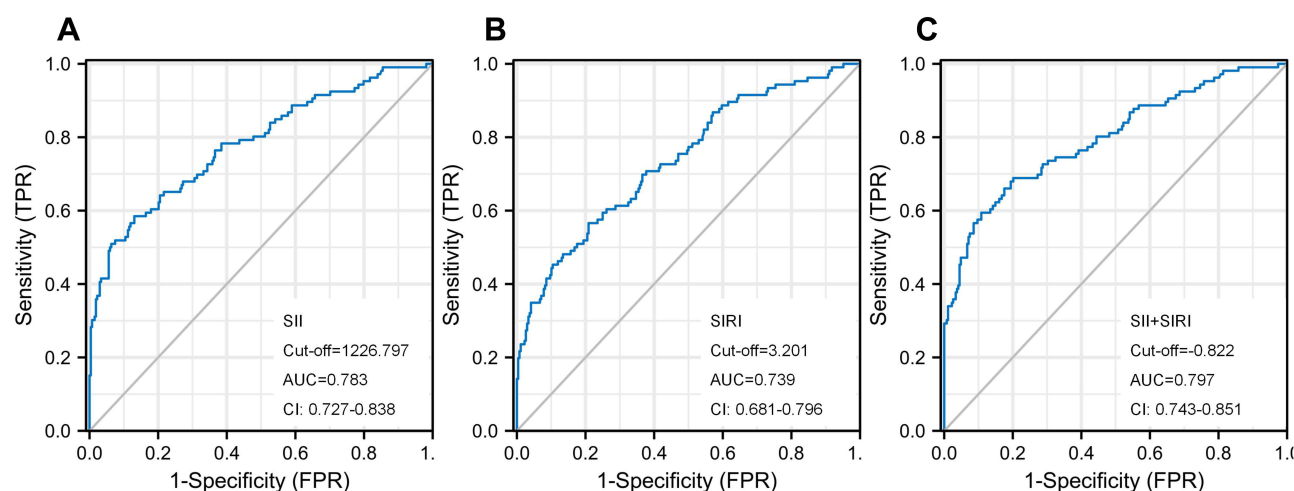
Variable		WBC	Neutrophils	Lymphocyte	Monocyte	Platelet	SII	SIRI
Cervical cerclage to delivery interval (days)	r-value	-0.307	-0.343	0.089	-0.138	0.020	-0.332	-0.351
	p-value	<0.001	<0.001	0.085	0.008	0.693	<0.001	<0.001
Cesarean delivery	r-value	0.028	-0.005	-0.013	0.054	-0.021	-0.05	-0.017
	p-value	0.587	0.916	0.807	0.293	0.685	0.330	0.748
Postpartum hemorrhage	r-value	0.015	0.024	0.021	0.022	-0.092	-0.066	-0.005
	p-value	0.771	0.642	0.686	0.669	0.077	0.204	0.918
GA at delivery (week)	r-value	-0.176	-0.224	0.049	0.021	-0.088	-0.329	-0.278
	p-value	0.001	<0.001	0.347	0.687	0.090	<0.001	<0.001
Birth weight (g)	r-value	-0.163	-0.174	0.068	0.067	-0.114	-0.319	-0.208
	p-value	0.002	<0.001	0.194	0.200	0.030	<0.001	<0.001
Apgar score (1 min)	r-value	-0.073	-0.099	0.007	-0.020	0.048	-0.080	-0.053
	p-value	0.178	0.070	0.899	0.711	0.376	0.141	0.327
Apgar score (5 min)	r-value	-0.077	-0.104	-0.054	-0.011	-0.072	-0.113	-0.079
	p-value	0.159	0.056	0.324	0.834	0.187	0.038	0.146
Apgar score (10 min)	r-value	-0.044	-0.079	-0.057	0.014	-0.115	-0.119	-0.021
	p-value	0.415	0.148	0.295	0.793	0.035	0.029	0.696
NICU admission	r-value	-0.092	0.129	-0.039	-0.044	-0.002	0.142	0.137
	p-value	0.087	0.016	0.469	0.416	0.968	0.008	0.011
Mortality	r-value	-0.166	-0.170	0.102	-0.037	-0.039	-0.319	-0.259
	p-value	0.001	0.001	0.049	0.437	0.455	<0.001	<0.001

**Note:** Analysis was performed using Spearman's rank correlation analysis.

**Abbreviations:** GA, gestational age; WBC, white blood cell; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; NICU, neonatal intensive care unit.

reliable indicators to predict the outcome of cervical cerclage and provide guidance measurements to improve the success rate.

In this study, 268 (71.7%) participants obtained successful cervical cerclage, proving that cervical cerclage can reduce the rate of preterm birth. And then, the neonatal mortality rate in the present study was 11.0%, which is similar to other studies, ranging from 12.7–47.5%.<sup>30,31</sup> Interestingly, this study found that inflammatory markers, such as the neutrophils counts, the SII, and the SIRI, in the maternal peripheral blood were significantly associated with the success rate of



**Figure 1** ROC curve analysis of the SII and SIRI level to predict the outcome of cervical cerclage. (A) Cut-off, the optimal SII according to the ROC curve. (B) Cut-off, the optimal SIRI according to the ROC curve. (C) Cut-off, the optimal combination with SII and SIRI level according to the ROC curve.

**Abbreviations:** SII, systemic immune inflammation index; SIRI, systemic inflammation response index; AUC, the area under the ROC curve; ROC, receiver operator characteristic; CI, confidence interval.



**Table 4** Independent Risk Factors for Predicting the Unsuccessful Cervical Cerclage

Factors	OR	95% CI	p-value
BMI(cm <sup>2</sup> /kg)	1.022	0.841–1.494	0.053
Bulging membrane	1.546	0.428–4.641	0.694
Cervical dilation(≥2cm)	3.477	1.458–10.844	0.007
Amniotic sac herniation	1.796	0.473–4.975	0.032
Neutrophils (×10 <sup>9</sup> /L)	1.119	0.903–4.480	0.240
SII (×10 <sup>9</sup> /L) (≥1226.797)	4.626	2.500–8.560	<0.001
SIRI (×10 <sup>9</sup> /L) (≥3.201)	3.795	1.989–7.242	<0.001

**Abbreviations:** BMI, body mass index; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; CI, confidence interval.

cervical cerclage. Moreover, we found that the AUC for the SII level (0.783) was higher than that for the SIRI level (0.739). Also, the optimal cut-off of the SII level was 1226.797, and the optimal cut-off of the SIRI level was 3.201.

Furthermore, we found the combination of SII and SIRI had a higher AUC (0.797) by ROC analysis. Finally, multivariable logistic regression analysis demonstrated that the SII and SIRI levels were independent risk factors associated with outcome after cervical cerclage. These non-invasive markers could assist in making clinical decisions to manage cervical cerclage.

As we know, infection is a significant etiologies in up to 50% of cases in PTB.<sup>32</sup> It has recently been suggested that preoperative inflammatory indicators may predict pregnancy outcomes after cervical cerclage. Because the cervical opening is often accompanied by infection, uterine contraction, or rupture of the fetal membranes, which often leads to poor postoperative prognosis for cervical insufficiency. It is reported that up to 40% of PTB cases had inflammation of the uterine cavity or membranes, which is considered the pathological basis for the occurrence of PTB.<sup>33</sup> Recently, some studies revealed that intrauterine infection and inflammation are important risk factors for postoperative prognosis after cervical cerclage.<sup>11–13</sup> Importantly, WBC counts and C-reactive protein (CRP) in maternal peripheral blood have been reported to reflect infection in women with preterm labor or premature rupture of membranes.<sup>34,35</sup> Importantly, recent studies have revealed that the blood neutrophil-lymphocyte ratio (NLR) is an independent diagnostic and prognostic factor of clinical inflammatory diseases, such as preterm labor and gestational diabetes (GDM).<sup>15,16</sup> Yilmaz et al<sup>15</sup> points out that NLR level was significantly higher in GDM women compared with without GDM. Logistic regression analysis showed that elevated NLR was an independent variable for predicting GDM in pregnancy. Our previous research also suggested that platelet-lymphocyte ratio (PLR) can be a valuable predictor of cerclage failure.<sup>36</sup> However, unfortunately, our previous study did not elaborate on the relationship between inflammatory markers in maternal peripheral blood and maternal and child outcomes.

Many scholars have recently suggested that the number of neutrophils, platelets, and lymphocytes from peripheral blood is closely associated with various tumors and inflammatory diseases.<sup>37,38</sup> Accumulated evidence suggests that inflammation and immune responses play a crucial role in cancer development, including tumor development, malignant transformation, invasion, metastasis, and even combination therapy and immune defense responses.<sup>39</sup> Another study mentions that six biological factors play a crucial role in the cancer response.<sup>40</sup> Inflammatory markers and cell-to-cell matrix interactions constitute a tumor microenvironment (TME) that influences tumorigenesis and development.<sup>40</sup>

Recent studies have shown that SII and SIRI are comprehensive indicators based on peripheral platelet, neutrophil, monocyte, and lymphocyte counts that more fully reflect the balanced state of local immunity and systemic inflammatory response.<sup>17–19</sup> SII, a new prognostic indicator of systemic immune inflammation, is associated with many tumors and inflammatory diseases, including pancreatitis and novel coronavirus pneumonia.<sup>41–43</sup> Elevated SII levels suggest a poor prognosis.<sup>44</sup> Similarly, SIRI is a new type of inflammatory index. And numerous studies have shown that it can be a good predictor of prognosis in patients with tumors. Its ability to predict prognosis has certain advantages over a traditional inflammatory index, tumor markers, and pathological tumor stages.<sup>45–47</sup> Wei et al<sup>48</sup> reported that a high SIRI level is associated with a poor disease prognosis. And those cancer patients with high levels of SIRI suggested poor prognosis



with shortened survival, accelerated tumor progression, and high rates of recurrence or metastasis. SII and SIRI are easy to obtain and less cost-effective, so they are gradually applied to clinical research. What is more, current studies have confirmed that SII and SIRI can better reflect the chronic inflammatory state in the body than NLR and other inflammatory indicators.<sup>20,21</sup>

Additionally, our results indicate that cervical dilation and amniotic sac herniation are independent potential risk factors to predict the subsequent cervical cerclage outcome. Fortner et al<sup>49</sup> demonstrated that pregnancies with cervical dilatation were more significant than 2 cm suggested with a higher rate of PTB and delivered before 27 weeks of pregnancy on average, which is consistent with our study. According to our research, higher WBC counts, higher neutrophils counts, lower lymphocyte counts, higher monocyte counts, higher platelet counts, a higher SII, and higher SIRI levels significantly represent poor prognostic maternal-neonatal outcome, with an earlier delivery age, lower birth weight, a lower neonatal Apgar score (5 min), a lower neonatal Apgar score (10 min), a lower rate of NICU admission, and a lower mortality rate.

There are some limitations to this study. Firstly, this study did not explore twin and multiple pregnancies because the surgical indications for twin and multiple pregnancies are unclear. So the conclusions in this study do not apply to twin and multiple pregnancies. Secondly, some inflammatory indicators were not included, such as NLR, platelet to lymphocyte (PLR), and lymphocyte to monocyte rate (LMR). Thirdly, this is a retrospective study, so temporality cannot be ascertained. Therefore, a prospective study and a randomized controlled trial are necessary for the future.

In conclusion, this study demonstrated that the baseline SII level and SIRI level in maternal peripheral blood emerged as important biochemical markers for predicting the outcome of the cervical cerclage. Moreover, our data prove they are closely related to maternal-neonatal outcomes. We advocate maternal peripheral blood from non-invasive procedures and combined measurement of baseline SII level and SIRI level as a suitable and practical method to predict the outcome of cervical cerclage. Our results may offer additional prognostic information in clinical, which helps to provide a personalized treatment before surgery and enhance postoperative surveillance.

## Patient Consent for Publication

The Hospital Ethics Committee of Fujian Provincial Maternity and Children's Hospital, an affiliated hospital of Fujian Medical University, approved the study (2022KYLLR03050) and complied with the Declaration of Helsinki. And all individuals participating in this study signed written informed consent.

## 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 report has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was funded by grants from the Fujian Science and Technology Innovation Joint Fund Project (2020Y9148), Natural Science Foundation of Fujian Province (No.2021J01406) and Fujian Provincial Technology Innovation Project (grant no. 2020Y9147), Natural Science Foundation of Fujian Province (No.2021J01420).

## Disclosure

All authors declare that they have no competing interests in this work.

## References

1. Walani SR. Global burden of preterm birth. *Int J Gynaecol Obstet.* 2020;150(1):31–33. doi:10.1002/ijgo.13195
2. American College of Obstetricians and Gynecologists. ACOG practice bulletin no.142: cerclage for managing cervical insufficiency. *Obstet Gynecol.* 2014;123:372–379. doi:10.1097/01.AOG.0000443276.68274.cc
3. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. *Semin Fetal Neonatal Med.* 2016;21(2):68–73. doi:10.1016/j.siny.2015.12.011



4. Song J-E, Lee K-Y, Jun H-A. Repeat cerclage prolongs pregnancy in women with prolapsed membranes. *Acta Obstet Gynecol Scand.* 2011;90(1):111–113. doi:10.1111/j.1600-0412.2010.01006.x
5. Gonzales SK, Adair CD, Torres C, et al. Robotic-assisted laparoscopic abdominal cerclage placement during pregnancy. *J Minim Invasive Gynecol.* 2018;25(5):832–835. doi:10.1016/j.jmig.2017.12.014
6. Witt MU, Joy SD, Clark J, et al. Cervicoisthmic cerclage: transabdominal vs transvaginal approach. *Am J Obstet Gynecol.* 2009;201(1):105.e1–4. doi:10.1016/j.ajog.2009.03.020
7. Berghella V, Rafael TJ, Szychowski JM, Rust OA, Owen J. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. *Obstet Gynecol.* 2011;117:663–671. doi:10.1097/AOG.0b013e31820ca847
8. Alfirevic Z, Stampalija T, Roberts D, Jorgensen AL. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database Syst Rev.* 2012;4:CD008991.
9. Brown R, Gagnon R, Delisle M-F. Cervical insufficiency and cervical cerclage. *J Obstet Gynaecol Can.* 2013;35(12):1115–1127. doi:10.1016/S1701-2163(15)30764-7
10. Sundtoft I, Uldbjerg N, Steffensen R, et al. Polymorphisms in genes coding for cytokines, mannose-binding lectin, collagen metabolism and thrombophilia in women with cervical insufficiency. *Gynecol Obstet Invest.* 2016;81(1):15–22. doi:10.1159/000381620
11. Again E, Aguin T, Cordoba M, et al. Amniotic fluid inflammation with negative culture and outcome after cervical cerclage. *J Matern Fetal Neonatal Med.* 2012;25(10):1990–1994. doi:10.3109/14767058.2012.667177
12. Lee KY, Jun HA, Kim HB, Kang SW. Interleukin-6, but not relaxin, predicts the outcome of rescue cerclage in women with cervical incompetence. *Am J Obstet Gynecol.* 2004;191(3):784–789. doi:10.1016/j.ajog.2004.04.019
13. Park JC, Kim DJ, Kwak-Kim J. Upregulated amniotic fluid cytokines and chemokines in emergency cerclage with protruding membranes. *Am J Reprod Immunol.* 2011;66(4):310–319. doi:10.1111/j.1600-0897.2011.00991.x
14. Bashiri A, Burstein E, Mazor M. Cerebral palsy and fetal inflammatory response syndrome: a review. *J Perinat Med.* 2006;34(1):5–12. doi:10.1515/JPM.2006.001
15. Yilmaz H, Celik HT, Namuslu M, et al. Benefits of the neutrophil-to-lymphocyte ratio for the prediction of gestational diabetes mellitus in pregnant women. *Exp Clin Endocrinol Diabetes.* 2014;122(1):39–43. doi:10.1055/s-0033-1361087
16. Kim MA, Lee BS, Park YW, Seo K. Serum markers for prediction of spontaneous preterm delivery in preterm labor. *Eur J Clin Invest.* 2011;41(7):773–780. doi:10.1111/j.1365-2362.2011.02469.x
17. Wang J, Zhou D, Dai Z, Li X. Association between systemic immune inflammation index and diabetic depression. *Clin Interv Aging.* 2021;16:97–105. doi:10.2147/CIA.S285000
18. Zhang F, Niu M, Wang L, et al. Systemic-immune inflammation index as a promising biomarker for predicting perioperative ischemic stroke in older patients who underwent non-cardiac surgery. *Front Aging Neurosci.* 2022;14:865244. doi:10.3389/fnagi.2022.865244
19. Tian T, Lu J, Zhao W, et al. Associations of systemic inflammation markers with identification of pulmonary nodule and incident lung cancer in Chinese population. *Cancer Med.* 2022;11:2482–2491. doi:10.1002/cam4.4606
20. Goyal N, Tsivgoulis G, Chang JJ, et al. Admission neutrophil-to-lymphocyte ratio as a prognostic biomarker of outcomes in large vessel occlusion strokes. *Stroke.* 2018;49(8):1985–1987. doi:10.1161/STROKEAHA.118.021477
21. Weng Y, Zeng T, Huang H, et al. Systemic immune inflammation index predicts 3-month functional outcome in acute ischemic stroke patients treated with intravenous thrombolysis. *Clin Interv Aging.* 2021;16:877–886. doi:10.2147/CIA.S311047
22. Rust O, Odibo A. American college of obstetricians and gynecologists, practice bulletin no. 142: cerclage for managing cervical insufficiency. *Obstet Gynecol.* 2014;123:372–379.
23. Fang J, Chen L, Chen Z, et al. Association of the vaginal microbiota with pregnancy outcomes in Chinese women after cervical cerclage. *Reprod Biomed Online.* 2020;41(4):698–706. doi:10.1016/j.rbmo.2020.06.016
24. American College of Obstetricians and Gynecologists. Prelabor rupture of membranes: practice bulletin no. 188. *Obstet Gynecol.* 2018;131:e1–e14. doi:10.1097/AOG.0000000000002455
25. Nam KW, Kwon HM, Jeong HY, et al. High neutrophil to lymphocyte ratio is associated with white matter hyperintensity in a healthy population. *J Neurol Sci.* 2017;380:128–131. doi:10.1016/j.jns.2017.07.024
26. Benedetti F, Palladini M, Paolini M, et al. Brain correlates of depression, post-traumatic distress, and inflammatory biomarkers in COVID-19 survivors: a multimodal magnetic resonance imaging study. *Brain Behav Immun Health.* 2021;18:100387. doi:10.1016/j.bbih.2021.100387
27. Wu Y, Liang X, Cai M, Gao L, Lan J, Yang X. Development and validation of a model for individualized prediction of cervical insufficiency risks in patients undergoing IVF/ICSI treatment. *Reprod Biol Endocrinol.* 2021;19(1):6. doi:10.1186/s12958-020-00693-x
28. Kassanos D, Salamalekis E, Vitoratos N, Panayotopoulos N, Loghis C, Creatsas C. The value of transvaginal ultrasonography in diagnosis and management of cervical incompetence. *Clin Exp Obstet Gynecol.* 2001;28(4):266–268.
29. Kurup M, Goldkrand JW. Cervical incompetence: elective, emergent, or urgent cerclage. *Am J Obstet Gynecol.* 1999;181(2):240–246. doi:10.1016/S0002-9378(99)70542-9
30. Galyean A, Garite TJ, Maurel K, et al. Removal versus retention of cerclage in preterm premature rupture of membranes: a randomized controlled trial. *Am J Obstet Gynecol.* 2014;211:399.e1–399.e7. doi:10.1016/j.ajog.2014.04.009
31. Aguin E, Van De Ven C, Cordoba M, Albayrak S, Bahadur-Singh R. Cerclage retention versus removal following preterm premature rupture of membranes and association with amniotic fluid markers. *Int J Gynaecol Obstet.* 2014;125:37–40. doi:10.1016/j.ijgo.2013.10.005
32. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* 2008;371(9606):75–84. doi:10.1016/S0140-6736(08)60074-4
33. Lee SE, Romero R, Park CW, Jun JK, Yoon BH. The frequency and significance of intraamniotic inflammation in patients with cervical insufficiency. *Am J Obstet Gynecol.* 2008;198(6):633.e1–633.e8. doi:10.1016/j.ajog.2007.11.047
34. Jung HJ, Park KH, Kim SN, et al. Non-invasive prediction of intra-amniotic inflammation in women with preterm labor. *Ultrasound Obstet Gynecol.* 2011;37(1):82–87. doi:10.1002/uog.8869
35. Park KH, Kim SN, Oh KJ, Lee SY, Jeong EH, Ryu A. Non-invasive prediction of intra-amniotic infection and/or inflammation in preterm premature rupture of membranes. *Reprod Sci.* 2012;19(6):399.e1–399.e7. doi:10.1177/1933719111432869
36. Pan M, Fang J-N, Wang -X-X, et al. Predictors of cerclage failure in singleton pregnancies with a history of preterm birth and a sonographic short cervix. *Int J Gynaecol Obstet.* 2022;156(2):316–321. doi:10.1002/ijgo.13640



37. Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. *Cancer Cell*. 2011;20(5):576–590. doi:10.1016/j.ccr.2011.09.009
38. Cools-Lartigue J, Spicer J, McDonald B, et al. Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. *J Clin Invest*. 2013;123(8):3446–3458. doi:10.1172/JCI67484
39. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883–899. doi:10.1016/j.cell.2010.01.025
40. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674. doi:10.1016/j.cell.2011.02.013
41. He K, Si LX, Pan XH, et al. Preoperative systemic immune-inflammation index (SII) as a superior predictor of long-term survival outcome in patients with stage I-II gastric cancer after radical surgery. *Front Oncol*. 2022;12:829689. doi:10.3389/fonc.2022.829689
42. Liu XM, Guan GX, Cui XY, et al. Systemic immune-inflammation index (SII) can be an early indicator for predicting the severity of acute pancreatitis: a retrospective study. *Int J Gen Med*. 2021;14:9483–9489. doi:10.2147/IJGM.S343110
43. Hamad DA, Aly MM, Abdelhameid MA, et al. Combined blood indexes of systemic inflammation as a mirror to admission to intensive care unit in COVID-19 patients: a multicentric study. *J Epidemiol Glob Health*. 2022;12(1):64–73.
44. Adiguzel A, Arsava EM, Topcuoglu MA. Temporal course of peripheral inflammation markers and indexes following acute ischemic stroke: prediction of mortality, functional outcome, and stroke-associated pneumonia. *Neurol Res*. 2022;44(3):224–31.
45. Kwon HC, Kim SH, Oh SY, et al. Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. *Biomarkers*. 2012;17(3):216–222. doi:10.3109/1354750X.2012.656705
46. Wei XL, Wang FH, Zhang DS, et al. A novel inflammation-based prognostic score in esophageal squamous cell carcinoma: the C-reactive protein/albumin ratio. *BMC Cancer*. 2015;15:350. doi:10.1186/s12885-015-1379-6
47. Ku JH, Kang M, Kim HS, et al. The prognostic value of pretreatment of systemic inflammatory responses in patients with urothelial carcinoma undergoing radical cystectomy. *Br J Cancer*. 2015;112(3):461–467. doi:10.1038/bjc.2014.631
48. Wei L, Xie H, Yan P. Prognostic value of the systemic inflammation response index in human malignancy: a meta-analysis. *Medicine*. 2020;99(50):e23486. doi:10.1097/MD.00000000000023486
49. Fortner KB, Fitzpatrick CB, Grotegut CA, et al. Cervical dilation as a predictor of pregnancy outcome following emergency cerclage. *J Matern Fetal Neonatal Med*. 2012;25(10):1884–1888. doi:10.3109/14767058.2012.668582

## Journal of Inflammation Research

Dovepress

### Publish your work in this journal

The Journal of Inflammation Research is an international, peer-reviewed open-access journal that welcomes laboratory and clinical findings on the molecular basis, cell biology and pharmacology of inflammation including original research, reviews, symposium reports, hypothesis formation and commentaries on: acute/chronic inflammation; mediators of inflammation; cellular processes; molecular mechanisms; pharmacology and novel anti-inflammatory drugs; clinical conditions involving inflammation. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-inflammation-research-journal>