Predictability of Hematological Parameters in the Diagnosis of Cesarean Scar Pregnancy

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Abstract

Introduction Cesarean scar pregnancy (CSP) is an increasing clinical condition that causes serious maternal morbidity and mortality. This study aimed to evaluate if inflammation markers measured by hemogram can aid in the diagnosis of CSP.

Materials and Methods A total of 86 patients were included in the study. The cases were divided as CSP (*n*: 42) and normal pregnancy (NP) (*n*: 44). At the time of admission, peripheral blood neutrophils, lymphocytes, monocytes, thrombocytes, systemic inflammatory index (SII) (neutrophil × platelet/lymphocyte), neutrophil–lymphocyte ratio, monocyte–lymphocyte ratio, and platelet–lymphocyte ratio were all measured. CSP and NP diagnoses were made by transabdominal or vaginal ultrasonography.

Results In the CSP group, mean age ($p < 0.001$), gravida ($p < 0.001$), parity ($p < 0.001$), number of surviving children ($p < 0.001$), number of abortions ($p < 0.001$), cesarean number ($p < .001$), dilatation and curettage count ($p = 0.013$), monocyte (M) value ($p = 0.039$) and monocyte/lymphocyte value (MLR) ($p = 0.035$) were significantly higher than the control group. The optimal M value cut-off value was found to be > 0.40, the sensitivity value was 78.57, and the specificity value was 50.00. AUC = 0.632 (SE = 0.061) for the MLR value. The optimal MLR cut-off value was found to be > 0.232, the sensitivity value was 61.90, and the specificity value was 63.64.

Conclusion Hemogram parameters, which are simple, inexpensive, and easily accessible, M and MLR are significantly higher in the diagnosis of CSP and can be used as an auxiliary parameter for ultrasonography.

Keywords
- cesarean scar pregnancy
- hemogram parameters
- systemic inflammatory index

Introduction

Cesarean scar pregnancy (CSP) refers to pregnancies that occur in the scar area of a previous cesarean section. Its incidence is increasing all over the world due to the increasing number of cesarean sections in recent years.[1] The true incidence is unknown. According to the literature, its prevalence among all cesarean section patients is estimated to be between 1/1800 and 1/2500. It constitutes 6.1% of all ectopic pregnancies with a history of one or more cesarean

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sections.[2,3] Increasing awareness among physicians on this issue has increased the incidence rates. Its clinical presentation can be quite variable. Many women are asymptomatic at presentation. Diagnosis is not always simple. Although ultrasonography is the primary diagnostic method, magnetic resonance imaging can assist in some cases.[4] The presence of a pregnancy sac in the lower segment of the first trimester, as well as a history of cesarean delivery, is predictive of the diagnosis. It should be kept in mind that CSP is the precursor of the spectrum of placenta accreta (PAS).

Although the pathogenesis of CSP is unknown, it is known that the nitabuch layer does not develop in the defective decidua, posing a risk for the spectrum of CSP and placenta accreta.[5,6] The pathophysiology of CSP and PAS is known to be the same.[7,8] It is well understood that increased but insufficient trophoblast invasion at the vascularized cesarean section scar causes some inflammatory responses. Recent research has shown that the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and monocyte–lymphocyte ratio (MLR) can be used as inflammation markers. Neutrophil (N) counts reflect active inflammation, whereas lymphocyte (L) counts regulate this inflammation. While PLR is a thrombosis and inflammation marker, it is also a chronic inflammation marker.[9]

The purpose of this study was to determine whether blood inflammation parameters are effective in predicting and early diagnosing cesarean scar pregnancies, which can be missed and cause serious morbidity and mortality when missed.

Materials and Methods

This study covers the first trimester of CSP and normal pregnancies (NP) followed retrospectively in the Perinatology and Pregnancy Outpatient Clinic of Necmettin Erbakan University (NEU) Meram Medical Faculty Hospital between January 2018 and October 2021. Patients' information was obtained electronically from the NEU Meram Medical Faculty Hospital. Approval for this study was obtained from the NEU ethics committee (decision no: 2022/3577).

A total of 86 patients were included in the study. Demographic data and obstetric histories of all patients were recorded. The patients were divided into two groups CSP and NP patients. Patient numbers were matched one-to-one. The gestational week for both groups was accepted as the first trimester (0–14 weeks). In both groups, those with a history of hyperemesis, imminent abortion diagnosis, twin pregnancy, a history of preeclampsia in a previous pregnancy, those with maternal systemic disease (diabetes, renal diseases, thyroid, heart and blood diseases, chronic hypertension, history of cancer, maternal teratogenic drug including those with autoimmune diseases) and those who smoke and consume alcohol were excluded from the study. Cases were included in the CSP group if its located on the anterior wall of the uterus in the isthmic region, the uterus and cervical canal were empty, and the myometrial thickness was absent or decreased between the bladder and gestational sac, and there was trophoblastic vascular blood flow around the sac. Following diagnosis, dilatation and curettage (D&C) were performed in all these cases. Only the early gestational week with the sac and intrauterine located first-trimester ultrasonography scans with normal fetal heartbeat were included in the NP group. For normal pregnancies, pregnant women with a previous cesarean section history and healthy delivery were randomly included from the electronic record system. All pregnant women had their peripheral venous complete blood count values taken at the time of admission. Hemoglobin (H)(mg/dL), lymphocyte (L)(10^3/L), neutrophil (N)(10^3/L), platelet (P)(10^3/L), and monocytes (M)(10^3/L) values were calculated, as well as NLR, PLR, MLR, and SII ($N \times P$ /L) ratios. Blood samples were collected in sterile ethylenediaminetetraacetate (EDTA) tubes for measurements. All measurements were made using the Mindray BC6200 automated blood count analyzer (Mindray Headquarters, China).

Statistical Analysis

In the descriptive statistics of continuous variables, mean, standard deviation, median, minimum, and maximum values are given in the definition of categorical variables, frequency (n) and percentage (percent) values are given. The normality assumptions of the variables were tested using skewness and kurtosis coefficients, the Kolmogorov–Smirnov test, and the histogram.

The Mann–Whitney U test was performed to compare the non-normally distributed continuous variables between the two groups, and when the normality assumption was met, an independent samples t-test was completed. The variables predicting scar status were determined using logistic regression analysis, and the sensitivity and specificity values were calculated using receiver operating characteristics (ROC) analysis. In all analyses, the IBM SPSS.25 program was used, and $p < 0.05$ was accepted as the level of significance.

Results

A total of 86 patients, with 44 (51.2%) in the control group and 42 (48.8%) in the scar group, were included in the study. ►**Table 1** shows a comparison of the patients included in the study based on obstetric and hematological parameters. As shown in ►**Table 1**, the mean age of the patients in the scar group ($p < 0.001$), gravida value ($p < 0.001$), parity value ($p < 0.001$), number of surviving children ($p < 0.001$), number of abortions ($p < 0.001$), cs number ($p < 0.001$), dc value ($p = 0.013$), monocyte value ($p = 0.039$) and mono/lymph value ($p = 0.035$) were significantly higher than the control group (►**Table 2**). The gestational week of the patients in the scar group ($p = 0.021$) was found to be significantly lower than the control group.

To examine the parameters that predict scar condition, a logistic regression analysis was performed. The gestational week was added as a covariate variable to the first step, and monocyte and mono/lymph parameters, which showed significant differences between groups, were added to the second and final steps. As shown in ►**Table 3**, while the gestational week covariantly predicted scar status

Table 1 Obstetric parameters of study and control groups

Parameters	*n*	Mean ± SD	Median (Min–Max)	*p*-Value
Age* < 0.001				
control	44	26.70 ± 5.20	27.00 (18.00–38.00)	
Scar	42	35.31 ± 5.23	34.00 (24.00–49.00)	
Gravida**				
control	44	2.45 ± 1.11	2.50 (1.00–5.00)	<.001
Scar	42	3.93 ± 1.50	4.00 (2.00–8.00)	
Parity**				
control	44	1.07 ± 0.85	1.00 (0.00–3.00)	<.001
Scar	42	2.07 ± 0.75	2.00 (1.00–4.00)	
Abortion**				
Control	44	.07 ± 0.33	0.00 (0.00–2.00)	<.001
Scar	42	.83 ± 1.10	0.50 (0.00–4.00)	
Cesarean**				
Control	44	.52 ± 0.76	0.00 (0.00–2.00)	<.001
Scar	42	2.02 ± 0.68	2.00 (1.00–3.00)	
D&C**				
Control	44	.30 ± 0.51	0.00 (0.00–2.00)	.013
Scar	42	.76 ± 0.96	0.50 (0.00–4.00)	
Gestational age**				
Control	44	7.50 ± 1.17	8.00 (5.00–10.00)	.021
Scar	42	6.86 ± 1.69	7.00 (4.00–11.00)	

Abbreviation: D&C, dilatation curettage.
*Independent *t*-test; **Mann–Whitney *U* test.

significantly ($p = 0.03$), the monocyte and mono/lymph parameters did not significantly predict the scar status ($p > 0.05$).

ROC analysis was used to calculate the diagnostic value by calculating the AUC (area under the ROC curve). AUC = 0.629 (SE = 0.061) for the M value. The optimal M value cut-off value was found to be > 0.40, the sensitivity value was 78.57, and the specificity value was 50.00. AUC = 0.632 (SE = 0.061) for the MLR value. The optimal MLR cut-off value was found to be > 0.232, the sensitivity value was 61.90, and the specificity value was 63.64. ROC curves of M and MLR values are shown in ►**Fig. 1** and ►**Fig. 2**, respectively.

Discussion

The purpose of this study was to compare the inflammatory parameters of patients with scar pregnancy to those with normal pregnancy using blood inflammation markers, which have predictive value in many obstetric conditions and gynecological cancers. Although the N, P, and SII rates in scar pregnancies were high, they were not statistically significant. M and MLR were found to be significantly higher. When the gestational age was taken into account, it was discovered that these parameters had no predictive value. This demonstrated that while ultrasonography remains the gold standard in the diagnosis of CSP, blood parameters that are quick, inexpensive, and available everywhere do not aid in the diagnosis.

The use of Doppler with abdominal and vaginal ultrasonography (USG) is still the gold standard for CSP diagnosis. Typical scar pregnancy findings may not always be seen on USG, which may lead to misdiagnosis or delay in diagnosis in CSP, which is the precursor of placental invasion anomalies (PAS). The diagnosis of scar pregnancies is easier between the 5th and 7th gestational weeks than between the 11 and 14th gestational weeks.[10] In one examination of the CSP case series, the mean gestational age at diagnosis was 7.5 ± 2.5 weeks.[11] The diagnosis may be missed in the following weeks of pregnancy because the gestational sac and fetus will grow toward the upper fundus. In this case, close attention should be paid to the placental tissue that remains in the incision line and the vascularization that surrounds it. Differentiating CSP from unavoidable miscarriages and cervical pregnancies is not always simple. Delays in diagnosis can result in uterine rupture and bleeding, which can result in serious maternal morbidity and mortality.[11,12] In a series of 751 CSP cases, 107 (13.6%) underwent hysterectomy because they could not be misdiagnosed or diagnosed, and as a result, these patients lost their fertility.[13] Another study found that 17 (15.4%) of 111 CSP cases were misdiagnosed as an incomplete abortion or cervical pregnancy.[11] Cali et al reported that the lower segment located sac image, which they detected in the first

Table 2 Blood parameters of study and control groups

Parameters	*n*	Mean ± SD	Median (Min–Max)	*p*-Value
Platelet*				
Control	44	273.36 ± 56.21	269.00 (156.00–459.00)	0.734
Scar	42	277.76 ± 63.40	273.50 (154.00–388.00)	
Neutrophil*				
Control	44	6.36 ± 1.83	6.50 (3.50–10.88)	0.183
Scar	42	6.93 ± 2.15	6.75 (2.89–12.91)	
Lymphocyte**				
Control	44	2.12 ± 0.66	2.15 (1.25–4.06)	0.622
Scar	42	2.05 ± 0.69	2.08 (0.49–3.74)	
Monocyte**				
Control	44	.48 ± 0.17	0.41 (0.28–1.06)	0.039
Scar	42	.55 ± 0.24	0.51 (0.28–1.80)	
Hemoglobin**				
Control	44	12.83 ± 1.25	12.80 (9.20–15.20)	0.836
Scar	42	12.67 ± 1.50	12.80 (8.20–15.90)	
Neutrophil/lymphocyte**				
Control	44	3.20 ± 1.20	2.78 (1.59–6.03)	0.207
Scar	42	4.02 ± 2.71	3.25 (1.15–14.04)	
Platelet/lymphocyte**				
Control	44	131.88 ± 37.56	128.70 (20.69–206.92)	0.342
Scar	42	153.41 ± 71.21	139.44 (64.29–422.22)	
Monocyte/lymphocyte**				
Control	44	.24 ± 0.10	.21 (0.13 - 0.60)	0.035
Scar	42	.35 ± 0.50	.26 (0.11–3.33)	
Neutrophil x platelet/lymphocyte**				
Control	44	834.46 ± 341.96	752.65 (161.40–1643.77)	0.099
Scar	42	1093.37 ± 649.09	898.78 (185.79–2921.61)	

*Independent *t*-test; **Mann–Whitney *U* test.

Table 3 Parameters predicting scar condition

	B	SE	Wald	Exp (B)	*p*-Value	%95 CI	
						Lower	Upper
Gestational age	−0.335	0.162	4.261	0.716	0.039	0.521	0.983
Monocyte	1.398	1.676	0.696	4.045	0.404	0.152	107.952
Monocyte/lymphocyte	2.197	2.483	0.783	8.995	0.376	0.069	1.167.291

11 weeks and is the most important finding of CSP in the first trimester, is also a very important finding for PAS in the subsequent weeks.[10] A few CSP cases were followed up on as expectant, and their hysterectomy rates ranged from 50 to 100%, even though PAS was found in almost all of them.[14] This situation necessitates that the physicians involved gain more experience in the diagnosis of CSP.

Recent research on obstetric and gynecological cancers has demonstrated that inflammatory indices obtained in peripheral blood using L, N, M, and P parameters can be an indicator of local and systemic inflammatory response. When these parameters were examined in preeclampsia patients, it was discovered that they could be used to monitor the disease's severity and prognosis. It has been demonstrated that M is elevated in preeclampsia cases and is a good indicator of chronic inflammation, and MLR is a prognostic factor reflecting poor outcomes and body condition.[15] Syncytiotrophoblast microparticles released by the placenta effectively activate

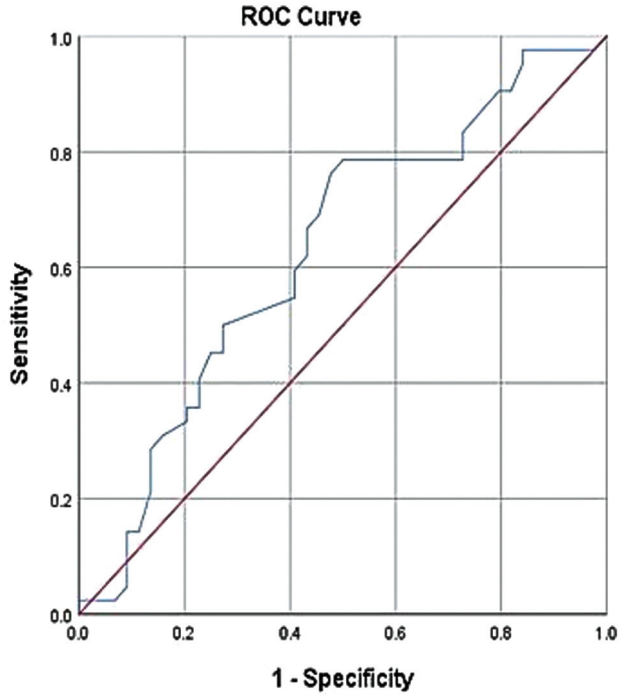

Fig. 1 Receiver operating characteristic curves monocyte for the diagnosis of scar pregnancy.

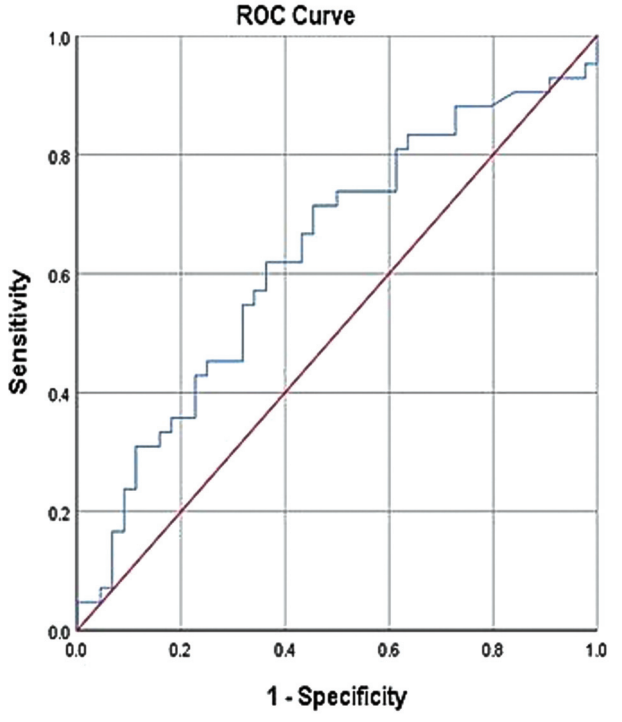

Fig. 2 Receiver operating characteristic curves monocyte to lymphocyte ratio (MLR) for the diagnosis of scar pregnancy.

neutrophils and stimulate neutrophil formation. It is well known that neutrophils serve as a vital link between syncytiotrophoblasts and vascular endothelial cells and that an increase in N in preeclampsia patients triggers a systemic inflammatory response.[16,17] In third-trimester studies of PAS cases with the same pathophysiology as CSP, NLR was significantly higher than in normal pregnant women, N and PLR ratios were higher, and L ratios were the same.[18–20] In the study conducted by Eskicioglu et al, which compared ectopic and normal pregnancies, N and M values were found to be high, but only M values were found to be statistically significant. PDW (platelet distribution width) is assumed to be low in ectopic pregnancies, M ratios are high, and monocytes may play a role in the pathophysiology of tubal ectopic pregnancies.[21] This result is consistent with the results we found in scar pregnancies, which are considered ectopic pregnancies. Kan et al discovered that NLR and PLR levels were significantly higher in ruptured ectopic pregnancies.[9] In our case series, although L ratios were low and N and P were high, they were not statistically significant. Even though M and MLR values were significantly higher, they were insufficient to establish a cut-off. Perhaps the fact that we did not perform an early D&C due to the risk of complicating pregnancies influenced these results. According to studies, the L ratio is low, and the PLR and NLR are significantly higher in pregnant women with hyperemesis compared with the control group, and these markers can help in the diagnosis.[22]

The limitations of our study include the early detection of scar pregnancies, the early termination of pregnancy, the failure to analyze detailed inflammatory cytokine responses, and the fact that it is retrospective. To examine detailed cytokine response, we believe that laboratory studies and large patient populations are required.

Conclusion

As a result, while systemic inflammatory markers may aid in the diagnosis, they are not predictive. Ultrasonography is an indispensable diagnostic method in the diagnosis of CSP. To avoid fatal complications, public awareness should be raised.

Consent to Publish

The participant has consented to the submission of the case report to the journal.

Informed Consent

Informed consent was obtained from all individuals included in this study.

Ethical Approval

Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013).

Authors' Contributions

S.D.: study design, patient management, and manuscript writing/editing; F.A.: data analysis, patient management. A.A.A.: data analysis, patient management; A.C.E.: data collection. A.A.: contributed to and approved of the final version of the manuscript.

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Conflict of Interest
None declared.

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