The European Research Journal 2023;9(5):1048-1055 Original Article

DOI: 10.18621/eurj.1315705 *Obstetrics and Gynecology*

Exploring the role of inflammatory parameters in predicting isthmocele formation following planned cesarean section: a study in patients with a history of one previous cesarean

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ABSTRACT

Objectives: Isthmocele is a hypoechoic area within the lower uterine segment myometrium, resulting from a discontinuation of the myometrium at the site of a previous cesarean scar. The aim of this study was to examine the influence of maternal cellular and inflammatory status prior to Cesarean Section (CS) on isthmocele formation.

Methods: This prospective observational study was conducted in a tertiary hospital and included women with a history of one previous CS. The inflammatory and cellular parameters were collected and ultrasonographic examinations were conducted in the 6th postpartum month and then analyzed. Logistic regression analysis was performed to identify potential factors influencing isthmocele formation.

Results: Of the 106 patients, 31 (29.2%) were diagnosed with isthmocele after one previous CS. There were no significant differences in terms of demographical variables between the groups. However, the duration of CS was significantly longer in the isthmocele group compared to the group without isthmocele (42.58 ± 8.77 vs. 38.42 ± 9.50 minutes, $p = 0.03$). The neutrophil-to-lymphocyte ratio (NLR) was higher and platelet-to-lymphocyte ratio (PLR) was lower in the isthmocele group ($p < 0.001$). Logistic regression analysis revealed that, NLR (OR [odds ratio]: 0.23, 95% CI [confidence interval]: 0.117- 0.473, $p < 0.001$) and PLR (OR: 1.05, 95% CI: 1.027-1.078, $p < 0.001$) were identified as independent predictors for isthmocele formation after planned CS.

Conclusions: Inflammatory markers, such as NLR and PLR, may contribute to the formation of isthmocele in women with a history of one previous CS, shedding light on the underlying pathophysiology.

Keywords: Cesarean scar defect, isthmocele, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

Uterine scar defects, also known as isthmoceles or niches, have gained significant attention in recent years due to their connection to adverse reproductive outcomes and potential clinical implications [1]. Isthmocele refers to a specific type of cesarean scar defect characterized by a localized pouch or indentation

Received: ***June 16, 2023;*** *Accepted:* ***July 18, 2023;*** *Published Online:* ***August 10, 2023***

How to cite this article: *Erturk A, Gokce G, Kender Erturk N. Exploring the role of inflammatory parameters in predicting isthmocele formation following planned cesarean section: a study in patients with a history of one previous cesarean. Eur Res J 2023;9(5):1048-1055. DOI: 10.18621/eurj.1315705*

e-ISSN: 2149-3189

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within the anterior uterine wall. This condition can occur when the healing process after a cesarean section (CS) delivery is incomplete or when the scar formation is faulty, leading to various gynecological symptoms and reproductive complications [2]. Understanding the risk factors associated with isthmocele development is essential for optimizing patient care, guiding prevention strategies, and improving reproductive outcomes. Furthermore, the presence of isthmoceles has been linked to several clinical manifestations, including abnormal uterine bleeding, chronic pelvic pain, infertility, and complications during subsequent pregnancies, such as cesarean scar pregnancy and placenta accreta spectrum disorders [3, 4].

The formation of isthmoceles is believed to have a multifactorial etiology, involving a complex interaction of patient-related, surgical, and obstetric factors [5]. Although the precise mechanisms responsible for isthmocele formation have yet to be fully understood, it is widely accepted that impaired scar healing, insufficient vascularization, and suboptimal tissue repair play a role in their development and persistence [3, 6]. Uterine wound healing is a complex and dynamic process that plays a critical role in the development of isthmoceles. After a CS, the uterine incision goes through a series of intricate biological events, including inflammation, cell migration, extracellular matrix remodeling, and tissue regeneration [7, 8]. The delicate balance between these processes is vital for achieving optimal scar formation and subsequent healing. Disruption of this intricate healing process can result in impaired scar tissue formation and contribute to the development of isthmoceles [6, 8, 9]. Understanding the mechanisms and factors that influence uterine wound healing is crucial for identifying key determinants of isthmocele formation. Previous animal studies have consistently demonstrated the critical roles of neutrophils, platelets, and monocytes in the process of wound healing and tissue maturation [10]. Furthermore, peripheral blood cells, such as neutrophils, lymphocytes, and monocytes, serve as essential biomarkers for evaluating systemic immunity. The ratios between these different cell types, namely the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), have been extensively used as markers for assessing the systemic inflammatory response [11].

This study aimed to investigate the potential impact of maternal cellular and inflammatory status on isthmocele formation.

METHODS

This prospective observational study was conducted at a university-affiliated tertiary hospital from March 2020 to February 2022. The study obtained approval from the local ethics committee (2011-KAEK-25 2019/02-18), and informed consent was obtained from the participating patients, adhering to the principles outlined in the Declaration of Helsinki.

The study focused on women between the ages of 20 and 40 years who had a scheduled CS due to a history of one previous CS. Inclusion criteria consisted of term pregnancies between 37 and 40 weeks, singleton pregnancies, a body mass index (BMI) of 18-25 kg/m2, pregnancy follow-up and delivery at the study hospital, and no known history of isthmocele. Exclusion criteria included emergency CS, multiple previous CSs, connective tissue diseases, a history of gestational diabetes or preeclampsia, uterine anomalies, fetal anomalies, a previous history of isthmocele, smoking, and the use of any medication.

Initially, 217 patients were assessed for eligibility. Demographic characteristics, preoperative laboratory values, intraoperative and postoperative data were recorded for these patients before the planned CS. Ultrasonographic examinations were performed in the 6th month postpartum to evaluate the presence of isthmocele. A total of 106 patients were included in the final analysis after excluding those who underwent CS surgery other than the standard procedure, those who experienced intraoperative complications, those who required additional treatment in the postoperative period, those who needed blood transfusion, those who underwent additional medical or surgical interventions within the 6-month period, and those who were lost to follow-up (Fig. 1).

The CS technique utilized in our hospital follows a standardized approach for all patients. Prior to the procedure, each patient receives intravenous 2 gr cefazolin antibiotic prophylaxis. The surgery begins with a pfannenstiel incision, and the subcutaneous tissue and fascia are separated through sharp dissection. The abdominal cavity is then accessed using a blunt tech-

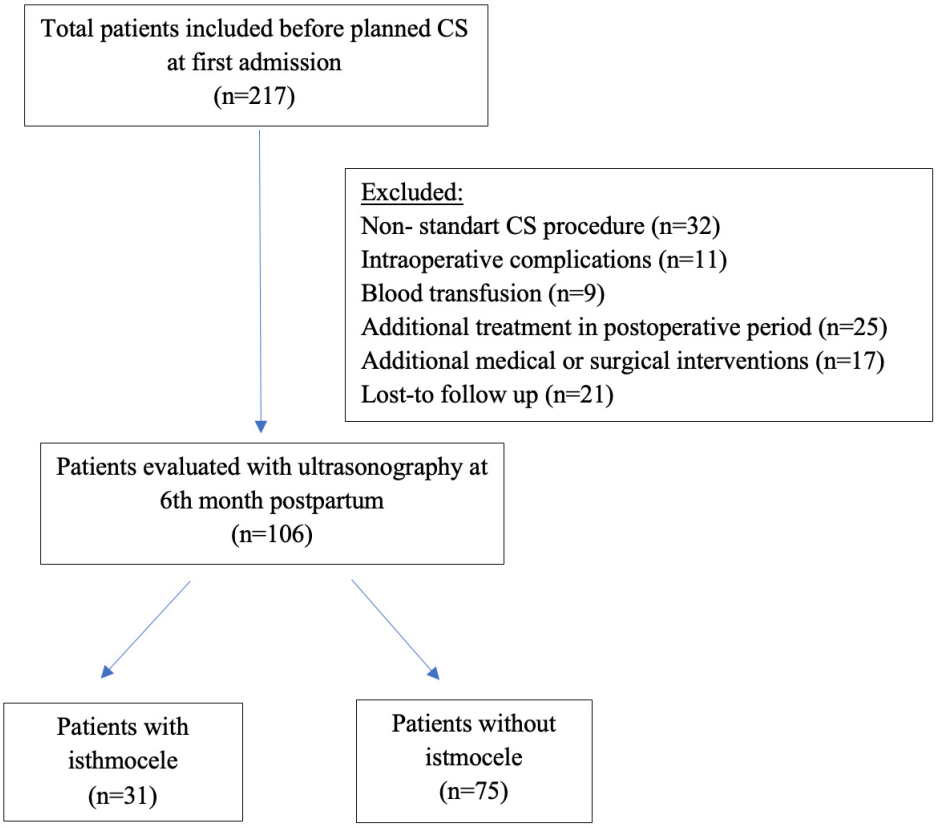

Fig. 1. Flowchart of the study.

nique. For the uterine incision, a lower segment transverse-Kerr incision is made without detaching the bladder. Following the delivery of the baby, the placenta and its attachments separate naturally, and the cervical opening is examined using sterile gloves. The placental bed is cleaned using dry gas, and the uterine scar is closed using a single-layered continuous polyglactin suture. Once bleeding is controlled, the peritoneum is closed with 2/0 polyglactin sutures, and the fascia is closed using a number 1 polyglactin suture. In cases where the subcutaneous tissue thickness is less than 2 cm, the skin is closed subcuticularly using 3/0 sharp prolene sutures, and the wound is dressed without further skin suturing.

In the postpartum 6th month, transvaginal ultrasonography (TVUSG) was conducted by a single doctor (G.G.) to ensure consistency and minimize interobserver differences. Various measurements were taken, including uterine length, width, endometrial thickness, niche-istmocele depth, residual myometrial thickness, and myometrial tissue adjacent to the scar.

Patients with a uterine scar depth of 2 mm or more in the sagittal section of ultrasonography were considered positive for the presence of isthmocele. At the end of the 6th month, the patients were categorized into two groups based on TVUSG findings: those with isthmocele and those without isthmocele. These two groups were then compared in terms of clinical, demographic, cellular, and inflammatory variables. Inflammatory parameters, including the NLR, MLR and PLR, were among the variables considered and analyzed.

Statistical Analysis

The statistical analysis was performed using SPSS version 25.0 (Statistical Package for Social Sciences Inc., Chicago, IL, USA). The normality of the distribution of variables was assessed using the Shapiro-Wilk test. For the comparison of continuous variables between groups, the Mann-Whitney U test was utilized. The chi-square test was employed for categorical variables. Logistic regression analysis was conducted to identify potential cofactors that may influence the formation of isthmocele. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In the study, out of the 106 patients included, 75 (70.7%) did not have an isthmocele, while 31 (29.2%) were diagnosed with an isthmocele. The demographic and clinical characteristics of the patient groups are summarized in Table 1. There were no significant differences between the groups in terms of age, BMI, presence of systemic disease, gestational week, placental position, fetal presentation, and birth weight (Table 1). However, the duration of the CS was longer in the isthmocele group compared to the group without isthmocele (42.58 ± 8.77 vs. 38.42 ± 9.50 minutes, $p = 0.03$) (Table 1). Blood loss, duration of hospitalization, and breastfeeding were similar between the groups.

The laboratory results of the two groups are presented in Table 2. Preoperative hemoglobin (Hb) and fibrinogen values showed no significant differences between the groups. However, the preoperative

Table 1. Comparison of clinical and demographic characteristics and birth follow-up outcomes among patient groups.

	Patients without isthmocele (n = 75)	Patients with isthmocele (n = 31)	*p* value
Age (years)	28.85 ± 4.99	30.06 ± 4.87	0.260
Gravida	2 (2-6)	2 (2-4)	**0.013**
Parity	1 (1-3)	1 (1-3)	**0.015**
BMI (kg/m^2)	29.31 ±2.55	28.88 ± 0.50	0.316
Systemic disease, n (%)			
No	62 (82.7)	28 (90.3)	0.386*
Yes	13 (17.3)	3 (9.7)	
Birth week	38.48 ± 0.50	38.58 ± 0.50	0.348
Placental position, n (%)			
Fundal/lateral	58 (77.3)	21 (67.7)	0.271*
Anterior extending incision	5 (6.7)	1 (3.2)	
Posterior	12 (16.0)	9 (29.0)	
Fetal presentation, n (%)			
Vertex	72 (96.0)	29 (93.5)	0.533*
Breech	2 (2.7)	2 (6.5)	
Podolic	1 (1.3)	0 (0)	
Anesthesia type, n (%)			0.419*
Spinal	65 (86.7)	24 (77.4)	
Combined	3 (4.0)	3 (9.7)	
General	7 (9.3)	4 (12.9)	
Duration of C- section (min)	38.42 ± 9.50	42.58 ± 8.77	**0.030**
Volume of blood loss (mL)	436.80 ± 120.02	424.19 ± 99.89	0.617
Birth weight (g)	3406.40 ± 283.78	3339.83 ± 299.34	0.272
Duration of hospitalization (h)	50.32 ± 7.30	49.54 ± 5.99	0.620
Duration of breast-feeding (days)	187.25 ± 42.73	184.61 ± 39.13	0.542

Values are given mean ± standard deviation or median (minimum-maximum). BMI = body mass index
Mann whitney-U test was performed unless otherwise specified.
$P < 0.05$ was significant. *Chi-square test was used.

Table 2. Comparison of laboratory results among patient groups

	Patients without isthmocele (n = 75)	Patients with isthmocele (n = 31)	*p* value
Preoperative Hb (g/dL)	10.76 ± 1.13	11.20 ± 1.21	0.101
Preoperative WBC ($\times10^3$/μL)	9.81 ± 2.53	9.63 ± 2.13	0.997
Preoperative neutrophils ($\times10^3$/μL)	7.78 ± 1.73	8.43 ± 1.30	0.051
Preoperative lymphocytes ($\times10^3$/μL)	2.02 ± 0.56	1.90 ± 0.63	0.221
Preoperative monocytes ($\times10^3$/μL)	0.54 ± 0.18	0.57 ± 0.20	0.582
Preoperative platelets ($\times10^3$/μL)	323.58 ± 323.12	216.87 ± 29.78	**< 0.001**
Preoperative fibrinogen (mg/dL)	428.81 ± 63.70	445.41 ± 77.17	0.326
NLR	4.12 ± 1.36	4.91 ± 1.67	**0.015**
MLR	0.28 ± 0.12	0.32 ± 0.12	0.183
PLR	183.52 ± 260.21	126.01 ± 40.92	**0.045**

Hb = hemoglobine, WBC = White blood cell, NLR = Neutrophil-to-lymphocyte ratio, MLR = Monocyte-to-lymphocyte ratio, PLR = Platelet-to-lymphocyte ratio

platelet count was higher in the group without isthmocele compared to the isthmocele group (323.58 ± 323.12 vs. 216.87 ± 29.78, $p < 0.001$) (Table 2). The NLR and PLR also exhibited significant differences between the groups. In patients with isthmocele, the NLR was higher, while the PLR was lower compared to those without isthmocele (Table 2).

Logistic regression analysis was conducted to determine factors associated with isthmocele formation, considering age, NLR, MLR and PLR. Among patients with a history of one previous CS, NLR (OR [odds ratio]: 0.23, 95% CI [confidence interval]: 0.117- 0.473, $p < 0.001$) and PLR (OR: 1.05, 95% CI: 1.027-1.078, $p < 0.001$) were identified as independent predictors for isthmocele formation after planned CS (Table 3).

DISCUSSION

The objective of this study was to investigate the cellular and inflammatory factors involved in the development of isthmocele following planned CS in patients with a history of one previous CS. Among the 106 patients included in the analysis, 29.2 % were diagnosed with isthmocele, while 70.7 % did not have isthmocele. The demographic and clinical characteristics of the patient groups were comparable, indicating a similar baseline between the two groups. However, it was observed that the duration of CS was significantly longer in the isthmocele group compared to the group without isthmocele. Interestingly, the laboratory analysis revealed distinct differences between the groups. Specifically, the preoperative platelet count

Table 3. Logistic regression analysis of factor effecting isthmocele presence

Variables	OR	95 % CI	*p* value
Age	1.01	0.907-1.136	0.796
NLR	0.23	0.117-0.473	**< 0.001**
MLR	0.55	0.003-114.318	0.826
PLR	1.05	1.027-1.078	**< 0.001**

NLR = Neutrophil-to-lymphocyte ratio, MLR = Monocyte-to-lymphocyte ratio, PLR = Platelet-to-lymphocyte ratio, Model summary: R^2 =0.46, $p < 0.001$

was significantly lower in patients with isthmocele, suggesting a potential role of platelet dysfunction in the pathogenesis of isthmocele. Additionally, the elevated NLR and decreased PLR observed in the isthmocele group may serve as biomarkers reflecting the inflammatory and immune response associated with isthmocele formation. Logistic regression analysis further identified key factors contributing to isthmocele formation, including NLR and PLR.

The prevalence of isthmocele can vary significantly, ranging from 6.9% to 69%, depending on the study population and methodology employed [1, 12]. It is crucial to acknowledge that the reported prevalence may be subject to change based on the criteria used to define isthmocele. Different diagnostic techniques, such as gel/saline instillation sonohysterography, have been associated with higher prevalence rates of up to 84% [12, 13]. The presence of symptoms can also impact the incidence of isthmocele. Asymptomatic patients with isthmocele may be underestimated, as clinicians may not always recognize it as a potential cause of symptoms, possibly due to a lack of awareness [14]. Furthermore, the prevalence of isthmocele tends to increase with an increasing number of previous CSs [1]. In our study, we observed an incidence of 29.2% for isthmocele in patients with one previous CS. Additionally, it is important to consider the technique used for uterine closure during CS, as it can potentially influence the development of isthmocele. In our study, we specifically utilized one-layer continuous sutures for uterine closure, which may have implications for the occurrence and prevalence of isthmocele.

To the best of our knowledge, this is the first study to investigate the relationship between NLR, MLR, PLR and isthmocele formation. Our findings revealed that higher NLR and lower PLR during the peripartum period were associated with an increased risk of isthmocele formation. It is worth noting that isthmocele formation can be considered as a condition related to inadequate healing of the uterine wound. In normal circumstances, when an injury occurs, neutrophils migrate to the wound site through chemotaxis. They release enzymes to fight infection and remove dead tissue [15]. However, if neutrophils become exhausted, abnormal fibrin fibers can accumulate, delaying wound healing [16]. Increased NLR may indicate impaired healing. Additionally, the balance between platelets and lymphocytes, derived from the same stem cells, is crucial for homeostasis. Abnormal platelet levels caused by systemic inflammation can directly impair wound healing. In cases of abnormal blood cell production, the PLR may temporarily decrease due to faster platelet depletion [17]. Maintaining proper functioning and balance of neutrophils, platelets, and lymphocytes is vital for optimal wound healing and immune response.

In a study investigating wound healing after neck surgery, a higher NLR and lower PLR were found to be associated with postoperative wound complications [18]. Similarly, another study involving pregnant women reported significantly higher NLR and lower PLR in women with preeclampsia compared to healthy pregnancies [19]. The authors of these studies linked these altered levels to impaired inflammation [19]. Another study conducted in people who had elective mesh surgery for groin hernia, high NLR in the preoperative period was found to be significantly associated with postoperative surgical site infection and decrased wound healing [20]. All these mentioned studies show that NLR and PLR are important markers in predicting the course of the inflammatory process. Therefore, it can be inferred that an enhanced inflammatory response during pregnancy could lead to endothelial dysfunction and incomplete wound healing, potentially contributing to the formation of isthmocele.

Limitations

This study has several limitations that should be acknowledged. Firstly, the data was collected from a single center, which may limit the generalizability of the findings to other settings. Secondly, the diagnosis of isthmocele was based solely on TVUSG, without the use of additional diagnostic modalities such as saline infusion sonography or hysteroscopy, which could potentially impact the accuracy of the isthmocele diagnosis. Moreover, the study focused specifically on patients with one previous CS, and it is unclear whether these patients had a previous diagnosis of isthmocele before the current pregnancy. This information could have provided further insights into the relationship between previous isthmocele and its recurrence.

Despite these limitations, there are notable strengths to our study. The prospective nature of the data collection allowed for the accurate assessment of variables and minimized the potential for recall bias. Additionally, the standard surgical methods used for every patient ensured consistency in the surgical approach, reducing the confounding effects of different techniques. Furthermore, the inclusion of patients with comparable demographic characteristics enhanced the validity of the findings. Importantly, this study is the first to evaluate the relationship between inflammatory parameters and isthmocele formation, providing novel insights into the potential mechanisms underlying its development.

CONCLUSION

In conclusion, there was a significant difference in the preoperative NLR and PLR values between patients who developed isthmocele and those who did not. These findings suggest that the inflammatory parameters NLR and PLR may serve as potential biomarkers for predicting isthmocele formation. Further research is needed to validate these findings and explore the underlying mechanisms linking inflammation to inadequate wound healing and isthmocele development. Nevertheless, these results contribute to our understanding of isthmocele pathogenesis and may have implications for risk assessment and preventive strategies in patients undergoing CS with a history of one previous cesarean.

Authors' Contribution

Study Conception: AE; Study Design: AE, NKE; Supervision: NKE; Funding: AE; Materials: AE, GG; Data Collection and/or Processing: GG; Statistical Analysis and/or Data Interpretation: NKE; Literature Review: GG; Manuscript Preparation: AE and Critical Review: NKE.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The author disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Antila-Långsjö RM, Mäenpää JU, Huhtala HS, Tomás EI, Staff SM. Cesarean scar defect: a prospective study on risk factors. Am J Obstet Gynecol 2018;219:458.e1-e8.
2. Kremer TG, Ghiorzi IB, Dibi RP. Isthmocele: an overview of diagnosis and treatment. Rev Assoc Med Bras (1992) 2019;65:714-21.
3. Kulshrestha V, Agarwal N, Kachhawa G. Post-caesarean niche (isthmocele) in uterine scar: an update. J Obstet Gynaecol India 2020;70:440-6.
4. Tulandi T, Cohen A. Emerging manifestations of cesarean scar defect in reproductive-aged women. J Minim Invasive Gynecol 2016;23:893-902.
5. Iannone P, Nencini G, Bonaccorsi G, Martinello R, Pontrelli G, Scioscia M, et al. Isthmocele: from risk factors to management. Rev Bras Ginecol Obstet 2019;41:44-52.
6. Vervoort AJ, Uittenbogaard LB, Hehenkamp WJ, Brölmann HA, Mol BW, Huirne JA. Why do niches develop in Caesarean uterine scars? Hypotheses on the aetiology of niche development. Hum Reprod 2015;30:2695-702.
7. Lofrumento DD, Di Nardo MA, De Falco M, Di Lieto A. Uterine wound healing: a complex process mediated by proteins and peptides. Curr Protein Pept Sci 2017;18:125-8.
8. Buhimschi CS, Zhao G, Sora N, Madri JA, Buhimschi IA. Myometrial wound healing post-Cesarean delivery in the MRL/MpJ mouse model of uterine scarring. Am J Pathol 2010;177:197-207.
9. Roeder HA, Cramer SF, Leppert PC. A look at uterine wound healing through a histopathological study of uterine scars. Reprod Sci 2012;19:463-73.
10. Baum CL, Arpey CJ. Normal cutaneous wound healing: clinical correlation with cellular and molecular events. Dermatol Surg 2005;31:674-86; discussion 86.
11. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget 2017;8:75381-8.
12. Vikhareva Osser O, Valentin L. Risk factors for incomplete healing of the uterine incision after caesarean section. BJOG 2010;117:1119-26.
13. van der Voet LF, Bij de Vaate AM, Veersema S, Brölmann HA, Huirne JA. Long-term complications of caesarean section. The niche in the scar: a prospective cohort study on niche prevalence and its relation to abnormal uterine bleeding. BJOG 2014;121:236-44.
14. Setubal A, Alves J, Osório F, Guerra A, Fernandes R, Albornoz J, et al. Treatment for uterine isthmocele, A pouchlike defect at the site of a cesarean section scar. J Minim Invasive Gynecol 2018;25:38-46.
15. Park JE, Barbul A. Understanding the role of immune regulation in wound healing. Am J Surg 2004;187(5a):11s-6s.
16. Kaitu'u-Lino TJ, Morison NB, Salamonsen LA. Neutrophil depletion retards endometrial repair in a mouse model. Cell Tissue Res 2007;328:197-206.
17. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Renewal by multipotent stem cells: Blood cell formation. Molecular Biology of the Cell. 4th edition. Garland Science; 2002.
18. Maruyama Y, Inoue K, Mori K, Gorai K, Shimamoto R, Onit-

suka T, et al. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as predictors of wound healing failure in head and neck reconstruction. Acta Otolaryngol 2017;137:106-10.
19. Mannaerts D, Heyvaert S, De Cordt C, Macken C, Loos C, Jacquemyn Y. Are neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and/or mean platelet volume (MPV) clinically useful as predictive parameters for preeclampsia? J Matern Fetal Neonatal Med 2019;32:1412-9.
20. Zhuo Y, Cai D, Chen J, Zhang Q, Li X. Pre-surgical peripheral blood inflammation markers predict surgical site infection following mesh repair of groin hernia. Medicine (Baltimore) 2021;100:e25007.