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Diagnostic value of systemic inflammatory indices in ectopic pregnancy

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Abstract

This study aims to evaluate the diagnostic and prognostic utility of systemic inflammatory indices in patients with ectopic pregnancy, and to assess whether they may serve as readily obtainable indicators for early diagnosis and informed clinical decision-making. This retrospective case-control study was conducted at Aksaray Training and Research Hospital between January 2020 and November 2025. The study group consisted of 116 patients who underwent surgical treatment for tubal ectopic pregnancy, while 101 healthy pregnant women with similar demographic characteristics and gestational age served as controls. Hematologic and systemic inflammatory indices were calculated and compared in both groups. A statistically significant difference was found between the patient and control groups in terms of Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), Aggregate Index of Systemic Inflammation (AISI) values ($p<0.05$). Comparative analysis revealed no significant intergroup variation in Systemic Inflammation Modulation Index (SIMI) scores ($p>0.05$). ROC analysis showed that all inflammatory indices except SIMI had statistically significant discriminatory ability. SIRI demonstrated the highest specificity (92.2%) with a PPV of 79.5%, NPV of 61.8%, and the largest AUC (0.68, 95% CI: 0.60–0.75, $p<0.001$), whereas NLR had the highest sensitivity (97.0%) with a high NPV (91.7%), PPV of 54.1%, and an AUC of 0.66 (95% CI: 0.59–0.73, $p<0.001$). AISI, SII, and PLR showed moderate diagnostic performance (AUC: 0.60–0.63) with PPV and NPV values ranging between 54–56% and 64–71%, respectively ($p<0.05$). SIMI did not demonstrate significant predictive value (AUC: 0.53, $p=0.399$; PPV 69.2%, NPV 56.5%). The results of the current study highlight the potential role of several inflammatory indices in the clinical assessment of ectopic pregnancy.

Keywords: Ectopic pregnancy, inflammation, biomarkers, diagnostic value

Introduction

Ectopic pregnancy (EP), defined as the implantation of a fertilized ovum outside the endometrial cavity, remains a prominent etiological factor underlying maternal risk in the first trimester morbidity and mortality [1]. Its incidence varies between 1–2% of all pregnancies, with tubal implantation accounting for more than 90% of cases [2]. Despite advancements in diagnostic imaging and biochemical markers, EP continues to pose a significant clinical challenge due to its heterogeneous presentation, delayed diagnosis, and potential for life-threatening complications such as tubal rupture and hemorrhagic shock [3]. Early identification of women at high risk is therefore essential to prevent adverse outcomes and guide timely medical or surgical intervention.

The pathophysiology of EP is complex and multifactorial, involving altered tubal motility, microenvironmental changes of the fallopian tube, defective embryonic transport, and abnormal trophoblastic invasion [4]. Nevertheless, increasing evidence suggests that inflammation plays a central role in the initiation and progression of EP [5]. Pelvic inflammatory disease, prior tubal infection, sexually transmitted pathogens such as *Chlamydia trachomatis*, and chronic subclinical inflammation all contribute to tubal damage, ciliary dysfunction, and changes in the tubal epithelial milieu [6]. These processes create a pro-inflammatory environment that facilitates ectopic implantation. Moreover, local immune responses triggered by the misplaced trophoblast may further amplify systemic inflammatory pathways, suggesting a bidirectional relationship between EP and systemic inflammation [7].

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In recent years, hematological systemic inflammatory indices derived from routine complete blood count (CBC) parameters have gained significant attention as low-cost, accessible, and reproducible biomarkers in various gynecologic and obstetric disorders [8-10]. Several hematological inflammatory indices have been investigated in multiple inflammatory and pregnancy-related conditions [9,11-16]. These markers are considered reflections of the balance between innate and adaptive immune responses and provide insight into the systemic inflammatory state of the patient. Due to their simplicity and widespread availability, they have emerged as promising adjuncts in the diagnostic and prognostic evaluation of a wide range of diseases.

Understanding the relationship between EP and systemic inflammatory indices is clinically relevant for several reasons. First, current diagnostic tools—ultrasound imaging and serial serum β-hCG measurements—may be inconclusive during the early gestational period, leading to delayed or missed diagnoses. Incorporating systemic inflammatory indices as complementary biomarkers may improve diagnostic accuracy, particularly in ambiguous cases. Second, these indices may assist in distinguishing ruptured from unruptured EP, thereby guiding the urgency and type of intervention. Third, inflammatory markers may help identify patients at risk for treatment failure with methotrexate, a commonly used medical therapy that is sensitive to the degree of trophoblastic activity and systemic inflammation. Lastly, since these biomarkers are inexpensive and widely available in emergency settings, they offer practical advantages, especially in resource-limited environments.

nvestigating systemic inflammatory indices in women diagnosed with EP may provide deeper insights into the underlying pathophysiology and support the development of more accurate diagnostic strategies. A comprehensive evaluation of these indices may contribute to earlier detection, better risk stratification, and improved clinical decision-making, ultimately enhancing maternal outcomes. Therefore, the present study aims to examine the roles of various systemic inflammatory indices in the diagnosis, and management of EP, and to determine their potential value as readily accessible biomarkers in clinical practice.

Materials and Methods

Study design and population

This study was designed as a retrospective case-control study and included patients who presented to the Department of Obstetrics and Gynecology at Aksaray Training and Research Hospital during early pregnancy between 2020 and 2025. Patients diagnosed with EP and with a surgical indication were assigned to the case group, while patients with similar demographic characteristics and gestational age were selected as the control group. In the present study, the patient cohort comprised individuals diagnosed with ruptured tubal ectopic pregnancy who were managed surgically. Surgical intervention was undertaken based on established clinical indications, including intra-abdominal hemorrhage, sonographic and/or clinical evidence of tubal rupture, and/or hemodynamic instability. Inflammatory indices were derived from complete blood count parameters obtained preoperatively, after the clinical onset of rupture and prior to surgical management.

Demographic data, including maternal age, parity, and gestational age, as well as hematological parameters (hemoglobin, neutrophil, lymphocyte, monocyte, and platelet counts), were obtained from the hospital automation system. CBC measurements were carried out with an automated hematological analyzer. Blood specimens from the case group were drawn in the preoperative setting, while those from the control group were acquired during scheduled obstetric follow-ups matched for gestational age. Recorded hematological data were used to compute systemic inflammatory indices, including Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), Aggregate Index of Systemic Inflammation (AISI), and Systemic Inflammation Modulation Index (SIMI). No additional blood samples were drawn specifically for the study.

Based on these parameters, the following systemic inflammatory indices were calculated:

NLR: neutrophil count / lymphocyte count

PLR: platelet count / lymphocyte count

SII: (neutrophil × platelet) / lymphocyte

SIRI: (neutrophil × monocyte) / lymphocyte

AISI: (neutrophil × platelet × monocyte) / lymphocyte

SIMI: (monocyte × platelet) / lymphocyte

Inclusion and exclusion criteria

Patients aged 18–41 years with histopathologically confirmed EP, preoperative CBC, and available serum β-hCG measurements were included in the final cohort, with participant eligibility restricted according to the exclusion criteria detailed below: patients with incomplete or inaccurate medical records; those with conditions that could affect hematological parameters, such as acute or chronic infections, malignancies, chronic hematologic, nephrological, or rheumatologic disorders; patients with chronic anemia; and cases of EP managed medically rather than surgically.

Statistical Analysis

A power analysis was performed using the G-Power (v3.1.2) program to determine sample sizes. For evaluation between two independent groups, when Cohen's effect size (d=0.50), alpha=0.05 level, and the number of n in each group (ectopic pregnancy=116, control=101) were determined, the power of the study was calculated as Beta=0.95.

SPSS v26.0 program was used for statistical analysis. The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. Normally distributed continuous variables were expressed as mean ± standard deviation and compared between groups using the independent samples t-test.

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Non-normally distributed variables were presented as median with 25th and 75th percentiles and analyzed using the Mann–Whitney U test.

Receiver Operating Characteristic (ROC) analysis was performed to evaluate and compare the diagnostic performance of inflammatory index parameters. The Youden J index was used to obtain the optimal cutoff value, and the relevant sensitivity, specificity, positive predictive and negative predictive values, area under the curve (AUC), and 95% confidence intervals (CI) were presented. A significance level of $p<0.05$ was used for interpreting the results.

Ethics Considerations

The study was approved by the Aksaray University Ethics Committee. (Protocol No: SAGETİK 2025-160, Date: 11/12/2025).

Results

No statistically meaningful differences were observed between the study groups with respect to age or parity, indicating comparable demographic characteristics. ($p>0.05$) (Table 1). In the comparison of hematological and biochemical parameters, several systemic inflammatory markers showed significant differences between the groups. Neutrophil and monocyte counts were significantly higher in the patient group, while lymphocyte levels did not differ between the groups ($p=0.503$). Hemoglobin levels were slightly but significantly lower in the control subjects ($p=0.029$). Platelet counts were notably elevated in the patient group compared with controls ($p<0.001$). Regarding biochemical parameters, both urea and creatinine levels were higher in patients ($p<0.001$ for both). Evaluation of systemic inflammatory indices demonstrated distinct patterns between the groups. NLR, SIRI, and AISI values were significantly higher in the patient group (all $p<0.001$). Similarly, SII and PLR levels were also elevated in patients with EP ($p=0.016$ and $p=0.006$, respectively). Conversely, SIMI values did not differ significantly between the groups ($p=0.403$) (Table 2).

Table 1. Demographic information of the study groups

Parameters	Control (n=101)	Patient (n=116)	p
Age (year), Mean ± SD	30.2 ± 5.8	30.6 ± 6.4	0.619 †
Parity, Median (25P-75P)	1 (0-2)	1 (0-2)	0.140*

† Independent samples t-test; *Mann- Whitney U test

Table 2. Comparison of the blood parameters of the study and control groups.

Parameters	Control (n=101) Median (25P-75P)	Patient (n=116) Median (25P-75P)	p*
Neutrophil (10^3/µL)	5.9 (3.99-8.17)	7.8 (6.3-12.3)	<0.001
Lymphocyte (10^3/µL)	1.93 (1.43-2.27)	1.96 (1.49- 2.5)	0.503
Monocyte (10^3/µL)	0.44 (0.35-0.57)	0.54 (0.41-0.71)	<0.001
Hemoglobin (g/dL)	11.8 (10.8-12.8)	12.3 (11.0-13.3)	0.029
Platelet (10^3/µL)	225.0 (185-262)	260.1 (211-320.2)	<0.001
Urea (mg/dL)	16.0 (14-20)	22.0 (19-26)	<0.001
Creatinine (mg/dL)	0.55 (0.48-0.63)	0.60 (0.55-0.69)	<0.001
B-hCG [mIU/mL]		4678.5 (1839.7 -8893)	
NLR	2.98 (1.7-4.8)	4.3 (2.7-8.4)	<0.001
PLR	118.9 (91.5-151.6)	140.2 (108.2-170.8)	0.006
SII	823.3 (489.6-1242.6)	939.2 (658.4 -1668.3)	0.016
SIRI	1.30 (0.74- 2.52)	1.99 (1.16-5.68)	<0.001
AISI	359.9 (199.9-634.2)	477.9 (302.9-1063.8)	<0.001
SIMI	61.8(44.7-79.8)	64.6 (45.1-94.2)	0.403

*Mann- Whitney U test; NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, SII: systemic inflammatory index (neutrophil x platelet / lymphocyte count), SIRI: systemic inflammatory response index (neutrophil × monocyte / lymphocyte count) and AISI: The aggregate index of systemic inflammation (neutrophil × platelet x monocyte /lymphocyte count), SIMI: systemic inflammation modulation index (Monocyte x Platelet) / Lymphocyte counts)

ROC analysis was performed to assess the diagnostic performance of the inflammatory markers. In the ROC analysis was performed to assess the diagnostic performance of the inflammatory indices in relation to EP the optimal cut-off value for NLR was determined to be ≤2.07, with 34.5% sensitivity and 91.1% specificity. For PLR the optimal cut-off value was found to be >133.58, with 55.2% sensitivity and 65.4% specificity. For SII, the optimal cut-off value was determined to be ≤629.71 with

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41.4% sensitivity and 80.2% specificity. For SIRI the optimal cut-off value was found to be ≤0.98, with 38.8% sensitivity and 88.1% specificity. For AISI the optimal cut-off value was found to be ≤295.61, with 43.1% sensitivity and 78.2% specificity. For SIMI the optimal cut-off value was found to be ≤119.81, with 93.1% sensitivity and 17.8% specificity (Table 3 and Figure 1).

Table 3. Diagnostic performance of inflammatory markers

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)		P-Value
NLR	>1.7	97.0	28.5	54.1	91.7	0.66	(0.59-0.73)	<0.001
PLR	≤133.6	65.4	55.2	55.9	64.6	0.61	(0.53- 0.68)	0.005
SII	>629.7	80.2	41.4	54.4	70.6	0.60	(0.52-0.67)	0.014
SIRI	>4.1	34.7	92.2	79.5	61.8	0.68	(0.60-0.75)	<0.001
AISI	>295.6	78.2	43.1	54.5	69.4	0.63	(0.56-0.71)	<0.001
SIMI	>119.8	17.8	93.1	69.2	56.5	0.53	(0.46-0.61)	0.399

AUC: area under curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

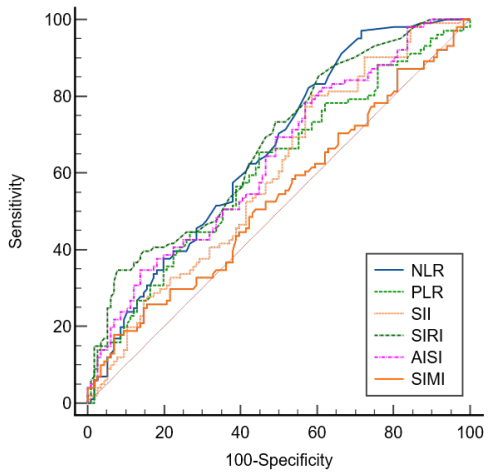

Figure 1. ROC curve comparison of inflammatory markers

The AUC values of NLR PLR, SII, SIRI, AISI and SIMI which are inflammatory indices were found to be 0.657, 0.608, 0.595,0.674,0.634 and 0.533 respectively (Figure 2).

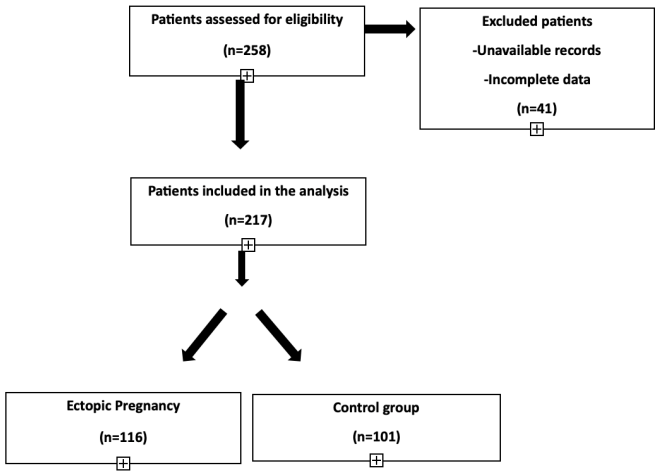

Figure 2. Flowchart of patient selection and group allocation in the study

Discussion

Our results showed statistically significant differences in various hematologic and composite inflammatory markers, and ROC analysis indicated that SIRI, NLR, and AISI had limited ability among the examined indices. In this study, we indicated that NLR, PLR, SII, SIRI and AISI were statistically significant in patient group compare to the control. However, no significant difference was detected in SIMI between the study groups. The results of this research point toward an association between ectopic gestation and systemic inflammatory responses.

EP is a potentially life-threatening condition in which a fertilized ovum implants outside the uterine cavity, most commonly within the fallopian tube. Because the tubal environment cannot support normal embryonic development, progressive growth of the gestational tissue may lead to tubal rupture and significant intraperitoneal bleeding. Clinically, patients may present with abdominal pain, vaginal bleeding, or hemodynamic instability, although early cases can be asymptomatic and resemble a normal intrauterine pregnancy. Emerging scientific data increasingly demonstrate that inflammatory processes constitute a central component in the pathogenesis of ectopic pregnancy. Moreover, systemic inflammatory activation becomes detectable through alterations in hematological indices. These parameters serve as indirect surrogates of amplified immune responses and tissue injury occurring during abnormal gestation. Taken together, current data support the concept that inflammation is not merely a secondary phenomenon but may play a contributory and potentially predictive role in the development and progression of EP.

In the study by Sarıkaya and colleagues evaluated systemic immune inflammation index in 140 patients with EP and reported the NLR value in Group II who underwent surgical treatment, was significantly lower than in Group I receiving MTX treatment. However, they found the SII value in Group II was significantly higher than in Group I. They suggested that the SII may help guide the selection of appropriate management strategies in EP [15].

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With respect to inflammatory markers, NLR and MLR values were significantly lower in the surgically treated group, whereas SII values were significantly higher, while PLR showed no significant intergroup difference. These heterogeneous patterns highlight that individual inflammatory indices may reflect distinct aspects of the underlying inflammatory and immunologic response in EP rather than following a uniform trend. The lower NLR observed in surgically managed patients may reflect differences in disease stage, immune response, or hemodynamic status at presentation, whereas elevated SII values may indicate a more pronounced systemic inflammatory burden associated with advanced ectopic implantation.

In this context, our findings align with the broader observation that indices such as NLR, SIRI, and AISI demonstrate moderate discriminatory capacity in the diagnostic evaluation of EP. The significant intergroup differences observed across these markers support their potential utility as adjunctive tools in therapeutic decision-making, particularly in distinguishing patients more likely to require surgical intervention from those suitable for medical management. However, the variability observed among different indices underscores the necessity for cautious interpretation. These markers should be viewed as complementary parameters rather than definitive determinants of treatment strategy.

Consistent with our data, the moderate discriminatory performance of SIRI, NLR, and AISI suggests that their greatest clinical value may lie in supporting established diagnostic modalities, including transvaginal ultrasonography and serial quantitative β-hCG measurements. When integrated into a multimodal assessment framework, these readily available and low-cost indices may enhance early risk stratification and assist clinicians in tailoring management approaches, especially in emergency and outpatient settings. Nevertheless, prospective validation and longitudinal studies are required to clarify their predictive value, optimal cut-off points, and role in guiding treatment selection in EP.

Another study conducted by Dinc et al. on rupture risk in tubal ectopic pregnancies, they reported that ROC curve evaluation demonstrated that an SII cutoff point of 792 provided the strongest predictive performance for identifying stage III trophoblastic invasion. However, they indicated that there was no significant difference in NLR and PLR values between the groups. They concluded that SII may serve as a useful indicator for anticipating rupture in tubal EP [16].

A study conducted by Callıoglu and colleagues to predict early pregnancy loss, they reported that SIRI values were higher and statistically significant in the patient group compared to the control group. They concluded that SIRI as a potentially more robust prognostic marker than NLR, PLR, MLR, and SII [17]. In our study, it was determined that NLR, PLR, SII, SIRI, and AISI values were statistically significant in patients with EP. These indicators demonstrate that they play a significant role in the diagnosis of EP.

The present findings suggest that systemic inflammatory indices such as SIRI, NLR, and AISI may offer additional value in the diagnostic evaluation of EP, demonstrating moderate discriminatory performance among the evaluated markers. From a practical standpoint, these indices are derived from routine complete blood count parameters and therefore represent readily available, inexpensive, and rapidly obtainable tools in both emergency and outpatient clinical settings. When interpreted in conjunction with established diagnostic modalities, including transvaginal ultrasonography and serial quantitative β-hCG measurements, these markers may assist clinicians in risk stratification and early clinical decision-making, particularly in cases with indeterminate imaging findings.

However, the moderate diagnostic accuracy observed in the present study underscores the need for cautious clinical interpretation. These inflammatory indices should not be considered standalone diagnostic tests but rather as complementary parameters that may enhance diagnostic confidence when used within a multimodal assessment framework. Their potential utility may be greatest in resource-limited settings or during early presentation, when definitive imaging findings are not yet apparent.

Future research should focus on prospective, multicenter studies with larger and more diverse patient populations to validate the diagnostic performance of SIRI, NLR, and AISI in EP. Longitudinal investigations assessing dynamic changes in these indices over time, in parallel with β-hCG trends, may further clarify their role in monitoring disease progression and treatment response. Additionally, integrating these markers into predictive models or composite scoring systems alongside clinical and imaging variables may improve overall diagnostic accuracy and clinical applicability. Such efforts could ultimately facilitate earlier detection and more individualized management strategies for patients with suspected EP.

Conclusion

The observed intergroup differences in NLR, SIRI, and AISI suggest that these inflammatory indices may have a potential supportive role in therapeutic decision-making. In our study, SIRI, NLR, and AISI demonstrated the limited diagnostic evaluation of EP. However, given their limited diagnostic performance, these markers should be interpreted cautiously and considered only as complementary tools alongside established methods such as imaging and serial quantitative β-hCG measurements. Further large-scale, prospective studies are required to clarify their clinical utility and determine whether they can serve as practical and cost-effective adjuncts in emergency and outpatient settings**.**

Limitations

This study has several limitations. First, the retrospective design may introduce selection bias and restrict the ability to establish causal relationships between systemic inflammatory indices and EP. Second, the lack of adjustment for potential confounders, including previous pelvic infections, smoking status, chronic

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inflammatory diseases, or medication use, which could affect inflammatory marker levels. Finally, the study was conducted in a single center, which may limit the generalizability of the findings to broader and more diverse populations. Prospective, multicenter studies with larger sample sizes are needed to validate these results and further clarify the diagnostic value of systemic inflammatory indices in EP.

Ethical Approval
The study was approved by the Aksaray University Ethics Committee. (Protocol No: SAGETİK 2025-160, Date:11/12/2025).

Patient Consent
Informed consent was waived due to the retrospective design of the study.

Conflict of Interest
The authors confirm the absence of any conflicts associated with this work.

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