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OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

The Predictive Role of Neutrophil Percentage to Albumin Ratio (NPAR) and Systemic Inflammatory Markers in Methotrexate Treatment Outcomes for Ectopic Pregnancy

Metotreksat Tedavisi Almış Ektopik Gebeliklerde Nötrofil Yüzdesi Albümin Oranı (NPAR) ve Diğer Sistemik İnflamatuvar Markerların Prediktif Değeri

Sitki Ozbilgec[1], Fatih Akkus[2], Emin Erhan Donmez[3]

[1]Konya City Hospital, Department of Gynecologic Oncology, Konya, Türkiye
[2]Kütahya City Hospital, Department of Obstetrics and Gynecology, Department of Perinathology, Kütahya,Türkiye
[3]İstanbul training and Research Hospital, Department of Gynecologic Oncology, İstanbul, Türkiye

ÖZET

Amaç: Bu çalışma, ektopik gebelikte (EP) metotreksat (MTX) tedavi başarısını öngörmede Nötrofil Yüzdesi Albümin Oranı (NPAR), Platelet-Lenfosit Oranı (PLR) ve Sistemik İmmün-İnflamasyon İndeksi'nin (SII) prediktif rolünü incelemeyi amaçlamaktadır. MTX tedavisinin başarısını önceden tahmin edebilecek biyobelirteçlerin tanımlanması, klinik uygulamada daha doğru ve etkin kararlar alınmasını sağlayabilir.

Gereçler ve Yöntemler: Bu retrospektif çalışma, 1 Ocak 2020 ile 1 Mayıs 2024 tarihleri arasında üçüncü basamak bir hastanede MTX ile tedavi edilen 166 ektopik gebelik hastasını kapsamaktadır. Hastalar tedavi sonuçlarına göre iki gruba ayrılmıştır: MTX tedavisiyle başarıya ulaşanlar ve ek dozlar veya cerrahi müdahale gerektiren tedavi başarısızlığı yaşayanlar. Çalışmada, hastaların başlangıç kan parametrelerinden NPAR, PLR ve SII değerleri hesaplanmış ve bu markerların tedavi sonuçlarını öngörme potansiyeli değerlendirilmiştir. İstatistiksel analizler, lojistik regresyon ve ROC eğrisi analizlerini içermektedir. Optimal eşik değerler, klinik karar verme süreçlerini desteklemek için belirlenmiştir.

Bulgular: NPAR ve PLR değerleri, MTX tedavi sonuçlarının anlamlı prediktörleri olarak bulunmuş ve yüksek değerlerin MTX başarısızlığı ile ilişkili olduğu gösterilmiştir ($p < 0.05$). ROC analizi, NPAR ve PLR'nin sırasıyla 0.777 (95% CI: 0.690-0.864) ve 0.659 (95% CI: 0.548-0.770) AUC değerlerine sahip olduğunu göstermiştir. Buna karşın, SII değerleri ile MTX tedavi başarısı arasında anlamlı bir ilişki bulunamamıştır. NPAR ve PLR'nin yüksekliği, tedavi başarısızlığı ile güçlü bir şekilde ilişkilendirilmiştir.

Sonuç: NPAR ve PLR, ektopik gebelikte MTX tedavisinin başarısını öngörmede etkili biyobelirteçler olarak öne çıkmaktadır. Bu markerlar, risk taşıyan hastaların erken dönemde belirlenmesine olanak sağlayarak, daha kişiselleştirilmiş ve etkili bir tedavi yönetimi sunabilir. Ancak, bu bulguların farklı popülasyonlarda daha geniş kapsamlı çalışmalarda doğrulanması gerekmektedir. Ayrıca, ek biyobelirteçlerin değerlendirilmesi ve bu markerların klinik algoritmalara entegrasyonu tedavi süreçlerini daha da iyileştirebilir.

Anahtar Kelimeler: Ektopik gebelik, metotreksat tedavisi, nötrofil yüzdesi albümin oranı (NPAR), platelet-lenfosit oranı (PLR), sistemik inflamatuvar markerlar

ABSTRACT

Objective: This study investigates the predictive role of the Neutrophil Percentage to Albumin Ratio (NPAR), Platelet-to-Lymphocyte Ratio (PLR), and Systemic Immune-Inflammation Index (SII) in determining methotrexate (MTX) treatment outcomes in patients with ectopic pregnancy (EP).

Materials and Methods: We conducted a retrospective analysis of 166 patients with ectopic pregnancy treated with MTX at a tertiary hospital between January 1, 2020, and May 1, 2024. Patients were categorized into two groups: those achieving successful MTX treatment and those experiencing treatment failure, necessitating additional MTX doses or surgical intervention. NPAR, PLR, and SII values were calculated from baseline blood parameters and analyzed to assess their predictive value. Statistical analyses included logistic regression and ROC curve analysis to determine optimal cutoff values.

Results: NPAR and PLR were significant predictors of MTX treatment outcomes, with higher values correlating with increased likelihood of MTX failure ($p < 0.05$). In contrast, SII did not show a significant association with treatment outcomes. ROC analysis showed that NPAR and PLR had satisfactory predictive performance, with AUC values of 0.777 (95% CI: 0.690-0.864) and 0.659 AUC (95% CI: 0.548-0.770), respectively. Optimal cutoff values for NPAR and PLR were determined to guide clinical decision-making.

Conclusion: This study identified NPAR and PLR as valuable markers for predicting MTX treatment outcomes in ectopic pregnancy, whereas SII was not predictive in this context. NPAR and PLR may aid in early identification of patients at risk for MTX treatment failure, enabling more personalized and effective management of ectopic pregnancy. Further research is needed to validate these findings in larger, prospective studies.

Keywords: Ectopic pregnancy, methotrexate treatment, neutrophil percentage to albumin ratio (NPAR), platelet-to-lymphocyte ratio (PLR), systemic Inflammatory markers

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Sorumlu Yazar/Corresponding Author: Sitki Ozbilgec, Konya City Hospital, Department of Gynecologic Oncology, Konya, Türkiye
e-mail: sozbilgec@yahoo.com

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INTRODUCTION

Ectopic pregnancy (EP), defined as the implantation of a fertilized ovum outside the uterine cavity, remains a significant cause of morbidity and, in severe cases, mortality in reproductive-aged women. Accounting for approximately 1-2% of all pregnancies, ectopic pregnancies often require timely intervention to prevent life-threatening complications, such as tubal rupture and hemorrhage (1). Methotrexate (MTX) therapy, a non-surgical treatment option that selectively targets trophoblastic tissue, has become an established approach for managing unruptured ectopic pregnancies in clinically stable patients. By inhibiting DNA synthesis, MTX effectively halts the proliferation of trophoblasts, allowing the EP to resolve without the need for invasive surgery (2,3).

Despite the clinical efficacy of MTX in many cases, a subset of patients does not respond adequately to this therapy, requiring additional MTX doses or eventual surgical intervention. Predicting MTX treatment outcomes early in the management process could improve clinical decision-making, optimize treatment strategies, and potentially reduce the need for repeat interventions. Recently, systemic inflammatory markers have emerged as potential predictors of various clinical outcomes, including treatment response in ectopic pregnancy. These markers are accessible, cost-effective, and easily derived from standard blood tests, making them appealing candidates for predictive analysis (4,5).

The Neutrophil Percentage to Albumin Ratio (NPAR), although unstudied in the context of ectopic pregnancy, has shown promise in prognosticating other medical conditions. Elevated NPAR levels are often indicative of systemic inflammation and immune activation, factors that could impact MTX treatment efficacy. In addition to NPAR, other indices such as the Systemic Inflammatory Index (SII), Neutrophil-to-Lymphocyte Ratio (NLR), and Platelet-to-Lymphocyte Ratio (PLR) have been linked to clinical outcomes in other systemic diseases (6,7). However, no previous studies have explored the predictive role of NPAR specifically in EP.

This study is the first to evaluate the potential of NPAR as a predictive marker for MTX treatment outcomes in EP. We hypothesize that higher baseline levels of NPAR, as well as elevated SII, NLR, and PLR, may correlate with an increased likelihood of MTX treatment failure, necessitating either repeat MTX doses or surgical intervention.

MATERIALS AND METHODS

Study Design and Population

This retrospective study was conducted in a tertiary care hospital between 1 January 2020 and 1 May 2024 and included 166 patients with EP receiving MTX treatment. Ectopic pregnancy was confirmed by a combination of transvaginal ultrasound findings and serum beta-hCG levels, interpreted by experienced obstetricians. Patients were categorised according to their response to MTX treatment as follows:

1. Successful MTX treatment: 136 patients who achieved treatment success with MTX without further intervention. (A beta hCG drop of at least 15% between day 4 and day 7 of treatment was considered successful MTX treatment) (8).

2. Unsuccessful MTX treatment: 30 patients requiring additional MTX doses or surgical intervention due to treatment failure. (A beta hCG decline of less than 15% between day 4 and day 7 of treatment was considered failed MTX therapy)

Inclusion and Exclusion Criteria

Patients were included if they met the following criteria: Confirmed diagnosis of EP (no intrauterine GS and GS in the right or left tuba uterina, with or without embryo), all patients had an ectopic pregnancy diagnosed by an obstetrician and gynaecologist with more than 10 years of experience using transvaginal ultrasound. Haemodynamic stability, eligibility for MTX therapy according to clinical guidelines (8) and complete medical and laboratory records. Exclusion criteria included cases of ruptured EP, first surgical treatment, concomitant inflammatory conditions or infections that may confound inflammatory marker levels.

Data Collection

Data collected from electronic medical records included patient age, clinical parameters and laboratory results. Systemic inflammatory indices were calculated using baseline and MTX treatment day laboratory values:

- NPAR: Percent neutrophils to albumin ratio.
- NLR: Neutrophil/lymphocyte ratio.
- PLR: Platelet-to-lymphocyte ratio.
- SII: Systemic Immune-Inflammation Index calculated as (Neutrophils × Platelet /Lymphocyte count
- SIRI: Systemic Inflammation Response Index (Neutrophils × monocytes/lymphocytes)
- MLR: Monocyte/lymphocyte ratio.
- Aggregate Index: Neutrophils × platelets × monocytes/lymphocytes).

Outcome Measures

The primary outcome was MTX treatment success or failure. Success was defined as complete resolution of the EP with MTX treatment alone, whereas failure was defined as the need for additional doses of MTX or surgical intervention.

Ethical approval was obtained from the Ethics Committee of the local Institutional Ethics Committee and the study adhered to the principles outlined in the Declaration of Helsinki.

Statistical analysis

SPSS 26 was used for statistical analysis. Normality of data distribution was assessed using Kolmogorov-Smirnov, Shapiro-Wilk tests and histograms. Independent t-test was used to compare between independent groups for normally distributed data, and results were presented as mean ± standard deviation (mean ± SD). The Mann-Whitney U test was used for non-normally distributed data, and results are presented as median (minimum-maximum). Logistic regression analysis was performed to determine the independent risk factors for predicting MTX treatment failure. As a result of the analysis, NPAR and PLR were found to be independent risk factors. ROC analysis was performed to evaluate the diagnostic performance of NPAR and PLR in predicting MTX treatment failure. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve

(AUC) values were reported with 95% confidence intervals. Cut-off values for NPAR and PLR were determined according to Youden index. A two-sided p-value of 0.05 was considered statistically significant.

RESULTS

A total of 166 patients were included in this study, including 136 patients in the successful treatment group and 30 patients in the unsuccessful treatment group. When clinical and laboratory parameters were compared, age, hCG, haemoglobin, Monocyte, Lymphocyte, Platelet, Immature Granulocyte at admission did not differ significantly between the groups (p>0.05). However, MTX day hCG levels (1887.65 ± 1636.15 vs. 2640.47 ± 1864.65, p=0.028), WBC count (9.18 ± 2.57 vs. 10.30 ± 2.27, p=0.029) and neutrophil levels (6.20 ± 2.09 vs. 7.32 ± 1.72, p=0.006) were significantly higher in the failed group. Albumin levels were lower in the failed group (45.00 (26.4-51.0) vs. 43.50 (24.0-51.0), p=0.025) (Table 1).

In Table 2, inflammatory and immune response indices were significantly elevated in the failed group. NPAR (1.47

Table 1. Comparison of Clinical and Laboratory Parameters According to the Success of Methotrexate Treatment in Ectopic Pregnancy

Variable	Successful Group (n=136)	Failed Group (n=30)	p-value
Age	31.79 ± 6.08	31.96 ± 7.33	0.893[α]
Admission hCG	1810.56 ± 1620.71	1948.23 ± 1461.56	0.669[α]
Mtx day hCG	1887.65 ± 1636.15	2640.47 ± 1864.65	0.028[α]
WBC	9.18 ± 2.57	10.30 ± 2.27	0.029[α]
Hemoglobin	12.85 (9.0-15.0)	12.70 (9.0-15.1)	0.515[β]
Neutrophil	6.20 ± 2.09	7.32 ± 1.72	0.006[α]
Monocyte	0.64 ± 0.59	0.62 ± 0.22	0.894[α]
Lymphocyte	2.88 ± 2.06	2.25 ± 0.77	0.103[α]
Platelet	259.97 ± 80.00	287.84 ± 80.55	0.086[α]
IG	0.30 (0.1-0.8)	0.30 (0.1-0.8)	0.740[β]
Albumin	45.00 (26.4-51.0)	43.50 (24.0-51.0)	0.025[β]

WBC: White Blood Cells, IG: Immature Granulocyte α:independet t test (Mean ± SD), β:Mann Whitney U test (Median(Min-Max)

Table 2. Comparison of Inflammatory and Immune Response Indices Between Successful and Failed Methotrexate Treatment in Ectopic Pregnancy

Variable	Successful Group (n=136)	Failed Group (n=30)	p-value
NPAR	1.47 (1.00-1.93)	1.68 (1.29-3.87)	0.001
NLR	2.33 (0.99-4.65)	3.13 (2.25-9.51)	0.001
PLR	108.52 (11.64-297.58)	138.64 (67.60-279.33)	0.007
MLR	0.25 (0.04-0.86)	0.29 (0.09-0.86)	0.030
SII	573.04 (98.49-3827.34)	979.88 (254.73-3827.34)	0.001
SIRI	1.20 (0.40-9.68)	2.30 (0.53-7.47)	0.001
Agregate index	358.45 (90.69-2440.82)	601.50 (146.64-1640.86)	0.001

All comparisons were conducted using the Mann-Whitney U test. NPAR: Neutrophil % -to- Albumin Ratio, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, MLR: Monocyte-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index

Table 3. Binary Logistic Regression Analysis to Predict Failure of Methotrexate Treatment in Ectopic Pregnancy

Predictor	Estimate	SE	Z	p-value	Odds Ratio	95% CI Lower	95% CI Upper
Intercept	-11.43	2.65	-4.31	0.001			
NPAR	3.4	1.14	2.99	0.003	30.02	3.23	279.07
NLR	0.62	0.39	1.56	0.118	1.85	0.85	4.01
PLR	0.02	0.01	2.08	0.038	1.01	1.00	1.03
MLR	-0.44	6.38	-0.07	0.946	0.65	2.38	175376.42
SII	-0.0	0.0	-0.07	0.945	1.00	1.00	1.00
SIRI	0.86	0.79	1.09	0.276	2.36	0.50	11.13
Agregate index	-0.0	0.0	-0.93	0.354	1.00	0.99	1.00
IG	-1.3	1.94	-0.67	0.504	0.27	0.01	12.31
Admission hCG	-0.0	0.0	-1.03	0.304	1.00	1.00	1.00
Mtx day hCG	0.0	0.0	1.9	0.058	1.00	1.00	1.02

IG: Immature Granulocyte, NPAR: Neutrophil % -to- Albumin Ratio, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, MLR: Monocyte-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index

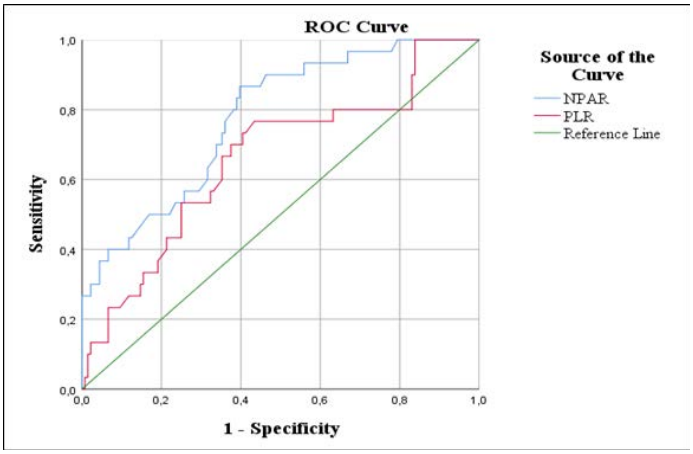

Figure 1. ROC Curve Analysis for NPAR and PLR in Predicting Methotrexate Treatment Failure in Ectopic Pregnancy

(1.00-1.93) vs. 1.68 (1.29-3.87), p=0.001), NLR (2.33 (0.99-4.65) vs. 3.13 (2.25-9.51), p=0.001), PLR (108.52 (11.64-297.58) vs. 138.64 (67.60-279.33), p=0.007), MLR (0.25 (0.04-0.86) vs. 0.29 (0.09-0. 86), p=0.030), SII (573.04 (98.49-3827.34) vs. 979.88 (254.73-3827.34), p=0.001), SIRI (1.20 (0.40-9.68) vs. 2.30 (0.53-7.47), p=0.001) and aggregate index (358.45 (90.69-2440.82) vs. 601.50 (146.64-1640.86), p=0.001).

There were independent risk factors identified by logistic regression analysis to predict failed MTX treatment, including NPAR with an odds ratio of 30.02 (p=0.003) and PLR with an odds ratio of 1.01 (p=0.038) (Table 3).

It demonstrates the diagnostic performance of NPAR and PLR in predicting MTX treatment failure. With a cut-off point of 1.5, NPAR achieved a sensitivity of 86.67%, specificity of 60.29% and AUC of 0.777 (95% CI: 0.690-0.864). With a cut-off point of 120.17, PLR achieved 76.67% sensitivity, 56.62% specificity and 0.659 AUC (95% CI: 0.548-0.770) (Table 4 & Figure 1).

Table 4. Diagnostic Performance of NPAR and PLR in Predicting Methotrexate Treatment Failure in Ectopic Pregnancy

Variables	Cutpoint	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95 % CI)
NPAR	1.5	86.67	60.29	32.5	95.35	0.777 (0.690-0.864)
PLR	120.17	76.67	56.62	28.05	91.67	0.659 (0.548-0.770)

NPAR: Neutrophil % -to- Albumin Ratio, PLR: Platelet-to-Lymphocyte Ratio

DISCUSSION

This study demonstrates the significance of the NPAR and PLR as independent predictors of MTX treatment failure in EP. Both NPAR and PLR were significantly associated with treatment outcomes, while the Systemic Immune-Inflammation Index (SII) did not show a meaningful association in predicting MTX success. This finding refines our understanding of inflammatory markers in EP management, highlighting the value of NPAR and PLR over broader indices like SII.

The role of inflammatory markers in MTX outcomes aligns with findings by Dereli et al., who reported that higher SII and NLR values correlated with MTX treatment failure, likely due to increased inflammation and trophoblastic invasion (5). Although our study found SII to be less predictive, the importance of NLR and similar markers in EP prognosis is underscored by our significant findings for NPAR and PLR. This suggests that while broader indices like SII may capture general inflammatory status, specific ratios such as NPAR may be more sensitive to the nuances of EP pathophysiology.

Similarly, Dinc and Issın evaluated SII in predicting tubal rupture in EP and found a correlation between high SII levels and severe trophoblastic invasion (9). In contrast, our study found no significant link between SII and MTX treatment failure, suggesting that the role of SII may vary depending on the endpoint studied-rupture risk versus MTX responsiveness. In this context, our findings reinforce the specificity of NPAR and PLR as markers that directly inform MTX success rather than rupture risk, supporting the idea that these markers may reflect distinct inflammatory pathways.

Research by Reis et al. further supports the predictive utility of NLR and PLR in EP cases, where elevated levels were associated with increased rupture risk (10). Although their focus was on rupture, the association of PLR with treatment failure in our study is consistent with their findings, emphasizing PLR's role in identifying more complex or treatment-resistant EP cases. This aligns with the observed odds ratio of 1.01 for PLR in our logistic regression analysis, underlining its potential as a clinically useful parameter for MTX outcome prediction.

Seyfettinoglu and Adıguzel also highlighted NLR's importance as a predictor for EP rupture, linking higher levels with greater inflammatory activity and an aggressive EP course (4). By incorporating NPAR, our study builds on these insights and provides an alternative marker with potentially higher specificity in the context of MTX treatment, offering a new avenue for enhancing patient selection and monitoring.

Sarikaya et al. emphasized SII's role in distinguishing between medical and surgical treatments in EP, correlating elevated levels with the need for surgical intervention (11). However, our study did not find a significant association between SII and MTX outcomes, suggesting that while SII might be valuable in evaluating cases progressing to surgery, NPAR and PLR could offer more precise information when

assessing MTX responsiveness specifically. This discrepancy reinforces the need to tailor marker selection to the treatment endpoint and underscores the importance of NPAR and PLR as focused predictors of MTX treatment success.

This study has several limitations. First, as a retrospective analysis, it is subject to selection bias and relies on the accuracy of recorded data. Additionally, the relatively small sample size may limit the generalizability of our findings, and larger, prospective studies are needed to validate the predictive value of NPAR and PLR in diverse populations. Finally, while we focused on specific inflammatory markers, other factors influencing MTX response in ectopic pregnancy, such as hormonal levels and genetic markers, were not assessed. Future research incorporating these factors may provide a more comprehensive understanding of treatment outcomes.

CONCLUSION

In conclusion, our study identified NPAR and PLR as potential predictors of MTX treatment failure patients with EP. These findings suggest that integrating inflammatory markers into routine assessment could offer a valuable approach for anticipating treatment outcomes and tailoring clinical management. This study bridges a critical knowledge gap by introducing NPAR, alongside established markers like PLR, as a potential biomarker for predicting MTX treatment outcomes in EP. Further studies with larger cohorts and prospective designs are essential to validate the utility of NPAR and PLR in diverse clinical settings. Future research should explore the combination of these indices with other biochemical markers to develop a more robust predictive model, with the ultimate goal of enhancing patient care in EP management.

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Address correspondence to: *Sitki Ozbilgec, Konya City Hospital, Department of Gynecologic Oncology, Konya, Türkiye*
e-mail: *sozbilgec@yahoo.com*

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