Original Article

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Enhancing Diagnostic Accuracy of Adnexal Masses: The Prognostic Value of Systemic Immune-inflammatory Index in Conjunction with CA125

Adneksiyal Kitlelerin Tanısal Doğruluğunun Artırılması: CA125 ile Birlikte Sistemik İmmün-enflamatuvar İndeksin Prognostik Değeri

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ABSTRACT

Objective: This retrospective study aimed to investigate the predictive role of the systemic immune-inflammatory index (SII) in distinguishing between benign and malignant adnexal masses in women.

Methods: A total of 268 female patients with adnexal masses who underwent surgical intervention were included. Patient data, including complete blood count and cancer antigen 125 (CA125) levels, were collected, and final pathological examinations were assessed. Patients with prior cancer diagnoses, non-epithelial ovarian cancer, and inflammatory, hematologic, or autoimmune diseases were excluded.

Results: The study included 177 women with benign and 91 women with malignant ovarian tumors. SII and CA125 showed significant differences between the two groups, with both markers found to be significantly higher in the malign group (p<0.001). The area under the curve for SII and CA125 in predicting malignancy were 0.779 and 0.814, respectively. Univariate and multivariate logistic regression analyses demonstrated that a higher preoperative CA125 level (>160) and elevated SII (>5.63) were associated with increased risks of having a malignant tumor (p<0.001).

ÖZ

Amaç: Bu çalışmada, kadınlarda benign ve malign adneksiyal kitleleri ayırt etmede sistemik immün-enflamatuvar indeksin (SII) öngörücü rolünün araştırılması amaçlanmıştır.

Yöntemler: Adneksiyal kitle nedeniyle opere edilen, final patoloji sonuçlarına göre benign tümör veya epitelyal over kanseri tanısı alan 268 kadın çalışmaya dahil edildi. Hastaların tam kan sayımı ve kanser antijeni 125 (CA125) düzeyleri gibi verileri retrospektif olarak toplandı ve değerlendirildi. Bilinen kanser tanısı olan, non-epitelyal over kanseri olan, enflamatuvar, hematolojik veya otoimmün hastalığı olan hastalar çalışmadan çıkarıldı.

Bulgular: Çalışmaya, 177 benign ve 91 malign epitelyal over tümörü olan kadın dahil edildi. SII ve CA125, iki grup arasında anlamlı farklılık gösterdi ve her iki belirteç de malign grupta anlamlı şekilde daha yüksek bulundu (p<0,001). SII ve CA125'in maligniteyi öngörmedeki eğri altında kalan alanları sırasıyla 0,779 ve 0,814 idi. Univaryant ve multivaryant lojistik regresyon analizleri, yüksek preoperatif CA125 düzeyi (>160) ve yüksek SII (>5,63) ile malign tümörlere sahip olma riskinin arttığını gösterdi (p<0,001).

Sonuç: Bulgularımız, SII'nın CA125 ile birlikte, benign ve malign adneksiyal kitleleri ayırt etmek için umut vaat eden öngörücü

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ABSTRACT

Conclusion: Our findings indicate that the SII, in conjunction with CA125, holds promise as a predictive marker for distinguishing between benign and malignant adnexal masses. While CA125 remains a cornerstone biomarker, the integration of SII provides valuable information about the inflammatory and immune response within the tumor microenvironment, enhancing diagnostic accuracy.

Keywords: Adnexal mass, ovarian cancer, systemic immune-inflammatory index, predictive biomarker

ÖZ

bir belirteç olduğunu göstermektedir. CA125 ile birlikte SII'nın entegrasyonu, tümör mikro çevresindeki enflamatuvar ve immün yanıt hakkında değerli bilgiler sağlayarak tanısal doğruluğu artırır.

Anahtar Kelimeler: Adneksiyal kitle, over kanseri, sistemik immün-enflamutuvar indeks, öngörücü belirteç

Introduction

Adnexal masses are common in women and are often detected during routine gynecological examinations or imaging studies (1). Most adnexal masses are benign, but a small percentage are malignant, and accurate diagnosis is essential for optimal patient management (2,3). However, traditional diagnostic methods such as imaging and tumor markers have limitations in their ability to distinguish between benign and malignant adnexal masses, and new biomarkers are needed to improve diagnostic accuracy (4,5).

The inflammatory and immune response within the tumor microenvironment plays a crucial role in cancer development and progression (6). Chronic inflammation has been implicated in various cancer types, and ovarian cancer is no exception (7). Tumor-associated neutrophils and platelets can release pro-inflammatory mediators, such as cytokines and chemokines, promoting angiogenesis, tumor growth, and metastasis (8). Conversely, lymphocytes are essential components of the immune system and play a pivotal role in tumor surveillance and suppression. An imbalance between these immune and inflammatory components can lead to an altered SII, reflecting the dynamic changes within the tumor microenvironment (9).

In recent years, systemic immune-inflammatory index (SII) has been suggested as a novel biomarker for predicting the prognosis of various types of cancer (10-12). SII is a composite index based on peripheral blood counts, which includes neutrophil, lymphocyte, and platelet counts. It reflects the systemic inflammatory response to the tumor and has been found to be associated with the prognosis of several types of cancer, including ovarian cancer (10-15).

Despite the potential diagnostic value of SII in predicting the likelihood of malignancy in adnexal masses, there is limited research on its predictive role. Therefore, this study aims to investigate the predictive role of SII in woman with adnexal masses from benign to malign. The primary objective of this study is to determine whether SII can be used as a diagnostic biomarker for distinguishing between benign and malignant adnexal masses in women.

Methods

This retrospective study included 268 female patients who presented with adnexal masses and subsequently underwent surgical intervention at tertiary referral center and whose final pathological results were epithelial ovarian cancer. Data were collected from patient records and the hospital's electronic database. All procedures were performed in accordance with the Declaration of Helsinki and in compliance with relevant ethical guidelines.

Approval was obtained from the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (decision number: AEŞH-EK1-2023-194, date: 17.05.2023).

Inclusion criteria were as follows: female patients aged 18 years and above, patients with adnexal masses confirmed through imaging studies (ultrasound, magnetic resonance imaging, or computed tomography scan), patients who underwent surgical exploration (laparoscopy or laparotomy) to determine the nature of the adnexal mass, patients with available complete blood count and cancer antigen 125 (CA125) data, including neutrophil (NEUT) count, lymphocyte count, and platelet count, within one week before the surgery. The final pathological examinations and diagnoses of adnexal masses were based on the International Federation of Obstetrics and Gynecology (FIGO) classification (16). Patients with a prior cancer diagnosis, non-epithelial ovarian cancer, inflammatory, hematologic, and autoimmune diseases were excluded from the study. Patients with incomplete medical records or missing laboratory data were excluded from the study also.

The SII was calculated for each patient using the following formula: SII = (Platelet count × NEUT count)/lymphocyte count. NEUT to lymphocyte ratio (NLR), platelet to lymphocyte (PLR) were calculated by dividing the total NEUT or platelet count by the total lymphocyte count.

Statistical Analysis

Statistical analysis was performed using the SPSS version 26 program (SPSS, Chicago, Illinois, United States of America). The normality of the data was analyzed with histogram and with Skewness and Kurtosis values. Descriptive statistics were

presented as mean ± standard deviation. X^2 tests were used to compare categorical variables. Qualitative data were presented as number (n) and percentage (%). Receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal cut-off value for SII in predicting malignancy. Area under the curve (AUC), sensitivity and specificity were calculated to evaluate the diagnostic performance of SII. Univariate analysis was performed after univariate analysis, a model for multivariate logistic regression analysis was formed, 95% confidence interval (CI) and a p-value of <0.05 were considered significant.

Results

A total of 268 women were included in study. Women were divided into two groups according to the final pathological results as benign and malign ovarian tumors. The benign group included 177 women with benign results, and the malign group included 91 women with malign results. Of the women 56.7% (n=152) were postmenopausal.

Table 1 shows the comparison of the two groups. There were no differences in terms of age and body mass index between the groups (p>0.05). However, significant differences were observed in laboratory results, particularly in CA125, SII, PLR, and NLR levels. All values were found to be significantly higher in the malign group (Table 1). Figure 1 shows the comparison of the SII levels of the women with benign and malign tumors.

Table 2 presents the characteristics of malignant ovarian tumors. The most frequently observed histologic type of the malignant tumors was serous histology (47, 51.6%), followed by the endometrioid type (26, 28.6%). Most of the women with malign ovarian tumors were in Stage IB (31, 34.1%).

According to the ROC analysis, AUC of CA125, SII, PLR and NLR in predicting malign ovarian tumors were 0.814, 0.779, 0.694 and 0.655, respectively (Figure 2). Women were divided into two groups based on the optimal cut-off values determined by ROC curve. Table 3 shows the univariate and multivariate logistic regression analyses of the variables. Women with preoperative CA125 level > 160 (95% CI: 9.13-42.08, p<0.001) had a 19.6-fold increased risk and SII >5.63 (95% CI: 2.3-11.52, p<0.001) had a 5.15 increased risk of having malignant tumor (Table 3).

Table 1. Comparison of the groups

	Benign group (n=177)	Malign group (n=91)	p-value
Age (y)	49.29±9.95	50.75±9.49	0.250
BMI (kg/m²)	27.96±4.78	28.79±5.52	0.207
Gravidity (median, range)	3 (0-6)	3 (0-7)	0.059
Parity (median, range)	3 (0-6)	2 (0-7)	0.085
Ca125 (mean, range)	171.68 (7-1393)	494.32 (58-5812)	**<0.001**
SII (mean, SD)	5.45±2.69	10.27±6.22	**<0.001**
PLR (mean, SD)	137.37±59.39	171.13±51.1	**<0.001**
NLR (mean, SD)	2.06±1.03	3.08±2.56	**<0.001**
Postmenopausal (n%)	96 (54.2)	56 (61.5)	0.253

SII: Systemic immune inflammatory index, NLR: Neutrophil lymphocyte ratio, PLR: Platelet to lymphocyte, SD: Standard deviation, BMI: Body mass index

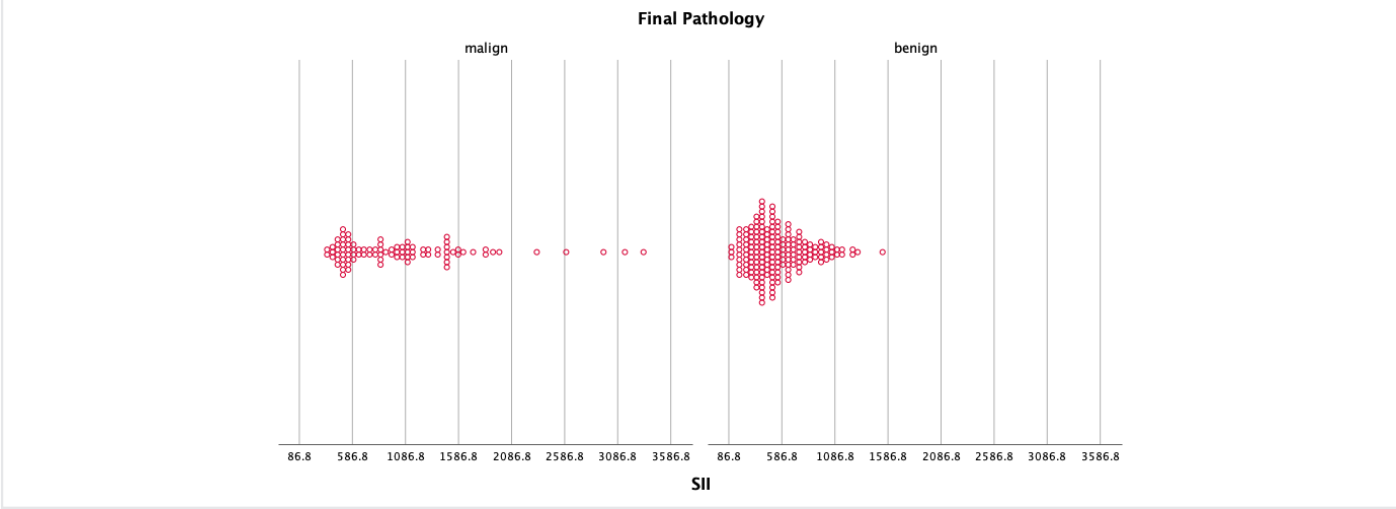

Figure 1. SII levels of patients with malign and benign ovarian tumors
SII: Systemic immune inflammatory index

Table 2. Characteristics of malign ovarian tumors

	(n=91)
Histology	
Serous	47 (51.6)
Endometrioid	26 (28.6)
Mucinous	8 (8.8)
Clear cell	5 (5.5)
Mixed	3 (3.3)
Undifferentiated	2 (2.2)
FIGO stage	
IA	26 (28.6)
IB	31 (34.1)
IC1	11 (12.1)
IC2	9 (9.9)
IC3	7 (7.7)
IIA	4 (4.4)
IIB	3 (3.3)

FIGO: International Federation of Obstetrics and Gynecology

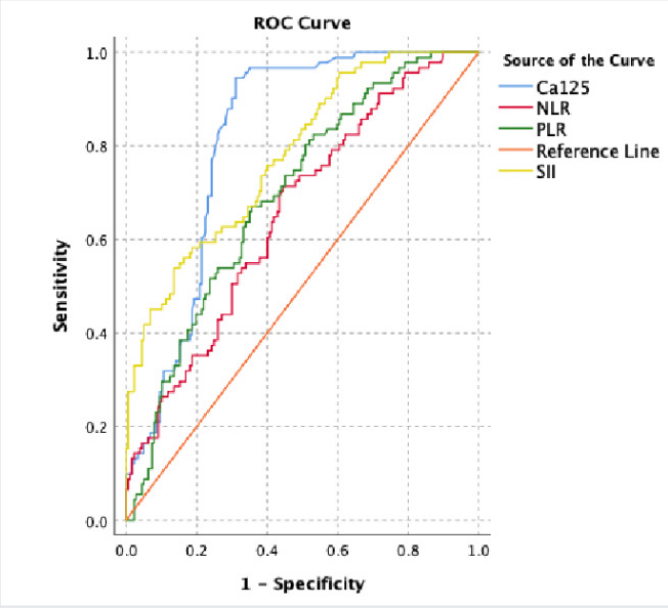

Figure 2. ROC analysis of CA125, SII, PLR and NLR for predicting the malign ovarian tumors

AUC=0.814, an optimal cut-off point of Ca125=160, sensitivity=80.2%, specificity=74.6%; AUC=0.779, an optimal cut-off point of SII=5.63, sensitivity=70.3%, specificity=63.1%; AUC=0.694, an optimal cut-off point of PLR=145.02, sensitivity=67%, specificity=62.6%; AUC=0.655, an optimal cut-off point of NLR=2.07, sensitivity=61.5%, specificity=60.3%

ROC: Receiver operating characteristic, CA: Cancer antigen, SII: Systemic immune inflammatory index, NLR: Neutrophil lymphocyte ratio, PLR: Platelet to lymphocyte, AUC: Area under the curve

Discussion

Adnexal masses are a common clinical challenge, and their accurate diagnosis is crucial for appropriate patient management (17). While CA125 has been widely used as a biomarker for ovarian tumors, its limitations in distinguishing between benign and malignant adnexal masses have prompted the search for additional predictive markers (18). In recent years, the SII has emerged as a novel and promising biomarker for various types of cancer, including ovarian cancer (19,20). Our study aimed to investigate the predictive role of SII in distinguishing between benign and malignant adnexal masses in women. We found that SII, along with CA125, showed significant potential in aiding the differentiation between these two groups of ovarian tumors. While CA125 has traditionally been considered more valuable due to its well-established role, our results suggest that SII can complement CA125 and enhance diagnostic accuracy.

Our findings are consistent with previous studies that have reported elevated SII levels in various malignancies, including ovarian cancer (19,20). These findings suggest that SII may not only serve as a general indicator of systemic inflammation but can also be indicative of the underlying pathological processes associated with malignancy. In a study by Bizzarri et al. (21) which evaluated the prognostic impact of baseline inflammatory markers in early-stage ovarian cancer, NLR and SII were found to be associated with worse disease-free survival. Additionally, SII was found to be associated with worse overall survival (OS). The study demonstrated that high levels of SII and NLR were significantly linked to the risk of recurrence, and, when combined with PLR, were associated with the risk of death in a population of early-stage ovarian cancer patients.

In a meta-analysis investigating the prognostic value of inflammatory markers in patients with ovarian cancer, the study revealed that markers like NLR and PLR were associated with ovarian cancer survival (22). Another review conducted by Zhang et al. (23) also supported these findings, highlighting that NLR and PLR could serve as reliable predictors of overall and progression-free survival (PFS) in patients with ovarian cancer. Furthermore, Prodromidou et al. (24) conducted a thorough review of 18 studies involving 3453 ovarian cancer patients and observed significant deviations in PLR and NLR values compared to healthy controls. These markers were found to potentially indicate disease stage and response to chemotherapy. Despite their potential clinical relevance, it's important to acknowledge that the diagnostic accuracy of NLR and PLR remains limited. While they have shown moderate sensitivity and specificity, further research is needed to enhance their predictive capabilities for ovarian cancer patients.

Feng and Wang (25) investigated the correlation of the systemic immune-inflammatory response index (SIRI) with clinical data in patients with malignant ovarian tumors. The group of patients who died exhibited notably higher NEUT and SIRI levels compared to the surviving group. SIRI showed a positive correlation with serum CA125, CA15-3, and HE4. The study identified age, FIGO stage, SIRI, and therapeutic regimen

Table 3. Univariate and multivariate logistic regression analysis of the variables for malignant ovarian tumors

Factor		Univariate logistic regression Odds ratio (95% CI)	p-value*	Multivariate logistic regression Odds ratio (95% CI)	p-value *
CA125	≤160 (n=150)	1 (reference)			
	>160 (n=118)	11.89 (6.42-22.04)	**<0.001**	19.6 (9.13-42.08)	**<0.001**
SII	≤5.63 (n=136)	1 (reference)			
	>5.63 (n=132)	3.8 (2.2-6.53)	**<0.001**	5.15 (2.3-11.52)	**<0.001**
PLR	≤145.02 (n=139)	1 (reference)			
	>145.02 (n=129)	3.25 (1.91-5.54)	**<0.001**	2.45 (1.09-5.54)	**0.03**
NLR	≤2.07 (n=131)	1 (reference)			
	>2.07 (n=137)	2.27 (1.35-3.82)	**<0.001**	0.683 (0.31-1.49)	0.339

CA: Cancer antigen, SII: Systemic immune inflammation index, PLR: Platelet to lymphocyte ratio, NLR: Neutrophil to lymphocyte ratio, *: Logistic regression analysis, CI: Confidence interval

as independent prognostic factors for the 5-year survival of ovarian cancer patients. In another meta-analysis that examined the prognostic significance of NLR and PLR in ovarian cancer patients, the results indicated that elevated NLR and PLR were associated with poorer outcomes. Specifically, higher NLR and PLR values were found to have an adverse effect on both PFS and OS in patients with ovarian cancer (26).

All of these studies in the literature have examined the impact of inflammatory markers on the prognosis of ovarian cancer cases. However, this study aims to evaluate whether inflammatory markers can be used to differentiate benign ovarian masses from malignant ones. With this characteristic, it offers a different perspective from other studies.

Study Limitations

Limitations of the study include retrospective design and single-center setting. Additionally, the relatively small sample size may impact the generalizability of the findings to larger populations. Prospective studies with larger cohorts and multi-center collaborations will be valuable to validate our results and establish the clinical utility of SII in adnexal mass evaluation.

Conclusion

In conclusion, our study demonstrates the potential significance of SII alongside CA125 in differentiating between benign and malignant adnexal masses in women. Although CA125 remains a cornerstone biomarker, SII offers an additional layer of information about the inflammatory and immune response within the tumor microenvironment. Healthcare providers should consider incorporating SII into their diagnostic evaluations, especially when faced with challenging cases or inconclusive CA125 results. The integration of SII and CA125 could lead to improved diagnostic accuracy and better patient outcomes by enabling more appropriate and timely management of women with adnexal masses. Future prospective studies should aim to confirm the clinical utility of SII and establish standardized guidelines for its use in ovarian tumor diagnostics.

Ethics

Ethics Committee Approval: Approval was obtained from the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (decision number: AEŞH-EK1-2023-194, date: 17.05.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.K., B.K., S.K.E., V.K., H.L.K., Concept: C.K., B.K., V.K., Design: H.L.K., Y.E.Ü., Data Collection or Processing: C.K., B.K., S.K.E., Analysis or Interpretation: B.K., S.K.E., Y.E.Ü., Literature Search: C.K., B.K., S.K.E., Writing: C.K., B.K., Y.E.Ü.

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