DOI: https://doi.org/10.2298/SARH221122057T
UDC: 618.11-006.6-074

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Novel inflammatory markers and prognostic importance of platinum-sensitive ovarian carcinoma relapse

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SUMMARY

Introduction/Objective Ovarian carcinomas are the deadliest gynecological tumors. Despite advances in treatment options, survival rates are still not at the desired level. Since clinical signs are not typical in early-stage disease, two-thirds of patients are diagnosed late. Carbohydrate Antigen 125 (CA125) does not have sufficient sensitivity and specificity in early-stage disease and early post-relapse progression. There is a need for a simple and cost-effective marker that correlates with CA125. For this purpose, we aimed to evaluate the potential of systemic inflammatory markers' as diagnostic aids.

Methods Patients with platinum-sensitive recurrent ovarian carcinomas were preferred because the treatment options were more diverse than the resistant group. Using retrospective data collection, 105 patients with platinum-sensitive recurrent ovarian carcinoma, admitted in the last four years were included in the study. Complete blood count data was recorded based on recurrence and progression periods.

Results When the systemic immune inflammatory index (SII) values were evaluated in combination with CA125 in terms of progression during the control visits after platinum-sensitive disease recurrence treatment, progression detection proportions increased to 97.5%, which was 82.9% when only CA125 was used. On the other hand, false positivity, which was 18.5% for CA125 alone, decreased to 2.5% when combined with SII. Furthermore, neutrophil lymphocyte ratio, white blood cells, and neutrophil values showed correlations with high CA125 values.

Conclusion The SII value could be used together with CA125 because it is easy to use, accessible, and has low cost in clinical practice, as well as to increase the accuracy rate and make precise corrections in the false positivity rate.

Keywords: ovarian cancer; CA125; relapse; inflammatory biomarkers; platinum sensitivity

INTRODUCTION

Ovarian cancer has the fifth-most cancer-related mortality in women in developed countries and is the deadliest gynecological tumor [1]. Although personalized treatment modalities, chemotherapeutic agents, and the addition of drugs such as bevacizumab (anti-vascular endothelial growth factor) to combination therapies in relapsed disease have positively contributed to progression-free survival in recent years, there has still not been enough contribution to overall survival [2]. While the five-year survival rate is 90% in patients detected in the early stage, this rate regresses to 20% in advanced-stage patients [3]. Approximately two thirds of the cases are diagnosed at later stages because of early onset, non-specific, and mostly constitutional complaints [3].

CA125 has low sensitivity and specificity, especially in ovarian cancers' earlier stages [4]. Furthermore, CA125 levels can elevate in benign situations such as endometriosis, menstruation, and coronary artery disease. As a result, high false-positivity may cause significant psychological problems in women who do not have ovarian cancer, leading to unnecessary additional treatment burdens [5]. Additionally, approximately 20% of epithelial ovarian cancer cases have typical CA125 measurements [6]. Considering these circumstances, CA125 alone cannot support the diagnosis during ovarian cancer recurrences. For this purpose, we aimed to evaluate biomarkers for recurrences in platinum-sensitive ovarian cancers that are simple, can be evaluated in correlation with CA125, and can be measured in any health institution without the need for additional laboratory expenses or a special infrastructure. Therefore, we analyzed inflammatory markers' contribution such as neutrophil lymphocyte ratio (NLR) and systemic immune inflammatory index (SII) in ovarian cancer patients' diagnosis and relapse periods.

METHODS

Using a retrospective database search, 105 patients with platinum-sensitive recurrent ovarian carcinoma, admitted in the last four years were included. The study was prepared per the declaration of Helsinki and was approved by the ethics committee of Health Sciences University, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, dated August 24, 2022, and numbered 2022-08/1930.

Received • Примљено: November 22, 2022
Revised • Ревизија: May 6, 2023
Accepted • Прихваћено: May 14, 2023
Online first: May 22, 2023

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Recurrence and progression timestamps were taken as a basis in processing the hemogram parameters. In addition, platelet-to-lymphocyte ratio (PLR), NLR, and Systemic immune inflammation index (SII) (with a formula of platelet × neutrophil / lymphocyte) were calculated.

Analyses were performed using the Statistical Package for the Social Sciences program [SPSS for Windows, Version 25.0, (IBM Corp., Armonk, NY, USA)]. Normality analises were performed to show the distribution of the variables. Continuous variables were reported using the median (interquartile range) and mean (SD), and categorical variables using the Pearson χ^2 or Fisher's exact test. ROC analysis was performed to calculate the best SII cut-off value. Finally, Spearman correlation analysis was performed for evaluating numerical variable relationships. A p-value of < 0.05 was accepted as significant.

RESULTS

A total of 105 patients with platinum-sensitive recurrent ovarian carcinoma were included. The median age was 55.81 (34–78). When evaluated for menopausal status, 34 (32.3%) patients were premenopausal, while 65 (67.6%) were postmenopausal. Progression developed in 16 (47%) of 34 premenopausal patients and 25 (35.4%) of 65 postmenopausal patients. When the patients were categorized according to their histopathological subtype, there were 90 (85.7%) high grade serous, six (5.7%) low grade serous, five (4.7%) endometrioid, two (1.9%) clear cell, and two (1.9%) other types.

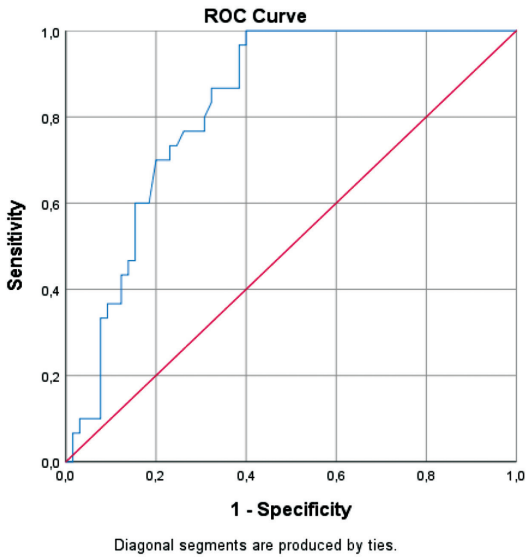
The relationship between laboratory parameters and progression is given in Table 1. Serum CA125 was converted into two separate categorical variables as 35 and below and above 35. CA125 cut-off value was taken as 35. NLR was higher in the group with CA125 > 35 U/ml compared to the group with CA125 ≤ 35 U/ml (p = 0.002) (Table 1). Also, white blood cells had been substantially elevated in CA125 > 35 U/ml cases compared to CA125 ≤ 35 cases (p = 0.05).

Table 1. Relationship of laboratory parameters to CA125

Parameters	CA125 ≤ 35 U/ml (n = 29) Median (range) (95% CI)	CA125 > 35 U/ml (n = 39) Median (range) (95% CI)	p-value
NLR	1.92 (1.47–2.26)	2.95 (3.12–4.52)	**0.002***
SII	722 (877–1999)	810 (580–1138)	0.621*
PLR	161 (134.91–216.35)	144 (141.48–211.77)	0.459*
WBC	6 (4.5–10.2) (x 10^3)	8.1 (7.9–9.7) (x 10^3)	**0.050***
Lymphocyte	1.7(1.57–2.14) (x 10^3)	1.48 (1.42–1.99) (x 10^3)	0.111*
CRP	4.0 (0.82–16)	6 (5.2–20)	0.986*

NLR – neutrophil lymphocyte ratio; SII – systemic immune inflammation index; PLR – platelet lymphocyte ratio; WBC – white blood cells; CA125 – Carbohydrate Antigen 125
*Mann Whitney U

Of our patients, 41 (39%) developed progression after relapse treatment. Serum CA125 was elevated in 34 (82.9%) of 41 patients with this progression. Measurements of CA125 and SII values were planned for these patients.



Progression	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	p
SII	0.825	0.744–0.906	929.5	73.3	75.4	**< 0.001**

AUC – area under the receiver operating curve; CI – confidence interval

Figure 1. Roc analysis results in determining the progression of the systemic immune inflammation index variable

As a result of the ROC analysis performed, the value of 929.5 was accepted as the best cut-off (Figure 1), and disease progression was detected in 40 (97.5%) patients when CA125 and elevated SII were evaluated simultaneously. There were five patients (18.5%) with CA125 > 35 and no recurrence on imaging. When CA125 was evaluated together with SII, one (2.5%) of 41 patients with progression was marked as "no progression" (Table 2).

Table 2. Relationship between age, CA125, SII, and performance status with progression

Progression				
Parameters		Present n = 41 (%)	Absent n = 64 (%)	p-value
Age	≤ 50	14 (34.1)	15 (23.4)	0.23[1]
	> 50	27 (65.8)	49 (76.5)	
CA125*	≤ 35	7 (17.1)	22 (81.5)	0.35[2]
	> 35	34 (82.9)	5 (18.5)	
(SII ≥ 929.5 + CA125 > 35)*		40 (97.5)	1 (2.5)	
Eastern Cooperative Oncology Group Performance Status	0	4 (20)	16 (80)	0.13[2]
	1	30 (44.7)	37 (55.2)	
	2	7 (38.8)	11 (51.1)	

CA125 – Carbohydrate Antigen 125; SII – systemic immune inflammation index
[1]Pearson's χ^2; [2]Fisher's exact test;
*Measurement values in patients with progression after relapse treatment

According to Figure 1, the SII parameter estimation was significant in differentiating additional parameters in progression development (p < 0.001). The area under the ROC curve (AUC) for SII to diagnose the presence of progression was 0.825 (95% [CI], 0.744–0.906). For predicting progression, the SII at a cut-off value of ≥ 929.5 had a sensitivity of 73.3% and a specificity of 75.4%.

The Spearman correlation analysis for interactions between the laboratory parameters' numerical variables

Table 3. Correlation between laboratory parameters

Parameters	p	Lymphocyte	Neutrophil	SII	NLR	PLR	CA125 (recurrence)
Lymphocyte	r	1					
	p						
Lymphocyte	r	0.125	1				
	p	0.226					
Lymphocyte	r	-0.266**	0.134	1			
	p	**0.009**	0.196				
Lymphocyte	r	-0.540**	0.637**	0.351**	1		
	p	**< 0.001**	**< 0.001**	**< 0.001**			
Lymphocyte	r	-0.319**	-0.098	0.393**	0.318**	1	
	p	**0.002**	0.343	**< 0.001**	**0.002**		
Lymphocyte	r	-0.152	0.233	-0.005	0.262*	-0.130	1
	p	0.250	**0.076**	0.972	**0.045**	0.325	

CA125 – carbohydrate antigen 125; SII – systemic immune inflammation index; NLR – neutrophil lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; *Spearman correlation analysis

showed a significant and low relationship among NLR and CA125 (r = 0.26, p = 0.045). Besides, serum neutrophil and CA125 values were also evaluated as having a significant relationship (r = 0.23, p = 0.076) (Table 3).

DISCUSSION

Despite many efforts to find the most appropriate biomarker for ovarian cancers, early detection methods still rely on serum CA125 level measurement [7]. CA125 is elevated in 83% of ovarian cancers, but it has low sensitivity and specificity in very early-stage ovarian cancers, and this rate drops to 50–60%. The premenopausal ages had a sensitivity of 50–74%, and a specificity of 69–78%. Additionally, the postmenopausal ages had a sensitivity of 69–87%, and a specificity of 81–93% [8, 9]. Due to various factors, there is a need for biomarkers that can increase the sensitivity and specificity of CA125. To address this issue, Ke Huang et al. [10] have shown that the combination of CA125 with biomarkers such as NLR and PLR is more effective than using CA125 alone in detecting the subgroup of borderline epithelial ovarian tumors that can potentially become malignant. In our study, we aimed to fill this gap by examining the contribution of NLR, PLR, and SII values. While we found that all three biomarkers provided significant contributions, unlike the study by Ke Huang et al. [10], we observed that the SII value, which combines neutrophil, lymphocyte, and platelet values, further enhances the sensitivity and specificity of CA125 when used in combination. Our study observed progression in 47% of premenopausal patients and 35.4% of postmenopausal patients.

CA125 can elevate in benign situations like endometriosis, menstruation, and pregnancy, in addition to ovarian carcinomas. However, it is also used as a marker in hematological malignancies such as lymphoma [11, 12, 13]. Therefore, it is not recommended for population screenings because of its low reliability [14]. Gschwantler et al. [15] in 2017 evaluated leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitor factor, and HE4 together in addition to CA125, and their 94.3% sensitivity and 92.3% specificity rate are important for the combined evaluation of several biomarkers to yield more reliable results, even in a highly complicated tumor. However, it takes work to measure these parameters and causes an additional cost burden. Therefore, evaluating the markers should be accessible and cost-effective in all health institutions. Our study aims to shed light on this gap and to obtain easily accessible biomarkers to be used in earlier diagnosis and progression detection.

There was a total of 47 patients with disease progression with CA125 > 35, and when the imaging and clinical findings were evaluated together, six patients (18.5%) were not considered to have progression. On the other hand, only one (2.5%) of the patients with high CA125 + SII values did not show any progression. Therefore, it was determined that our CA125 false positive rate decreased from 18.5% to 2.5%. Furthermore, when SII values of recurrence patients' progression were evaluated in combination with CA125, the rate of progression detection increased to 97.5%, which was 82.9% compared to the evaluation of CA125 alone.

Patients with ovarian cancers whose first recurrence timing (platinum-free follow-up interval-PTA) occurs within six months are considered to have a platinum-resistant disease, and platinum-based regimens are not preferred in the treatment options of these patients. In the follow-up of patients after adjuvant therapy, using CA125 in combination with other biomarkers will increase the reliability of recurrence detection, thus providing earlier recognition and reducing the additional platinum exposure of the patients.

CONCLUSION

Considering all these data, the SII value could be used together with CA125 because it is easy to use, accessible, and has low cost in clinical practice, as well as to increase the accuracy rate and make precise corrections in the false positivity rate. Furthermore, in the analyses performed, it was determined that NLR, white blood cells, and Neutrophil values were parallel with high CA125 values.

Conflict of interest: None declared.

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Нови инфламаторни маркери и прогностички значај релапса карцинома јајника осетљивог на платину

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Болница за обуку и истраживање онкологије у Анкари „Абдурахман Журтаслан", Одељење за медицинску онкологију, Анкара, Турска

САЖЕТАК

Увод/Циљ Карциноми јајника су најсмртоноснији гинеколошки тумори. Упркос напретку у опцијама лечења, стопе преживљавања још увек нису на жељеном нивоу. Пошто клинички знаци нису типични у раној фази болести, 2/3 болесница се дијагностикује касно. Антиген угљених хидрата 125 (*CA*125) нема довољну осетљивост и специфичност у раној фази болести и раној прогресији после релапса. Постоји потреба за једноставним и исплативим маркером који корелира са *CA*125. У ту сврху, желели смо да проценимо потенцијал системских инфламаторних маркера као дијагностичких помагала.

Методе Болеснице са рекурентним карциномом јајника осетљивим на платину су биле у предности јер су опције лечења биле разноврсније од резистентне групе. Користећи ретроспективно прикупљање података, у студију је укључено 105 болесница са рекурентним карциномом јајника осетљивим на платину, примљених у последње четири године. Подаци комплетне крвне слике су снимљени на основу периода рецидива и прогресије.

Резултати Када су вредности системског имунолошког инфламаторног индекса процењене у комбинацији са *CA*125 у смислу прогресије током контролних посета после третмана рецидива болести осетљиве на платину, пропорције откривања прогресије су порасле на 97,5%, што је било 82,9% када је био коришћен само *CA*125. С друге стране, лажна позитивност, која је била 18,5% само за *CA*125, смањена је на 2,5% када се комбинује са системским имунолошким инфламаторним индексом. Штавише, однос вредности неутрофила и лимфоцита, вредности белих крвних зрнаца и неутрофила показале су корелацију са високим вредностима *CA*125.

Закључак Вредност системског имунолошког инфламаторног индекса би се могла користити заједно са *CA*125 јер је лака за употребу, приступачна и има ниску цену у клиничкој пракси, као и за повећање стопе тачности и прецизне корекције у стопи лажне позитивности.

Кључне речи: рак јајника; *CA*125; релапс; инфламаторни биомаркери; осетљивост на платину