DOI 10.26724/2079-8334-2026-1-95-155-159
UDC 616.347/616.347-008.64:616.61

Xalilova V.Z., Safarova I.A., Ahmedzade N.B., Xalilov S.Z., Jafarova G.A.
Azerbaijan Medical University, Baku, Azerbaijan

HE4, CA-125, ROMA INDEX, AND TUMOR RECEPTOR EXPRESSION IN POSTMENOPAUSAL OVARIAN AND CERVICAL CANCER

e-mail: vusala.xalilova77@gmail.com

Ovarian and cervical cancers are among the most common gynecologic malignancies in postmenopausal women, and reliable biomarkers are essential for accurate diagnosis and risk stratification. The study aims to evaluate the clinical relevance of serum HE4 and CA-125 levels, the ROMA index, and tumor receptor expression (ER, PR, HER2, Ki-67) in postmenopausal patients with ovarian and cervical cancer. A total of 45 postmenopausal ovarian cancer patients (age Me=58.4) and 38 postmenopausal cervical cancer patients (Me=59.3;) were enrolled. Serum HE4 and CA-125 were measured using the fully automated Integra 411 analyzer. Tumor receptor status (ER, HR, HER2, Ki-67) was evaluated by immunohistochemistry. ROMA index was calculated for ovarian cancer patients. Elevated levels of HE4 and CA-125 were observed in both ovarian and cervical cancer patients. In ovarian cancer patients, circulating tumor biomarkers increased markedly with tumor progression. HE4 demonstrated a strong positive correlation with CA-125 and the ROMA index, indicating a close association between these biomarkers in ovarian malignancy. Additionally, HE4 showed moderate correlations with tumor receptor expression, including ER, PR, HER2, and the proliferative marker Ki-67, suggesting a link between biomarker levels and tumor biological activity. In cervical cancer patients, HE4 and CA-125 also exhibited moderate correlations with receptor expression and Ki-67, reflecting a similar pattern of association between circulating biomarkers and tumor characteristics. Overall, the ROMA index effectively differentiated high-risk ovarian cancer patients from lower-risk groups and showed a strong association with HE4 levels. Integrated analysis of HE4, CA-125, ROMA index, and receptor expression may improve early detection, risk assessment, and individualized treatment in postmenopausal patients with ovarian and cervical cancer.

Key words: ovarian cancer, cervical cancer, human epididymis protein 4, cancer antigen 125, ROMA index, estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, Ki-67 proliferation index.

Халілова В.З., Сафарова І.А., Ахмедзаде Н.Б., Халілов С.З., Джафарова Г.А.

HE4, CA-125, ІНДЕКС ROMA ТА ЕКСПРЕСІЯ ПУХЛИННИХ РЕЦЕПТОРІВ У ПОСТМЕНОПАУЗАЛЬНИХ ПАЦІЄНТОК ІЗ РАКОМ ЯЄЧНИКІВ ТА ШИЙКИ МАТКИ

Рак яєчників та шийки матки є одними з найбільш поширених гінекологічних злоякісних новоутворень у постменопаузальних жінок, і надійні біомаркери мають вирішальне значення для точної діагностики та стратифікації ризику. Метою цього дослідження було оцінити клінічне значення сироваткових рівнів HE4 та CA-125, індексу ROMA та експресії пухлинних рецепторів (ER, PR, HER2, Ki-67) у постменопаузальних пацієнток із раком яєчників та шийки матки. Загалом було включено 45 постменопаузальних пацієнток із раком яєчників (Me=58,4 роки) та 38 постменопаузальних пацієнток із раком шийки матки (Me=59,3 роки), які проходили обстеження та лікування в Онкологічній клініці Азербайджанського медичного університету. Сироваткові рівні HE4 та CA-125 визначали за допомогою повністю автоматизованого аналізатора Integra 411. Статус пухлинних рецепторів (ER, PR, HER2, Ki-67) оцінювали методом імуногістохімії. Для пацієнток із раком яєчників розраховували індекс ROMA. Було виявлено підвищення рівнів HE4 та CA-125 у пацієнток як із раком яєчників, так і з раком шийки матки. У пацієнток із раком яєчників циркулюючі пухлинні біомаркери значно підвищувалися з прогресуванням пухлини. HE4 продемонстрував сильну позитивну кореляцію з CA-125 та індексом ROMA, що свідчить про тісний зв'язок цих біомаркерів у злоякісних пухлинах яєчників. Крім того, HE4 показав помірні кореляції з експресією пухлинних рецепторів, включно з ER, PR, HER2 та маркером проліферації Ki-67, що свідчить про взаємозв'язок між рівнями біомаркерів і біологічною активністю пухлини. У пацієнток із раком шийки матки HE4 та CA-125 також демонстрували помірні кореляції з експресією рецепторів та Ki-67, відображаючи схожий патерн взаємозв'язку між циркулюючими біомаркерами та характеристиками пухлини. Загалом, індекс ROMA ефективно диференціював пацієнток із високим ризиком раку яєчників від груп із нижчим ризиком та показав сильну асоціацію з рівнями HE4. Інтегрований аналіз HE4, CA-125, індексу ROMA та експресії рецепторів може покращити раннє виявлення, оцінку ризику та індивідуалізоване лікування постменопаузальних пацієнток із раком яєчників та шийки матки.

Ключові слова: рак яєчників, рак шийки матки, білок епідидимісу людини 4, раковий антиген 125, індекс ROMA, естрогеновий рецептор, прогестероновий рецептор, рецептор епідермального фактора росту людини 2, індекс проліферації Ki-67.

Funding. *This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The study was conducted at the authors' primary place of work and was funded from their income there.*

Ovarian and cervical cancers remain among the most significant causes of morbidity and mortality in postmenopausal women globally, with ovarian cancer consistently ranking as one of the deadliest gynecologic malignancies due to late-stage diagnosis and limited early detection tools. While cervical cancer incidence has declined in regions with organized screening programs, it continues to pose a major clinical challenge worldwide, especially in low-resource settings where access to regular screening and advanced diagnostics remains limited [14]. Early diagnosis and precise risk stratification are critical for improving clinical outcomes, tailoring individualized treatment strategies, and reducing overall treatment-related morbidity and mortality.

Serum biomarkers have emerged as indispensable tools in the diagnostic workup of gynecologic cancers. Cancer antigen 125 (CA-125) has been used extensively in ovarian cancer detection, monitoring therapeutic response, and identifying recurrence; however, its specificity is limited by elevations in various benign gynecologic and non-gynecologic conditions [7]. In contrast, human epididymis protein 4 (HE4) demonstrates greater specificity for ovarian malignancy and maintains diagnostic value across diverse patient subgroups, including postmenopausal women [4]. Recent large multicenter studies have confirmed that HE4 alone offers improved specificity compared with CA-125 and reduces false positives in benign disease cohorts [4, 11].

To address diagnostic limitations of individual markers, the Risk of Ovarian Malignancy Algorithm (ROMA) was developed to integrate serum HE4 and CA-125 levels with menopausal status, thereby improving risk stratification for ovarian malignancy. Several validation studies have demonstrated that ROMA outperforms CA-125 or HE4 alone in differentiating malignant from benign ovarian masses, particularly in postmenopausal populations [10].

In addition to serum biomarkers, tumor receptor profiling – such as estrogen receptor (ER), hormone receptor (HR), human epidermal growth factor receptor 2 (HER2), and the proliferation marker Ki-67 – provides valuable prognostic and predictive information that informs clinical decision-making and individualized therapeutic planning. Emerging evidence suggests that combined evaluation of serum markers and receptor status may yield a more comprehensive understanding of tumor biology, disease aggression, and likelihood of treatment resistance [9, 13].

Despite extensive research on individual biomarkers or receptor profiles in gynecologic malignancies, there is a paucity of studies systematically examining the interplay between serum biomarkers (HE4, CA-125), ROMA index, and receptor expression in postmenopausal women with ovarian and cervical cancer. Most cervical cancer biomarker research has focused on high-risk HPV detection and screening rather than on integrated biomarker-receptor correlations [2].

The present study aims to address this gap by investigating the complex associations among HE4, CA-125, ROMA index, and tumor receptor status in a well-defined cohort of postmenopausal women with ovarian and cervical malignancies, potentially offering novel insights into integrated biomarker assessment for improved diagnostic precision and personalized care.

The purpose of the study was to evaluate the clinical relevance of serum HE4 and CA-125 levels, the ROMA index, and tumor receptor expression (ER, PR, HER2, Ki-67) in postmenopausal patients with ovarian and cervical cancer.

Materials and methods. This study included a total of 83 postmenopausal women diagnosed with gynecologic malignancies, who were examined and treated at the Oncology Clinic of Azerbaijan Medical University: 45 patients with ovarian cancer (age range 52–72 years; median 58.4 years, Q1=57, Q3=69) and 38 patients with cervical cancer (age range 54–75 years; median 59.3 years, Q1=59, Q3=71). The control group consisted of 20 apparently healthy postmenopausal women (age range 53–71 years; median 59.8 years, Q1=58, Q3=69) with no history of oncological or significant gynecological diseases. The participants were selected from individuals undergoing routine medical examinations. The control group was age-matched to the patient groups. All control subjects had no clinical or laboratory signs of malignant or inflammatory diseases.

Inclusion criteria were: postmenopausal status, histologically confirmed ovarian or cervical cancer, and availability of complete clinical and laboratory data. Exclusion criteria included the presence of other malignancies, severe comorbid conditions, prior oncological treatment before enrollment, and incomplete medical records.

The diagnosis was established based on clinical examination, imaging methods (ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI)), and histopathological verification in accordance with international clinical guidelines.

All participants were recruited between 2022 and 2024, and the study was approved by the Ethics Committee of Azerbaijan Medical University (protocol No. 4, dated May 18, 2020). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Peripheral blood samples were collected prior to any therapeutic intervention. Serum levels of HE4 and CA-125 were measured using a fully automated immunoassay analyzer (COBAS Integra 411, Roche Diagnostics, Germany) with reagents provided by the manufacturer, according to the manufacturer's instructions. The ROMA index was calculated for all patients using the standard algorithm incorporating HE4, CA-125, and menopausal status.

Formalin-fixed, paraffin-embedded tumor tissue samples were assessed for estrogen receptor (ER), hormone receptor (HR), HER2, and Ki-67 expression by immunohistochemistry following standard protocols. Staining intensity and percentage of positive tumor cells were scored independently by two experienced pathologists blinded to serum biomarker levels.

Statistical analysis was performed using SPSS software version 26.0 (IBM Corp., USA). Continuous variables were expressed as median values with interquartile ranges (Me, Q1–Q3) due to non-normal distribution of the data. Comparisons between independent groups were performed using the Mann–Whitney U test, while comparisons among multiple groups were evaluated using the Kruskal–Wallis test. Spearman rank correlation coefficients (ρ) were calculated to assess relationships between serum biomarkers (CA-125, HE4), the ROMA index, and tumor receptor expression (ER, PR, HER2, Ki-

67). Statistical significance was defined as $p<0.05$. The applied analytical approach enabled an integrated evaluation of serum biomarker levels and tumor receptor profiles, providing a comprehensive assessment of diagnostic and prognostic markers in postmenopausal gynecological cancers.

Results of the study and their discussion. The following section presents the serum levels of tumor biomarkers measured in postmenopausal women with ovarian and cervical cancer, as well as in healthy control subjects. These data provide insight into differences in biomarker expression associated with tumor type and disease progression. Analysis of serum tumor biomarkers revealed statistically significant differences between the study groups, reflecting tumor progression, metastatic status, and cancer type. In the control group, baseline median serum concentrations of tumor biomarkers were relatively low. The median CA 125 level was 12.5 U/ml, HE4 concentration 38.7 pmol/l, and the ROMA index 6.5 %, indicating a low predicted risk of malignancy (Table 1).

Table 1

Biomarkers in postmenopausal ovarian and cervical cancer patients, Me (Q1:Q3)

Groups		CA-125 (U/ml),	HE4 (pmol/l),	ROMA Index, %
Control		12.5(4.8;18.6)	38.7 (14.26; 65.82)	6.5 (1.23;19.8)
Ovarian cancer	Non-metastatic primary malignant	68.9 (35.8; 76.5) ($p<0.001$)	128.9 (67.8; 976.4) ($p<0.001$)	51.5 (5.64; 67.9) ($p<0.001$)
Ovarian cancer	Metastatic	598.6 (85.6; 3176.6) ($p<0.001$)	847.9 (96.7; 5125) ($p<0.001$)	97.4 (10.54; 118.5) ($p<0.001$)
Cervical cancer	Early-stage	23.1 (12; 36) ($p<0.001$)	52.6 (40; 68) ($p<0.001$)	18.5 (12; 20) ($p<0.001$)
Cervical cancer	Advanced-stage	312 (60; 980) ($p<0.001$)	416 (110; 840) ($p<0.001$)	42 (35; 50) ($p<0.001$)

Note: p – compared with the control group.

Among patients with ovarian cancer, serum biomarker levels increased markedly with tumor progression and metastatic dissemination. In non-metastatic primary malignant ovarian tumors, the median CA 125 level was 68.9 U/ml, a 5.5-fold increase compared with the control group ($p<0.001$). Similarly, HE4 concentration increased to 128.9 pmol/l, representing a 3.3-fold increase compared with controls ($p<0.001$). The ROMA index rose to 51.5 %, corresponding to an almost 7.9-fold increase relative to the control group ($p<0.001$), reflecting a substantially elevated risk of ovarian malignancy.

A pronounced increase in tumor biomarker levels was observed in patients with metastatic ovarian cancer. The median CA 125 concentration was 598.6 U/ml, 8.7-fold higher than in non-metastatic ovarian tumors and approximately 47.9-fold higher than in the control group ($p<0.001$). HE4 levels were significantly elevated to 847.9 pmol/l, representing a 6.6-fold increase over non-metastatic ovarian cancer and nearly 21.9-fold higher than controls ($p<0.001$). The ROMA index also reached extremely high values, with a median of 97.4 %, corresponding to an increase of almost 89.1 % compared with non-metastatic ovarian cancer and approximately 15-fold higher values than in the control group ($p<0.001$). These findings demonstrate that both CA 125 and HE4, together with the composite ROMA index, strongly correlate with tumor burden and metastatic spread in ovarian cancer patients.

In cervical cancer, serum biomarker levels were generally lower than those observed in ovarian cancer; however, they still showed a clear dependence on tumor stage. In early-stage cervical cancer, the median CA 125 level was 23.1 U/ml, representing 85.0 % increase compared with controls ($p<0.001$). HE4 concentration was 52.6 pmol/l, corresponding to a 36.0 % increase relative to the control group ($p<0.001$). The ROMA index reached 18.5 %, approximately 2.8-fold higher than in controls. Although these values were significantly elevated compared with the control group, they remained markedly lower than those detected in ovarian cancer patients.

In contrast, advanced-stage cervical cancer demonstrated substantial increases in biomarker levels. The median CA 125 concentration was 312 U/ml, representing a 13.5-fold increase over early-stage cervical cancer and approximately 25-fold higher than in the control group ($p<0.001$). HE4 increased to 416 pmol/l, corresponding to a 7.9-fold increase compared with early-stage cervical cancer and nearly 10.7-fold higher levels than in the control group ($p<0.001$). The ROMA index also rose significantly to 42 %, representing a 2.3-fold increase over early-stage disease and approximately 6.5-fold higher than in the control group ($p<0.001$).

Analysis of hormonal receptor expression and proliferative activity markers also revealed distinct differences between cancer types and disease stages (Table 2). In non-metastatic ovarian cancer, the median expression levels of ER and PR were 45 % and 40 %, respectively. HER2 positivity was relatively low, with a median of 10 %, while the proliferative marker Ki-67 showed a median of 20 %.

In metastatic ovarian cancer, receptor expression levels increased significantly compared with non-metastatic tumors. Median ER expression increased to 70 % and PR to 65 % ($p_1<0.001$ for both comparisons). HER2 positivity also increased to 20 % ($p_1<0.001$), while Ki-67 expression rose markedly to 55 % ($p_1<0.001$), indicating significantly enhanced proliferative activity in metastatic disease.

In cervical cancer, receptor expression levels were generally lower but demonstrated stage-

dependent variation. In early-stage disease, the median ER expression was 35 % (25–50) and PR 25 % (15–40), while HER2 positivity was 5 %. The proliferative index Ki-67 had a median value of 30 %.

Table 2

Receptor profiles in postmenopausal ovarian and cervical cancer patients, Me (Q1:Q3)

Cancer type	Group	ER, (%)	PR, (%)	HER2, (%)	Ki-67, (%)
Ovarian cancer	Non-metastatic primary malignant	45 (40; 60)	40 (35; 55)	10 (5; 15)	20 (15; 30)
Ovarian cancer	Metastatic	70 (65; 80) (p_1<0.001)	65 (60; 75) (p_1<0.001)	20 (15; 25) (p_1<0.001)	55 (45; 70) (p_1<0.001)
Cervical cancer	Early-stage	35 (25; 50)	25 (15; 40)	5 (2; 10)	30 (25; 40)
Cervical cancer	Advanced-stage	45 (35; 50) (p_2=0.026)	35 (25; 40) (p_2=0.048)	8 (5; 10) (p_2=0.039)	65 (50; 70) (p_2=0.001)

Note: p_1 – compared with non-metastatic primary malignant ovarian cancer; p_2 – compared with early-stage cervical cancer.

Patients with advanced cervical cancer demonstrated significant increases in receptor expression and proliferative activity. ER expression increased to 45 % (p_2=0.026), PR to 35 % (p_2=0.048), and HER2 to 8 % (p_2=0.039). The most pronounced difference was observed for the proliferative marker Ki-67, which increased to 65 % (p_2=0.001), indicating substantially enhanced tumor cell proliferation in advanced disease.

Spearman correlation analysis revealed significant associations between tumor biomarkers and receptor expression profiles in both ovarian and cervical cancers. In ovarian cancer, a strong positive correlation was observed between HE4 and CA-125 (ρ=0.654; p<0,001), indicating that increases in HE4 levels were accompanied by parallel elevations in CA-125 concentrations. An even stronger correlation was identified between HE4 and the ROMA index (ρ=0.721; p<0.001), supporting the close relationship between HE4 and the composite risk assessment model for ovarian malignancy.

Moderate positive correlations were also found between HE4 and several receptor markers. Specifically, HE4 showed correlations with ER (ρ=0.485; p=0,006), PR (ρ=0.523; p=0.001), HER2 (ρ=0.504; p=0.008), and the proliferative marker Ki-67 (ρ=0.568; p<0.001). These findings suggest that elevated HE4 levels are associated not only with tumor burden but also with increased receptor expression and proliferative activity in ovarian cancer.

In cervical cancer, correlation patterns differed slightly but still demonstrated meaningful associations. A moderate correlation was observed between HE4 and CA-125 (ρ=0.458; p=0.009), indicating a weaker but still positive relationship between these biomarkers compared with ovarian cancer.

HE4 also showed moderate correlations with hormonal receptor expression, including ER (ρ=0.604; p<0.001) and PR (ρ=0.526; p=0.004), suggesting that HE4 levels may partially reflect hormonal receptor activity in cervical tumors. Additionally, correlations were observed between HE4 and HER2 (ρ=0.443; p=0.012) as well as Ki-67 (ρ=0.572; p<0.001), indicating an association between elevated HE4 levels and increased tumor proliferative potential.

This study demonstrates that serum HE4 and CA-125 levels, together with the ROMA index, reliably differentiate primary malignant and metastatic ovarian tumors in postmenopausal women. The progressive increase of HE4 and CA-125 from non-metastatic to metastatic disease aligns with prior reports, confirming their utility for risk stratification and early diagnosis [2, 12, 15]. Our findings are consistent with Shi H. et al. and Zhang L. et al., who reported that HE4 is more specific than CA-125 in distinguishing malignant ovarian masses, while the ROMA index integrates both markers to improve predictive accuracy [12, 15]. Additional recent studies have reinforced the predictive role of HE4 and CA-125 in postmenopausal ovarian cancer patients, particularly for identifying high-risk and metastatic cases [3].

Receptor profiling in ovarian cancer showed that ER and PR expression increased with tumor aggressiveness, HER2 overexpression remained relatively rare, and Ki-67 proliferation index correlated positively with HE4 and CA-125 levels. This supports the concept that tumor biology and proliferative activity are partially reflected by serum biomarkers, a notion highlighted in multicenter studies and meta-analyses [3]. These correlations suggest that integrating serum biomarkers with receptor expression may enhance individualized prognosis and therapeutic planning. Recent work by Ahmed A.A. et al. further confirmed that high Ki-67 and elevated HE4 levels identify tumors with aggressive biology [1].

In cervical cancer, although CA-125 and HE4 levels were lower than in ovarian malignancies, they still correlated moderately with tumor stage and Ki-67, consistent with observations by Hwang et al. and Papadatou et al. [6, 8]. These data indicate that HE4 and CA-125 can serve as adjunct biomarkers in cervical cancer, especially when combined with proliferation and receptor profiling, even though their diagnostic specificity is lower than in ovarian cancer. Similar findings were reported by Guo M. et al. highlighting the potential role of HE4 and CA-125 in risk assessment for cervical malignancies [10].

Compared with previous studies, our data emphasize the combined use of serum biomarkers and tumor receptor profiling for both gynecologic malignancies. Integration of the ROMA index with ER, PR, HER2, and Ki-67 provides a more nuanced understanding of tumor aggressiveness and metastatic potential, supporting personalized treatment decisions [6, 15]. Notably, our study

expands upon prior work by including postmenopausal cervical cancer patients, a population often underrepresented in biomarker research [5, 8]. Recent investigations further suggest that combined biomarker and receptor profiling can improve early detection and therapeutic stratification in both ovarian and cervical cancers.

Limitations. The sample size was relatively small and limited to postmenopausal women from a single center, which may affect the generalizability of the findings. Additionally, the study relied on specific biomarkers and imaging methods, and the short follow-up period may have limited the assessment of long-term outcomes.

Conclusion

Overall, the results of this study indicate that circulating tumor biomarkers progressively increase with tumor progression and metastatic dissemination. The most pronounced elevations were observed in metastatic ovarian cancer, where serum levels of CA-125 and HE4, as well as the ROMA index, were markedly higher than in the control group. In cervical cancer, although absolute biomarker levels were generally lower than in ovarian malignancies, significant stage-dependent increases were also observed. Correlation analysis demonstrated that HE4 is strongly associated with CA-125 and the ROMA index in ovarian cancer, and shows moderate correlations with receptor expression (ER, PR, HER2) and the proliferative marker Ki-67 in both ovarian and cervical malignancies. These findings underscore the clinical relevance of CA-125, HE4, the ROMA index, and tumor receptor markers in postmenopausal women, supporting their role not only in differentiating cancer types, disease stages, and metastatic status, but also in reflecting tumor biological behavior and aggressiveness. By highlighting statistically significant associations between serum biomarkers, ROMA index, and receptor expression, the study provides a foundation for integrated diagnostic strategies. Future research should aim to validate these findings in larger cohorts and explore how these biomarkers can guide targeted therapies, individualized patient monitoring, and prognostic assessment.

References

1. Ahmed AA, Abdou AM. Diagnostic accuracy of CA125 and HE4 in ovarian carcinoma patients and the effect of confounders on their serum levels. Curr Probl Cancer. 2019 Oct;43(5):450-460. doi: 10.1016/j.currproblcancer.2018.12.004.
2. Barr CE, Funston G, Jeevan D, Sundar S, Mounce LTA, Crosbie EJ. The Performance of HE4 Alone and in Combination with CA125 for the Detection of Ovarian Cancer in an Enriched Primary Care Population. Cancers (Basel). 2022 Apr 24;14(9):2124. doi: 10.3390/cancers14092124.
3. Braicu EI, Krause CL, Torsten U, Mecke H, Richter R, Hellmeyer L, et al. HE4 as a serum biomarker for the diagnosis of pelvic masses: a prospective, multicenter study in 965 patients. BMC Cancer. 2022 Jul 30;22(1):831. doi: 10.1186/s12885-022-09887-5.
4. Chudecka-Głaz A, Strojna A, Michalczyk K, Wieder-Huszla S, Safranow K, Skwirczyńska E, et al. Evaluation of He4 Use in the Diagnosis of Ovarian Cancer: First and Second Recurrence, and an Analysis of HE4 Concentration during Second- and Third-Line Chemotherapy. Diagnostics (Basel). 2023 Jan 26;13(3):452. doi: 10.3390/diagnostics13030452.
5. Guo M, Liang L, Wu L, Xie D, Li J. Application Value of Real-Time Ultrasonic Elastograph with Serum Human Epididymis Protein 4, Interleukin-33, and Carbohydrate Antigen 153 in Diagnosis of Early Cervical Cancer. J Healthc Eng. 2022 Apr 12;2022:4880874. doi: 10.1155/2022/4880874.
6. Hwang WY, Suh DH, Kim K, Kim YB, No JH. Serum Human Epididymis Protein 4 as a Prognostic Marker in Cervical Cancer. Cancer Control. 2022 Jan-Dec;29:10732748221097778. doi: 10.1177/10732748221097778.
7. Momenimovahed Z, Mazidimoradi A, Allahqoli L, Salehiniya H. The Role of CA-125 in the Management of Ovarian Cancer: A Systematic Review. Cancer Rep (Hoboken). 2025 Mar;8(3):e70142. doi: 10.1002/cnr2.70142.
8. Papadatou K, Perros P, Thomakos N, Haidopoulos D, Rodolakis A, Pergialiotis V. Biomarkers in Cervical Cancer. Hellenic Journal of Obstetrics & Gynecology. 2022;21(14): doi: 10.33574/hjog.0401.
9. Pînzaru V, Mărițoi T, David V, Foca E, Șaptefrați L. Expression of estrogen and progesterone receptors and their clinicopathological correlations in serous ovarian carcinoma. Mold J Health Sci. 2025;4(12):3-11. https://doi.org/10.52645/MJHS.2025.4.01.
10. Salim E, Zubairi AM, Danish SH, Ali U. Diagnostic Accuracy of Risk of Ovarian Malignancy Algorithm (ROMA) in Post-Menopausal Patients with Ovarian Mass. J Coll Physicians Surg Pak. 2018 Jun;28(6):440-444. doi: 10.29271/jcpsp.2018.06.440.
11. Serdar CC, Osmanoglu S. Comparison of CA-125 and HE4 in ovarian cancer recurrence detection. Acıbadem Univ. Sağlık Bilim. Derg. 2025;16(1):83-97. https://doi.org/10.31067/acusaglik.1539955
12. Shi H, Liu L, Deng X, Xing X, Zhang Y, Djouda Rebecca Y, et al. Exosomal biomarkers in the differential diagnosis of ovarian tumors: the emerging roles of CA125, HE4, and C5a. J Ovarian Res. 2024 Jan 5;17(1):4. doi: 10.1186/s13048-023-01336-6.
13. Shi Q, Xu L, Yang R, Meng Y, Qiu L. Ki-67 and P16 proteins in cervical cancer and precancerous lesions of young women and the diagnostic value for cervical cancer and precancerous lesions. Oncol Lett. 2019 Aug;18(2):1351-1355. doi: 10.3892/ol.2019.10430.
14. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023 Jan;73(1):17-48. doi: 10.3322/caac.21763.
15. Zhang L, Chen Y, Wang K. Comparison of CA125, HE4, and ROMA index for ovarian cancer diagnosis. Curr Probl Cancer. 2019 Apr;43(2):135-144. doi: 10.1016/j.currproblcancer.2018.06.001.

Conflict of interest. The authors have no conflicts of interest to declare.

ORCID: Xalilova V.Z. https://orcid.org/0009-0007-2673-6322, Safarova I.A. https://orcid.org/0009-0004-8059-0852, Ahmedzade N.B. https://orcid.org/0009-0005-3448-8723, Xalilov S.Z. https://orcid.org/0009-0005-7131-7747, Jafarova G.A. https://orcid.org/0000-0001-8318-7920.

Article received: 27.01.2025.