Regulatory Mechanisms in Biosystems

ISSN 2519-8521 (Print)
ISSN 2520-2588 (Online)
Regul. Mech. Biosyst.

Combined prognostic utility of serum CA-125, HE4, and hormonal receptor expression in predicting tumor aggressiveness and clinical outcome in advanced cervical cancer

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Article info

Received 12.04.2026
Received in revised form 26.05.2026
Accepted 30.06.2026

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Almzil, N. R. H., Ali, Z. H., Ali, A. K., & Mohsein, O. A. (2026). Combined prognostic utility of serum CA-125, HE4, and hormonal receptor expression in predicting tumor aggressiveness and clinical outcome in advanced cervical cancer. Regulatory Mechanisms in Biosystems, 17(6), e26108. doi:10.15421/0226108

Advanced cervical cancer remains a major cause of cancer-related morbidity and mortality among women worldwide. Reliable biomarkers capable of predicting tumor aggressiveness and clinical outcome are needed to improve risk stratification and therapeutic decision-making. Serum tumor markers and hormonal receptor expression may provide valuable prognostic information regarding disease progression and metastatic potential. The objective of the present study was to evaluate the combined prognostic utility of serum CA-125, HE4, and hormonal receptor (ER and PR) expression in predicting tumor aggressiveness, disease stage, metastatic behavior, and clinical outcome in patients with advanced cervical cancer. A case–control study was conducted between July 2025 and April 2026 involving 150 women with FIGO stage III–IV cervical cancer and 50 healthy controls. Serum CA-125, HE4, and SCC-Ag levels were measured using ELISA. Estrogen receptor (ER) and progesterone receptor (PR) expression were assessed by immunohistochemistry in cervical tissue specimens. Associations between biomarkers, FIGO stage, metastatic status, and clinicopathological characteristics were statistically analyzed. The patients with advanced cervical cancer exhibited significantly higher serum CA-125, HE4, and SCC-Ag levels than the controls. Tumor marker concentrations were significantly elevated in stage IV compared with stage III disease and in the metastatic compared with nonmetastatic patients. The positivity of ER and PR was significantly lower among metastatic cases. HE4 demonstrated the strongest correlation with FIGO stage (r = 0.511) and metastatic status (r = 0.486), while the combined CA-125 + HE4 score showed the highest overall correlations with FIGO stage (r = 0.548) and metastasis (r = 0.503). Serum CA-125 and HE4, particularly when combined, are valuable indicators of tumor aggressiveness and metastatic potential in advanced cervical cancer. Reduced ER and PR expression is associated with unfavorable clinicopathological features. Integrating serum tumor markers with hormonal receptor status may enhance prognostic assessment and facilitate personalized management strategies for patients with advanced cervical cancer.

Keywords: advanced cervical cancer; CA-125; HE4; SCC-Ag; estrogen receptor; progesterone receptor; tumor aggressiveness; metastasis; prognostic biomarkers.

Introduction

Cervical cancer is one of the most common gynecologic cancers, and it is a leading cause of cancer-related deaths among women worldwide, especially in low- and middle-income countries where screening, vaccination, and early therapeutic intervention is limited. Even though there are significant improvements in preventive measures and oncological management, advanced cervical cancer still has a poor prognosis, frequent recurrence, invasion by tumor, and spread of metastasis at a distance. Although the persistence of high-risk human papillomavirus (HPV) 16 and 18 is well established as the main etiological cause of cervical carcinogenesis, viral infection alone does not completely account for the differences in the aggressiveness of tumors, clinical behavior, and the outcome of the disease (Arbyn et al., 2020; Momenimovahed et al., 2023). There are multiple biological pathways of inflammation, angiogenesis, endocrine regulation, and interactions within the tumor microenvironment that are now being identified as factors that contribute to the progression of cervical cancer (Jiang et al., 2020).

The highest morbidity and mortality rates in advanced cervical cancer are due to tumor invasion and metastasis. The aggressiveness of tumor develops as a complex cascade of biological events including increased cell proliferation, degradation of extracellular matrix, epithelial-mesenchymal transition, angiogenesis, immune escape, and metastasis colonization (Arbyn et al., 2020). As a result, there is a need to identify reliable biomarkers that can predict the behavior of the tumor and the outcome of the disease for the management of cervical cancer. The ability to stratify risk using biomarkers, to make informed therapeutic choices, and to identify patients early who are at higher risk of disease progression may help improve the efficacy of the prognostic assessment (George et al., 2023).

In gynecologic oncology, cancer antigen-125 (CA-125) has been an area of great interest with respect to the various circulating tumor markers. It is a typical indicator of ovarian carcinoma, but high levels of CA-125 have also been seen in cervical cancer, especially in late stage, extension into the pelvis, involvement of lymph nodes and metastatic spread (Charkhchi et al., 2020). Raised CA-125 may be due to tumor disease, irritation of the peritoneum, activation of inflammatory mechanisms, and to the presence of malignant cells in the peritoneum. Several studies have suggested that CA-125 levels are associated with poor prognosis, higher clinical stage, and decreased survival in patients with cervical cancer. However, contradictory results on its sensitivity and prognostic specificity suggest that there is a need for further complementary biomarkers to confer more accurate prediction (Razmi & Hasanzadeh, 2018).

Another promising tumor biomarker in gynecologic malignancies is human epididymis protein-4 (HE4). It is a secretory glycoprotein originally detected in reproductive tissues but also found to be over-

expressed in some cancers, such as ovarian, endometrial, and certain cervical cancers. Recent evidence indicates that HE4 may be involved in tumor proliferation, invasion, angiogenic, and metastatic signaling pathways (Jia et al., 2016; Li et al., 2016). High levels of serum HE4 have been linked to high tumor aggressiveness, advanced stage, and poor clinical outcome in gynecologic cancers. The advantage of HE4 over conventional tumor markers is that it has lower levels in noncancerous inflammatory conditions, which may mean that it offers greater diagnostic and prognostic discrimination. The role of HE4 in advanced cervical cancer is however not fully understood and needs further study (Qu et al., 2016).

Hormonal receptor signaling also may play a role in cervical cancer biology. The expression of estrogen receptor (ER) and progesterone receptor (PR) has been extensively investigated in hormone-dependent malignancies such as breast and endometrial cancers but not in cervical cancer, the expression of which is controversial (Rani et al., 2025). Estrogen and progesterone regulate cellular differentiation, proliferation, and immune regulation, as well as tissue remodeling through receptor-mediated mechanisms. Changes in ER and PR expression in cervical tissues can occur due to endocrine dysfunction, a shift in tumor differentiation, and modulation of oncogenic pathways. Various studies have found that advanced cervial cancer shows reduced or heterogeneous expression of hormone receptors, which may indicate that loss of receptors may be linked with more aggressive tumor phenotypes, poor differentiation, invasion, and worse prognosis. Other studies, however, showed inconsistent or weak prognostic significance of the expression of hormonal receptors, possibly due to the heterogeneity of the tumor histologies, to the different immunohistochemical methods, to the different stage of the disease, and to the different characteristics of the patient populations (Ren et al., 2020).

Serum tumor markers, in addition to tissue-based hormonal receptor testing, may help to more completely assess the aggressiveness of cervical cancer than any single tumor marker. When associated with tissue hormonal receptor typing, circulating tumor markers (CA-125 and HE4) may help to better predict invasion, metastatic potential, and clinical outcome as the progression of tumor is a result of several interacting molecular pathways. However, there are not many studies to date that have examined this combined biomarker approach in advanced cervical cancer (Gawełczyk et al., 2025; Gupta, 2025).

Thus, the present study was designed to assess the combined prognostic value of serum CA-125, HE4, and the expression of hormonal receptors in stage III–IV cervical cancer. In particular, their relationship with tumor aggressiveness, FIGO stage, metastatic behavior, and indicators of clinical outcome were studied to explore the possibility of developing an integrated biomarker model that could enhance the prognostic evaluation and help to understand the mechanisms underlying advanced cervical cancer.

Materials and methods

The study was approved by the relevant institutional ethics committee in accordance with the Declaration of Helsinki (Approval No. 558, January 1, 2025). Written informed consent was obtained from all participants prior to enrollment, and all personal information was handled confidentially throughout the study.

This case–control study was carried out in the Oncology Unit and the Gynecology Unit of Al-Habboubi Teaching Hospital and the Histopathology Laboratory Center in Nasiriyah, Iraq, from 15 July 2025 to 20 April 2026. A total of 200 female patients participated in the study, incluing 150 patients with advanced cervical cancer and 50 apparently healthy women, matched as closely as possible by age and body mass index (BMI) as the control. Cervical cancer diagnosis was made on the basis of a gynaecological clinical assessment, radiological evaluation, histopathological verification of the biopsy specimens from the cervix, and oncological assessment by specialists. Patients with cervical cancer were staged based on the classification of the International Federation of Gynecology and Obstetrics (FIGO) and only advanced stage cases (FIGO III–IV) were included. On imaging, pathologic studies and clinical oncology records, tumor invasion status, lymph node involvement, and distant metastatic spread were characterized. To reduce the confounding effect of tumor markers and hormonal receptor expression, patients with other types of gynecological cancers, chronic inflammatory diseases, autoimmune disorders, chronic renal disease, chronic liver disease, hematological disorders, pregnancy, recent blood transfusion, hormonal replacement therapy, and current immunosuppressive therapy were excluded. The clinicopathological and demographic data such as age, BMI, menopausal status, smoking history, stage (FIGO), treatment history, metastatic status, and lymph node involvement were obtained from medical records and direct interviews with the patients.

Venous blood was drawn aseptically by trained laboratory personnel under standardized conditions. From each study participant, approximately 7 mL of fasting venous blood was collected in sterile disposable syringes. Blood samples were drawn and put into EDTA tubes for routine hematological investigations and plain gel tubes for serum preparation. Serum was separated by centrifugation at 3,000 rpm for 10 minutes, aliquoted, and stored at −20 °C until biochemical and immunological analyses were performed. The levels of serum CA-125 and HE4 were determined using enzyme-linked immunosorbent assay (ELISA) kits (Elabscience Biotechnology Inc., Wuhan, China) according to the manufacturer's instructions. The serum SCC-Ag level was determined with the ELISA kit, purchased from MyBioSource Inc., California, USA. Blood parameters were measured using an automatic hematology analyzer (Mindray BC-5300, Mindray Bio-Medical Electronics Co., Shenzhen, China).

Immunohistochemical (IHC) staining was used to assess the expression of hormonal receptors in formalin-fixed paraffin-embedded cervical tissue sections. Tissue samples were processed routinely, sectioned at about 4 μm thickness, and placed on high-quality glass slides, dewaxed, rehydrated, and subjected to antigen retrieval procedures. Standardized immunohistochemical protocols were used for primary monoclonal antibodies against estrogen receptor (ER) and progesterone receptor (PR) (Dako/Agilent Technologies, Glostrup, Denmark). The receptor expression was evaluated by highly experienced histopathologists under the microscope and staining intensity and percentage of positive tumor nuclei were noted. The cases were classified as positive or negative based on predetermined scoring criteria. The prognostic value of the combination of serum CA-125, HE4, and hormonal receptor expression with established clinical outcome and tumor aggressiveness and invasion markers was then analyzed using conventional statistical methods.

Quantitative data were analyzed using SPSS version 26. Results are presented as frequencies and percentages. For normally distributed variables, independent and dependent t-tests (two-tailed) were used. For non-normally distributed variables, the Mann-Whitney U-test, Wilcoxon test, and Chi-square test were applied. A P-value of < 0.05 was considered statistically significant.

Results

The sociodemographic and clinical baseline data of the study participants are shown in Table 1. No significant differences were observed between advanced cervical cancer patients and healthy controls regarding age (53.86 ± 9.74 against 51.92 ± 8.66 years, $P = 0.214$), postmenopausal status (64.0% against 58.0%, $P = 0.452$), hypertension prevalence (34.0% against 26.0%, $P = 0.296$), or family history of cancer (16.0% against 10.0%, $P = 0.301$). However, the cancer patients had a significantly elevated BMI compared with the controls (28.94 ± 4.51 against 27.38 ± 3.96 kg/m², $P = 0.033$). FIGO stage III and stage IV accounted for 64.0% and 36.0% of the cervical cancer patients, respectively. In addition, 48.0% had lymph node involvement, and 27.3% had distant metastasis, which was indicative of the advanced disease and aggressive clinical course of the disease in the study population.

As shown in Table 2, the patients with advanced cervical cancer had significantly higher levels of all tumor markers assessed than the healthy controls. Serum CA-125 levels were markedly increased in the cancer patients (54.82 ± 21.46 U/mL) relative to the controls (18.75 ± 6.92 U/mL, $P < 0.001$). Also, the cancer patient group had significantly higher HE4 levels (108.64 ± 38.27 pmol/L) than the

control group (54.18 ± 15.33 pmol/L, P < 0.001). The levels of SCC-Ag were also significantly higher in the cervical cancer patients (3.86 ± 1.52 ng/mL) than in the healthy control women (1.14 ± 0.46 ng/mL, P < 0.001). The results reveal significant expression of these tumor-associated biomarkers in cervical cancer with advanced disease and suggest these could be clinically useful as markers of tumor burden and disease progression.

Table 1
Sociodemographic and clinical characteristics
of the advanced cervical cancer patients and healthy controls

Variable	Advanced cervical cancer (n = 150)	Healthy controls (n = 50)	P-value
Age, years	53.86 ± 9.74	51.92 ± 8.66	0.214
BMI, kg/m²	28.94 ± 4.51	27.38 ± 3.96	0.033
Postmenopausal status	96 (64.0%)	29 (58.0%)	0.452
Hypertension	51 (34.0%)	13 (26.0%)	0.296
Family history of cancer	24 (16.0%)	5 (10.0%)	0.301
FIGO stage III	96 (64.0%)	N/A	N/A
FIGO stage IV	54 (36.0%)	N/A	N/A
Lymph node involvement	72 (48.0%)	N/A	N/A
Distant metastasis	41 (27.3%)	N/A	N/A

The distribution of hormonal receptor expression among the patients with advanced cervical cancer demonstrated a predominance of receptor-negative tumors. Estrogen receptor (ER) positivity was observed in 57 patients (38.0%), whereas 93 patients (62.0%) were ER-negative. Similarly, progesterone receptor (PR) positivity was identified in 49 patients (32.7%), while PR negativity was present in 101 patients (67.3%). Combined receptor analysis revealed that only 34 patients (22.7%) exhibited concurrent ER and PR positivity, whereas 78 patients (52.0%) were negative for both receptors. Overall, these findings indicate that loss of hormonal receptor expression is common in advanced cervical cancer, suggesting reduced endocrine responsiveness and supporting the association between receptor negativity and a more aggressive tumor phenotype.

Table 2
Comparison of serum tumor marker levels
between the advanced cervical cancer patients and healthy controls

Marker	Patients (n = 150)	Controls (n = 50)	P-value
CA-125, U/mL	54.8 ± 21.5	18.8 ± 6.9	<0.001
HE4, pmol/L	108.6 ± 38.3	54.2 ± 15.3	<0.001
SCC-Ag, ng/mL	3.86 ± 1.52	1.14 ± 0.46	<0.001

Table 3
Distribution of estrogen receptor (ER) and progesterone receptor (PR) expression among the patients with advanced cervical cancer

Receptor status	Patients (n = 150)
ER positive	57 (38.0%)
ER negative	93 (62.0%)
PR positive	49 (32.7%)
PR negative	101 (67.3%)
ER/PR double positive	34 (22.7%)
ER/PR double negative	78 (52.0%)

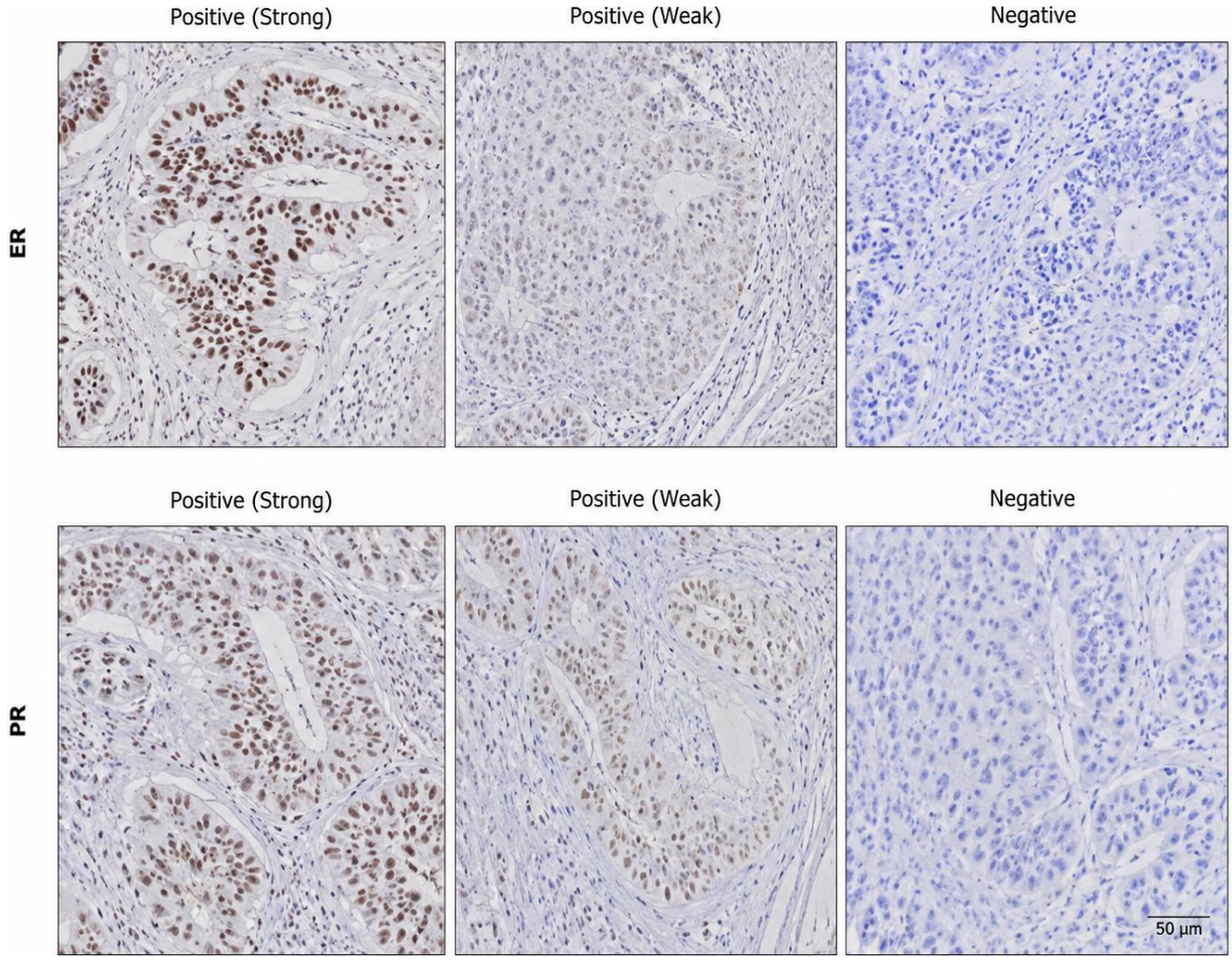

Fig. 1. Representative immunohistochemical staining of advanced cervical cancer tissues showing differential expression patterns of estrogen receptor (ER) and progesterone receptor (PR): strongly positive, weakly positive, and negative staining profiles are illustrated for each receptor; positive expression is identified by variable degrees of brown chromogenic nuclear immunoreactivity in malignant epithelial cells, whereas negative tissues demonstrate absence of specific immunostaining; the heterogeneity of ER and PR expression may reflect endocrine pathway involvement in tumor progression, invasion, and clinical outcome in cervical cancer; hematoxylin counterstaining was used for nuclear visualization; scale bar – 50 µm

As seen in Table 3, serum tumor marker levels were significantly elevated at increasing severity of the disease. The CA-125 level of the patients with cervical cancer stage IV was significantly higher than that of the patients with stage III (67.61 ± 23.18 vs. 47.63 ± 17.84 U/mL, $P < 0.001$). Similarly, stage IV patients had significantly higher level of HE4 than the stage III patients (131.58 ± 39.72 against 95.72 ± 31.46 pmol/L, $P < 0.001$). SCC-Ag was increased similarly, and significantly higher in stage IV disease (4.87 ± 1.56 ng/mL against 3.29 ± 1.21 ng/mL, $P < 0.001$). The results indicate that the levels of CA-125, HE4, and SCC-Ag are strongly related to the disease progression and might be associated with higher tumor burden and metastatic disease in advanced cervical cancer.

Table 4
Association of serum tumor markers with FIGO stage in the advanced cervical cancer patients

Marker	Stage III (n = 96)	Stage IV (n = 54)	P-value
CA-125, U/mL	47.6 ± 17.8	67.6 ± 23.2	<0.001
HE4, pmol/L	95.7 ± 31.5	131.6 ± 39.7	<0.001
SCC-Ag, ng/mL	3.29 ± 1.21	4.87 ± 1.56	<0.001

Table 4 shows that there are significant differences in biomarker profiles between metastatic and nonmetastatic patients. The patients with distant metastasis exhibited substantially higher serum levels of CA-125 (69.6 ± 24.3 against 49.3 ± 18.7 U/mL, $P < 0.001$), HE4 (135.9 ± 41.8 against 98.4 ± 32.9 pmol/L, $P < 0.001$), and SCC-Ag (5.03 ± 1.63 against 3.42 ± 1.28 ng/mL, $P < 0.001$) compared with the nonmetastatic patients. However, the expression of hormonal receptors was significantly decreased in metastatic cases, with 24.4% of the metastatic patients expressing estrogen receptor (ER) positivity compared with 43.1% of the nonmetastatic patients ($P = 0.037$); progesterone receptor (PR) positivity was 17.1% in the metastatic group and 38.5% in the nonmetastatic group ($P = 0.014$). The findings here suggest that the elevated level of tumor markers is linked to metastatic progression, and the low level of hormonal receptor expression may be linked to the more aggressive tumor phenotype in advanced cervical cancer.

Table 5
Relationship between tumor markers, hormonal receptor expression, and metastatic status in the advanced cervical cancer

Marker	Nonmetastatic (n = 109)	Metastatic (n = 41)	P-value
CA-125, U/mL	49.3 ± 18.7	69.6 ± 24.3	<0.001
HE4, pmol/L	98.4 ± 32.9	135.9 ± 41.8	<0.001
SCC-Ag, ng/mL	3.42 ± 1.28	5.03 ± 1.63	<0.001
ER positivity	47 (43.1%)	10 (24.4%)	0.037
PR positivity	42 (38.5%)	7 (17.1%)	0.014

As shown in Table 5, there are significant correlations between the investigated biomarkers and the indicators of the severity of the disease. CA-125 showed moderate positive correlations with both clinical parameters ($P < 0.001$), while SCC-Ag also showed moderate positive correlation with both clinical parameters ($P < 0.001$), with serum HE4 showing a stronger correlation. However, ER and PR expression showed significant negative correlations with FIGO stage and metastatic status, suggesting that lower levels of hormone receptor expression are linked to higher stage and metastatic disease. Specifically, the CA-125-HE4 score yielded the highest correlation with FIGO stage ($r = 0.548$, $P < 0.001$) and metastatic status ($r = 0.503$, $P < 0.001$), suggesting that the two markers in combination were more effective at predicting tumor progression and metastatic potential than either marker alone in advanced cervical cancer patients.

Discussion

In the present study, the serum levels of CA-125, HE4, and SCC-Ag were found to be significantly higher in the patients with advanced cervical cancer than in the healthy controls, suggesting the presence of correlation between these biomarkers and tumor burden, as well as the aggressive biological behavior of the tumor. The elevation of CA-125 has been correlated with gynecological cancers, and may be attributed to the extension of the tumor, pelvic involvement, and inflammatory irritation of the peritoneum in advanced cervical cancer (Charkhchi et al., 2020). Likewise, in the patients, HE4 exhibited significant increase, indicating its potential use as an additional marker of prognosis, in addition to its established use in ovarian cancer (Ghose et al., 2024). SCC-Ag was also found to be significantly elevated, which is a natural consequence of many cervical cancers being of squamous type. Moreover, SCC-Ag is closely related to tumor mass, lymph node involvement, and risk of recurrence (Salvatici et al., 2016).

Table 6
Correlation of tumor markers and hormonal receptor expression with disease severity in the advanced cervical cancer

Variable	FIGO Stage (r)	P-value	Metastatic status (r)	P-value
CA-125	0.462	<0.001	0.418	<0.001
HE4	0.511	<0.001	0.486	<0.001
SCC-Ag	0.449	<0.001	0.437	<0.001
ER expression	−0.231	0.004	−0.198	0.015
PR expression	−0.256	0.002	−0.221	0.007
CA-125 + HE4 combined score	0.548	<0.001	0.503	<0.001

Only a portion of the cervical cancer tissues was found to be positive for hormonal receptor, while negativity was more common, based on the analysis. The discovery implies that cancer of the cervix may lose the hormone receptors as the cancer progresses. Previous studies have shown that ER and PR expression varies in cervical cancer, and tumors with less expression of the receptors are more aggressive and poorly differentiated (Waqar et al., 2018). Other studies, however, have shown no significant prognostic significance of ER/PR expression, perhaps because the histological type, the scoring of the immunohistochemical staining, and the clones of the antibodies used varied, as well as tumor stage and population characteristics (Sinn et al., 2017; Smith et al., 2018).

CA-125, HE4, and SCC-Ag were significantly higher among the stage IV patients than the stage III patients when compared by the FIGO stage. This lends support to the notion that there is a corresponding increase in tumor burden, deeper infiltration, lymphovascular infiltration, and systemic release of biomarkers with increasing tumor stage. Raised levels of HE4 in stage IV disease may suggest that HE4 is not just a marker of the disease but may also be associated with tumor biology and metastases (Scaletta et al., 2017). This is in accordance with the results of previous studies that high levels of tumor markers are correlated with advanced stage, lymph node metastasis, and low survival rate in cervical cancers (Mais et al., 2022).

Levels of tumor markers were also significantly higher in the metastatic patients compared with the nonmetastatic patients. The elevation of CA-125 and HE4 in the metastatic cases could be attributed to the dissemination of the tumor, invasion of the stromal tissue, and the initiation of angiogenesis and systemic inflammatory response. Increase in these parameters as markers of the aggressiveness of the disease and the risk of recurrence is further supported by SCC-Ag elevation in metastatic disease (Salvatici et al., 2016). However, ER and PR positivity was lower in the metastatic patients, which implies that the absence of these receptors may be related to an aggressive and less differentiated type (Luo et al., 2024). This corroborates reports that receptor-negative tumors may exhibit more aggressive characteristics and lack more endocrine regulation (Peng et al., 2021).

The CA-125, HE4, and SCC-Ag levels were revealed to be significantly and positively correlated with the tumor aggressiveness parameters such as FIGO stage and metastatic status, which enabled us to confirm these relationships. The correlation between combined CA-125 + HE4 score was the highest, suggesting that combination of markers may yield more prognostic data than single marker assessment (Guo et al., 2017). This is a scientific reasonable thought, due to the fact that cancer cells in the cervix start to grow, squamous (covering) cells differentiate, along with inflammation, angiogenesis (formation of new blood vessels), and hormonal imbalance. Thus, it may be advantageous to use markers in combination to predict invasion and clinical outcome (Zhang et al., 2023).

The strong prognostic value of the CA-125 and HE4 in cervical cancer has been challenged by some studies in which the authors claim a minor or lackluster diagnostic or prognostic value. Limited or no diagnostic or prognostic value of CA-125 or HE4 has been reported in cervical cancer (Ghose et al., 2024). The differences could be due to sample size, tumor histology, distribution of disease stages, treatment status, menopausal status, assay sensitivity, and cutoff values adopted. However, differences in the results reported may be due to the less robust study of HE4 in cervical cancer compared with ovarian cancer. Furthermore, there may be some nonmalignant gynecological diseases that alter CA-125 levels, which will limit the specificity of CA-125 in some population groups (Potenza et al., 2020).

Conclusion

The overall results indicate that CA-125, HE4, and SCC-Ag are significantly linked to the stage of cervical cancer, the stage of the tumor, and presence of metastasis, and low expression of ER/PR may be related to the more aggressive behavior of the tumor. A joint evaluation of serum tumor markers and hormonal receptor status may be helpful in establishing a useful prognosis model to identify patients at higher risk for invasion, metastasis, and poor clinical outcome. The results should be interpreted as associations rather than causations, and further multicenter studies with survival follow-up are warranted to confirm the clinical usefulness of this biomarker panel.

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