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Performance of HE4 and CA125 Alone and in Combination in Predicting Ovarian Cancer

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Abstract

Background: Ovarian cancer is a leading cause of gynaecologic cancer mortality worldwide, due to asymptomatic early stages and lack of effective screening for early detection. Early diagnosis is crucial for survival rates, as advanced-stage ovarian cancer involves poorer outcomes. The identification of reliable biomarkers for early detection has been a significant research focus. This study evaluates the performance of HE4 and CA125 alone and combined in predicting ovarian cancer.

Methods: This prospective cross-sectional analytic study was conducted at the Department of Gynaecological Oncology and Department of Obstetrics and Gynaecology, BSMMU, from August 2023 to July 2024. Forty patients with ovarian tumors were admitted and selected for surgical treatment. Serum CA-125 levels were estimated before admission, and HE4 levels were measured in the Department of Microbiology and Immunology, BSMMU, Dhaka, and surgery was performed. The final histopathological report was recorded. Patients were divided into two groups based on pathological findings: women with benign conditions and those with ovarian cancer. CA125 and HE4 levels alone and combined were calculated and compared in both groups.

Result: Serum HE4 and CA125 concentrations were significantly higher in ovarian cancer patients compared with those seen in patients with benign disease. In the receiver operating characteristic analysis (ROC), sensitivity was found to be 73.33% and 86.36% for HE4 and CA-125, respectively, and specificity was found to be 90.91% and 60% for HE4 and CA-125, respectively. Combined HE4 and CA-125 was found to have 86% sensitivity and specificity.

Conclusion: Measuring serum HE4 and CA125 concentrations may provide higher accuracy than HE4 and CA-125 alone for detecting epithelial ovarian cancer.

Keywords: HE4, CA-125, Benign tumor, Malignant tumor

Introduction

Ovarian cancer (OC) is recognized as the deadliest malignancy affecting the female reproductive system worldwide [1]. It represents the seventh most common gynaecological cancer globally and has the highest mortality rate [2]. The GLOBOCAN 2020 report documented 313,969 new cases of ovarian cancer, alongside 207,252 deaths from the disease worldwide. The incidence and mortality rates are notably higher in the Asian region. In Bangladesh, the annual mortality rate from ovarian cancer has risen by 40.3% since 1990, with

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an average yearly increase of 1.8% [3]. The overall 5-year survival rate for ovarian cancer is approximately 40% [4], and despite advances in diagnosis and treatment over the past 40 years, survival rates have only improved by around 10%. Survival largely depends on the stage of diagnosis: women diagnosed at stage I have a 93% 5-year survival rate, compared to just 13% for those diagnosed at stage IV [5]. Current methods for detecting ovarian cancer involve pelvic examination and transvaginal ultrasounds, typically carried out in patients showing symptoms. However, the signs and symptoms, such as dyspepsia, bloating, early satiety, and backaches, are generally nonspecific and usually only appear in the later stages of the disease [6].

Women with early-stage ovarian cancer typically exhibit few apparent clinical symptoms, which results in 80% of cases being diagnosed at advanced stages [7]. Common symptoms, such as bloating, abdominal pain, and frequent urination, are nonspecific and often occur in women without cancer [5]. Because the early signs of ovarian cancer are subtle, the disease usually progresses to an advanced stage by the time of diagnosis, leading to missed opportunities for timely treatment and higher mortality rates [8]. Simple tests to triage patients for urgent specialist referral or provide reassurance are needed, but early detection remains challenging, with only 30% of cases currently diagnosed at stage I. Despite ongoing research, screening efforts have yet to demonstrate a significant improvement in ovarian cancer survival rates. Most women are diagnosed with relevant symptoms after presenting to primary care [5]. To reduce the high mortality associated with ovarian cancer, numerous studies have focused on identifying sensitive and specific indicators to differentiate benign from malignant ovarian tumors [9]. Prompt diagnosis and treatment of ovarian masses are crucial for ensuring timely referral to a gynecologic oncologist. Although several diagnostic tests are currently available, their reliability remains limited, highlighting the need for more accurate methods [7].

Unfortunately, there are still no practical screening tools for the early detection of ovarian cancer. While most gynecologic oncologists use multimodal screening with transvaginal ultrasound and CA125 testing, these methods are costly and lack the necessary sensitivity and specificity [10]. Various tumor biomarkers have been studied, with CA125, first identified in the early 1980s [11], being widely used to predict malignancy in patients with a pelvic mass. CA125 levels are elevated (>35 U/mL) in 80% of advanced cancer cases but in fewer than 50% of early-stage cases, making it less sensitive for early detection [12]. Additionally, CA125 can be elevated in non-cancerous conditions, such as menstruation, pregnancy, endometriosis and inflammatory diseases of the peritoneum [13]. Unlike imaging, serum analysis is noninvasive, low-cost, and less subject to operator variability. Therefore, considerable research is focused on identifying new serum biomarkers that, alone or combined with CA125, could improve the diagnosis of epithelial ovarian cancer [14]. Other biomarkers, such as Human Epididymis Protein 4 (HE4), have been developed to enhance the specificity for detecting ovarian carcinomas [13]. Recently, Human Epididymis 4 (HE4) has been recognized as one of the most promising biomarkers for the early diagnosis of ovarian cancer [15]. HE4 is a whey-acidic protein produced by the epithelial cells of the respiratory and reproductive tracts [16]. It is known to be overexpressed in cases of ovarian cancer [13]. Unlike CA125, HE4 levels are less influenced by endometriosis [17]. Combining HE4 and CA125 enhances the sensitivity and specificity for detecting ovarian cancer [18]. This study aims to investigate the performance of HE4 and CA125 alone and in combination in the diagnosis of ovarian tumors.

Objective

This study aimed to evaluate the performance status of HE4 and CA125 alone and in combination in predicting ovarian cancer.

Methodology & Materials

This cross-sectional analytical study was conducted at the Department of Gynaecological Oncology, and Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from August 2023 to July 2024. A total of 40 patients with clinically diagnosed ovarian tumors were admitted to the Department of Gynaecological Oncology and the Department of Obstetrics and Gynaecology, BSMMU, Dhaka, for surgical purposes.

Enrollment Criteria

Inclusion criteria

- Patients clinically diagnosed with ovarian tumors who were selected for surgical treatment.
- Women more than 18 years.

Exclusion criteria

- Pregnant women
- Women who received radiotherapy or chemotherapy for ovarian neoplasm.
- Women with any other known malignancy.

Study procedure: IRB approval was obtained from the Institutional Review Board of BSMMU. The study subjects were patients clinically diagnosed with cases of ovarian tumor who were selected for surgical treatment. All patients received an explanation of the nature of the study, and a written informed consent was obtained from all the participants to collect and analyze their data for scientific

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papers. In every patient, a 5ml blood sample was taken after admission and before operation and sent to the Department of Microbiology and Immunology to estimate HE4. The blood was allowed to clot for 10 minutes, centrifuged for 30 minutes, and serum and plasma were separated, and serum HE4 levels were determined using a fully automated chemiluminescence immunoassay analyzer. The serum CA125 level of every patient was already estimated before admission. Patients were divided into two groups based on pathological findings: women with benign conditions and those with ovarian cancer. CA125 and HE4 levels of all patients alone and in combination were calculated.

Statistical analysis: The data were analyzed with the SPSS version 26.0. For descriptive statistics means, medians, standard deviations & ranges were analyzed for numerical data and frequencies & proportions for categorical data were calculated as required. Sensitivity, specificity, PPV, NPV and accuracy of HE4 and CA125 alone and in combination were calculated. A "p" value <0.05 was considered significant.

Ethical consideration: Ethical clearance was obtained from the Institutional Review Board (IRB) of BSMMU. According to the Helsinki Declaration for Medical Research involving Human Subjects 1964, all the patients were informed about the study design and the right of the participants to withdraw from the research at any time, for any reason. Informed written consent was obtained from each subject who voluntarily consented to participate in this study. There is minimal physical, psychological, social, and legal risk when taking history, performing physical examinations, and conducting investigations. Strict confidentiality and security of data related to patients were maintained. For safeguarding confidentiality and protecting anonymity each of the patients were given a special ID number which will be followed during examination and each and every step of the procedure.

Results

Figure 1 shows that 41% of the study subjects were benign, and 59% of the cases were malignant.

Figure 1: Histopathology of the study participants

Table 1 presents a comparative analysis of two groups among the participants with benign (n=15) and malignant (n=22) cases. Participants under 50 comprised 37.9% of the benign group and 62.1% of the malignant group, while those over 50 made up 50.0% in both groups. The mean age of participants in the benign group was 39.27±18.72, compared to 34.41±15.41 in the malignant group. However, this difference in mean age between the two groups was not statistically significant. Regarding menopausal status, 44.0% of the benign group were premenopausal, and 56.0% of the malignant group were premenopausal. Among postmenopausal participants, 33.3% were in the benign group, and 66.7% were in the malignant group. The differences in menopausal status were not statistically significant.

Table 1: Distribution of the participants according to sociodemographic characteristics (n=37)

Variables		Types of tumors		P value
		Benign (n=15)	Malignant (n=22)	
Age (in year)	<50	11 (37.9)	18 (62.1)	0.53
	>50	4(50.0)	4 (50.0)	
Mean±SD		39.27±18.72	34.41±15.41	0.39
Menopausal status	Premenopausal	11 (44.0)	14 (56.0)	0.53
	Postmenopausal	4 (33.3)	8 (66.7)	

Table 2 compares the levels of two biomarkers, CA-125 and HE4, between participants with benign and malignant conditions. The mean value of CA-125 in the benign group was 133.75 ± 188.93, while in the malignant group, it was 372.90 ±466.82. This difference was statistically significant, indicating that higher CA-125 levels are associated with malignant conditions. Similarly, the mean level of HE4 was 61.95 ± 32.69 in the benign group, compared to 208.46 ± 272.95 in the malignant group. This difference was also statistically significant, suggesting that elevated HE4 levels are strongly associated with malignant ovarian tumors.

Table 2: Distribution of the participants according to biochemical parameter (n=37)

	Types of tumors		
Variables	Benign (15)	Malignant (22)	P value
CA-125	133.75(188.93)	372.90(466.82)	0.01
HE4	61.95(32.69)	208.46(272.95)	0.003

Table 3: Cross tabulation of Ovarian cancer with HE4 value based on derived cut-off value

HE4	Ovarian tumor		Total
	Malignant	Benign	
≥72.20	20	4	24
<72.20	2	11	13
Total	22	15	37

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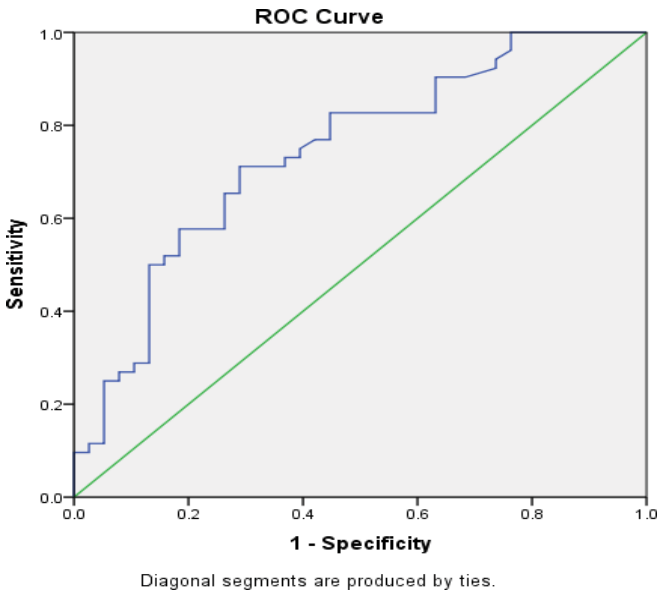

Figure 2: Receiver operator characteristics (ROC) curve of HE4 to predict Ovarian cancer

ROC analysis of preoperative HE4 to predict Ovarian cancer had an AUC value of 0.791 (95% CI 0.636-0.946), which was statistically significant.

Table 4: Sensitivity, specificity, PPV, NPV, and accuracy gained by the derived cutoff of HE4 with a 95% confidence interval for predicting ovarian cancer

Statistic	Value	(95% Confidence Interval)
Sensitivity	73.33%	70.84% to 98.88%
Specificity	90.91%	44.90% to 92.21%
PPV	83.33%	68.13% to 92.12%
NPV	84.62%	58.63% to 95.53%
Accuracy	83.78%	67.99% to 93.81%

Sensitivity [73.33% (95% Confidence Interval: 70.84% to 98.88%)] and specificity [90.91% (95% Confidence Interval: 44.90% to 92.21%)] found from the derived cutoff supported that the derived cutoff of HE4 can predict ovarian cancer with about 83.78% accuracy.

Table 5 shows that 19 out of 22 patients who had ovarian cancer had a CA-125 value ≥56.45 U/mL.

ROC analysis of preoperative CA-125 to predict Ovarian cancer had an AUC value of 0.74 for CA125 (95% CI 0.57-0.91), which was statistically significant.

Sensitivity [86.36% (95% Confidence Interval: 65.09% to 97.09%)] and specificity [60.00% (95% Confidence Interval: 32.29% to 83.66%)] found from the derived cutoff supported that the derived cutoff of CA125 can predict ovarian cancer

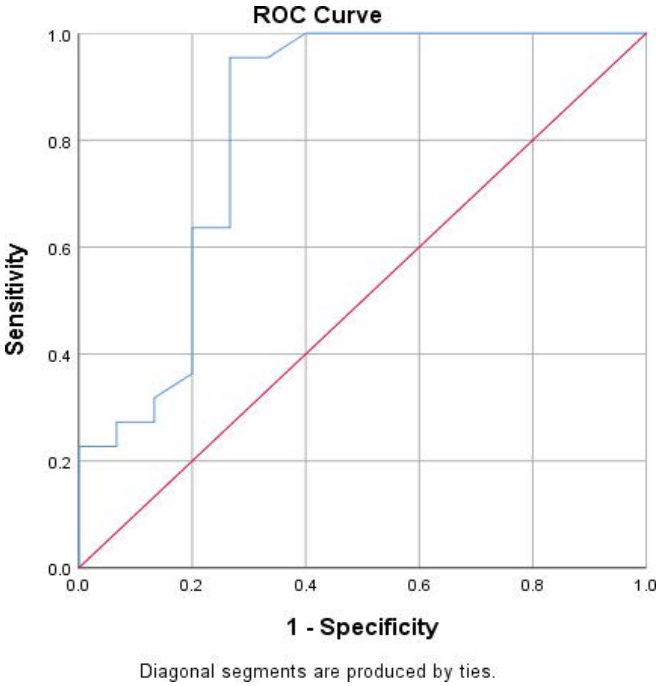

Figure 3: Receiver operator characteristics (ROC) curve of CA-125 to predict Ovarian cancer

with about 75.68% accuracy.

It appears from Tables 5 and 9 that 19 out of 22 patients who had ovarian cancer had both HE4 (≥72.20 pg/ml) and CA-125(≥56.45 U/mL).

Sensitivity [86.36% (95% Confidence Interval: 65.09% to 97.09%)] and specificity [86.67% (95% Confidence Interval: 56.54% to 98.34%)] found from the derived cutoff supported that the derived cutoff of combined HE4 and CA125 can predict ovarian cancer with about 86.49% accuracy.

Table 5: Cross tabulation of Ovarian cancer with CA-125 value based on derived cut-off value

CA-125	Ovarian tumor		Total
	Malignant	Benign	
≥56.45	19	6	25
<56.45	3	9	12
Total	22	15	37

Table 6: Sensitivity, specificity, PPV, NPV, and accuracy gained by the derived cutoff of CA 125 with a 95% confidence interval for predicting ovarian cancer

Statistics	Value	(95% Confidence Interval)
Sensitivity	86.36%	65.09% to 97.09%
Specificity	60.00%	32.29% to 83.66%
PPV	76.00%	62.50% to 85.75%
NPV	75.00%	49.22% to 90.28%
Accuracy	75.68%	58.80% to 88.23%

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Table 7: Cross tabulation of Ovarian cancer with combined HE4 and CA-125 value based on derived cut-off value

Combined HE4(≥72.20) and CA-125(≥56.45)	Ovarian tumor		Total
	Malignant	Benign	
Yes	19	2	**21**
No	3	13	16
Total	**22**	**15**	**37**

Table 8: Sensitivity, specificity, PPV, NPV, and accuracy gained by the derived cutoff of HE4 and CA 125 (combined) with a 95% confidence interval for predicting ovarian cancer

Statistics	Value	(95% Confidence Interval)
Sensitivity	86.36%	65.09% to 97.09%
Specificity	86.67%	56.54% to 98.34%
PPV	90.48%	72.12% to 97.21%
NPV	81.25%	59.78% to 92.67%
Accuracy	86.49%	71.23% to 95.46%

Discussion

This cross-sectional study was conducted over a period of one year and aimed to evaluate patients with clinically diagnosed ovarian tumors who were selected for surgical management. Initially, 40 patients were identified for inclusion in the study. However, three patients were excluded for specific reasons: two patients could not undergo surgery due to the presence of significant co-morbid conditions, making the surgical procedure too risky, and another patient was excluded due to the detection of a double primary cancer before the scheduled surgery, altering the clinical approach. As a result of these exclusions, the study ultimately focused on 37 patients. In this study, benign cases were found in 41% and malignant cases in 59%. Among these, under 50 comprised 37.9% of the benign group and 62.1% of the malignant group, while those over 50 made up 50.0% in both groups. Another study conducted by Anderson et al found that participants under 50 years old comprised 22(26%) of the healthy group and 12(16%) of the ovarian cancer group, while those over 50 years old made up 80% in both groups which is not similar to this study [19]. In this study, the mean age of participants in the benign group was 39.27±18.72 SD, compared to 34.41±15.41 SD in the malignant group. However, this difference in mean age between the two groups was not statistically significant. A study carried out by Barr et al found that the mean age of healthy participant was 37 years in less than 50 years with a standard deviation of 8.6. And for more than 50 years, the mean age was 63, with a standard deviation of 10.1. In the cancer group less than 50 years, the mean age was 44, with a standard deviation of 4.0, and the mean age in the more than 50 years group was 65 years, with a standard deviation of 9.5 [5].

In the benign group, 44.0% were premenopausal, and in the malignant group, 56.0% were premenopausal. Among postmenopausal participants, 33.3% were in the benign group, and 66.7% were in the malignant group, as found in this study. The differences in menopausal status were not statistically significant. A study by Hamed et al showed that 30% of premenopausal patients were in the malignant group and 25% were in the benign group [20]. The mean value of CA-125 in the benign group was 133.75 ± 188.93, while in the malignant group, it was significantly higher (372.90 ± 466.82). This difference was statistically significant, indicating that higher CA-125 levels were associated with malignant conditions. The mean level of HE4 was 61.95 ± 32.69 in the benign group, compared to 208.46 ± 272.95 in the malignant group. This difference was also statistically significant, suggesting that elevated HE4 levels are strongly associated with malignant ovarian tumor.

CA125 is still the widely used tumor marker recommended as a diagnostic or prognostic indicator and for the monitoring of disease recurrence after surgery and adjuvant chemotherapy. CA125's main disadvantage is its known lack of specificity. As a result, many attempts have been made to enhance its diagnostic capabilities. The HE4 has recently been identified as one of the most significant and promising markers for increasing sensitivity and specificity. In this study, we investigated the role of HE4 alone and in combination with CA125 in assessing patients with ovarian cancer. Initial results on HE4 testing confirm that sensitivity was 73.33%, specificity was 90.91%, PPV was 83.33%, NPV was 84.62%, and accuracy was 83.78%. In CA-125, Sensitivity was 86.36%, specificity was 60.00%, PPV was 76%, NPV was 75%, and accuracy was 75.68%. The diagnostic performance of CA125 and HE4 in discriminating ovarian cancer from benign gynaecologic conditions was verified using ROC analysis. In this study, the resultant AUC values were 0.79 for HE4 (95% CI 0.63-0.94) and 0.74 for CA125 (95% CI 0.57-0.91) ($p < 0.01$), which would make them feasible for use as tumor markers to differentiate ovarian cancers from benign and malignant gynaecological conditions. In combined HE4 and CA-125, sensitivity was 86.36%, and specificity was 86.67%, as found from the derived cutoff, which supported that the derived cutoff of combined HE4 and CA-125 predicts ovarian cancer with about 86.49% accuracy. According to Hamed et al, sensitivity for HE4 was 90% and specificity was 95%, for CA-125, sensitivity was 83.3%, and specificity was 85%. Combined HE4 and CA-125 had a 69.7% sensitivity and 80% specificity, slightly similar to this study [20]. Another study by Barr et al showed sensitivity was 80.5% for CA-125 and specificity was 92.2%. Sensitivity of HE4 was 90%. In combination, the sensitivity and specificity of CA-125 and HE4 were 78% and 98.7%, respectively, which is close to this study [5].

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Limitations of the study

The study was conducted among a cross-sectional group using a purposive sampling technique, which may introduce selection bias. Additionally, the small sample size limits the generalizability of the findings and may not accurately represent the broader population or the national context.

Recommendations

The combined measurement of serum HE4 and CA-125 appears to be a promising tool for predicting ovarian cancer and should be considered in the evaluation of all ovarian tumor cases. To validate these findings and enhance their applicability, larger-scale studies involving more extensive sample sizes and diverse population subsets from different geographical regions of the country are recommended.

Conclusion

This study demonstrates that both HE4 and CA-125 are significantly elevated in malignant ovarian tumors compared to benign cases, with each marker showing distinct sensitivity and specificity profiles. When used in combination, HE4 and CA-125 significantly improved diagnostic accuracy, yielding 86.36% sensitivity and 86.67% specificity. The combined use of these biomarkers outperformed either marker alone, offering a more reliable method for distinguishing malignant from benign ovarian tumors. These findings support the clinical utility of dual-marker testing as a non-invasive approach to enhance early detection and improve diagnostic confidence in suspected cases of epithelial ovarian cancer.

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Conflicts of interest

There are no conflicts of interest.

Ethical approval

The study was approved by the Institutional Ethics Committee.

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