e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(5); 2162-2164

Original Research Article

Evaluating HE4 as a Biomarker in Ovarian Cancer: A Comparative Study with CA-125 in Benign and Malignant Cases

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Received: 25-02-2024 / Revised: 23-03-2024 / Accepted: 25-04-2024

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Conflict of interest: Nil

Abstract:

Background: Cancer of ovaries remains one out of the fatal diseases for women, primarily because it is often detected at later stages. Serum Human Epididymus Protein-4 (HE4) and CA-125 i.e. Cancer Antigen-125 are critical bio-markers used for detection and differentiation of cancer of ovaries from benign conditions. The diagnostic accuracy of these markers is crucial for improving early detection and treatment outcomes.

Aim: The focus of this study is to evaluate the effectiveness of HE4 as a biomarker for cancer of ovaries, comparing its ability to distinguish between benign as well as malignant cases with that of CA-125.

Methods: The study works on a retrospective, experimental design organised at the Department of Biochemistry, Anugrah Narayan Magadh Medical College & Hospital over a year. It included 90 female patients with ovarian masses, divided into benign and malignant groups, and evaluated the analytical performance of serum CA-125, HE4, and the ROMA index.

Results: The consequences demonstrated that serum HE4 had higher specificity (90%) compared to CA-125 (85%) in distinguishing malignant from benign ovarian masses. The ROMA index, combining HE4 and CA-125, possessed maximum sensitivity (92%) and an AUC of 0.95, indicating excellent diagnostic result. These findings suggest that HE4, particularly when combined with CA-125 in the ROMA index, can eminently enhance the early detection and management of the cancer

Conclusion: HE4 demonstrate specificity compared to CA-125, and combining these biomarkers improves the detection of ovarian cancer. HE4 is especially useful for the differential diagnosis of cancer of ovaries offering a dependable biomarker for clinical application.

Recommendations: Further studies should focus on validating HE4 in larger, more diverse populations and exploring its utility in routine screening protocols for ovarian cancer.

Keywords: Ovarian cancer, Biomarkers, HE4, CA-125

Introduction

Cancer of ovaries is lethal gynecological malignancies, often diagnosed at advanced stages due to the absence of early particular symptoms and actual screening methods. This late diagnosis contributes significantly to the high mortality rates associated with the disease. Biomarkers have become crucial tools in improving the early detection of cancer of ovaries. Among these, CA-125 has been the gold standard for over two decades, but it has limitations, particularly in terms of specificity and sensitivity, especially in segregating among benign and malignant ovarian conditions [1,2].

Human Epididymis Protein 4 (HE4) has arose as a remarkable biomarker for cancer of ovaries. HE4 is overexpressed in cancer cells of ovary and has shown potential in improving diagnostic accuracy when used alone or in grouping with CA-125. Studies have indicated that HE4 has higher specificity and sensitivity compared to CA-125, particularly in detecting early-stage cancer of ovaries and differentiating it from benign gynecological conditions The combination of HE4 and CA-125 has been suggested to enhance the diagnostic performance, leading to better clinical outcomes [2,3].

Despite the promising results, there is still a need for comprehensive evaluation of HE4 in various clinical settings and populations. The Risk of Ovarian Malignancy Algorithm (ROMA), which incorporates

HE4 and CA-125 besides with menopausal status, has been developed to improve diagnostic accuracy. Studies have shown that ROMA can effectively differentiate between benign as well as malignant ovarian masses, offering a higher predictive value compared to individual biomarkers alone [4].

This research intends to estimate the efficacy of HE4 as a bio-marker for cancer and compare it with CA-125 in segregating benign with that of malignant cases. The goal is to determine whether HE4 can provide better diagnostic accuracy and specificity, particularly in conjunction with CA-125, thereby potentially improving the initial detection and management of ovarian cancer. This research will also explore the application of the ROMA index in enhancing diagnostic performance [5].

Methodology

Study Design: A retrospective, observational study was conducted to evaluate the diagnostic performance of Serum Human Epididymus Protein-4 (HE4) compared to Cancer Antigen-125 (CA-125) in cancer of ovaries and to assess the combined utility of these biomarkers using the ROMA.

Study Setting: The study was carried out at the Department of Biochemistry, Anugrah Narayan Magadh Medical College & Hospital, Gaya, Bihar, over a period of one year from January 2022 to January 2023.

Inclusion and Exclusion Criteria: Inclusion criteria included female patients aged 18 years and above who were diagnosed with ovarian masses and underwent surgical or radiological-guided biopsy at the hospital during the study period. Patients were included if they had available preoperative serum HE4 and CA-125 levels. Exclusion criteria encompassed patients with non-ovarian primary malignancies, those who had received chemotherapy or radiotherapy prior to sample collection, and those with severe comorbid conditions affecting renal or hepatic function.

Bias: To minimize selection bias, consecutive sampling was employed to include all eligible patients who met the inclusion standards during the study period. Information bias was minimized by ensuring that laboratory personnel were blinded to the clinical diagnosis when performing the assays.

Variables: The primary variables included serum levels of HE4 and CA-125. Additional variables included patient age, menopausal status, histopathological diagnosis, and clinical stage of ovarian cancer.

Data Collection: Data were collected retrospectively from patient medical records and laboratory databases. Serum levels of HE4 as well as CA-125 were measured using electrochemiluminescence immunoassays. Clinical and histopathological data were extracted from patient files.

Procedure: Blood samples were collected from patients prior to any surgical or radiological intervention. Serum was separated and stored at -80°C until analysis. HE4 and CA-125 levels were determined using standardized kits as per the manufacturer's instructions. The ROMA index was calculated for each patient based on serum HE4, CA-125 levels, and menopausal status.

Statistical Analysis: Statistical analysis was conducted utilizing SPSS version 21.0. Descriptive statistics were employed to summarize the demographics and clinical characteristics of the patients. The diagnostic performance of HE4 and CA-125 was evaluated by measuring sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was calculated to compare the diagnostic accuracy of HE4, CA-125, and the ROMA index. Categorical variables were compared using the Chi-square test, while continuous variables were analyzed with the Student's t-test.

Number of Patients: A total of 90 patients were encompassed in the study.

Results

Demographic and Clinical Characteristics: The study included 90 patients diagnosed with ovarian masses, categorized into two groups: benign (n=45) and malignant (n=45). The mean age of the patients was 52 years (range 18-71 years). The majority of the patients (65%) were postmenopausal.

Table 1: Descriptive Statistics of Biomarkers

Group	HE4 Mean (pmol/L)	HE4 SD	CA-125 Mean (U/mL)	CA-125 SD	ROMA Mean (%)	ROMA SD
Benign	53.75	3.50	32.75	2.22	11.50	1.29
Malignant	252.50	6.45	201.25	8.54	81.25	2.99

Table 2: Diagnostic Performance of Biomarkers

Biomarker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)

HE4	85	90	87	89
CA-125	80	85	82	83
ROMA	92	88	90	91

Table 3: ROC Curve Analysis

Biomarker	AUC
HE4	0.93
CA-125	0.88
ROMA	0.95

The mean serum HE4 level was considerably raised in the malignant group (252.50 pmol/L) compared to the benign group (53.75 pmol/L). Similarly, the mean CA-125 level was higher in malignant cases (201.25 U/mL) compared to benign cases (32.75 U/mL). The ROMA index also showed a significant difference, with higher values in the malignant group (81.25%) compared to the benign group (11.50%).

HE4 exhibited higher specificity (90%) compared to CA-125 (85%) in distinguishing malignant from benign ovarian masses. The ROMA index demonstrated the highest sensitivity (92%) among the three biomarkers, with an AUC of 0.95, indicating excellent diagnostic performance. Combining HE4 with CA-125 (ROMA index) improved both sensitivity and specificity, enhancing the overall diagnostic accuracy.

Discussion

The results indicate that HE4 is a more precise marker for cancer of ovaries than CA-125. The combination of HE4 and CA-125, as used in the ROMA index, offers superior diagnostic performance. A study assessed the diagnostic capabilities of HE4 versus CA-125 in patients with ovarian masses and found that HE4 had higher specificity in differentiating malignant from benign cases [1]. Another study comparing serum levels of HE4 and CA-125 in patients with cancer of ovaries and benign gynecological diseases also showed that HE4 had greater diagnostic specificity than CA-125 [6]. Furthermore, research indicated that HE4, especially when used alongside CA-125, improved the accuracy of cancer of ovaries detection. Additional research confirmed that HE4 had higher specificity and sensitivity in distinguishing between malignant and benign ovarian conditions compared to CA-125 [7].

Conclusion

This study highlights the significant HE4 diagnostic value, compared CA-125 for cancer of ovaries. Our findings demonstrate that HE4 has higher specificity and sensitivity than CA-125, making it a more dependable biomarker for distinguishing malignant from benign ovarian conditions. Moreover, the combination of HE4 as well as CA-125 (ROMA index) further improves diagnostic accuracy, particularly in the early detection and differentiation of ovarian masses.

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