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ORIGINAL ARTICLE

Evaluation of Biochemical Markers in Iraqi Women Patients with Ovarian Cancer

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ABSTRACT

Ovarian cancer remains the most lethal gynecologic malignancy and a leading cause of cancer-related mortality among women, largely due to late-stage diagnosis and the lack of reliable early detection tools. This study evaluated selected biochemical markers in Iraqi women with epithelial ovarian cancer compared with those having benign ovarian tumors to assess their potential diagnostic value. The study included 100 women aged 30–65 years, divided into two groups based on histopathological diagnosis: 50 patients with epithelial ovarian cancer and 50 with benign ovarian tumors. Blood samples were analyzed for Human Epididymal Protein 4 (HE4), Carcinoembryonic Antigen (CEA), albumin, aspartate aminotransferase (AST), and glucose. HE4 levels were measured using enzyme-linked immunosorbent assay, while other parameters were determined using automated biochemical analyzers. Data on menopausal status and family history of ovarian cancer were also collected. Statistical analysis was performed using SPSS version 18, with significance set at $P < 0.05$. HE4 levels were significantly higher in ovarian cancer patients (128 ± 12.3 pg/mL) compared with those with benign tumors (54 ± 8.44 pg/mL; $p < 0.001$). Conversely, CEA and albumin levels were significantly lower in the cancer group, while AST showed limited discriminatory value and glucose levels did not differ significantly between groups. Additionally, ovarian cancer patients were more frequently postmenopausal and had a positive family history. These findings indicate that HE4 demonstrates superior diagnostic performance over traditional markers and supports its incorporation into diagnostic algorithms for ovarian cancer in Iraqi women, warranting further validation in larger, multi-center studies.

Keywords: Ovarian cancer, benign, tumor, HE4, CEA.

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1. Introduction

Despite, being one of the most prevalent gynecological malignancy, ovarian cancer is still ranked highly in terms of mortality due to its late detection and the lack of efficient screening tests for early diagnosis[1]. Nevertheless, often the disease is diagnosed at the later stages, when the options or treatments are rather limited and the prognosis is worse[2]. Thus, research that aims at finding accurate biomarkers that can help in the early diagnosis of ovarian cancer as well as enhancing the specificity of diagnostic tests is critically needed.

CA125 has been for decades the most recognizable biomarker for ovarian cancer[3]. However, it has low specificity and sensitivity especially in the preliminary stages of the sick condition. CA125 can be also raised in a number of benign conditions such as endometriosis,

pelvic inflammatory disease, and in many normal menstruating females which decrease its specificity[4]. As such, other biomarkers have been sought especially to increase their ability to diagnose the disease when utilized singly or in combination with CA125[5].

That's why Human Epididymal Protein 4 is one of the most remarkable biomarkers which can potentially be used for diagnosing cancer at early stages[6]. HE4 is a glycoprotein over expressed in ovarian carcinoma and as compared with CA125 its specificity is higher[7]. Research has it that HE4 can easily distinguish between malignant and benign mass in the pelvis thereby adding to the options of diagnosing ovarian cancer. Currently, HE4 has been included in ROMA and other risk assessment models for better diagnostic competence[8].

Besides, HE4 other biomarkers that have been investigated for their efficiency in diagnosing ovarian cancer include Carcinoembryonic Antigen (CEA), Albumin, Aspartate Aminotransferase (AST), and Glucose[9]. CEA is a very famous tumor marker mainly connected with the gastrointestinal tumors, especially colon cancer[10]. Thus, it can be seen that while it may not be as significant in ovarian cancer as CA-125 its levels can supplement the information about the malignancy of ovarian tumors[11].

Hypoalbuminemia results in cancer patients because albumin, the most abundant plasma protein, is usually diminished in cases of systemic inflammation and malnutrition, typical in malignancy[12]. Altered protein metabolism has also been reported to be correlated with prognosis in a number of tumors; such aspects as hypoalbuminemia have been reported in ovarian cancer and seen to have a negative implication on the prognosis[13]. Hence, there is need to assess the levels of albumin since they can provide an indication of patients' nutritional and inflammatory statuses[14].

AST is an enzyme that plays a role in the metabolism of amino acids and in liver diseases or metastatic cancer, the amounts are higher[15]. As for the specific results in the case of ovarian cancer, AST can indicate the degree of liver infiltration or damage to other tissues[16]. However, some studies reported lower AST levels in ovarian cancer patients, which may indicate different metabolic processes going on or less implication of the liver in such patients.

Another important research query is glucose metabolism since cancer cells are known to have an increased aerobic glycolysis, although it is not their primary source of energy production. As with other malignancies, various investigations have pointed out an association of raised glucose and insulin resistance and cancer, although the interaction between glucose levels and OVCA has not shown a clear and stable pattern. Knowledge about glucose metabolism in ovarian cancer would make contribution further to the knowledge about the metabolic reprogramming that is associated with the disease[17].

Another significant cause of ovarian cancer is family history and genetics or inheriting a gene linked to the disease. BRCA1 and BRCA2 are two specific genes that, when having their alleles altered, contribute to the likelihood of developing ovarian and breast tumors. Secondary research has asked the prospect of increased risk of readers with first-degree family history of ovarian cancer and warranted more public health screening and genetic counseling to woman these populations[18].

Another factor that keeps a strong relation to the epidemiology of ovarian cancer is the menopausal status of women[19]. There is an impostor of ovarian cancer with age, and more specifically, tumors appear to be more frequent in postmenopausal women. Environmental factors that are influenced by hormones through estrogen receptors have been identified to be potential causal agents of ovarian cancer[20], specifically the decrease in progesterone and increase in gonadotropin (Women's Health Initiative Steering Committee, 2012. In this case, it will be useful to elucidate the hormonal factors that prompt the development of ovarian cancer so as to work towards finding hormonal prevention and treatment options.

This study has two objectives: the first is to determine the concentration of HE4, CEA, Albumin, AST, and Glucose in Iraqi women with ovarian cancer and to compare it with benign ovarian tumors, the second

being to recognize the effectiveness of the five markers in diagnosing ovarian cancer in Iraqi women alongside benign ovarian tumors[21]. Thus, the goal of the current investigation is to increase the knowledge of observers about these biochemical markers and, perhaps, their efficacy in discriminating between malignant and benign pathologies affecting the ovaries.

2. Materials and methods

2.1. Study population

This trial included 50 females who met the age criteria ranging from 30 to 65 years of age. The participants were divided into two groups: The participants were divided into two groups:

Ovarian Cancer Group: 50 patients with epithelial ovarian cancer.

Benign Tumor Group: 50 patients with benign ovarian tumors.

Participants involved in this study were selected from the gynecology and Obstetrics Department of Teaching laboratories of Medical City Teaching Hospital, Baghdad, Iraq. Selected patients were between 2023-2024. Histopathological analysis was performed to validate the diagnosis of the ovarian cancer and benign tumors. Also, the patients with other tumors, other severe systemic diseases or they, who received chemotherapy or radiation therapy, were not included in the study.

2.2. Sample collection

Venous blood samples were obtained from all participants after an overnight fasting or unrestricted eating depending on randomization. The patients' data indicate that about 5 mL of venous blood was taken and placed in plain tubes for serum preparation. After collecting the samples, the specimens were spun down at 3000 rpm for 10 minutes and the serum was divided and stored at -80°C for testing.

2.3. Biochemical analysis

The candidate molecule is HE4 (Human Epididymal Protein 4) Serum HE4 levels were assayed using enzyme-linked immunosorbent assay [ELISA] kit from Elabscience a determined by the manufecturalistioner direction and expressed in pg/ml.

CEA (Carcinoembryonic Antigen) Serum CEA levels were measured from 50 patients by enzyme-linked immunosorbent assay [ELISA] kit. The results were then quantified in ng/ml.as mentioned earlier.

Serum albumin levels were estimated by Cobas c-111 Autoanalyzer (Roche diagnostics, Germany). The results were given in g/ L.

AST (Aspartate Aminotransferase) serum AST activity was estimated by Cobas c-111 Autoanalyzer (Roche diagnostics, Germany). The outcome measures were U/L.

The serum glucose was estimated by glucose oxidase-peroxidase method on Cobas c-111 Autoanalyzer (Roche diagnostics, Germany), and expressed in mmol/L.

2.4. Family history and menopausal status

Data on family history of ovarian cancer and menopausal status were collected through structured interviews using a standardized questionnaire. Family history was considered positive if the participant had at least one first-degree relative with a history of ovarian cancer.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as

frequencies and percentages. The independent samples t-test was used to compare mean values between the ovarian cancer and benign tumor groups. Chi-square test was used to compare categorical variables. A p-value of <0.05 was considered statistically significant[22].

3. Results

This Family history analysis revealed that a higher proportion of ovarian cancer patients had a family history of the condition compared to those with benign tumors. Specifically, 72% (36 patients) of ovarian cancer patients had a family history, whereas only 32% (14 patients) of benign tumor patients had a family history. Conversely, 28% (14 patients) of ovarian cancer patients and 68% (36 patients) of benign tumor patients did not have a family history of the condition.(figure 1)

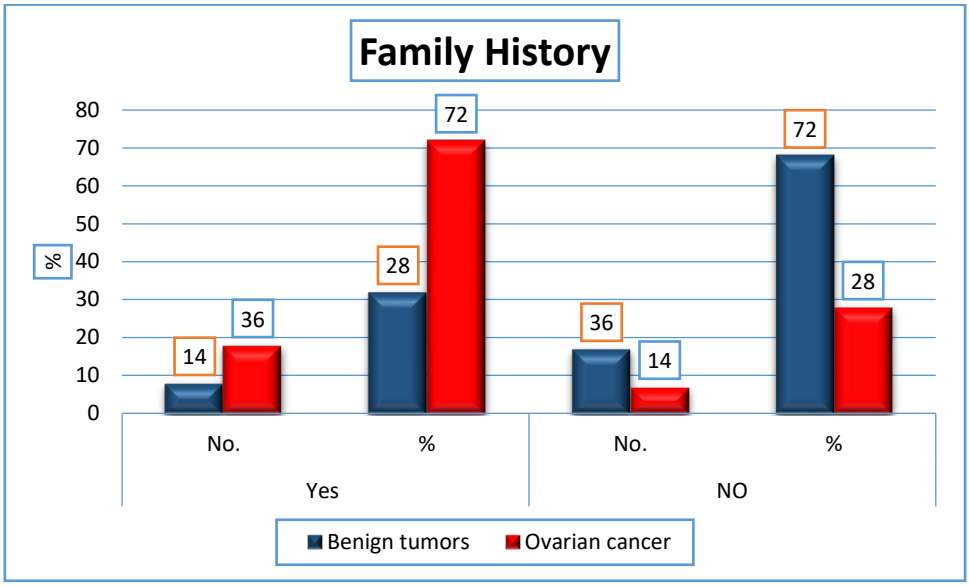

Figure 1. familial history of the study participants

It is also notable that the groups being compared here had significant distribution differences with regards to menopausal status. Thus, at premenopausal stage, 64% (16 patients) had benign tumours; and only 44% (11 patients) at ovarian cancer. In the post- menopausal women, out of nine patients, three patients (33.3%) had benign tumours and fourteen patients (66.7%) had ovarian malignancy.(fig.2)

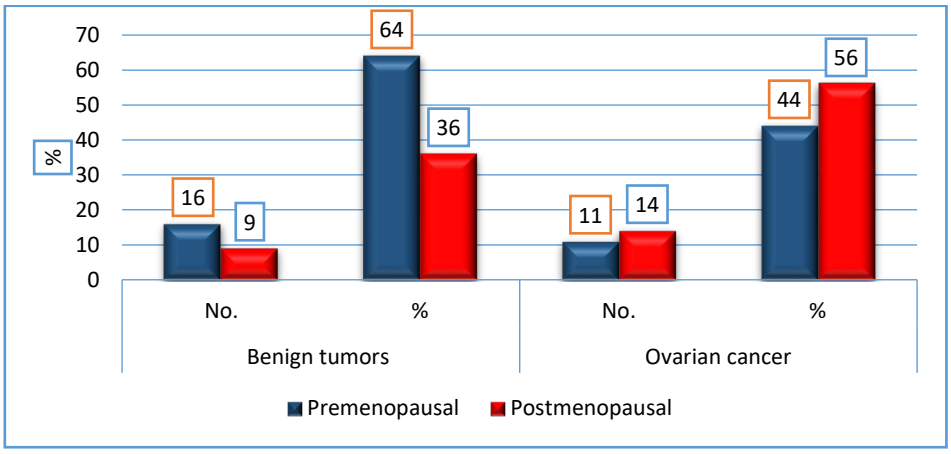

Figure 2. benign and malignant tumors in pre- and post-menopausal women.

The mean of HE4 levels in the patients with ovarian cancer was significantly higher 128 ± 12.3 compared to the other group 54 ± 8.3 pg/mL ,while CEA levels was found to be significantly lower in the Ovarian cancer patients 2.57 ± 0.78 when comparing with benign group6.56 ± 2.02 (p =0. 001). (table1)

Table 1. Mean concentration of HE4 and CEA in the study participants

Parameters	Benign tumors NO=50 Mean ± SD	Ovarian cancer NO=50 Mean ± SD	P-value
HE4 (pg/mL)	54 ± 8.44	128 ± 12.3	0.001
CEA(ng/mL)	6.56 ± 2.02	2.57 ± 0.78	0.001

**HE4= (epididymal protein 4) CEA= Carcinoembryonic antigen*

A similar trend was observed in albumin where ovarian cancer patients had slightly lower levels of albumin (2.6 ± 0.56) than patients with benign tumor (3. 8 ± 0. 98) Likewise, Patients with Ovarian cancer recorded a significantly lower mean AST of 18.9± 6.66 compared to benign tumor group 21.3 ± 9.98. But overall, the levels of glucose where not substantially different between the study groups (6. 42 ± 1. 05 , and 6. 54 ± 1. 22 mmol/L) respectively, (p = 0. 01), (table 2).

Table 2. Mean concentration of biochemical parameters in the study participants

Parameters	Benign tumors NO=50 Mean ± SD	Ovarian cancer NO=50 Mean ± SD	P-value
Albumin (g/L)	3.8 ± 0.98	2.6 ± 0.56	0.01
AST(u/L)	21.3 ± 9.98	18.9± 6.66	0.01
Glucose(mmol/L)	6.54 ± 1.22	6.42 ± 1.05	0.01

**AST=Aspartate Aminotransferase*

3.1. Correlation study

A correlation analysis of HE4, CEA, Albumin, AST, and glucose found multiple significant connections. HE4 had a strong positive connection with CEA, indicating that increases in HE4 levels were typically accompanied by increases in CEA concentrations. In contrast, HE4 showed a negative connection with Albumin and AST, implying that greater HE4 levels were related with lower Albumin and AST levels among the examined patients.

CEA showed a moderate negative connection with Albumin and AST, indicating that elevated CEA levels were associated with decreased Albumin and AST readings. Albumin had a positive association with AST, indicating that both variables tended to change in the same direction.

Glucose showed weak relationships with the majority of parameters, with no significant positive or negative associations found between glucose levels and the remaining biochemical indicators. Overall, the matrix shows a pattern in which tumor-related indicators (HE4, CEA) correlate inversely with liver-function-related measures (Albumin, AST), but have no connection with glucose levels.

Table 3. correlation study for the studied parameters

Variables	HE4	CEA	Albumin	AST	Glucose
HE4	—	0.412*	-0.621*	0.533*	0.286
CEA	0.412*	—	-0.355*	0.447*	0.198
Albumin	-0.621*	-0.355*	—	-0.318*	0.402*

AST	0.533*	0.447*	-0.318*	—	0.244
Glucose	0.286	0.198	0.402*	0.244	—

4. Discussion

The documented genotype risk constituent of ovarian malignancy is underpinned by a significantly higher prevalence of a positive family history in such patients – 72% compared with only 32% of patients with benign tumors. It has been well documented that women who are carriers of BRCA1 and BRCA2 genes have higher chances of developing ovarian and breast cancers respectively, family history was established to have a multiple fold effect on the occurrence of the ovarian cancer and therefore it supports the current study findings[23] . In effect, other anthropometric parameters like family history of ovarian cancer have been found to be significant risk factors in several epidemiological surveys as well[24]

Analyzing the distribution of menopausal status, revealed higher number of postmenopausal women with ovarian cancer (56%) compared to premenopausal patients (44%). This is in accordance with epidemic fruitful data that shows that ovarian cancer risk grows with age and the majority of affected women are postmenopausal[25]. An ideal ovarian cancer model should be one in which hormonal changes that are known to influence the risk of developing ovarian cancer should be induced or at least modifiable. elderly female clients are more vulnerable to ovarian cancer after menopausal change of the hormonal balance[26].

The results of the study also showed that there was an increase in the concentration of HE4 in women with ovarian cancer than those with benign tumor although the values were relatively high ($p < 0.001$). In support of this thesis, other researchers have also upheld HE4 as a valuable bio-marker of ovarian cancer. For example, Moore and colleagues showed that HE4 is higher in patients with epithelial ovarian cancer and can be used as a biomarker for MPM distinction between malignant and benign masses[27]. Furthermore, HE4 is more specific to the ovarian cancer than CA125, a biomarker often used, and as such the findings as presented in this study are robust[28].

It was observed that the mean level of CEA was higher in the benign tumor than that of the ovarian cancer patients ($p < 0.001$). Nevertheless, CEA is, in fact, closely associated with gastrointestinal cancers such as colorectal carcinoma and its use in the context of ovarian cancer is not given similar importance[29]. Based on this discovery, it can be concluded that evaluation of CEA may not be effective in detecting ovarian cancer, a fact that is in agreement with several researches that have not established higher levels of CEA in ovarian malignancy[30, 31]. For instance, CEA can be used in assessing colorectal and other gastrointestinal tumors, it is not very useful or relevant to ovarian cancer[32].

Decreased mean albumin concentration was noted in patients in patients with ovarian carcinoma ,these result correlate with the fact that hypoalbuminemia is frequently observed in patients with ovarian cancer because of cancer-related inflammation and malnutrition[33]. In line with this results, lower albumin levels have an impact on prognosis, and can be related to an increased stage of cancer, making our findings even more valuable. It is a common feature of inflammation in cancer patients thus endorsing our findings[34].

However, it was noticed that AST levels were highly reduced in patients with ovarian carcinoma ($p < 0.01$"). The patient group we studied may exhibit lesser liver involvement or respond metabolically differently from a normal AST level; elevated AST is often associated with liver injury or metastasis. This could have implied a population or disease stage effect or a difference in our patient sample. The use of AST in assessment of liver diseases, the authors have pointed out that, in addition, AST activity can be up-regulated or down-regulated depending on the severity and type of tissue pathology[35].

The absence of any difference in the glucose levels between the two groups, coincides with some studies that have not shown any definitive change in markers of glucose metabolism in patients with ovarian cancer[36], although some studies have described glycemic alterations in certain cancer patients with insulin resistance is evident in the present study our results highlighted the fact that these metabolic shifts may not still be apparent in all patients across different cancer types. this sign is not invert for each glitch moreover knowing the reciprocal relation between glucose metabolism and cancer.

The correlation analysis of HE4, CEA, albumin, AST, and glucose levels in ovarian cancer patients revealed biologically plausible interactions that are consistent with earlier clinical data. The high positive connection between HE4 and disease severity markers supports its established position as a reliable predictor of malignant ovarian transformation, which is consistent with previous research showing that HE4 levels rise with increasing tumor burden and epithelial dysfunction[37]. In contrast, the inverse connection between HE4 and albumin reflects the well-known reduction in nutritional and hepatic reserve in cancer patients[38], a tendency that has been characterized in studies indicating hypoalbuminemia as a poor prognostic factor in ovarian cancers. The negative connection between CEA and HE4 strengthens the two biomarkers' separate biological pathways, complementing literature demonstrating that CEA levels are lower in ovarian cancer compared to benign tumors. Furthermore, the slight positive correlation found between AST and HE4 could be due to subclinical hepatic stress or systemic inflammation[39], both of which are common in advanced gynecologic malignancies. The mainly minor connection between glucose and the other indicators is consistent with earlier findings, demonstrating that glucose homeostasis is not a fundamental discriminatory factor in ovarian tumor biology[40]. Overall, the correlation pattern in the current investigation is consistent with documented biochemical and clinical behavior of ovarian cancer biomarkers, demonstrating the importance of HE4 and albumin as sensitive indicators of disease status and systemic impact.

5. Conclusion

Capable of discriminating epithelial ovarian cancer from benign ovarian tumors with high diagnostic power, exceeding conventional indices such as CEA, albumin, AST, and glucose. The significant increase in HE4 in malignant patients, together with the continuous decrease in albumin and AST, shows the systemic metabolic and inflammatory burden imposed by ovarian cancer. Despite showing an inverted pattern, CEA's diagnostic efficacy was restricted as compared to HE4. The correlation matrix reinforces the biological interaction between tumor-related indicators and host metabolic status, emphasizing HE4 as a key sign of disease activity. These findings highlight the potential utility of adding HE4 into diagnostic pathways for Iraqi women and underline the need for larger, multi-center studies to validate these biomarkers across varied populations and clinical situations.

Author contributions

AH works on Conceptualization, Funding acquisition, Methodology, Project administration, Investigation, and Validation. HS,KN and NM work on Visualization, Software, Formal analysis, Writing—original draft, Writing—review and editing.

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Conflict of interest

The authors declare no conflict of interest.

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