

The Role of S100 Calcium-binding Protein A1 and Some Biochemical markers in Patients with Ovarian Cancer

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ABSTRACT

Patients with epithelial ovarian cancer (EOC) typically receive a late-stage diagnosis since there are insufficient early diagnostic markers. The biomarker that is most commonly used is ovarian cancer antigen 125 (CA125). In order to increase sensitivity and specificity, particularly in cases of early illness, complementing markers are therefore required. The current study concentrated on the diagnosis of ovarian cancer patients using specific biochemical markers found in blood serum. Serum albumin, calcium, and phosphorus were among these markers that were thought to increase sensitivity and specificity, especially in early stages of the disease and facilitate effective early identification. Serum calcium-binding protein S100 A1 (S100A1) enhanced the growth and migration of ovarian cancer cells. When ovarian cancer patients are evaluated, serum levels of fibroblast growth factor 23 (FGF23) are recommended as a helpful indicator of advanced disease. Consequently, treatment for patients with ovarian cancer is aided by the early identification and diagnosis of metastases.

Key words: Epithelial ovarian cancer (EOC), S100 calcium-binding protein A1 (S100A1), Fibroblast growth factor 23 (FGF23), and Calcium(Ca²⁺)

INTRODUCTION

There are several types of ovarian cancer, and each has its own etiology, molecular biology, and other traits. Most ovarian epithelial malignancies are discovered in stages III or IV. Even though ovarian cancer incidence has decreased, more study is still required to identify the best methods for early identification⁽¹⁾. Despite the fact that a number of markers have been researched and utilized to evaluate the status, development, and prognosis of ovarian cancer (OC), but is frequently detected at a late stage. This can be partially explained by the absence of an effective screening method⁽²⁾. Serum albumin and calcium levels are used to predict malignancy in women with ovarian cancer because hypercalcemia has been associated to an increased risk of malignancy⁽³⁾. Clinical and epidemiological studies have linked ovarian cancer to decreased blood albumin and elevated serum calcium levels. It's unclear if low albumin and high calcium levels cause ovarian cancer or if they are symptoms of an already existing malignancy⁽⁴⁾. Because hypercalcemia is associated with ovarian cancers. This suggests that a higher risk of ovarian cancer overall may be linked to elevated blood calcium levels. Elevated amounts of calcium in the serum may indicate ovarian cancer. This suggests that there may be a correlation between ovarian cancer and serum calcium indices⁽⁵⁾. In patients with epithelial ovarian cancer (EOC), serum albumin may be utilized as a separate indicator of overall survival⁽⁶⁾. Human S100 is an extensive subfamily of low-molecular-weight calcium-binding proteins that differs in many functional areas but shares certain structural commonalities. The S100 members play a number of roles in a healthy cell, including the transport and storage of calcium, a process known as calcium homeostasis. This process, which can occur extracellularly, intracellularly, or both, is necessary for cellular homeostasis as well as inflammation⁽⁷⁾. The S100 protein regulates a multitude of cellular functions, including differentiation, proliferation, homeostasis of Ca²⁺, and inflammation. Growth and advancement of multiple diverse cancer types is promoted by the S100 protein. As a result, research indicates that members of the S100 family are useful markers for diagnosis and may be used as novel targets for treatment⁽⁸⁾. Because it can be challenging to differentiate between ovarian pathology based solely on histopathology, some researchers have started using novel markers, like the S100 calcium-binding protein A1 (S100A1), to distinguish between benign and malignant ovarian disease⁽⁹⁾. The S100 family members, S100A1, S100A2, S100A4, and S100A5 levels of expression which are often uncontrolled in human malignancies, were significantly higher in ovarian cancer (OC) patients⁽¹⁰⁾. Because the S100 proteins are involved in biological processes that are closely linked to the genesis and evolution of malignancies, there is growing interest in the association between these proteins and different types of cancer.

The S100 members are potential cancer prognostic indicators ⁽¹¹⁾. In ovarian cancer, the calcium-binding protein S100 A1, which is a member of the S100 protein family, is significantly expressed. S100A1 was found to enhance the migration and proliferation of ovarian cancer cells. Findings indicated that S100A1 is a critical component in the ovarian cancer development process and a useful marker for ovarian cancer detection ⁽¹²⁾. Tumor markers can be a highly useful tool for treatment of patients when used properly. Patients with ovarian cancer have been connected to the search for novel tumor indicators, such as the up-regulation of the S100A1 protein ⁽¹³⁾. Fibroblast growth factor 23 (FGF23), a phospho-directing hormone mostly present in bone, lowers serum phosphate levels by preventing the absorption of phosphate in the intestine as well as by reducing 1,25-dihydroxy vitamin D and phosphate reabsorption in the proximal tubule ⁽¹⁴⁾. In the past, more control of phosphorus in the body has been subjected to stricter management of calcium using parathyroid hormone and vitamin D. Nonetheless, a great deal of work has been made in understanding how the phosphatonin system, of which FGF 23 is the primary component, controls the phosphate cycle ⁽¹⁵⁾. Tumor-induced osteomalacia is one happen disease because of hypophosphataemia. Patients with ovarian cancer should think about tumor-induced osteomalacia ⁽¹⁶⁾. Patients with advanced epithelial ovarian cancer had higher serum or plasma levels of FGF23. Patients with ovarian tumors who have elevated FGF23 levels may have a more advanced stage of the disease ⁽¹⁷⁾. In order to maintain phosphate homeostasis, 1,25-dihydroxy vitamin D metabolism is regulated by FGF-23. Since it has been demonstrated that vitamin D metabolites possess anti-cancer properties, it is possible that FGF-23 influences cancer. Far more FGF-23 was found in women with advanced ovarian cancer than in those with early-stage disease ⁽¹⁸⁾.

Aspects of Ethics: In compliance with Iraqi ethical standards, the authorization of the institutional ethical board and the executed written permission of each participant were acquired prior to the commencement of study-related operations.

MATERIALS AND METHODS:

The participants of this study comprised 46 women with ovarian cancer patients with a mean age of (52.5 ± 8.7) years and 46 women with benign ovarian mass (pathological controls) with a mean age of (49.8 ± 7.9) years. Other 46 women were considered normal healthy controls with mean age (51.6 ± 7.8) years, who attended for treatment in Al-Amal National Cancer Hospital from January, 2024 till July, 2024. Pathological examination determined that all patients were either benign epithelial ovarian tumors or epithelial ovarian malignancy. Patients were diagnosed and treated for cancer after evaluation. The operation records were sufficiently detailed and unique to secure the 2015. International Federation of Gynecology and Obstetrics (FIGO) standard clinical staging for ovarian cancer, as shown in figure (1).
 Stage 0 : Carcinoma in situ , intraepithelial Carcinoma.
 Stage 1: Confined to the vagina.

Stage II: Involvement of paravaginal tissue but not pelvic sidewall.

Features	Patients. No	Features	Patients. No
Total No. of subjects	46	Patients with ovarian cancer	stage I(31), stage II,(15)
Stage 0	No	Carcinoma in situ , intraepithelial Carcinoma.	0
Stage 1	31	1.No malignant disease in family 2. Confined to the vagina.	30%
stage II	15	1. Malignant disease in family 2. Involvement of paravaginal tissue but not pelvic sidewall.	65%

Figure (1) General features of patients with ovarian cancer

After the blood had coagulated at room temperature, it was centrifuged for ten minutes at 3000 rpm. The acquired serum was separated, and manual testing was done. Using its kits, serum levels of albumin, phosphorus, and calcium were measured. Serum S100A1 , FGF23 were examined using of ELISA kits .

RESULTS & DISCUSSION:-

Additional study is required to advance our knowledge of the illness, identify modifiable risk factors, and create strategies for ovarian cancer early identification and improved treatment.

In comparison to healthy controls, table (1) indicated a significant drop in albumin levels and an increase in calcium levels in ovarian cancer sera. While there was no significant difference in the levels of albumin or calcium in the serum when comparing pathological controls with healthy controls, there was a significant increase in the calcium level and a significant decrease in the albumin level when ovarian cancer sera were compared to pathological controls. It is possible to distinguish between benign and malignant ovarian cancers using these values .

Table (1) biostatistical calculations for some biochemical markers and the comparison of levels of healthy controls , pathological controls and ovarian cancer.

Serum biochemical markers	Ovarian cancer (n = 46)	Pathological controls (n = 46)	Healthy controls (n = 46)	P Value
Calcium(mg/dL)	12.9± 5.4	9.4±2.2	9.2±1.3	P<0.001 NS
Albumin (g/L)	32.3 ±3.3	40.1±4.2	41.5±3.6	P<0.001 NS
S100A1 (ng/mL)	6.38 ± 1.26	1.85 ± 0.65	1.53± 0.78	P<0.001 NS
FGF23 (pg/mL)	290.6 ±27.5	60.7 ±14.5	54.3 ±15.8	P<0.001 NS
Phosphorus (mg/dL)	2.3 ±1.5	3.6 ± 1.7	3.9 ± 1.3	P<0.001 NS

*Significant using student t-test between two independent means at 0.05 level of significance.

Serum albumin and calcium levels significantly changed in women with early-stage ovarian cancer. These results are consistent with those published by Gary G. Schwartz and others in 2020. Low blood albumin and hypercalcemia have been related to ovarian cancer in both clinical and epidemiological research. Whether low albumin and high calcium enhance the risk of ovarian cancer is unclear ⁽⁴⁾. Diagnostic indicators that help in the differential identification of malignant from benign tumors are needed in order to properly classify women with malignancy for specialized therapy. A cut-off value of 10.5 mg/dL was used to measure the predictive qualities of the calcium level.

Table (2) demonstrated that the serum calcium had high validity values (77.7% sensitivity , 80.5% specificity , 65.6% positive predictive value , 45.3% negative predictive value and 80.2% accuracy test). These values make the parameter with highly significance in the study. Calcium level provides useful information for patients in a diagnosis of ovarian cancer especially in early stage disease. The predictive values of serum albumin was measured using a cut-off value (37.9) (g/L).

Table (2) demonstrated the high validity values of the serum albumin. (80.5% sensitivity , 77.7% specificity , 64.4% positive predictive value , 44.4% negative predictive value and 80.1% accuracy test). These values make the parameter with highly significance in the study. When ovarian cancer is diagnosed, especially in its early stages, albumin levels can be a valuable diagnostic tool for patients.

Table (2) predictive values of biochemical parameters levels in ovarian cancer women as compared to pathological control using (mean+ 1SD) of healthy control as (a cut off).

Serum Chemical tests	*Sensitivity	*Specificity	*Positive predictive	*Negative predictive	*Accuracy test
Calcium	77.7 %	80.5%	65.6%	45.3%	80.2%
Albumin	80.5%	77.7%	64.4%	44.4%	80.1%
S100A1	83.3%	86.1%	69.8%	47.7%	84.7%

FGF23	80.6%	83.0%	67.4%	46.1%	82.2%
Phosphorus	77.8%	80.5%	65.1%	44.6 %	80.1%

*Sensitivity : It is a percentage of True Positive result.

*Specificity : It is a percentage True Negative result

* Positive predictive : It is the percentage of all Positive tests that are true positive.

*Negative predictive :It is a percentage of all Negative values.

* Accuracy : Percentage of patients correctly classified by the test results as having or not having the disease.

These results are consistent with those reported by Kelly et al. (2015). In comparison with females with benign ovarian masses, those with malignant ovarian masses, including patients with early-stage cancer, have considerably lower levels of blood albumin and greater levels of serum calcium. ⁽³⁾

According to table (1), there was a noteworthy rise in S100A1 levels in ovarian cancer sera relative to healthy controls, a similar increase in S100A1 levels in ovarian cancer sera relative to pathological controls, and no significant differences in serum S100A1 levels between pathological and healthy controls. These values can be used in differentiation between benign tumors from malignant ovarian tumors. Numerous biological processes, such as proliferation, apoptosis, migration, inflammation, and differentiation, are displayed by members of the S100 family. A higher expression of S100A1 in ovarian cancer patients is linked to a better prognosis. Patients with ovarian cancer that have elevated S100A1 expression have a better prognosis. Further research on the S100 family members may be helpful for the diagnosis and evaluation of ovarian cancer patients levels significantly changed in women with early-stage ovarian cancer ⁽¹⁹⁾. The calcium-binding protein (S100A1) is abundantly expressed with ovarian cancer. The results demonstrated that S100A1 increased the migration and multiplication of ovarian cancer cells. S100A1 is a useful marker for ovarian cancer identification, is highly expressed in ovarian cancer, and contributes significantly to the aggressiveness of ovarian cancer ⁽¹²⁾. The predictive values of serum S100A1 was measured using a cut-off value (2.31) (ng/mL).

Table (2) showed that the serum S100A1 had high validity values (83.3% sensitivity , 86.1% specificity , 69.8% positive predictive value , 47.7% negative predictive value and 84.7% accuracy test). These values make the parameter with highly significance in the study. Patients can diagnose ovarian cancer with the help of the S100A1 level, particularly in cases of early-stage disease. These results are in agreement with those published by Hong-Yu Xu et al. in 2020. S100A1, S100A2, S100A4, and S100A5, members of the S100 family that are usually dysregulated in human malignancies, were considerably overexpressed in ovarian cancer (OC) patients ⁽¹⁰⁾. Novel biomarkers are therefore helpful for managing cancer . Numerous intracellular and extracellular activities, such as calcium homeostasis, cell proliferation, apoptosis, invasion, and motility, are regulated by the S100 protein, according to Hongyan C. et al. (2014). Tumor formation has been associated with changes in the expression of S100 proteins caused by autoimmunity, inflammation, protein phosphorylation, and cells ⁽²⁰⁾.

As indicated by table (1), there were no significant differences in the serum levels of FGF 23 and phosphorus when comparing pathological controls to healthy controls, but there was a significant increase in FGF 23 and a significant decrease in phosphorus in ovarian cancer sera when compared to pathological controls and when ovarian cancer sera were compared to healthy controls. These values for FGF 23 levels can be used in differentiation between benign tumors from malignant ovarian tumors. Women with ovarian cancer in the early stages showed significant alterations in their serum levels of phosphorus and FGF 23. These results were consistent with those reported by Xuegong Ma et al. (2018). Even though diverse cases of hypercalcemia in ovarian cancer may resemble one another. During the examinations, a lower blood phosphorus level and a greater serum calcium level were observed ⁽²¹⁾. Hung-An Lin, et al . 2014. Elevated serum FGF 23 levels were reported in a group of patients with ovarian cancer and hypophosphataemia ⁽¹⁶⁾.

The predictive values of serum phosphorus was measured using a cut-off value (2.6) (mg/dL).

Table (2) showed that the serum phosphorus had high validity values (77.8% sensitivity , 80.5% specificity , 65.1% positive predictive value , 44.6% negative predictive value and 80.1% accuracy test). These values make the parameter with highly significance in the study. Phosphorus level provides useful information for patients in a diagnosis of ovarian cancer especially in early stage disease. The predictive values of serum FGF-23 was measured using a cut-off value (70.1) (pg/mL).

Table (2) showed that the serum FGF-23 had high validity values (80.6% sensitivity, 83.0% specificity, 67.4% positive predictive value, 46.1% negative predictive value and 82.2% accuracy test). These values make the parameter with highly significance in the study. Shu Feng and Michael Ittmann.2014. Patients with advanced ovarian cancer were observed to have higher levels of FGF-23 in comparison to those with early-stage disease⁽¹⁸⁾.

Serum or plasma FGF23 levels were elevated in patients with advanced epithelial ovarian cancer. Findings from the 2005 study by Peter J. T., et al. Increased FGF23 levels in ovarian tumor patients likely indicate advanced disease⁽¹⁷⁾. Serum or plasma FGF23 levels provides useful information for patients in a diagnosis of ovarian cancer especially in advanced ovarian cancer.

CONCLUSION:

It needs a lot of research to ascertain the usefulness of each tumor marker for screening, diagnosing, evaluating treatment response, and detecting recurrence of cancer, as well as markers produced by tumor cells in response to cancer or certain benign diseases. In this study, calcium, S100A1 and FGF-23 levels increased significantly, and albumin and phosphorus levels decreased significantly compared to the pathological controls and healthy controls. These values can be used in differentiation between benign tumors from malignant ovarian tumors. The calcium, S100A1, albumin and phosphorus levels provide useful information for patients in the diagnosis of ovarian cancer, especially in the early stages of the disease. At the same time, the concentration of FGF-23 provides useful information for patients when ovarian cancer is diagnosed, especially in the advanced stage.

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