ISSN: 0067-2904

The Role of Some Enzymes and Vitamin C in Diagnosis of Ovarian Cancer in Iraqi Patients

Noor L. Dawood*, Firas A. Hassan
Department of Chemistry, College of Sciences, Al-Nahrain University, Jadriya, Baghdad, Iraq

Received: 6/5/2024 Accepted: 11/12/2024 Published: 30/12/2025

Abstract:

Ovarian cancer stands out as the most lethal gynecological cancer, characterized by its aggressive nature, which is largely attributed to the fact that it is often diagnosed at a late stage. Patients with ovarian cancer, particularly those with early-stage tumors, currently face challenges in obtaining a clear and efficient pre-surgical diagnosis. This paper aimed to determine the role of acetyl-CoA carboxylase, fatty acid synthase, matrix metalloproteinase-14, and Vitamin C in patients with ovarian cancer. One hundred patients diagnosed with ovarian cancer at Al-Amal Hospital for Radiation and Nuclear Medicine and Oncology Teaching Hospital at Baghdad Medical City aged from 35 to 65 years were included in this study, divided into 50 patients untreated as a group I, and 50 patients treated as group II and 40 healthy women as a control group. The findings revealed a notable increase in the concentrations of acetyl-CoA carboxylase, fatty acid synthase, and matrix metalloproteinase-14 (P-value <0.0001) among patients with ovarian cancer compared to the control group. In contrast, vitamin C concentration was significantly lower than in the control group, (P-value <0.0001). A receiver operating character curve analysis showed a high sensitivity according to the area under the curve. The present results conclude that acetyl-CoA carboxylase, fatty acid synthase, and matrix metalloproteinase-14 can be used as biomarkers for early-stage detection diagnostic markers for ovarian cancer.

Keywords: Ovarian cancer, Acetyl-CoA carboxylase, Fatty acid synthase, Matrix metalloproteinase-14, Vitamin C.

دور بعض الانزيمات وفيتامين ج في تشخيص سرطان المبايض في المريضات العراقيات

نور ليث داود*، فراس عبد الله حسن
قسم الكيمياء، كلية العلوم، جامعة النهرين، العراق

الخلاصة:

يبرز سرطان المبيض كأكثر أنواع السرطان النسائية فتكًا، ويتميز بطبيعته العدوانية، وهو ما يُعزى إلى حد كبير إلى أنه غالبًا ما يتم تشخيصه في مرحلة متأخرة. يواجه مرضى سرطان المبيض، وخاصة أولئك الذين يعانون من أورام في مراحل مبكرة، تحديات في الحصول على تشخيص واضح وفعال قبل الجراحة. هدفت هذه الورقة إلى تحديد دور أسيتيل–CoA كربوكسيلاز، سينثاز الأحماض الدهنية، والميتالوبروتيناز المادة الخلالية –14، وفيتامين ج في مرضى سرطان المبيض. مائة مريض تم تشخيصهم بسرطان المبيض في مستشفى الأمل للأشعة والطب النووي ومستشفى الأورام التعليمي في مدينة الطب ببغداد تتراوح أعمارهم

* Email: mscnoorlaith@gmail.com

بين 35 و65 عامًا شملهم هذا الدراسة، مقسمين إلى 50 مريضًا غير معالجين كمجموعة أولى، و50 مريضًا معالجين كمجموعة ثانية و40 امرأة سليمة كمجموعة ضابطة. كشفت النتائج عن زيادة ملحوظة في تركيزات أسيتيل-CoA كربوكسيلاز، ودهون الأحماض الدهنية، والميتالوبروتيناز المادة الخلالية -14(قيمة P <0.0001) بين مرضى سرطان المبيض مقارنة بمجموعة التحكم. على النقيض، كانت تركيزات فيتامين ج أقل بكثير مقارنة بمجموعة التحكم، (P-value <0.0001). أظهر تحليل منحنى التشغيل التلقائي حساسية عالية وفقًا للمساحة تحت المنحنى. تخلص النتائج الحالية إلى أن أسيتيل-CoA كربوكسيلاز، سينثاز الأحماض الدهنية، والميتالوبروتيناز المادة الخلالية -14 يمكن استخدامها كعلامات حيوية للكشف المبكر عن سرطان المبيض.

Introduction

Ovarian cancer is a significant public health challenge, claiming the lives of approximately 207,000 women worldwide annually out of the 314,000 who are diagnosed with the condition each year[1,2]. According to the Global Cancer Observatory (GCO) of the World Health Organization (WHO), ovarian cancer (OC) fatalities and cases are projected to increase globally by 36% and 47%, respectively[3]. One of the ten cancer types most common in Iraq, according to the Iraqi Cancer Registry 2016, is OC[4]. The OC is a cancer that starts in the ovaries, the female reproductive organs that produce eggs [5]. Despite multiple treatment options, the five-year survival rate is still very low. Ovarian cancer is often not diagnosed until it has expanded to other body parts, due to the non-specific symptoms that are often attributed to other conditions[6]. Additionally, there is currently no effective screening test for OC, which can also contribute to delays in diagnosis[7]. Clearly, early detection and treatment can improve the chances of survival [8].

Lipid metabolism, encompassing the synthesis, breakdown, and absorption of lipids from the environment, holds paramount significance in normal cellular biology and is essential in the genesis of pathological states, such as cancer [9]. In the case of ovarian tumorigenesis, lipids are dynamic and contribute to the growth of cancer cells as well as the suppression of the immune system[9,10].

Long-chain saturated fatty acids are produced by the fatty acid synthase (FAS) through the conversion of acetyl-CoA to malonyl-CoA, which is induced by the acetyl-CoA carboxylases (ACC) [11]. The FAS is an enzyme involved in synthesizing fatty acids, which are essential components of cell membranes and play important roles in various cellular processes[12]. Emerging evidence suggests that FAS may play a crucial role in the development of OC[13]. Matrix metalloproteinase-14 (MMP14), is an enzyme that plays a role in the breakdown of extracellular matrix during regular physiological processes like tissue regeneration, reproduction, and embryonic development[14]. It has also been implicated in various pathological conditions, including cancer. In the context of OC, MMP14 is overe-xpressed in OC tissues and is associated with tumor progression, invasion, and metastasis [15]. Research indicates that MMP14 is involved in facilitating the invasion of OC cells through the extracellular matrix and in promoting the formation of new blood vessels to support tumor growth[16]. Ascorbic commonly known as Vitamin C, is an essential water-soluble nutrient that humans cannot synthesize because a crucial enzyme in the biosynthetic pathway has been lost[17]. The vitamin C is used in the prevention and treatment of a broad spectrum of conditions, involving diabetes, stroke, COVID-19, atherosclerosis, glaucoma, heart disease, macular degeneration, and cancer[19]. The objective of this study was to biochemically analyze the levels of enzymes such as acetyl-CoA carboxylase, fatty

acid synthase, matrix metalloproteinase-14, and vitamin C levels in women with ovarian cancer.

2. Materials and Methods

2.1 Study design

This case-control study was conducted between 1 January 2023 and 1 June 2023 at Al-Amal Hospital for Radiation and Nuclear Medicine and Oncology Teaching Hospital at Baghdad Medical City. The study population consisted of 100 OC patients with age ranged between 35 and 65 years divided into two groups, untreated (group I) and treated (group II) with Taxol chemotherapy. In addition, 40 healthy females served as a control group, and the patient's verbal consent was written and documented in the questionnaire. The study excluded patients with congenital adrenal hyperplasia, diabetes, hyperprolactinemia, renal impairment, thyroid disorders, hypertension, and chronic smoking. The necessary permissions were acquired from the at Al-Amal Hospital for Radiation and Nuclear Medicine and Oncology Teaching Hospital at Baghdad Medical City and were approved by the institutional ethics council of Al-Nahrain University, College of Science (Reference Number COB 3298/2022). The subjects provided informed consent and/or agreement.

2.2 Blood samples procedures

Blood samples were collected from the subjects, and processed according to established protocols under the supervision of Chemistry Department, College of Science, Al-Nahrain University, Baghdad. In brief, using a disposable syringe, 5ml of blood was drawn by venipuncture in tubes having a clot activator. The tubes were centrifuged for 10 minutes at 0.31304xg, according to the equation G=(1.118 x 10-5) × R S Where :*R is the radius of the centrifuge, *S is the momentary speed, and the serum that was isolated was subsequently moved to Eppendorf tubes. For sample integrity, all tubes have been kept at -20°C until analysis.

2.3 Enzymes and Analytical Assessment

The concentrations of ACC, FAS, MMP-14, and vitamin C were determined using the commercially available enzyme-linked immunosorbent assay ELISA kits, which company and origin for all kits are, (CUSABIO\USA, ASSAY Genie \Ireland, ASSAY Genie \Ireland, Sunlong\ China), respectively.

The quantitative sandwich enzyme immunoassay technique involves binding ACC, Human FAS, MMP-14, and Vitamin C to a microplate using pre-coated antibodies, biotin-conjugated antibodies, avidin-conjugated Horseradish Peroxidase, and a substrate solution. The color develops proportionally to the bound amount, and absorbance is measured at 450 nm.

2.4 Statistical Analysis

Data were analyzed using GraphPad Prism Software, version 8.0.2 (San Diego, California, USA). The mean values across the three groups were compared using a one-way analysis of variance (ANOVA). The data have been considered significant at $p \leq 0.05$[20]. The receiver operating characteristic (ROC) curve was analyzed to determine whether the markers could accurately predict a disease. The AUC has been used to compare the markers.

3. Results and Discussion

The descriptive findings for the patients with OC in groups I (untreated), II (treated), and control are summarized in Table 1.

Table 1: Assessment of serum level acetyl-CoA carboxylase, fatty acid synthase, matrix metalloproteinase-14, and vitamin C in ovarian cancer patients and control group.

Variable	mean value ±SD			P-value (Anova)
	Control	Group I	Group II	
Acetyl-CoA carboxylase ng\L	167.80±62.10	536±137.3 [a]	225.0±112.9[c]	<0.0001 **
Fatty acid synthase ng\mL	1.52±1.50	44.07±8.62 [a]	39.59±11.82[b]	<0.0001 **
Matrix metalloproteinase-14 ng\mL	7.73±2.78	20.84±5.51 [a]	12.83±2.35 [b,c]	<0.0001 **
Vitamin C ng\mL	33.84±5.30	20.50±6.30 [a]	22.60±2.09 [b]	<0.0001 **

*Sig.*P < 0.05; high Sig. **P < 0.001; no sig: p>0.05. a: control vs group I, b: control vs group II, c: group I vs group II*

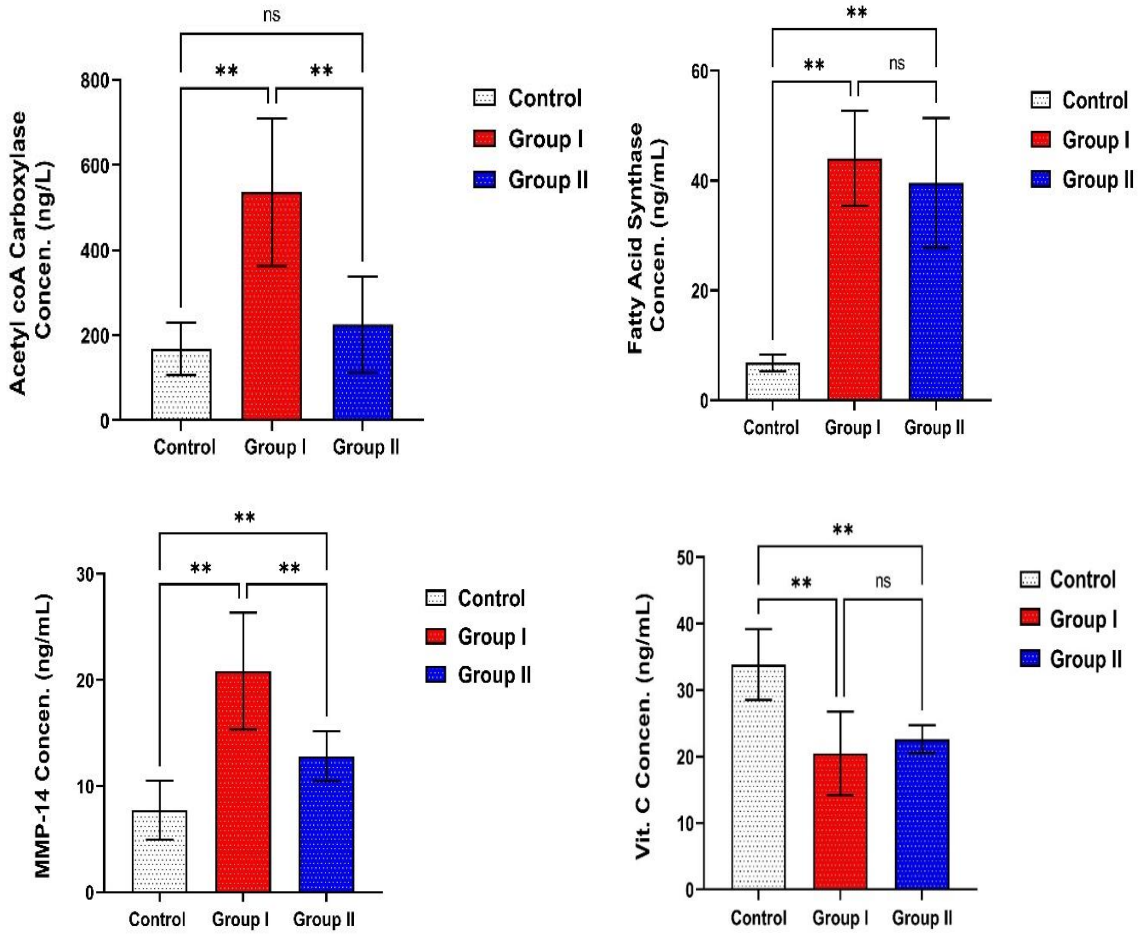


Figure 1 a- The concentration of a- acetyl coA carboxylase (ng/L), b- fatty acid synthase (ng\mL), c- matrix metalloproteinase-14 (ng\mL), d- vitamin C (ng/mL) in the control group, group I (untreated), and group II (treated).

The mean ± SD of ACC in patients of OC group I was found to be significantly high (536±137.3 ng\L) in contrast to the level recorded in the control group (167.80±62.10 ng\L), as illustrated in Figure 1-a, whereas, the result showed no significance between control and group II (P-value = 0.1046), as shown in Figure 1-a.

These results are consistent with other studies that concluded that have found acetyl-CoA carboxylase levels to be associated with initiation and progression of multiple malignancies [21]. Tumors exhibit a high energy flux and a strong reliance on the synthesis of fatty acids. As a result, blocking ACC has become more and more common as a cancer therapeutic[11,22].

Weijing He and his colleagues found that the expression level of ACC *in vitro* impacts cell migration and lipogenesis in OC[23]**.** Therefore, acetyl-CoA carboxylase levels may serve as a valuable biochemical marker, in conjunction with clinical and histopathological findings for monitoring ovarian cancer patients after surgery and chemotherapy. Additionally, elevated levels of this enzyme could help predict the probability of developing OC for women who have a high index of the enzyme.

The results of serum FAS in patients of OC group I(44.07±8.62 ng\mL) and group II (39.59±11.82ng\mL) were found to be significantly high compared to the control group's mean value (1.52±1.5 ng\mL), as illustrated in Figure 1-b. Whereas, the result showed no significance between group I and group II (P-value = 0.0518), as shown in Figure 1-b. Therefore, the result obtained in this research is consistent with the results of other studies, which stated that the synthesis of new fatty acids is the basis for the majority of cancers [24,25]. Especially, increased fatty acid levels are linked to an increased risk of cancer because they regulate multiple biological processes, such as preserving the integrity of cancer cell membranes and converting oncogenic signals [26]. Yoon and Lee reported that FAS is overe-xpressed in OC cells compared to normal ovarian tissue[27]. Multiple malignancies are associated with upregulated levels of FAS and de novo fatty acid synthesis, like breast, lung, prostate, pancreatic, liver, gastric, and ovarian[28,29]. Additionally, Recent studies have indicated that alterations in the metabolism of fatty acids could be significant in the pathogenesis and aggressiveness of OC and that OC can be inhibited in its growth by suppressing FAS[27,28,30]. Thus, FAS represents a potential target for cancer treatment.
Figure 1-c illustrates the serum levels of MMP-14 in group I and group II were found to be significantly high respectively (20.84±5.51 ng\mL) (12.83±2.35 ng\mL) compared to the mean value observed in the control group (7.73±2.78 ng\mL). MMP14 is involved in the degradation of the extracellular matrix a process that occurs during both healthy and pathological processes, including cancer and inflammatory motion[15]. MMP-14 acts at the level of tumor cells, producing intracellular effects at the level of the nucleus[31], epithelial-mesenchymal transition and proliferation[32], and even the tumor microenvironment, contributing to invasion, angiogenesis, and metastasis[33]. Recently, MMPs have been identified as biomarkers in many fields, including diagnosis, monitoring, and treatment efficacy[34,35]. Hua et al. reported that membrane-type 1 matrix metalloproteinase (MT1-MMP/MMP-14) was highly expressed in malignant tumor cells like atypical teratoid rhabdoid tumor (ATRT) and suggested that inhibition of MMPs may reduce the aggressiveness of cancer cells[36]. The results obtained from this work may support our knowledge and our conclusion about the effect of MMP-14 on human malignant tumors and their biomarkers for effective diagnosis and treatment.

Table 1 shows the serum level of vitamin C in patients of OC group I and group II and it was found to be significantly low respectively (20.50±6.30 ng\mL) (22.60±2.09 ng\mL) in contrast to the control group's mean value (33.84±5.30 ng\mL), as illustrated in Figure 1-d. Whereas, the result showed no significance between group I and group II (P-value =0.1390). The result obtained in this research is consistent with the results of other studies that describe the function of vitamin C and how it affects cancer cells. B. Abiri et al explain how vitamin C

may be used to prevent and treat cancer, but state that the evidence is still inconclusive [37]. In addition, J. Hunyady also notes that vitamin C deficiency is common in cancer patients, and receiving large doses of vitamin C intravenously may improve quality of life and alleviate symptoms [38]. However, additional clinical trials necessary to assess the effectiveness of high-dose vitamin C as a cancer adjuvant treatment [39]. A recent study has reported that vitamin C has potential novel functions in regulating anticancer immunity [40]. Kamranikheiri and Kosar reported that vitamin C and citrus sinensis fruit extract have potent anticancer effects [41].

Receiver Operating Characteristic

The Receiver Operating Characteristic (ROC) was performed to assess the diagnostic significance of ACC, FAS, MMP14, and vitamin C. The AUC in ROC analysis indicates the test's advantage. The results are tabulated in Table 2 and Figures 2,3,4 and 5 respectively.

Table 2: Diagnostic criterion values and coordinates of ROC curve analysis for ACC, FAS, MMP14, and vitamin C in the differentiation of study groups.

Parameters	Type of correlation	AUC	Sensitivity	Specificity	Cut-off value	P-Value
Acetyl-CoA carboxylase ng\L (ng\L)	control vs group I	0.9500	93.33%	96.97%	>478.7	<0.0001
	control vs group II	0.9469	100.0%	93.33%	>325.56	<0.0001
Fatty acid synthase ng\mL	control vs group I	1.0	100%	96.67%	>30.12	<0.0001
	control vs group II	0.7739	83.33%	60%	>24.68	<0.0003
Matrix metalloproteinase 14 ng\mL	control vs group I	0.9589	93.33%	96.97%	>15.56	<0.0001
	control vs group I	0.9322	93.33%	96.97%	>14.85	<0.0001
Vitamin C ng\mL	control vs group I	0.9773	95.5%	86.4%	>31.87	<0.0001
	control vs group I	1.0	100. %	95.5%	>24.91	<0.0001

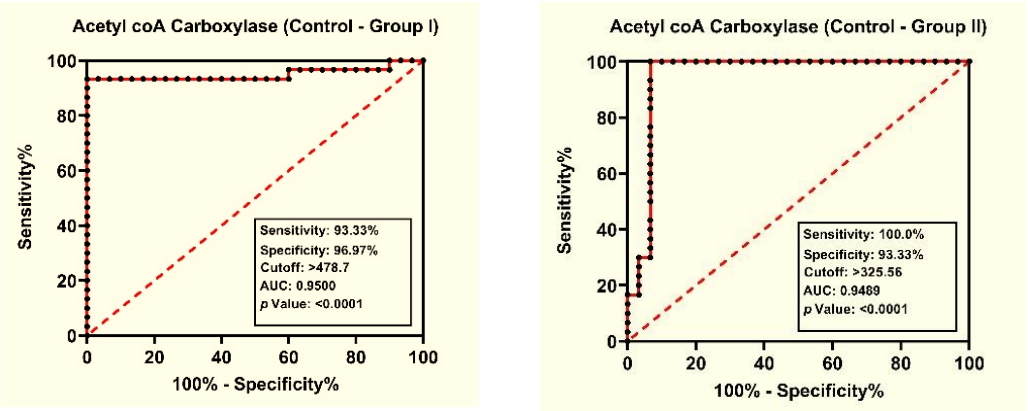
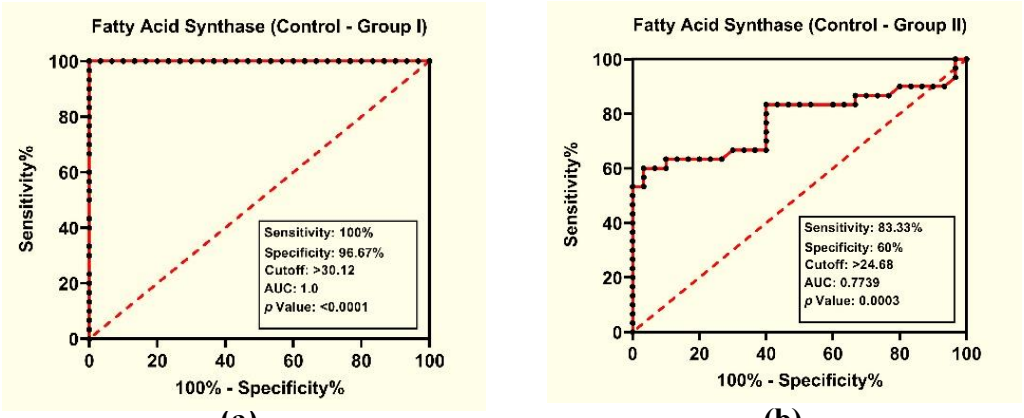
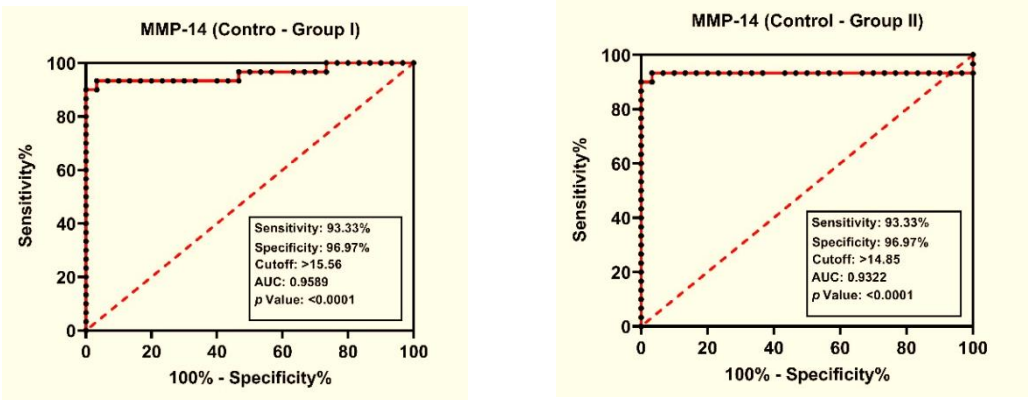


Figure 2: The ROC analysis of a- acetyl-CoA carboxylase in group I patients vs control b- acetyl-CoA carboxylase in group II patients vs control showing the AUC, p-value, sensitivity, specificity, and cut-off.



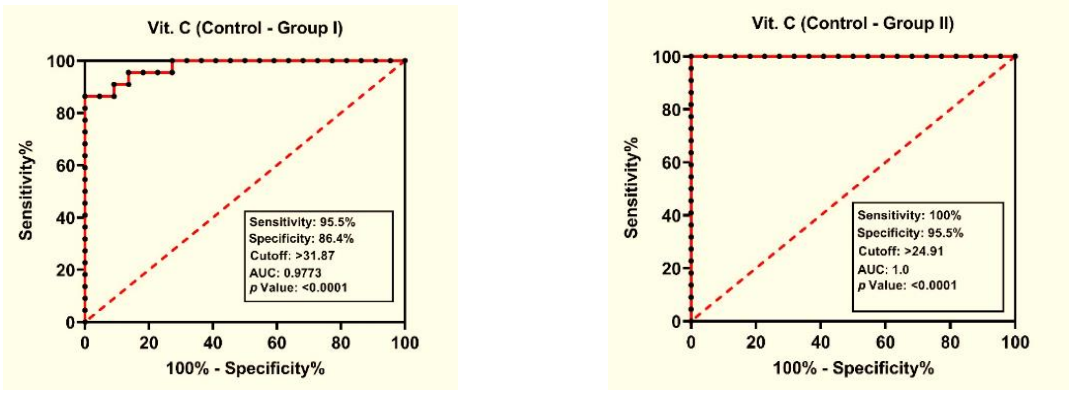
(a) (b)

Figure 3: The ROC analysis of a- fatty acid synthase in group I patients vs control b- fatty acid synthase in group II patients vs control showing the AUC, p-value, sensitivity, specificity, and cut-off.



(a) (b)

Figure 4: The ROC analysis of a-matrix metalloproteinase-14 in group I patients vs control b-matrix metalloproteinase-14 in group II patients vs control showing the AUC, p-value, sensitivity, specificity, and cut-off .



(a) (b)

Figure 5: The ROC analysis of a-vitamin C in group I patients vs control b- b-vitamin C in group II patients vs control showing the AUC, p-value, sensitivity, specificity, and cut-off.

The findings indicated that ACC, MMP-14, and vitamin C exhibited a high AUC in both control vs group I and control vs group II with a (P-value <0.0001). Based on the sensitivity and specificity measures, these markers demonstrated high sensitivity and specificity as shown in Table 1. These results indicate that ACC, MMP14, and vitamin C have a high level of specificity and statistical significance in detecting ovarian cancer. Furthermore, FAS occupied a significant AUC=1.0 in control vs group I, and the sensitivity and specificity were 100% and 96.67% respectively. Conversely, it showed a moderately significant prognostic value with AUC=0.7739 in control vs group II and sensitivity and specificity of 83.33 and 60 achieved at a cut-off value of >24.68.

Conclusion

The findings revealed that serum levels of ACC, FAS, and MMP-14 were significantly elevated in OC patients. In contrast, vitamin C levels were found to be lower in OC patients compared with controls. These findings suggest that the measurement of the concentration of these enzymes (ACC, FAS, MMP14), and vitamin C may have a diagnostic importance and potentially function as a prognostic indicator of ovarian carcinogenesis.

References

[1] M. Sideris, U. Menon, R. Manchanda, "Screening and prevention of ovarian cancer," The *Medical Journal of Australia*, vol. 221, no. 10, pp. 264-274, 2024. doi: 10.5694/mja2.52227.

[2] T. A. Subhi, F. A. Hassan, and A. H. J. Al-Qaisi, "Role of some enzymes in early diagnosis of ovarian cancer," *Indian Journal of Public Health Research & Development*, vol 10, no. 10, pp. 2206, 2019. doi: 10.5958/0976-5506.2019.03181.4.

[3] H. Sung, "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries," *A Cancer Journal for Clinicians*, vol. 71, no. 3, 2021. doi: 10.3322/caac.21660.

[4] B. J. Mohamad, F. A. Zghair, and Z. T. Fadhil, "Clinical and Histopathological Features of Ovarian Cancer in Iraq, Baghdad Between 2014-2020," *Iraqi Journal of Science*, vol. 63, no. 6, pp. 2354–2361, 2022. doi: 10.24996/ijs.2022.63.6.4.

[5] K. Coward, D. Wells, "Female reproductive tract and oocyte development," in Textbook of Clinical Embryology, *Cambridge University Press*, Amazon, 391 pages, 2013. doi: 10.1017/CBO9781139192736.006.

[6] J. Antony, J. P. Thiery, and R. Y. J. Huang, "Epithelial-to-mesenchymal transition: Lessons from development, insights into cancer and the potential of EMT-subtype based therapeutic intervention," *Physical Biology*, vol. 16, no. 4, 2019. doi: 10.1088/1478-3975/ab157a.

[7] J. M. Liberto, "Current and Emerging Methods for Ovarian Cancer Screening and Diagnostics: A Comprehensive Review," *Cancers*, vol. 14, no. 12, 2022. doi: 10.3390/cancers14122885.

[8] P. Samuel and D. R. F. Carter, "The Diagnostic and Prognostic Potential of microRNAs in Epithelial Ovarian Carcinoma," *Molecular Diagnosis & Therapy*, vol. 21, pp. 59–73, 2017. doi: 10.1007/s40291-016-0242-z.

[9] S. Chaudhry, S. N. Thomas, and G. E. Simmons Jr. "Targeting lipid metabolism in the treatment of ovarian cancer," *Oncotarget*, vol 13, pp. 768–783, 2022. doi: 10.18632/oncotarget.28241.

[10] R. S. Kadhim and F. A. Hassan, "Estimation of Fibulin-1, Chemerin and Omentin-1 in Iraqi Women with Polycystic Ovary Syndrome-Associated Infertility," *Al-Rafidain Journal of Medical Sciences*, vol. 5, no. 1, pp. S125–S131, 2023. doi: 10.54133/ajms.v5i1S.329.

[11] Y. Wang, W. Yu, S. Li, D. Guo, J. He, and Y. Wang, "Acetyl-CoA Carboxylases and Diseases," vol 12, 2022, Frontiers Media S.A. doi: 10.3389/fonc.2022.836058.

[12] C. de Carvalho, "The various roles of fatty acids," *Molecules*, vol 23, no. 10, pp. 2583, 2018. doi: 10.3390/molecules23102583.

[13] L. Jiang, "Up-regulated FASN expression promotes transcoelomic metastasis of ovarian cancer cell through epithelial-mesenchymal transition," *International Journal of Molecular Sciences*, vol. 15, no. 7, 2014. doi: 10.3390/ijms150711539.

[14] GA Cabral-Pacheco, "The roles of matrix metalloproteinases and their inhibitors in human diseases," *International Journal of Molecular Sciences*, vol. 21, no. 24, 2020. doi: 10.3390/ijms21249739.

[15] M. C. Vos, "The role of MMP-14 in ovarian cancer: a systematic review," *Journal of Ovarian Research*, vol. 14, no. 101, 2021. doi: 10.1186/s13048-021-00852-7.

[16] P. Carey, "Metalloproteinases in ovarian cancer," *International Journal of Molecular Sciences*, vol. 22, no. 7, 2021. doi: 10.3390/ijms22073403.

[17] M. Nishikimi, "Cloning and chromosomal mapping of the human nonfunctional gene for L-gulono-γ-lactone oxidase, the enzyme for L-ascorbic acid biosynthesis missing in man," *Journal of Biological Chemistry*, vol. 269, no. 18, 1994. doi: 10.1016/s0021-9258(17)36884-9.

[18] D. Martin, "Vitamin C—sources, physiological role, kinetics, deficiency, use, toxicity, and determination," *Nutrients*, vol. 13, no. 2, pp.615, 2021. doi.org/10.3390/nu13020615.

[19] A. Kükürt and V. Gelen, "Understanding Vitamin C: Comprehensive Examination of Its Biological Significance and Antioxidant Properties," *Ascorbic Acid - Biochemistry and Functions, Book*, 2024. doi: 10.5772/intechopen.114122.

[20] M. B. Ahmed and A. H. Ad'hiah, "Effects of age, Gender and Allergen Type on Immunoglobulin E Level in Asthma and Allergic Rhinitis Patients," *Iraqi Journal of Science,* vol. 63, no. 4, pp. 1498–1506, 2022. doi: 10.24996/ijs.2022.63.4.10.

[21] H. Ito, I. Nakamae, J. Kato, and N. Yoneda-Kato, "Stabilization of fatty acid synthesis enzyme acetyl-CoA carboxylase 1 suppresses acute myeloid leukemia development," *Journal of Clinical Investigation*, vol. 131, no. 12, 2021. doi: 10.1172/JCI141529.

[22] Y. Yu, Q. Nie, Z. Wang, Y. Di, X. Chen, and K. Ren, "Targeting acetyl-CoA carboxylase 1 for cancer therapy," *Frontiers in Pharmacology*, vol.14, 2023. doi: 10.3389/fphar.2023.1129010.

[23] W. He, Q. Li, and X. Li, "Acetyl-CoA regulates lipid metabolism and histone acetylation modification in cancer," *Biochimica Biophysica Acta (BBA) - Reviews on Cancer*, vol. 1878, no. 1, p. 188837, 2023. doi: 10.1016/J.BBCAN.2022.188837.

[24] Q. Du, "FASN promotes lymph node metastasis in cervical cancer via cholesterol reprogramming and lymphangiogenesis," *Cell Death & Disease*, vol. 13, no. 5, 2022. doi: 10.1038/s41419-022-04926-2.

[25] J. Nascimento, "Fatty acid synthase as a potential new therapeutic target for cervical cancer," *Anais da Academia Brasileira de Ciências*, vol. 94, no. 2, 2022. doi: 10.1590/0001-3765202220210670.

[26] Z. Li, "SLC27A4-mediated selective uptake of mono-unsaturated fatty acids promotes ferroptosis defense in hepatocellular carcinoma," *Free Radical Biology and Medicine*, vol. 201, pp. 41-54, 2023. doi: 10.1016/j.freeradbiomed.2023.03.013.

[27] H. Yoon and S. Lee, "Fatty Acid Metabolism in Ovarian Cancer: Therapeutic Implications," *International Journal of Molecular*, vol. 23, no. 4, 2022. doi: 10.3390/ijms23042170.

[28] A. Du, "Fatty acids in cancer: Metabolic functions and potential treatment," *MedComm-Oncology*, vol. 2, no. 1, 2023. doi: 10.1002/mog2.25.

[29] Z. Ji, "Deregulation of Lipid Metabolism: The Critical Factors in Ovarian Cancer," *Frontiers in Oncology*, vol. 10, 2020. doi: 10.3389/fonc.2020.593017.

[30] R.R Chen, "Targeting of lipid metabolism with a metabolic inhibitor cocktail eradicates peritoneal metastases in ovarian cancer cells," *Communications Biology*, vol. 2, no. 1, 2019. doi: 10.1038/s42003-019-0508-1.

[31] Y. Makutani, "Contribution of MMP14-expressing cancer-associated fibroblasts in the tumor immune microenvironment to progression of colorectal cancer," *Frontiers in Oncology*, vol. 12, 2022. doi: 10.3389/fonc.2022.956270.

[32] Y Makutani, "Immune Infiltration of MMP14 in Pan Cancer and Its Prognostic Effect on Tumors," *Frontiers in Oncology*, vol. 11, 2021. doi: 10.3389/fonc.2021.717606.

[33] S Nandadasa, "Degradomic Identification of Membrane Type 1-Matrix Metalloproteinase as an ADAMTS9 and ADAMTS20 Substrate," *Molecular and Cellular Proteomics*, vol. 22, no. 6, 2023. doi: 10.1016/j.mcpro.2023.100566.

[34] J. Liu and R. A. Khalil, "Matrix Metalloproteinase Inhibitors as Investigational and Therapeutic Tools in Unrestrained Tissue Remodeling and Pathological Disorders," *Progress in Molecular*

Biology and Translational Science, vol. 148, pp.355-420, 2017. doi: 10.1016/bs.pmbts.2017.04.003.

[35] Z. Shasha, "Effects of recombinant human collagen supplementation on extracellular matrix remodeling in mouse skeletal muscle after eccentric exercise," *Chinese Journal of Tissue Engineering Research*, vol. 28, no. 16, 2024. doi: 10.12307/2024.304.

[36] T. Hua, "Human Malignant Rhabdoid Tumor Antigens as Biomarkers and Potential Therapeutic Targets," *Cancers*, vol. 14, no. 15, 2022. doi: 10.3390/cancers14153685.

[37] B. Abiri, "Tea's anti-obesity properties, cardiometabolic health-promoting potentials, bioactive compounds, and adverse effects: A review focusing on white and green teas," *Food Science and Nutrition*, vol. 11, no. 10, 2023. doi: 10.1002/fsn3.3595.

[38] J. Hunyady, "The Result of Vitamin C Treatment of Patients with Cancer: Conditions Influencing the Effectiveness," *International Journal of Molecular Sciences*, vol. 23, no. 8, 2022. doi: 10.3390/ijms23084380.

[39] B. Abiri and M. Vafa, "Vitamin C and Cancer: The Role of Vitamin C in Disease Progression and Quality of Life in Cancer Patients," *Nutrition and Cancer*, vol. 73, no. 8, 2020. doi: 10.1080/01635581.2020.1795692.

[40] L. Yool, "Role of vitamin C in targeting cancer stem cells and cellular plasticity," *Cancers*, vol. 15, no. 23, pp. 5657, 2023. doi.org/10.3390/cancers15235657.

[41] M. Kamranikheiri and M. Kosar, "Potent anticancer effects of vitamin C and vitamin C-rich fruit extract (Citrus sinensis L.) on human lung cancer cells," *Journal of HerbMed Pharmacology*, vol. 12, no. 2, 2023. doi: 10.34172/jhp.2023.30.