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ORIGINAL ARTICLE

Serum Oxidative Stress Biomarkers as Prognostic Indicators of Tumor Aggressiveness in Ovarian Cancer: A Multicenter Clinical Study

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ABSTRACT

Background: Ovarian cancer remains the most lethal gynecologic malignancy, largely due to delayed diagnosis and the aggressive nature of advanced tumors. Emerging evidence suggests that oxidative stress plays a critical role in tumorigenesis and progression. However, the relationship between oxidative stress biomarkers and tumor aggressiveness in ovarian cancer remains underexplored, particularly in South Asian populations.

Objective: To evaluate the association between serum oxidative stress biomarkers and tumor aggressiveness in ovarian cancer patients.

Methods: This cross-sectional study was conducted from July 2022 to February 2023 at Shahbaz Sharif Hospital Multan, Liaquat National Hospital Karachi, and BMC Sandeman Provincial Hospital Quetta. Eighty histologically confirmed ovarian cancer patients aged 25–70 years were enrolled prior to therapy. Serum levels of malondialdehyde (MDA), total antioxidant capacity (TAC), superoxide dismutase (SOD), and glutathione peroxidase (GPx) were measured. Tumor grade and FIGO stage were used to define aggressiveness. Statistical analyses included t-tests and Pearson's correlation.

Results: High-grade and advanced-stage tumors showed significantly elevated MDA levels ($p<0.001$) and decreased TAC, SOD, and GPx (all $p<0.001$). MDA positively correlated with tumor grade ($r=0.69$) and stage ($r=0.72$), while antioxidant markers showed negative correlations ($p<0.001$).

Conclusion: Oxidative stress is strongly associated with increased tumor aggressiveness in ovarian cancer. Serum oxidative biomarkers may serve as valuable prognostic indicators and therapeutic targets. Further longitudinal studies are warranted to validate these findings and explore antioxidant-based interventions in clinical practice.

Keywords: Ovarian Cancer, Oxidative Stress, Malondialdehyde, Superoxide Dismutase, Glutathione Peroxidase, Tumor Grade, FIGO Stage.

INTRODUCTION

Ovarian cancer ranks as the fifth leading cause of cancer-related deaths among women worldwide and is the most lethal of all gynecological malignancies. Despite advances in surgical oncology, imaging techniques, and chemotherapy protocols, the prognosis for ovarian cancer remains poor, largely due to late-stage detection and the aggressive biological nature of the disease[1]. High-grade serous carcinoma, the most common subtype, is often diagnosed at an advanced stage, characterized by widespread peritoneal dissemination and chemoresistance. The clinical challenge lies not only in diagnosing the disease early but also in accurately predicting tumor behavior to guide individualized treatment plans. In recent years, there has been growing interest in understanding the molecular and biochemical mechanisms underlying tumor progression, with a particular emphasis on oxidative stress as a central player in cancer biology[2].

Oxidative stress is defined as a state of imbalance between the production of reactive oxygen species (ROS) and the ability of the body's antioxidant defense mechanisms to detoxify these harmful intermediates[3]. ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, are generated endogenously during mitochondrial respiration and exogenously through environmental toxins, inflammation, and radiation. While low levels of ROS play essential roles in cell signaling and immune responses, excessive ROS can damage cellular macromolecules, including DNA, proteins, and lipids. This oxidative damage contributes to genomic instability, mutagenesis, and the disruption of normal cell-cycle regulation hallmarks of carcinogenesis[4].

In ovarian cancer, the tumor microenvironment is characterized by chronic oxidative stress, driven by inflammatory cytokines, hypoxia, and abnormal angiogenesis. Studies have shown elevated levels of oxidative stress markers, such as malondialdehyde (MDA), in the serum and tumor tissues of ovarian cancer patients. MDA is a well-established byproduct of lipid peroxidation and serves as a sensitive indicator of oxidative damage[5]. Simultaneously, the levels and activity of key antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), are often reduced in these patients, indicating an overwhelmed or impaired antioxidant system. Total antioxidant capacity (TAC), which reflects the cumulative action of all antioxidants present in plasma, is also frequently diminished in cancer patients, particularly those with high-grade tumors[6].

The extent of oxidative stress not only reflects disease presence but may also correlate with disease severity. Aggressive tumors often exhibit higher metabolic rates, increased angiogenesis, and enhanced proliferation all of which contribute to excessive ROS generation[7]. It is postulated that a direct relationship exists between oxidative stress markers and the histopathological features of ovarian cancer, such as tumor grade, FIGO stage, lymphovascular invasion, and metastatic potential. However, despite these associations, limited data exist from the South Asian region, particularly from hospital-based clinical cohorts in Pakistan, where genetic, nutritional, and environmental factors may further influence oxidative stress status and tumor behavior[8].

Understanding the link between oxidative stress and tumor aggressiveness could have significant clinical implications. Oxidative biomarkers may serve not only as diagnostic tools but also as prognostic indicators and potential therapeutic targets[9]. The assessment of oxidative stress parameters could help oncologists stratify patients according to risk, tailor therapy more precisely, and potentially explore the use of antioxidant adjuvant treatments to mitigate tumor progression and improve clinical outcomes[10].

Therefore, the present study aims to evaluate the association between serum oxidative stress biomarkers specifically malondialdehyde, total antioxidant capacity, superoxide dismutase, and glutathione peroxidase and tumor aggressiveness in ovarian cancer patients admitted to tertiary care hospitals in Pakistan. By correlating these biochemical markers with clinical and

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histopathological parameters, this research seeks to contribute to the understanding of oxidative stress as a pivotal factor in ovarian tumor biology and to identify potential biomarkers for early detection and prognosis in ovarian cancer management[11].

MATERIALS AND METHODS

This hospital-based cross-sectional study was conducted from July 2022 to February 2023 across three tertiary care hospitals in Pakistan: Shahbaz Sharif Hospital, Multan, Liaquat National Hospital, Karachi, and Bolan Medical College (BMC) Sandeman Provincial Hospital, Quetta. These centers were selected based on their high-volume gynecologic oncology departments, diagnostic facilities, and surgical oncology units, ensuring a diverse patient population representative of various geographic and socioeconomic backgrounds. Ethical approval for the study was obtained from the Institutional Review Boards (IRBs) and informed written consent was secured from each participant prior to enrolment.

A total of 80 female patients diagnosed with ovarian cancer were enrolled using a non-probability consecutive sampling technique. Inclusion criteria were: females aged between 25 and 70 years, newly diagnosed with histopathologically confirmed epithelial ovarian carcinoma, and who had not yet received any form of chemotherapy, radiotherapy, or antioxidant supplementation at the time of enrollment. Exclusion criteria included patients with a history of chronic inflammatory diseases, autoimmune disorders, end-stage organ failure, concurrent malignancies, or current infections, as these conditions could independently alter oxidative stress parameters and confound study results.

Demographic and clinical data, including age, body mass index (BMI), parity, menopausal status, comorbidities, and clinical presentation, were recorded through a structured, pre-tested proforma. Detailed oncological profiles were collected from clinical and histopathological records, including tumor type, histological grade, FIGO stage, presence of lymphovascular invasion, and evidence of peritoneal carcinomatosis or metastasis.

Venous blood samples (5 mL) were collected aseptically from each participant in the morning after an overnight fast. The samples were allowed to clot at room temperature and then centrifuged at 3000 rpm for 10 minutes to separate serum. The serum was aliquoted and stored at −80°C until biochemical analysis. All oxidative stress biomarkers were measured in the central biochemistry laboratories of the respective hospitals using standardized protocols and commercial reagent kits.

Malondialdehyde (MDA) levels, a marker of lipid peroxidation, were determined using the thiobarbituric acid-reactive substances (TBARS) assay, and values were expressed in nanomoles per milliliter (nmol/mL). Total antioxidant capacity (TAC) was estimated using the ferric-reducing ability of plasma (FRAP) method and expressed in millimoles per liter (mmol/L). Superoxide dismutase (SOD) activity was measured by its ability to inhibit the autoxidation of pyrogallol and expressed in units per milliliter (U/mL). Glutathione peroxidase (GPx) activity was assessed spectrophotometrically based on the oxidation of NADPH and reported in units per liter (U/L). All assays were conducted in duplicate to ensure analytical reliability, and internal quality control standards were followed throughout.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 27.0. Continuous variables such as oxidative stress biomarkers were expressed as mean ± standard deviation (SD). Categorical variables including tumor grade and stage were presented as frequencies and percentages. The independent samples t-test was used to compare biomarker levels between low- and high-grade tumors, and between early (FIGO I–II) and advanced (FIGO III–IV) stages. Pearson's correlation coefficient was applied to examine the relationship between oxidative stress markers and tumor aggressiveness parameters. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 80 female patients newly diagnosed with ovarian cancer were included in this study. The mean age of participants was 52.6 ± 9.4 years, with the majority being postmenopausal (58.8%) and multiparous (76.3%). Most patients presented with abdominal distension, pelvic mass, or nonspecific lower abdominal pain. Based on histopathological findings, the most common histological subtype was high-grade serous carcinoma (HGSC), followed by endometrioid, mucinous, and clear cell carcinomas. The distribution of tumor grade and FIGO stage at diagnosis showed a predominance of advanced-stage (FIGO III–IV) and high-grade disease, reflecting the aggressive nature of the disease and the diagnostic delay frequently encountered in clinical practice.

Table 1 presents the demographic and clinical characteristics of the study population, stratified according to tumor aggressiveness (low-grade vs. high-grade). Patients with high-grade tumors tended to be older, with a higher proportion of FIGO stage III/IV disease, lymphovascular invasion, and peritoneal carcinomatosis compared to those with low-grade tumors. The mean body mass index (BMI) was also slightly higher in the high-grade group, although this difference did not reach statistical significance (p=0.068).

Table 1: Demographic and Clinical Characteristics of Patients Stratified by Tumor Grade

Parameter	Low-Grade Tumors (n=26)	High-Grade Tumors (n=54)	p-value
Mean Age (years)	48.1 ± 8.5	55.3 ± 8.9	<0.001
Postmenopausal (%)	11 (42.3%)	36 (66.7%)	0.031
Mean BMI (kg/m²)	26.1 ± 2.8	27.6 ± 3.1	0.068
FIGO Stage III–IV (%)	8 (30.7%)	44 (81.4%)	<0.001
Lymphovascular Invasion (%)	7 (26.9%)	37 (68.5%)	<0.001
Peritoneal Spread (%)	4 (15.3%)	32 (59.2%)	<0.001

As shown in Table 1, tumor grade correlated strongly with advanced disease features, especially FIGO staging and lymphovascular invasion, reinforcing the classification of high-grade tumors as biologically more aggressive.

The core focus of the study was the relationship between oxidative stress biomarkers and tumor aggressiveness. Table 2 summarizes the serum levels of malondialdehyde (MDA), total antioxidant capacity (TAC), superoxide dismutase (SOD), and glutathione peroxidase (GPx), stratified by tumor grade. The data reveal a striking oxidative imbalance in patients with high-grade tumors, with significantly elevated MDA levels and markedly reduced antioxidant defenses. The mean MDA concentration in the high-grade group was 6.84 ± 1.19 nmol/mL, nearly double that of the low-grade group (3.79 ± 0.73 nmol/mL, p<0.001). Likewise, TAC, SOD, and GPx levels were significantly lower in the high-grade group (all p<0.001).

Table 2: Serum Oxidative Stress Biomarkers According to Tumor Grade

Biomarker	Low-Grade Tumors (n=26)	High-Grade Tumors (n=54)	p-value
MDA (nmol/mL)	3.79 ± 0.73	6.84 ± 1.19	<0.001
TAC (mmol/L)	1.27 ± 0.19	0.84 ± 0.12	<0.001
SOD (U/mL)	146.3 ± 17.5	97.8 ± 14.9	<0.001
GPx (U/L)	67.5 ± 11.2	43.3 ± 8.6	<0.001

Table 2 clearly demonstrates a biochemical pattern of elevated oxidative damage and reduced antioxidant defense in high-grade tumors, underscoring the potential utility of these biomarkers in distinguishing between aggressive and indolent forms of ovarian cancer.

To further evaluate the clinical relevance of oxidative stress in disease progression, patients were also stratified according to FIGO staging, comparing early-stage disease (I–II) with advanced-stage disease (III–IV). Table 3 shows the mean biomarker levels in these two groups. A statistically significant increase in MDA and decrease in TAC, SOD, and GPx were observed in patients with

advanced-stage tumors. The oxidative stress burden appears to progressively worsen with disease advancement, further strengthening the correlation between redox status and tumor aggressiveness.

Table 3: Serum Oxidative Stress Biomarkers Stratified by FIGO Stage

Biomarker	FIGO Stage I–II (n=29)	FIGO Stage III–IV (n=51)	p-value
MDA (nmol/mL)	3.96 ± 0.82	6.55 ± 1.24	<0.001
TAC (mmol/L)	1.21 ± 0.15	0.88 ± 0.13	<0.001
SOD (U/mL)	142.7 ± 16.1	102.1 ± 15.2	<0.001
GPx (U/L)	65.3 ± 9.6	45.8 ± 8.9	<0.001

The findings in Table 3 indicate that oxidative stress markers can effectively distinguish between early and advanced disease states, which could be of diagnostic and prognostic significance in clinical practice. Finally, to quantify the strength of association between oxidative stress biomarkers and tumor aggressiveness, Pearson's correlation analysis was performed. As shown in Table 4, a strong positive correlation was observed between MDA levels and FIGO stage ($r=0.72$, $p<0.001$), while TAC, SOD, and GPx were all negatively correlated with tumor stage and histological grade ($p<0.001$ for all), indicating that as disease severity increases, antioxidant defense diminishes in a statistically predictable manner.

Table 4: Correlation Between Oxidative Stress Biomarkers and Tumor Aggressiveness Parameters

Biomarker	Tumor Grade (r)	Tumor Stage (r)	p-value (All)
MDA	+0.69	+0.72	<0.001
TAC	−0.65	−0.67	<0.001
SOD	−0.61	−0.63	<0.001
GPx	−0.68	−0.70	<0.001

In summary, the results of this hospital-based study strongly demonstrate that ovarian cancer patients with high-grade and advanced-stage tumors exhibit a profoundly dysregulated oxidative stress profile, characterized by elevated serum malondialdehyde and suppressed antioxidant enzyme activity. The robust correlations observed between redox biomarkers and tumor aggressiveness parameters such as histological grade and FIGO stage suggest that oxidative stress plays a central role in driving ovarian tumor progression. These findings not only validate the importance of oxidative imbalance in ovarian cancer pathophysiology but also propose that serum oxidative biomarkers may serve as reliable, non-invasive indicators of tumor behavior, with potential implications for prognostic assessment, treatment stratification, and future antioxidant-based therapeutic interventions.

DISCUSSION

The current hospital-based study provides robust evidence that oxidative stress plays a significant role in the biological aggressiveness of ovarian cancer[12]. Our findings demonstrate that patients with high-grade tumors and advanced-stage disease exhibit markedly higher levels of serum malondialdehyde (MDA), a marker of lipid peroxidation, along with significantly reduced levels of essential antioxidant parameters including total antioxidant capacity (TAC), superoxide dismutase (SOD), and glutathione peroxidase (GPx). These associations were statistically significant and suggest that oxidative stress is not only a feature of ovarian malignancy but also closely linked with its progression and severity[13].

Malondialdehyde is one of the most studied end-products of lipid peroxidation and has been widely accepted as a reliable marker of oxidative damage. In the present study, MDA levels were nearly doubled in patients with high-grade tumors compared to those with low-grade histology[14]. This observation indicates an excessive oxidative burden in aggressive ovarian cancers, likely driven by high metabolic rates, hypoxic tumor microenvironments, and ongoing inflammation. Previous literature supports this pattern. Previous studies have reported similar findings, emphasizing the association between lipid peroxidation and cancer cell proliferation, angiogenesis, and chemoresistance[15].

On the other hand, antioxidant defense mechanisms, particularly enzymatic antioxidants such as SOD and GPx, were significantly compromised in patients with more aggressive disease phenotypes. These enzymes serve as critical protectors against ROS-induced damage. Their reduced activity in high-grade ovarian tumors may be the result of enzyme consumption due to persistent oxidative stress, or it may reflect impaired antioxidant regulation in cancer cells. TAC, a global measure of non-enzymatic and enzymatic antioxidant potential, was also significantly lower in patients with advanced-stage and high-grade disease, suggesting a systemic oxidative imbalance[16, 17].

These findings suggest a clear inverse relationship between antioxidant levels and tumor aggressiveness. Importantly, Pearson's correlation analysis confirmed that MDA had a strong positive correlation with tumor stage and grade, while TAC, SOD, and GPx exhibited significant negative correlations with these clinical parameters. These patterns reinforce the hypothesis that redox status influences tumor behavior and could be used as a biochemical indicator of disease severity[18, 19].

From a pathophysiological perspective, chronic oxidative stress in the tumor microenvironment can enhance tumor progression through multiple mechanisms. Reactive oxygen species (ROS) promote DNA damage, genomic instability, and mutations in oncogenes and tumor suppressor genes such as p53 and BRCA1[20]. Furthermore, ROS modulate signaling pathways including NF-κB, MAPK, and HIF-1α, which are implicated in epithelial-mesenchymal transition (EMT), angiogenesis, and metastasis. These molecular alterations contribute to the enhanced proliferative and invasive capacity observed in aggressive ovarian tumors[21].

Clinically, these results support the potential utility of oxidative stress biomarkers as non-invasive tools for prognostication and disease monitoring. MDA, TAC, SOD, and GPx could be incorporated into risk stratification models to identify patients at higher risk of poor outcomes, allowing for earlier intervention and personalized treatment plans[22]. Additionally, these findings raise the possibility of antioxidant-based adjunct therapies aimed at restoring redox balance. Preclinical studies have shown promising results with agents such as N-acetylcysteine, resveratrol, and vitamin E, although clinical trials are needed to validate their effectiveness in ovarian cancer management[23].

Nonetheless, this study has several limitations. Being cross-sectional, it cannot establish causality or temporal relationships between oxidative stress and tumor progression[24]. Serum oxidative stress levels were measured at a single time point, which may not reflect fluctuations during disease course or treatment. Dietary factors, environmental exposures, and genetic predispositions that influence oxidative status were not fully controlled. Future longitudinal studies, with serial measurements and larger multicenter cohorts, are required to confirm these associations and explore their predictive value over time[25].

In conclusion, the present study underscores the significant association between oxidative stress and tumor aggressiveness in ovarian cancer. Elevated MDA and diminished antioxidant enzyme activity are strongly linked with higher histological grade and advanced FIGO staging, suggesting their potential role as biochemical indicators of disease severity. These findings open new avenues for research into oxidative stress as a target for diagnosis, prognosis, and therapeutic intervention in ovarian cancer[26].

CONCLUSION

This hospital-based study demonstrates a significant association between oxidative stress biomarkers and tumor aggressiveness in patients with ovarian cancer. Elevated serum levels of malondialdehyde (MDA), accompanied by reduced levels of total antioxidant capacity (TAC), superoxide dismutase (SOD), and

glutathione peroxidase (GPx), were observed in patients with high-grade histology and advanced FIGO stages. These findings reflect a marked redox imbalance in biologically aggressive tumors and highlight oxidative stress as both a potential driver and indicator of tumor progression. The strong correlations observed suggest that oxidative biomarkers could serve as valuable, non-invasive tools for clinical risk stratification, prognosis, and possibly therapeutic targeting in ovarian cancer management. Further longitudinal and interventional studies are needed to explore the predictive and therapeutic implications of these biomarkers across different tumor subtypes and treatment modalities.

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Authors' Contributions: HK conceptualized and led the study. NA and MM contributed to data collection and laboratory analysis. AT and HS managed clinical coordination and patient recruitment. FA supervised histopathological correlation and contributed to manuscript review. All authors critically reviewed, revised, and approved the final manuscript.

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REFERENCES

1. Liu Q, Yang X, Yin Y, Zhang H, Yin F, Guo P, et al. Identifying the Role of Oxidative Stress-Related Genes as Prognostic Biomarkers and Predicting the Response of Immunotherapy and Chemotherapy in Ovarian Cancer. Oxidative medicine and cellular longevity. 2022;2022(1):6575534.
2. Pal MK, Jaiswar SP, Dwivedi VN, Tripathi AK, Dwivedi A, Sankhwar P. MicroRNA: a new and promising potential biomarker for diagnosis and prognosis of ovarian cancer. Cancer biology & medicine. 2015;12(4):328-41.
3. Leone A, Roca MS, Ciardiello C, Costantini S, Budillon A. Oxidative stress gene expression profile correlates with cancer patient poor prognosis: identification of crucial pathways might select novel therapeutic approaches. Oxidative Medicine and Cellular Longevity. 2017;2017(1):2597581.
4. Martinez-Useros J, Li W, Cabeza-Morales M, Garcia-Foncillas J. Oxidative stress: a new target for pancreatic cancer prognosis and treatment. Journal of clinical medicine. 2017;6(3):29.
5. Baczewska M, Bojczuk K, Kołakowski A, Dobroch J, Guzik P, Knapp P. Obesity and energy substrate transporters in ovarian cancer. Molecules. 2021;26(6):1659.
6. Hoter A, Naim HY. Heat shock proteins and ovarian cancer: important roles and therapeutic opportunities. Cancers. 2019;11(9):1389.
7. Zhang W, Ye B, Liang W, Ren Y. Preoperative prognostic nutritional index is a powerful predictor of prognosis in patients with stage III ovarian cancer. Scientific reports. 2017;7(1):9548.
8. Tyagi K, Mandal S, Roy A. Recent advancements in therapeutic targeting of the Warburg effect in refractory ovarian cancer: a promise towards disease remission. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2021;1876(1):188563.
9. Ganjali S, Ricciuti B, Pirro M, Butler AE, Atkin SL, Banach M, et al. High-density lipoprotein components and functionality in cancer: state-of-the-art. Trends in Endocrinology & Metabolism. 2019;30(1):12-24.
10. Wilczyński JR, Wilczyński M, Paradowska E. Cancer stem cells in ovarian cancer—a source of tumor success and a challenging target for novel therapies. International Journal of Molecular Sciences. 2022;23(5):2496.
11. Kobayashi H, Imanaka S. Toward an understanding of tissue factor pathway inhibitor-2 as a novel serodiagnostic marker for clear cell carcinoma of the ovary. Journal of Obstetrics and Gynaecology Research. 2021;47(9):2978-89.
12. Yang L, Xie H-J, Li Y-Y, Wang X, Liu X-X, Mai J. Molecular mechanisms of platinum-based chemotherapy resistance in ovarian cancer. Oncology reports. 2022;47(4):1-11.
13. Falco M, Palma G, Rea D, De Biase D, Scala S, D'Aiuto M, et al. Tumour biomarkers: homeostasis as a novel prognostic indicator. Open biology. 2016;6(12):160254.
14. Chen S, Li Y, Qian L, Deng S, Liu L, Xiao W, et al. A review of the clinical characteristics and novel molecular subtypes of endometrioid ovarian cancer. Frontiers in oncology. 2021;11:668151.
15. Chon HS, Sehovic M, Marchion D, Walko C, Xiong Y, Extermann M. Biologic mechanisms linked to prognosis in ovarian cancer that may be affected by aging. Journal of Cancer. 2019;10(12):2604.
16. Shah F, Logsdon D, Messmann RA, Fehrenbacher JC, Fishel ML, Kelley MR. Exploiting the Ref-1-APE1 node in cancer signaling and other diseases: from bench to clinic. NPJ precision oncology. 2017;1(1):19.
17. Zhang M, Zhuang G, Sun X, Shen Y, Zhao A, Di W. Risk prediction model for epithelial ovarian cancer using molecular markers and clinical characteristics. Journal of Ovarian Research. 2015;8:1-12.
18. Berretta M, Cavaliere C, Alessandrini L, Stanzione B, Facchini G, Balestreri L, et al. Serum and tissue markers in hepatocellular carcinoma and cholangiocarcinoma: clinical and prognostic implications. Oncotarget. 2016;8(8):14192.
19. Ahmed N, Kadife E, Raza A, Short M, Jubinsky PT, Kannourakis G. Ovarian cancer, cancer stem cells and current treatment strategies: A potential role of magmas in the current treatment methods. Cells. 2020;9(3):719.
20. Kadhel P, Revaux A, Carbonnel M, Naoura I, Asmar J, Ayoubi JM. An update on preoperative assessment of the resectability of advanced ovarian cancer. Hormone Molecular Biology and Clinical Investigation. 2020;41(3):20190032.
21. Testa U, Petrucci E, Pasquini L, Castelli G, Pelosi E. Ovarian cancers: genetic abnormalities, tumor heterogeneity and progression, clonal evolution and cancer stem cells. Medicines. 2018;5(1):16.
22. Schwameis R, Grimm C, Brodowicz T, Petru E, Hefler-Frischmuth K, Staudigl C, et al. Gamma-glutamyltransferase as novel biomarker in patients with uterine leiomyosarcoma. Scientific reports. 2016;6(1):33757.
23. Mieulet V, Garnier C, Kieffer Y, Guilbert T, Nemati F, Marangoni E, et al. Stiffness increases with myofibroblast content and collagen density in mesenchymal high grade serous ovarian cancer. Scientific reports. 2021;11(1):4219.
24. Criscuolo D, Avolio R, Calice G, Laezza C, Paladino S, Navarra G, et al. Cholesterol homeostasis modulates platinum sensitivity in human ovarian cancer. Cells. 2020;9(4):828.
25. Ain Qu, Muhammad S, Hai Y, Peiling L. The role of urine and serum biomarkers in the early detection of ovarian epithelial tumours. Journal of Obstetrics and Gynaecology. 2022;42(8):3441-9.
26. Mancini A, Bruno C, Vergani E, d'Abate C, Giacchi E, Silvestrini A. Oxidative stress and low-grade inflammation in polycystic ovary syndrome: controversies and new insights. International Journal of Molecular Sciences. 2021;22(4):1667.

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