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ORIGINAL ARTICLE

Association between Oxidative Stress Biomarkers, Tumor Aggressiveness, and Hematological Abnormalities in Ovarian Cancer Patients: A Hospital-Based Study

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ABSTRACT

Background: Ovarian cancer remains a leading cause of gynecologic cancer-related mortality, often diagnosed at advanced stages. Oxidative stress is increasingly recognized as a key contributor to tumor progression, while hematological abnormalities frequently reflect underlying tumor biology and systemic inflammation.

Objective: To investigate the association between oxidative stress biomarkers, tumor aggressiveness, and hematological abnormalities in patients with epithelial ovarian carcinoma.

Methods: This hospital-based cross-sectional study included 70 patients diagnosed with histologically confirmed epithelial ovarian cancer, recruited from the Departments of Obstetrics and Gynecology at Nawaz Sharif Medical College, Bolan Medical College Hospital, and Gulab Devi Teaching Hospital between January 2022 and April 2023. Serum levels of malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx) were measured. Hematological parameters, including hemoglobin, white blood cell count, platelet count, red cell distribution width (RDW), and mean corpuscular volume (MCV), were analyzed. Tumor grade, FIGO stage, and Ki-67 index were used to assess tumor aggressiveness. Multivariate regression was used to identify independent predictors.

Results: MDA levels were significantly elevated in high-grade and advanced-stage tumors ($p < 0.001$), while SOD and GPx levels were significantly reduced ($p = 0.002$ and 0.004, respectively). Anemia (74.2%), thrombocytosis (32.8%), and elevated RDW (64%) were commonly observed and strongly associated with oxidative imbalance and tumor severity. MDA and platelet count independently predicted tumor grade, whereas SOD and hemoglobin were independent predictors of FIGO stage (adjusted $R^2 = 0.59$, $p < 0.001$).

Conclusion: Oxidative stress and hematological abnormalities are significantly associated with tumor aggressiveness in ovarian cancer. MDA, SOD, GPx, and routine hematologic indices may serve as accessible prognostic biomarkers, particularly in low-resource settings.

Keywords: Ovarian cancer, oxidative stress, malondialdehyde, superoxide dismutase, glutathione peroxidase, tumor aggressiveness, hematological abnormalities.

INTRODUCTION

Ovarian cancer remains one of the most lethal gynecological malignancies worldwide, accounting for approximately 3% of all female cancers but contributing disproportionately to cancer-related mortality among women. According to global cancer statistics, it is the eighth most common cause of cancer death in women, with more than 300,000 new cases and 200,000 deaths reported annually[1]. The insidious nature of ovarian cancer, characterized by vague or absent symptoms during early stages, often leads to late-stage diagnosis. By the time most patients are clinically evaluated, the disease has progressed to advanced stages (FIGO stage III or IV), significantly limiting therapeutic options and reducing survival rates[2].

Despite advancements in surgical techniques and chemotherapeutic regimens, the five-year survival rate for advanced-stage ovarian cancer remains dismally low, typically ranging from 30% to 40%. The heterogeneous nature of ovarian tumors, encompassing diverse histological subtypes and variable genetic and molecular profiles, further complicates effective management[3]. Among the various factors contributing to tumor development and progression, oxidative stress has garnered substantial research interest due to its fundamental role in cellular transformation, proliferation, angiogenesis, and metastasis[4].

Oxidative stress refers to the biochemical imbalance between the generation of reactive oxygen species (ROS) and the ability of endogenous antioxidant systems to neutralize them. ROS, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-), are highly reactive molecules that can damage DNA, proteins, and lipids, leading to genomic instability and tumorigenesis. In the context of ovarian cancer, chronic oxidative stress contributes to DNA strand breaks, base modifications, oncogene activation, and inhibition of tumor suppressor genes such as TP53[5]. Moreover, oxidative stress can stimulate the production of pro-inflammatory cytokines and angiogenic factors, promoting tumor invasion and metastasis[6].

Several oxidative stress biomarkers have been evaluated in cancer research, among which malondialdehyde (MDA) is a well-recognized product of lipid peroxidation and a direct indicator of cellular oxidative damage. In contrast, enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) represent the antioxidant defense mechanisms attempting to counteract ROS-mediated injury[7]. Elevated MDA levels and diminished antioxidant enzyme activity have been associated with aggressive tumor behavior, poor response to therapy, and worse prognosis in various cancers, including breast, cervical, and colorectal cancer. However, limited comprehensive data exist for such associations in ovarian cancer patients, especially in resource-limited healthcare settings[8].

Tumor aggressiveness is a multidimensional concept involving histological grade, stage, proliferation index (e.g., Ki-67), vascular invasion, and metastatic potential. Aggressive ovarian tumors are characterized by rapid growth, resistance to chemotherapy, and a higher likelihood of recurrence and mortality. Emerging evidence suggests that heightened oxidative stress correlates with these aggressive features by facilitating epithelial-to-mesenchymal transition (EMT), upregulating matrix

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metalloproteinases (MMPs), and disrupting the tumor microenvironment[9, 10].

In parallel, hematological abnormalities frequently accompany malignancies and serve as both diagnostic and prognostic indicators. Cancer-related anemia, leukocytosis, and thrombocytosis are often observed in ovarian cancer due to chronic inflammation, bone marrow suppression, and cytokine dysregulation[11]. For instance, elevated platelet counts have been linked to increased production of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), which promote tumor progression and angiogenesis. Anemia and elevated red cell distribution width (RDW) may reflect systemic oxidative stress and nutritional deficiencies, further complicating patient outcomes. Although hematological derangements are routinely monitored in cancer patients, their correlation with oxidative stress markers and tumor characteristics remains inadequately understood in ovarian malignancies[12].

Thus, there exists a compelling need to investigate the interconnected roles of oxidative stress, tumor aggressiveness, and hematological abnormalities in ovarian cancer. This integration may offer a novel approach for early risk stratification, monitoring disease progression, and evaluating therapeutic responses[13]. Biomarkers such as MDA, SOD, and GPx, in combination with routine hematological indices, could provide a cost-effective and non-invasive means of assessing tumor biology in clinical settings, particularly in low- and middle-income countries where advanced molecular testing may be inaccessible[14].

The present hospital-based study aims to bridge this critical knowledge gap by evaluating the association between oxidative stress biomarkers (MDA, SOD, GPx), tumor aggressiveness parameters (grade, stage, Ki-67 index), and hematological abnormalities (hemoglobin, WBC, platelets, RDW, MCV) in patients diagnosed with ovarian cancer. Understanding these relationships may not only contribute to better prognostication but also support the development of adjunct therapeutic strategies targeting oxidative stress and inflammation in ovarian cancer management[15].

MATERIALS AND METHODS

This hospital-based cross-sectional observational study was conducted over a period of sixteen months, from January 2022 to April 2023, in the Departments of Obstetrics and Gynecology at three tertiary care teaching hospitals: Nawaz Sharif Medical College, University of Gujrat; Bolan Medical College Hospital (BMCH), Quetta; and Gulab Devi Teaching Hospital, Lahore. The study aimed to assess the association between oxidative stress biomarkers, tumor aggressiveness, and hematological abnormalities in women diagnosed with ovarian cancer. A total of 70 female patients, aged between 25 and 70 years, with histopathologically confirmed epithelial ovarian carcinoma were enrolled using non-probability purposive sampling. Patients were included if they had not received any prior chemotherapy or radiotherapy, were not taking antioxidant supplements, and were free from comorbid autoimmune, infectious, or chronic inflammatory conditions that could confound oxidative or hematological parameters. Patients with non-epithelial tumors or known hematological disorders unrelated to malignancy were excluded from the study.

Ethical approval for the study was obtained from the institutional review boards of all participating institutions, and informed written consent was taken from each patient prior to enrollment. Clinical and demographic information, including age, menopausal status, tumor type, FIGO stage, and histological grade, was obtained through patient records and standardized case reporting forms. Tumor aggressiveness was evaluated based on histological grade, clinical staging according to the International Federation of Gynecology and Obstetrics (FIGO) classification, and proliferative activity assessed by the Ki-67 index using immunohistochemistry. Ki-67 expression levels were recorded as low (<20%), moderate (20–50%), or high (>50%) based on pathologist reports.

For biochemical assessment of oxidative stress, venous blood samples were drawn from fasting patients. The samples were processed to obtain serum, which was analyzed for malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx). MDA levels were measured using the thiobarbituric acid reactive substances (TBARS) assay, a well-established method that detects lipid peroxidation products. SOD activity was assessed spectrophotometrically based on the inhibition of pyrogallol oxidation, whereas GPx activity was quantified using enzyme-specific colorimetric assays. All biochemical tests were conducted in institutional biochemistry laboratories following standard operating procedures to ensure accuracy and reproducibility.

In parallel, hematological analysis was performed by collecting blood samples in EDTA tubes and evaluating them using fully automated hematology analyzers. Parameters assessed included hemoglobin concentration, total white blood cell (WBC) count, platelet count, red cell distribution width (RDW), and mean corpuscular volume (MCV). Hematological abnormalities such as anemia, leukocytosis, and thrombocytosis were recorded and categorized according to standard reference ranges.

All data were compiled and analyzed using IBM SPSS version 25. Quantitative variables were expressed as means and standard deviations, while qualitative variables were presented as frequencies and percentages. The relationship between oxidative stress biomarkers and tumor aggressiveness parameters was assessed using Pearson's correlation coefficient and analysis of variance (ANOVA), while associations between hematological abnormalities and tumor characteristics were evaluated using the chi-square test. Multivariate linear regression analysis was employed to identify independent predictors of tumor stage and grade. A p-value of less than 0.05 was considered statistically significant throughout the analysis.

RESULTS

This study involved 70 women diagnosed with epithelial ovarian carcinoma. The mean age of participants was 51.8 ± 9.6 years, and the majority (62.8%) were postmenopausal at the time of diagnosis. Histologically, serous carcinoma was the most common subtype, observed in 68.5% of cases, followed by mucinous carcinoma in 17.1%, endometrioid carcinoma in 8.5%, and clear cell carcinoma in 5.7%. Regarding tumor grade, 57.1% of the tumors were high-grade (Grade III), 27.1% were intermediate-grade (Grade II), and 15.7% were low-grade (Grade I). Clinical staging based on FIGO criteria revealed that 70% of patients were diagnosed at advanced stages (Stage III–IV), with only 30% detected in early stages (Stage I–II). These findings underscore the predominance of late-stage diagnosis and high-grade pathology in this patient population (Table 1).

Table 1: Demographic and Clinical Characteristics of Study Participants

Variable	Value
Mean Age (years)	51.8 ± 9.6
Postmenopausal Status (%)	62.8%
Histological Subtypes	
Serous Carcinoma	68.5%
Mucinous Carcinoma	17.1%
Endometrioid Carcinoma	8.5%
Clear Cell Carcinoma	5.7%
Tumor Grade	
Grade I (Low)	15.7%
Grade II (Intermediate)	27.1%
Grade III (High)	57.1%
FIGO Stage	
Stage I–II (Early)	30.0%
Stage III–IV (Advanced)	70.0%

When oxidative stress biomarkers were analyzed, serum malondialdehyde (MDA) levels were significantly higher in patients

with advanced-stage tumors (Stage III–IV) compared to those with early-stage disease. The mean MDA level was 7.1 ± 1.3 µmol/L in Stage III–IV versus 4.9 ± 1.1 µmol/L in Stage I–II ($p < 0.001$). Additionally, patients with high-grade tumors and higher Ki-67 proliferation index also exhibited elevated MDA levels. On the other hand, antioxidant enzymes showed an inverse pattern. Superoxide dismutase (SOD) levels declined from 2.5 ± 0.6 U/mL in early-stage to 1.7 ± 0.4 U/mL in advanced-stage tumors ($p = 0.002$), while glutathione peroxidase (GPx) levels dropped from 6.2 ± 1.0 U/mL to 4.1 ± 0.9 U/mL ($p = 0.004$). These patterns clearly demonstrate an imbalance between oxidative and antioxidative mechanisms as the disease progresses. These findings are summarized in Table 2.

Table 2: Oxidative Stress Biomarkers by Tumor Stage

Biomarker	Stage I–II	Stage III–IV	p-value
MDA (µmol/L)	4.9 ± 1.1	7.1 ± 1.3	<0.001
SOD (U/mL)	2.5 ± 0.6	1.7 ± 0.4	0.002
GPx (U/mL)	6.2 ± 1.0	4.1 ± 0.9	0.004

Hematological evaluation showed that anemia (Hb <11 g/dL) was the most common abnormality, present in 74.2% of the patients. Anemia was significantly more prevalent in those with advanced-stage tumors ($p = 0.008$). Thrombocytosis (platelet count >450,000/µL) was seen in 32.8% of patients, especially those with high-grade tumors (42.5%, $p = 0.021$). Leukocytosis (WBC >11,000/µL) was observed in 28.5% of patients, primarily in those with higher oxidative stress. Furthermore, 64% of patients had RDW >15%, and 39% had abnormal MCV values. These abnormalities were significantly associated with high MDA levels and low antioxidant enzyme activity, reflecting systemic inflammation and oxidative damage. Table 3 provides a detailed overview of these hematological patterns and their clinical correlations.

Table 3: Hematological Parameters and Their Association with Tumor Characteristics

Parameter	Frequency (%)	Higher Frequency In	p-value
Anemia (Hb <11 g/dL)	74.2%	Stage III/IV	0.008
Thrombocytosis (>450,000/µL)	32.8%	Grade III	0.021
Leukocytosis (>11,000/µL)	28.5%	Stage III/IV	0.034
RDW >15%	64.0%	High MDA / Low GPx	0.015
Abnormal MCV	39.0%	Advanced Stage	0.049

Multivariate regression analysis was conducted to identify independent predictors of tumor aggressiveness. MDA emerged as a strong independent predictor of tumor grade ($\beta = 0.51$, $p < 0.001$), while platelet count also contributed significantly ($\beta = 0.36$, $p = 0.004$). For FIGO stage, both SOD ($\beta = -0.42$, $p = 0.003$) and hemoglobin ($\beta = -0.39$, $p = 0.006$) were significant inverse predictors. The adjusted R^2 value of the model was 0.59, indicating that 59% of the variability in tumor stage and grade could be explained by these variables. These results are displayed in Table 4.

Table 4: Multivariate Regression Analysis Predicting Tumor Aggressiveness

Predictor	Predicts	Beta Coefficient	p-value
MDA	Tumor Grade	0.51	<0.001
Platelet Count	Tumor Grade	0.36	0.004
SOD	FIGO Stage	-0.42	0.003
Hemoglobin	FIGO Stage	-0.39	0.006

In summary, patients with advanced or high-grade ovarian cancer displayed elevated oxidative stress (higher MDA), compromised antioxidant defenses (lower SOD and GPx), and distinct hematological abnormalities, including anemia and thrombocytosis. These findings, as shown through Tables 1–4, demonstrate a strong interrelationship between oxidative stress, hematologic profile, and tumor aggressiveness, highlighting the clinical utility of these biomarkers for prognosis and therapeutic monitoring.

DISCUSSION

The present hospital-based cross-sectional study evaluated the relationship between oxidative stress biomarkers, tumor aggressiveness, and hematological abnormalities in patients diagnosed with epithelial ovarian cancer[16]. The findings highlight a strong and statistically significant association between elevated oxidative stress (indicated by high MDA levels), decreased antioxidant enzyme activity (SOD and GPx), and advanced clinical and histopathological parameters of ovarian cancer. These findings are consistent with prior literature suggesting that oxidative stress plays a central role in the pathogenesis and progression of malignancies, particularly through the promotion of DNA damage, angiogenesis, and immune evasion[17].

Malondialdehyde (MDA), a final product of lipid peroxidation, was significantly elevated in patients with advanced-stage (FIGO Stage III–IV) and high-grade tumors. This is consistent with studies by Dasgupta et al. and Khan et al., which demonstrated a positive correlation between MDA levels and tumor progression in ovarian and other gynecologic cancers[18]. The elevated MDA levels reflect the extensive oxidative damage occurring in tumor cells, leading to increased proliferation and invasiveness. Conversely, SOD and GPx, which are critical enzymatic antioxidants responsible for detoxifying reactive oxygen species (ROS), were significantly reduced in patients with more aggressive tumors. This inverse relationship underscores a redox imbalance, wherein antioxidant defenses are overwhelmed by excessive ROS production in the tumor microenvironment[19].

The Ki-67 proliferation index, used as a marker for tumor aggressiveness, showed a strong positive correlation with MDA levels and a negative correlation with antioxidant enzymes. This further strengthens the hypothesis that oxidative stress is not merely a by-product of cancer but an active participant in driving its progression[20]. These findings also suggest that MDA, SOD, and GPx may serve as useful prognostic biomarkers for stratifying patients based on tumor biology and risk[21].

In addition to oxidative stress parameters, hematological abnormalities were found to be prevalent in this cohort and closely linked with tumor behavior. Anemia was present in over 70% of patients, a finding that aligns with reports of cancer-related anemia caused by chronic inflammation, nutritional deficiencies, and myelosuppressive effects of tumor-secreted cytokines. Thrombocytosis was also significantly associated with high-grade tumors[22]. Elevated platelet counts have previously been shown to correlate with increased levels of interleukin-6 and vascular endothelial growth factor (VEGF), both of which promote tumor angiogenesis and metastasis. Leukocytosis, another common paraneoplastic finding, may reflect both tumor-induced inflammation and immune modulation[23].

Furthermore, red cell distribution width (RDW) and mean corpuscular volume (MCV) abnormalities were prevalent and showed statistically significant associations with oxidative stress levels. These parameters, although nonspecific, provide additional insight into systemic physiological disruption in advanced ovarian cancer and may offer value as adjunctive markers in routine evaluation[24].

The multivariate regression analysis identified MDA and platelet count as independent predictors of tumor grade, and SOD and hemoglobin levels as independent predictors of FIGO stage. This statistical model, which explained nearly 59% of the variance in tumor aggressiveness, highlights the potential of using a combination of biochemical and hematological markers to develop a clinically useful prognostic index[25].

From a clinical perspective, the integration of oxidative stress biomarkers and complete blood count-derived indices into standard diagnostic and prognostic workflows could offer a cost-effective, non-invasive means of patient risk stratification. This is particularly relevant in resource-limited settings such as Pakistan,

where access to advanced molecular diagnostics is restricted. Moreover, these findings open avenues for future research into the use of antioxidant therapies as adjuvants to conventional treatments in ovarian cancer, potentially enhancing treatment outcomes and reducing chemoresistance[26].

However, this study is not without limitations. The cross-sectional design limits the ability to draw causal inferences. The sample size, although adequate for primary analysis, may limit the generalizability of findings. Furthermore, dietary factors, lifestyle, and other comorbidities that can influence oxidative stress levels were not controlled for. Nonetheless, the multicenter nature of the study and the inclusion of both biochemical and clinical parameters enhance the strength and applicability of the findings[27].

CONCLUSION

This study demonstrates a clear and clinically significant association between oxidative stress biomarkers, hematological abnormalities, and tumor aggressiveness in ovarian cancer patients. Elevated MDA levels and reduced SOD and GPx activity were strongly correlated with higher tumor grade, advanced FIGO stage, and increased proliferative index. Hematological disturbances, particularly anemia and thrombocytosis, were also prevalent and aligned with more aggressive disease characteristics. Together, these findings suggest that oxidative stress markers and routine hematological parameters can serve as valuable, cost-effective adjuncts for prognostic evaluation in ovarian cancer. The combined use of these biomarkers may enhance early identification of high-risk patients, guide individualized therapy, and inform clinical decision-making especially in low-resource healthcare environments. Future prospective studies with larger populations and longitudinal follow-up are recommended to validate these results and explore their implications in therapeutic monitoring and patient survival.

Availability of Data and Materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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