Original Article

Ki-67 as a Prognostic Indicator in Serous Types of Ovarian Malignancies

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Abstract

Objective: To assess the frequency and distribution of Ki-67 immunoexpression across different histological subtypes and tumor grades of surface epithelial serous ovarian carcinomas.

Methodology: This descriptive cross-sectional study was conducted at the Department of Pathology, SZABMU (PIMS), Islamabad, Pakistan, from January 15, 2022, to July 14, 2022. All patients fulfilling the inclusion criteria visiting PIMS, Islamabad, during the study period. All specimens were fixed in 10% formalin, followed by gross examination, sectioning, embedding in paraffin blocks, and preparation of hematoxylin and eosin (H&E)–stained slides. The slides were examined under a light microscope, and the diagnosis was recorded. Immunohistochemistry for Ki-67 was performed and evaluated accordingly. Data were analyzed using SPSS version 20. All statistical analyses were performed using two-tailed tests, with a p-value <0.05 considered statistically significant.

Results: The mean age of the study cohort was 52.4 years (SD ± 12.7). High-grade serous carcinoma constituted the majority of cases (62.9%), while low-grade serous carcinoma accounted for 37.1%. Evaluation of Ki-67 immunoexpression revealed low proliferative activity (1–30% staining) in 34.3% of cases, intermediate activity (31–50%) in 15.0%, and high proliferative activity (>50%) in 50.7%.

Conclusion: High-grade serous carcinoma was identified as the predominant tumor grade, with Ki-67 immunoexpression >50% being the most consistent proliferative marker. These findings highlight the need for larger, multicenter studies in Pakistan to validate the observed trends and strengthen their clinical and prognostic significance.

Keywords: Ki-67 Antigen; Immunohistochemistry; Ovarian Surface Epithelial Neoplasms; Grading.

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Introduction

Ovarian cancer remains one of the most lethal malignancies affecting women worldwide. It is the seventh most commonly diagnosed cancer and ranks as the third most frequent gynecological malignancy following cervical and uterine cancers.[1] Globally, ovarian cancer accounts for approximately 239,000 new cases and 152,000 deaths annually.[2] In Pakistan, it is the third most prevalent malignancy among women, following breast and oral cancers.[3]

The etiology of ovarian cancer is multifactorial, encompassing genetic, hormonal, and environmental contributors. Key risk factors include increasing age, ethnicity, a personal or family history of breast or ovarian cancer, and mutations in BRCA1/2 and other susceptibility genes.[3] These factors underscore the importance of early identification and stratification of high-risk individuals to improve outcomes.

Ovarian tumors are histologically classified based on their presumed tissue of origin. Among these, epithelial tumors represent the most common subtype, with serous carcinoma accounting for nearly 70% of all epithelial ovarian malignancies.[2] High-grade serous

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carcinomas (HGSCs) are believed to originate from the distal fallopian tube epithelium and subsequently implant on the ovarian surface.[4]

Tumor stage and histological grade represent the most significant prognostic determinants in ovarian carcinoma, with accurate classification being essential for guiding therapeutic decision-making. Borderline serous tumors generally follow an indolent clinical course and often obviate the need for systemic therapy. In contrast, low-grade serous carcinomas typically demonstrate relative resistance to conventional chemotherapy, whereas high-grade serous carcinomas, despite their aggressive biological behavior, exhibit greater chemosensitivity and therefore require more intensive systemic treatment.[5]

Recent advances in molecular pathology have identified potential biomarkers that may aid in the prognostication and therapeutic stratification of ovarian tumors. Among these, Ki-67 has emerged as a robust marker of cellular proliferation.[6] Ki-67 is a non-histone nuclear protein encoded by a gene located on chromosome 10q25. It is expressed in all active phases of the cell cycle (G1, S, G2, and M), but absent in quiescent cells (G0 phase), making it a valuable marker of tumor proliferation. Immunohistochemical assessment of Ki-67 involves quantifying the proportion of positively stained tumor nuclei, regardless of staining intensity. High Ki-67 expression has been reported in 65% of high-grade serous carcinomas, correlating with aggressive tumor behavior and poor clinical outcomes.[7,8]

This study aims to evaluate the immunoexpression of Ki-67 across various grades of ovarian serous carcinoma, including borderline, low-grade, and high-grade subtypes. By assessing its correlation with tumor grade, we seek to establish the utility of Ki-67 as a predictive and prognostic biomarker. Such insights may facilitate the early identification of tumors with invasive potential and support more tailored surveillance and management strategies, ultimately contributing to improved patient outcomes.

While Ki-67 is a recognized proliferation marker, its expression across borderline, low-grade, and high-grade ovarian serous tumors remains underexplored. Most studies focus on high-grade lesions and use variable cutoffs, limiting clinical applicability. Our study provides region-specific data to clarify expression patterns and assess Ki-67 as a practical prognostic tool in resource-limited settings.

Methodology

This cross-sectional study was conducted in the Department of Pathology, Pakistan Institute of Medical Sciences (PIMS), SZABMU, Islamabad, from January 15, 2022, to July 14, 2022. A non-probability consecutive sampling technique was used. The sample size of 140 was estimated using the WHO sample size calculator, with an anticipated prevalence of 65.34%[7], a 95% confidence level, and an absolute precision of 8%.

Biopsies and resection specimens of all patients aged 15–70 years, diagnosed by histopathology as borderline serous tumors, low-grade serous cystadenocarcinoma, or high-grade serous cystadenocarcinoma, were included.

All benign ovarian lesions and other variants of ovarian surface epithelial tumors, such as mucinous carcinoma, clear cell carcinoma, and endometrioid adenocarcinoma, were excluded from the study.

After approval from the hospital's ethical committee and CPSP Ref. No. CPSP/REU/HSP-2021-042-811, patients fulfilling the inclusion criteria were enrolled. All ovarian biopsies and surgical resection specimens diagnosed as ovarian surface serous tumors and received in the Department of Pathology, PIMS, Islamabad, were included. The specimens were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Slides were examined under a light microscope by a consultant pathologist alongside a postgraduate resident, and the final diagnosis was recorded. Immunohistochemistry for Ki-67 was performed and evaluated according to predefined criteria. Patient registration numbers and relevant clinical details were documented in a structured proforma.

Data were analyzed using SPSS version 20. Qualitative variables, including Ki-67 immunoexpression, were expressed as frequencies and percentages, while quantitative variables, such as age, were reported as mean ± standard deviation. Effect modifiers, such as age and tumor grade, were controlled through stratification, followed by application of the Chi-square test. Fisher's exact test was employed when the expected cell count was <5. All statistical analyses were performed using two-tailed tests, with a p-value <0.05 considered statistically significant.

Ki-67 IMMUNOEXPRESSION

Ki-67 immunoexpression was considered negative when less than 1% were stained and positive when more than 1% of cells showed nuclear positivity. Grading interpretation is shown in the following table I.[14] Positive cell measurement was done for each case by counting 1000 cells in 10 HPF.[8]

Table I: Staining criteria for Ki67.

Percentage of tumor cells showing positive staining	Interpretation
1-30%	+
30-50%	++
>50%	+++

Results

Stratification of Ki-67 immunoexpression with age groups showed that among patients aged 15–50 years, 16 (11.4%) had low expression (1–30%), 7 (5.0%) had moderate expression (30–50%), and 24 (17.1%) demonstrated high expression (>50%). In contrast, among patients above 50 years, 32 (22.9%) had low expression, 14 (10.0%) had moderate expression, and 47 (33.6%) showed high expression. The difference across age groups was not statistically significant (p = 0.998), as shown in Table II.

Table II: Stratification of age group with Ki67 expression. (n = 140)

	AGE GROUP [In Years]		
Ki67 EXPRESSION	20 – 50	>50	**P-Value**
1 – 30%	16(11.4%)	32(22.9%)	0.998
30 – 50%	7(5.0%)	14(10.0%)	
>50%	24(17.1%)	47(33.6%)	

Stratification by marital status revealed that in married women, 35 (24.6%) had low expression, 18 (12.7%) had moderate expression, and 52 (36.6%) demonstrated high expression, while among unmarried women, 15 (10.6%) showed low expression, 3 (2.1%) moderate expression, and 19 (13.4%) high expression. The association was again statistically insignificant (p = 0.381) as shown in Table III.

Table III: Stratification of marital status with Ki67 expression (n = 140)

Ki67	**Marital Status**		
EXPRESSION	Married	Unmarried	**P-Value**
1 – 30%	35(24.6%)	15(10.6%)	0.381
30 – 50%	18(12.7%)	3(2.1%)	
>50%	52(36.6%)	19(13.4%)	

When analyzed by tumor grade, 20 (14.3%) of low-grade tumors had low Ki-67 expression, 7 (5.0%) had moderate expression, and 25 (17.9%) had high expression. In high-grade tumors, 28 (20.0%) demonstrated low expression, 14 (10.0%) moderate expression, and 46 (32.9%) high expression. No statistically significant association was observed between Ki-67 expression and tumor grade (p = 0.717) as shown in table IV.

Table IV: Stratification for grade of tumor with Ki67 expression. (n = 140)

Ki67	**Grade of Tumor**		
EXPRESSION	Low	High	**P-value**
1 – 30%	20(14.3%)	28(20.0%)	0.717
30 – 50%	7(5.0%)	14(10.0%)	
>50%	25(17.9%)	46(32.9%)	

Discussion

Ovarian masses present across a wide age range, with approximately 8% of women between 25 to 40 years remaining asymptomatic. Nearly 80% of ovarian tumors are benign and occur in younger women aged 20–45 years, whereas borderline tumors usually present in slightly older patients. Malignant ovarian tumors, on the other hand, are more common in peri- and postmenopausal women, with incidence rising with age. Globally, ovarian cancer is the seventh leading cause of cancer-related mortality in women and the sixth most common female malignancy.[9,10] Despite advances in diagnostic and therapeutic modalities, the overall 5-year survival remains approximately 40%, largely due to late-stage presentation in almost 70% of patients.[11]

Prognostic factors such as age, histological type, tumor grade, serum CA-125 levels, and residual disease after cytoreductive surgery strongly influence patient outcomes.[12,13] Ki-67 has emerged as a useful immunohistochemical marker of tumor proliferation, expressed in actively dividing cells but absent in quiescent ones. Its detection using the MIB-1 antibody correlates with tumor aggressiveness and metastatic potential.[14,15]

In the present study, the mean patient age was 52.4 ± 12.7 years, which is higher than the 40 years reported in a previous study.[7] Tumor grading revealed low-grade serous carcinoma in 37.1% and high-grade serous carcinoma in 62.9% of patients. Ki-67 expression was low (1–30%) in 34.3%, moderate (30–50%) in 15.0%, and high (>50%) in 50.7% of cases. These findings are broadly comparable to Mahadevappa et al., who demonstrated high Ki-67 expression in nearly 70% of high-grade tumors and in advanced-stage disease.[7]

However, unlike some earlier studies that reported significant associations between Ki-67 expression and clinicopathological parameters, our stratification analysis revealed no statistically significant relationship

between Ki-67 expression and age group (p = 0.998), marital status (p = 0.381), or tumor grade (p = 0.717). This lack of significance may be attributed to sample size, study design, or unmeasured biological variables. Nevertheless, the overall distribution still indicates that high Ki-67 expression (>50%) was the most frequent finding in our cohort, suggesting that proliferative activity remains an important feature of serous ovarian carcinomas.

Ovarian cancer is a heterogeneous disease, arising from diverse precursor lesions and genetic alterations. This heterogeneity complicates early detection, and the absence of reliable screening tools results in most cases being diagnosed at advanced stages, where 10-year survival drops to 15–30% compared to 90% in early disease.[16] Malpica et al. categorized epithelial ovarian carcinomas into low-grade and high-grade subtypes.[18] While high-grade serous carcinoma accounts for the majority of cases and demonstrates responsiveness to chemotherapy, low-grade tumors, though less common (≈5%), show chemoresistance but comparatively better survival outcomes.[19–21]

Current management strategies rely on optimal cytoreductive surgery followed by platinum-based chemotherapy.[22] Prognosis in low-grade tumors is influenced by age at diagnosis and residual disease post-surgery.[23] As a proliferative marker, Ki-67 continues to hold value in ovarian cancer biology; however, its role as an independent prognostic marker remains uncertain given conflicting results across studies.[24,25]

Our findings highlight the predominance of high-grade serous carcinoma and frequent high Ki-67 expression, but without statistically significant associations with clinical variables in this cohort. This underlines the need for larger, multicenter studies incorporating additional molecular and clinicopathological parameters to clarify the prognostic and predictive utility of Ki-67 in ovarian carcinoma.

Conclusion

High-grade serous carcinoma emerged as the most prevalent tumor subtype in our study, with Ki-67 expression >50% observed as the most common immunohistochemical finding. These results underscore the aggressive nature of ovarian carcinoma and the potential utility of Ki-67 as a prognostic marker. However, to substantiate these findings, larger multicenter studies involving broader patient populations and additional clinical and molecular parameters are warranted within the Pakistani context.

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