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Research Article

ROLE OF EPIDERMAL GROWTH FACTOR RECEPTOR AND KI67 IN EPITHELIAL OVARIAN TUMOR

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ABSTRACT

Objective: The objective of the study was to evaluate epidermal growth factor receptor (EGFR) and Ki67 expression in epithelial ovarian tumors and assess the existence of any correlation between overexpression of these markers and histological grades.

Methods: This prospective study was conducted in the Department of Pathology in a tertiary care hospital of G.S.V.M. Medical College from 2022 to 2024. The study included 50 patients with histologically confirmed epithelial ovarian tumors, whose post-resection specimens were subjected to immunostaining to determine the degree of expression of EGFR and Ki67 proliferation index. Details were noted pertaining to age, tumor type, and histological grade. Statistical analysis included the Chi-square test, which evaluated associations between age, histological grade, EGFR expression, and Ki67 proliferation index.

Results: Most of the participants were below 60 years of age (80%). Most tumors were benign (72%), with serous cystadenoma being the most common (66%). The association between histological grade and age was statistically significant; with benign tumors being more common in patients aged ≤50 years and malignant tumors more frequent in those aged >50 years ($p=0.018$). EGFR expression was observed in 18% of the tumors, predominantly malignant ones, showing a significant association with tumor malignancy ($p<0.001$). In addition, the Ki67 proliferation index was significantly higher in malignant tumors ($p<0.001$), and its levels were associated with EGFR expression ($p=0.026$).

Conclusion: The study findings suggest that molecular markers such as EGFR and Ki67 may be useful in predicting tumor behavior and guiding tailored treatment strategies for ovarian cancer patients.

Keywords: Ovarian tumors, Histological grade, Immunohistochemistry, Molecular marker.

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INTRODUCTION

Surface epithelial tumors of the ovary are a diverse group of neoplasms that make up the most prevalent form of ovarian cancer. They make up about two-thirds of all ovarian tumors, with their malignant variants accounting for nearly 90% of ovarian malignancy [1]. Epithelial ovarian cancer remains the third most lethal gynecologic malignancies worldwide, contributing significantly to cancer-related morbidity and mortality [2]. Despite advances in therapeutic techniques, the high mortality rate associated with epithelial ovarian cancers underscores the need for a better understanding of the molecular pathways involved in their development and progression [3]. This information is critical for designing tailored treatment plans for each ovarian cancer subtype.

Based on histology, epithelial ovarian cancer has different subtypes. The most common type is serous cancer, which has two types: High grade and low-grade. Less common subtypes are mucinous cancer, endometrioid cancer, or clear cell ovarian cancer. These histological subtypes are associated with different cancer-causing mutations [4]. Among the plethora of biomarkers investigated in ovarian cancer, epidermal growth factor receptor (EGFR) and Ki-67 have emerged as key players, offering valuable insights into tumor biology, prognosis, and therapeutic response [5,6]. EGFR, a transmembrane glycoprotein, plays a crucial role in regulating cellular proliferation, survival, and differentiation by activating downstream signaling pathways. EGFR signaling dysregulation has been linked to carcinogenesis, progression, and treatment resistance in a variety of cancer types. Likewise, Ki-67, a nuclear protein associated with cellular proliferation, is a marker of tumor aggressiveness and has prognostic significance in various malignancies. Despite their recognized roles, the precise involvement of EGFR and Ki-67 in epithelial ovarian tumors remains incompletely understood [7]. Moreover, the interplay between these biomarkers and their clinical implications in ovarian cancer warrants further investigation. Therefore, the present study aimed to evaluate the expression of EGFR and Ki67 in epithelial ovarian tumors and assess the existence of any correlation between overexpression of these markers and histological grades.

METHODS

The present work was an observational study, with cross-sectional study design, conducted in the Department of Pathology at G.S.V.M. Medical College from 2022 to 2024. The study protocol was approved by the Institutional Ethics Committee, and participants were enrolled after obtaining informed written consent. The study was conducted on patients with ovarian cancer, whose resection specimens were received from the gynecology department post-surgery and were confirmed to have epithelial ovarian tumors. Patients who did not consent to participate in the study or those with non-epithelial ovarian tumors such as germ cell tumors, sex cord-stromal tumors, or metastatic tumors were excluded from the study.

A total of 50 formalin-fixed, paraffin-embedded epithelial ovarian tumor specimens were studied. Sections of 4–5 μm were prepared and stained with hematoxylin and eosin. Histological classification was done based on the World Health Organization criteria, categorizing tumors into serous, mucinous, endometrioid, clear cell, transitional (Brenner), mixed, and undifferentiated types. Following this, tissue sections were prepared for immunohistochemistry (IHC) and staining for both EGFR and Ki67 markers using standard protocol.

Cells with cytoplasmic or membrane staining were counted in areas with the highest expression. The staining patterns are as follows:

- 0= No staining or faint membranous staining in <10% of tumor cells
- 1+=Weak membranous staining in ≥10% of tumor cells
- 2+=Moderate membranous staining in ≥10% of tumor cells
- 3+= Strong membranous staining in ≥10% of tumor cells.

Ki67 immunoreactivity in epithelial ovarian tumors was assessed quantitatively as:

- Grade 1 – up to 2%
- Grade 2 – 3–20%
- Grade 3 – More than 20%.

For all study participants, detailed history, including personal, family, investigation, and treatment history, was documented. Gross examination details such as tumor location, appearance, size, invasion, and nodal metastasis were also recorded.

Statistical analysis

Data entry was done in Microsoft Excel and analysis was performed using Statistical Package for the Social Sciences version 20.0. Descriptive statistics was used to calculate the means and standard deviations (SDs) of the data. Chi-square test was applied to evaluate associations between categorical variables; analysis of variance test was performed to compare continuous variables between categories of histological grades. A $p<0.05$ was considered as statistically significant.

RESULTS

Out of 50 study participants, the majority were between 41 and 50 years of age (n=16, 32%), followed by those between 51 and 60 years of age (n=14, 28%) and 31–40 years (n=10, 20%). Overall, 80% of the patients were aged <60 years. The majority of the participants had serous cystadenoma (n=33, 66%) while 8%, 8%, 6%, 4% and 4% participants had low-grade serous carcinoma, high-grade serous carcinoma, mucinous cystadenoma, borderline serous tumor, and borderline mucinous tumor, respectively. There was one case each of Brenner tumor and clear cell carcinoma. Analysis of epithelial tumors according to histological grade revealed that 72% had benign tumors (n=36), 20% had malignant tumors (n=10), and 8% of the patients had borderline tumors (n=4) (Fig. 1).

A significant association was observed between histological grade and age; where patients with age ≤50 years had a higher rate of benign tumors compared to those with age >50 years who had a higher rate of malignant tumors (p=0.018) (Table 1).

IHC staining of specimen revealed that tumors of 41 patients (82%) were negative for EGFR, while four patients (8%) had weak EGFR expression, three patients (6%) had moderate EGFR expression, and two patients (4%) had strong EGFR expression. While 100% of the benign tumors were EGFR negative, among malignant tumors, 40%, 30% and 20% had weak, moderate, and strong EGFR expression, respectively (p<0.001) (Table 2).

Among the study participants, 36 patients (72%) had Grade 1, 11 patients (22%) had Grade 2, and 3 patients (6%) had Grade 3 Ki67 proliferation index. Similar to EGFR, higher grades of Ki67 proliferation index were associated with malignant tumors (p<0.001) (Table 3).

The comparison of mean proliferation index among the different histological grades also revealed that KI67 proliferation index has a significantly higher value for malignant tumors (mean±SD: 15.4±17.3) while benign tumors have lower KI67 proliferation index (mean±SD: 2.0±2.1) (p<0.001) (Fig. 2).

The association between Ki67 (proliferation index) and EGFR expression was further explored. Fig. 3 shows the distribution of Ki67 (proliferation index in different categories of EGFR expression. EGFR expression was categorized into two groups – "Negative" and "Non-Negative" (combining "Weak," "Moderate," and "Strong"). The

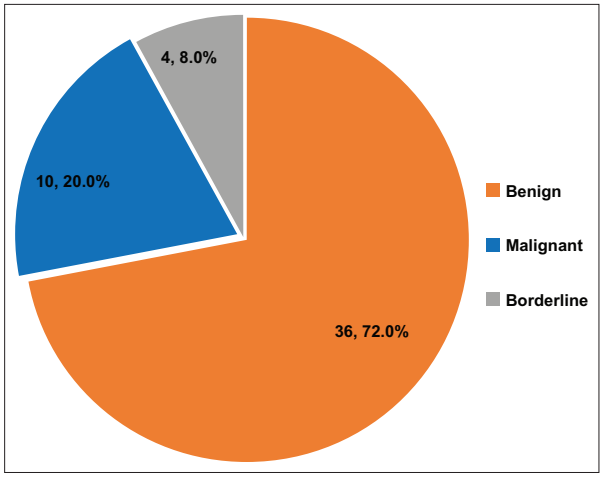

Fig. 1: Distribution of epithelial tumors according to histological grade

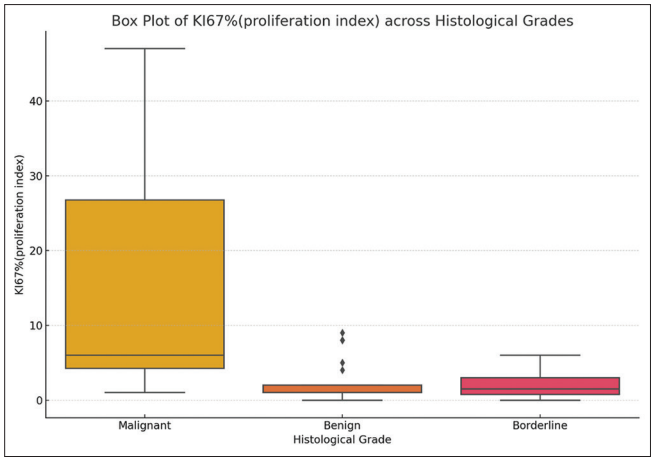

Fig. 2: Histological grade with Ki67 proliferation index

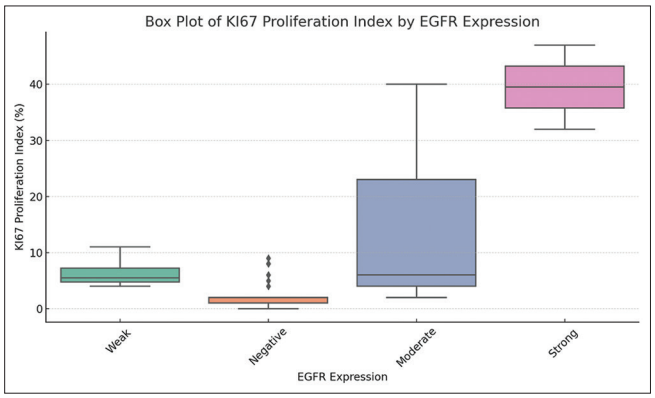

Fig. 3: Distribution of epidermal growth factor receptor expression and Ki67 proliferation index

Mann–Whitney U test was statistically significant between these two large groups (p=0.026).

DISCUSSION

Globally, ovarian cancer poses a significant public health burden, with disparities in incidence and mortality rates across regions. While industrialized nations report higher survival rates, many low- and middle-income countries face more significant challenges in

Table 1: Distribution of histological grade tumors according to age groups

Histological grade	Frequency (%)	Benign (n=36) n (%)	Borderline (n=4) n (%)	Malignant (n=10) n (%)	p-value
Age≤50 years	26 (54.0)	20 (55.6)	4 (100.0)	2 (20.0)	0.018*
Age>50 years	24 (48.0)	16 (44.4)	0 (0.0)	8 (80.0)	

*p-value was based on Chi-square test and p<0.05 was considered as statistically significant

Table 2: Distribution of histological grade tumors and EGFR expression

EGFR expression	Frequency (%)	Benign (n=36) n (%)	Borderline (n=4) n (%)	Malignant (n=10) n (%)	p-value
Negative	41 (82.0)	36 (100.0)	4 (100.0)	1 (10.0)	<0.001*
Weak	4 (8.0)	0 (0.0)	0 (0.0)	4 (40.0)	
Moderate	3 (6.0)	0 (0.0)	0 (0.0)	3 (30.0)	
Strong	2 (4.0)	0 (0.0)	0 (0.0)	2 (20.0)	

*p-value was based on Chi-square test and p<0.05 was considered as statistically significant

Table 3: Distribution of histological grade tumors and Ki67 (proliferation index)

KI 67(grading)	Frequency (%)	Benign (n=36) n (%)	Borderline (n=4) n (%)	Malignant (n=10) n (%)	p-value
Grade 1	36 (72.0)	31 (86.1)	3 (75.0)	2 (2.0)	<0.001*
Grade 2	11 (22.0)	5 (13.9)	1 (25.0)	5 (50.0)	
Grade 3	3 (6.0)	0 (0.0)	0 (0.0)	3 (30.0)	

*p-value was based on Chi-square test and p<0.05 was considered as statistically significant

diagnosis, treatment access, and overall patient outcomes [7]. Efforts are underway to uncover the molecular pathways causing cancer, offering hope for novel therapeutic interventions to augment survival rates and improve the quality of life for affected individuals. This study investigated the roles of EGFR and Ki-67 in epithelial ovarian tumors, aiming to understand their implications in tumor biology, prognosis, and therapeutic strategies. Using immunohistochemical analysis, the research evaluated EGFR and Ki-67 expression levels and correlated the same with histological grades of epithelial ovarian tumors.

Age is a well-known factor in ovarian tumor pathology. We observed that 80% of our participants were below 60 years old, a demographic peculiarity commonly seen in studies of epithelial tumors. Our observation aligns with the findings of Mahadevappa *et al*. [8], Mehner *et al*. [9], and Henzen-Logmans *et al*. [10]. Moreover, we noted that the majority of the patients had serous cystadenoma. In line with our observation, studies conducted by Wang *et al*. [11], Uribe *et al*. [12], and Farrag *et al*. [13] also highlighted the predominance of serous cystadenoma among epithelial tumors.

In the present study, most tumors were benign (72%), with 20% being malignant and 8% classified as borderline. Several studies have reported a greater likelihood of developing benign ovarian tumors in younger women, whereas the incidence of malignant tumors tends to increase with age. For instance, a study by Begum *et al*. [14] indicated that the mean age of women with benign tumors was significantly lower than those with malignant tumors. This aligns with the current study, where patients aged ≤50 years had a higher rate of benign tumors, while those >50 years showed a higher rate of malignant tumors.

The role of EGFR in ovarian cancer has been a topic of research, with some studies suggesting that EGFR overexpression is associated with poor prognosis in ovarian cancer [11]. In this study, 82% of the tumors were negative for EGFR expression, with higher levels of EGFR expression (weak, moderate, strong) observed in malignant tumors. Notably, a statistically significant association between EGFR expression and histological grade suggested that the majority of negative EGFR expression correlates with benign tumor, and malignant tumors had moderate to strong EGFR expression. Hence, EGFR expression may be a good predictor of tumor types and better health management and diagnosis. Our observation is consistent with the study by Psyrri *et al*. [15], which reported that high EGFR expression correlated with higher tumor grades and worse outcomes. However, other studies, such as those by Mehner *et al*. [9], have found variable results regarding the prognostic significance of EGFR expression, indicating that while EGFR may be overexpressed in ovarian carcinomas, its role as a biomarker remains controversial. This suggests that EGFR's impact may be influenced by additional genetic and molecular factors not accounted for in all studies.

We observed that the Ki67 proliferation index was significantly higher in malignant tumors than benign tumors (p<0.001). Association between higher Ki67 grades and malignancy was also statistically significant (p<0.001). The Ki67 index is widely recognized as a proliferation marker in cancer studies. High Ki67 labeling is associated with aggressive tumor behavior and poor prognosis across various cancer types, including ovarian cancer [16]. Our findings align with these observations, demonstrating that malignant tumors had higher Ki67 indices compared to benign ones. The concordance between this study and existing literature emphasizes the reliability of Ki67 as a marker for assessing tumor aggressiveness in ovarian cancer.

Moreover, a significant association was observed between Ki67 proliferation index and EGFR expression, with higher proliferation indices associated with increased EGFR expression (p=0.026). The interplay between EGFR signaling and Ki67 expression reflects underlying mechanisms driving tumor growth and progression. EGFR activation promotes cell proliferation through downstream signaling pathways such as MAPK and PI3K/AKT, which can increase the Ki67 index [17]. Moreover, other studies have indicated that both high EGFR expression and a high Ki67 index are indicative of poor prognosis and may contribute to therapy resistance in ovarian cancer [11,18]. The findings of our study highlight the potential role of both the molecular markers in stratifying patients based on risk and tailoring therapeutic approaches accordingly.

CONCLUSION

To summarize, the current work sheds light on the roles of EGFR and Ki67 in epithelial ovarian tumors. By understanding their expressions and correlations with histopathological parameters, clinicians can better predict tumor behavior, aiding in diagnosis, treatment planning, and prognosis. The findings pave the way for more personalized and targeted approaches in the management of ovarian cancer, ultimately aiming to improve patient outcomes and survival rates. However, variability in results across studies warrants the need for further multi-centric research on a larger sample size to refine these biomarkers' roles in diagnosis, prognosis, and treatment, while ensuring generalizability of the results.

AUTHORS' CONTRIBUTIONS

All authors contributed equally in the design of the study, data collection, analysis, and manuscript writing.

CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest.

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