Journal of Research in Applied and Basic Medical Sciences 2025; 11(1): 115-124

Original Article

RABMS Journal of Research in Applied and Basic Medical Sciences

A retrospective study of serous ovarian tumour with IHC correlation: a three-year study

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Abstract

***Background & Aims*:** Serous ovarian tumors account for 40% of all ovarian cancer cases and remain a major cause of cancer-related mortality in women due to late-stage diagnosis. This retrospective study aimed to analyze the clinicopathological features of serous ovarian tumors and their correlation with immunohistochemical (IHC) markers, including WT-1, CA-125, CK-7, CK-20, and CEA, to improve diagnostic accuracy and prognostic evaluation.

Materials & Methods: The study included pathology data from August 2020 to July 2023, focusing on patients with ovarian neoplasms. Clinical characteristics were correlated with IHC markers.

Results: Results showed that 62% of tumors occurred in women of reproductive age, with abdominal pain being the most common symptom (62%). The majority (88%) of tumors were benign, while 8% were malignant and 4% were borderline. Most tumors (88%) were unilateral, and the predominant tumor size ranged from 6 to 10 cm. High-grade serous carcinomas were identified in two cases, exhibiting Ki-67 labeling indices of 26–50% and >50%, respectively. Ki-67 expression was significantly higher in malignant tumors (50%) compared to borderline tumors (26%) ($p < 0.001$).

IHC analysis showed strong WT1 nuclear expression, CK7 cytoplasmic expression, and CA125 membrane staining in serous ovarian cancer cases. CK20 and CEA were negative in all cases of serous adenocarcinoma. Malignant tumors exhibited significantly higher Ki-67 expression than borderline tumors.

Conclusion: The study concluded that increasing age, postmenopausal status, bilaterality, and complex tumor morphology were associated with malignancy risk. The use of IHC markers such as WT1, CK7, CK20, CEA, and CA125 remains essential for accurate diagnosis and differentiation of serous ovarian tumors.

***Keywords*:** Hysterectomy, Ki-67 labeling, Ovarian tumors, postmenopausal malignancy

Received 17 September 2024; accepted for publication 25 October2024

Introduction

Globally, ovarian cancer ranks as the eighth most common cancer among women, accounting for 3.7% of all cancer cases and 4.7% of cancer-related deaths as of 2020 (1). In India, ovarian tumors are the fifth leading cause of cancer mortality in women, representing 6% of all cancers, with an annual incidence of 9 per 1,000,000 people (1). These tumors are more frequently observed in women from higher socioeconomic backgrounds, with studies suggesting a higher prevalence among Caucasian women compared to Black women, who have a lower risk (2).

Serous ovarian tumors constitute approximately 40% of all ovarian cancer cases (2). Several risk factors contribute to their development, including nulliparity, a positive family history, and inherited genetic abnormalities. In contrast, protective factors such as the use of oral contraceptives and tubal ligation are associated with a reduced risk of serous ovarian tumors (2). The poor prognosis associated with these tumors is primarily due to an incomplete understanding of their pathophysiology and late-stage diagnosis (2).

Serous ovarian tumors typically arise between the ages of 25 and 45, with additional risk factors such as genetic mutations, hormonal imbalances, and a familial predisposition playing significant roles (3). The ovarian epithelium undergoes cyclic changes throughout a woman's reproductive lifespan, which may contribute to neoplastic transformation. The repeated rupture and repair processes associated with ovulation have been linked to ovarian tumorigenesis, as malignant genetic alterations can arise over time. This mechanism explains why factors that suppress ovulation—such as oral contraceptive use, later onset of menarche, early menopause, multiparity, and breastfeeding—may confer a protective effect (1).

Cancer antigen 125 (CA125) remains one of the most widely utilized biomarkers in ovarian cancer diagnosis. Elevated CA125 levels are detected in approximately 50% of early-stage (type I) ovarian cancers and 92% of advanced-stage (type II) ovarian cancers. Ultrasonography and CA125 assays serve as essential tools for early detection, while fine-needle aspiration cytology (FNAC) plays a critical role in primary diagnosis and prognosis, demonstrating an accuracy rate of 90–95% in distinguishing benign from malignant lesions. Preventive strategies for ovarian cancer include lifestyle modifications, smoking and tobacco cessation, and prophylactic oophorectomy in high-risk populations (4).

Despite advancements in diagnostic and therapeutic approaches, ovarian cancer continues to have a high mortality rate, primarily due to late-stage presentation, with a five-year survival rate of less than 20% (5). Persistent ovarian enlargement requires timely surgical intervention, and histopathological examination remains the gold standard for confirming the diagnosis (5).

Immunohistochemical (IHC) markers play a crucial role in distinguishing serous ovarian tumors from other ovarian and metastatic neoplasms. WT1 is a key marker for surface epithelial tumors and aids in differentiating primary ovarian carcinoma from metastatic lesions. Other markers, including CK7, CEA, CA125, and CK20, assist in distinguishing serous tumors from mucinous ovarian neoplasms, while CK20 and CEA help differentiate serous ovarian cancer from colorectal adenocarcinoma (4).

According to the World Health Organization (WHO) classification, ovarian tumors are categorized as benign, borderline, or malignant, with this classification carrying significant implications for both treatment and prognosis (1). Additionally, histopathological patterns may vary between primary and metastatic ovarian tumors, emphasizing the importance of thorough histological and IHC evaluations.

This study aims to analyze the clinicopathological spectrum of serous ovarian tumors at our institution, focusing on age distribution, histopathological features, and immunohistochemical profiles. Specifically, we will evaluate the expression of WT-1, CA125, CK7, CK20, and CEA to assess their diagnostic and prognostic significance in differentiating primary serous ovarian carcinoma from other ovarian neoplasms.

Materials & Methods

Study Design and Period

This was a retrospective study conducted over a period of 3 years, from August 2020 to July 2023, in the Pathology Department at SVS Medical College, Mahabubnagar, Telangana. A total of 50 diagnosed cases of serous ovarian tumors were included in the study.

Data Collection

A comprehensive medical history of each patient was obtained from hospital records, which included demographic details such as age, menopausal status, and socioeconomic status. Clinical variables recorded included presenting symptoms, imaging findings, tumor size, and laterality. Relevant comorbidities and other clinical characteristics were also documented.

Study Inclusion and Exclusion Criteria

The inclusion criteria for the study consisted of female patients aged over 20 years who were admitted with clinical and radiological findings indicative of ovarian neoplasms. Additionally, hysterectomy specimens that included incidental ovarian tumors were also considered for inclusion. On the other hand, the exclusion criteria involved the exclusion of autolyzed samples and non-neoplastic ovarian lesions, such as simple ovarian cysts, tubo-ovarian masses, and polycystic ovaries.

Histopathological Examination

After fixation, serial gross sections of 1 cm thickness were taken from representative areas of the tumor, including both the periphery and the center, and fixed in 10% neutral buffered formalin for 24-48 hours. The tissues were then processed and embedded in paraffin. Thin sections measuring 4-5 microns in thickness were cut using a microtome.

The sections were stained with hematoxylin and eosin (H&E) using the following procedure:

1. Deparaffinization of sections followed by hydration.
2. Application of hematoxylin for nuclear staining.
3. Counterstaining with eosin for cytoplasmic and extracellular matrix details.
4. Dehydration, clearing, and mounting of sections.

Immunohistochemistry (IHC) Analysis

Immunohistochemistry was performed on 3-4 µm paraffin sections using the following markers: WT1, CK7, CK20, CEA, and CA125. The procedure involved antigen retrieval and staining with phosphate-buffered saline (PBS), horse radish peroxidase (HRP), and the chromogen 3,3′-diaminobenzidine (DAB).

The results of IHC staining were scored as follows:

- **Score 0:** No staining or fewer than 5% positive cells (negative).
- **Score 1+:** 5-25% positive cells (focal staining, positive).
- **Score 2+:** 25-50% positive cells (focal staining, positive).
- **Score 3+:** 50-75% positive cells (diffuse staining, positive).
- **Score 4+:** 75-100% positive cells (diffuse staining, positive).

Data Analysis

The correlation between clinical parameters (such as age and laterality), tumor types, and IHC expression of WT1, CK7, CK20, CEA, and CA125 was assessed. Histopathological classification followed WHO guidelines. Statistical analysis was performed using the chi-square test.

Results

The majority were benign tumors (88%), followed by 4% malignant tumors (serous cystadenocarcinoma + papillary serous cystadenocarcinoma) and 4% borderline tumors. The majority of tumors, i.e., 34%, were present in the age group of 31–40 years. Approximately 62% of the tumors occurred in the reproductive age group (Table 1).

The majority of the patients, i.e., 80%, attained menarche after the age of 12 years. The remaining 20% attained menarche before the age of 12 years. The premenopausal age group was more common than the postmenopausal group, accounting for 78% of the tumors. Malignant tumors were more common in the postmenopausal age group.

Abdominal pain was the most common presentation in malignant tumors, followed by mass per abdomen. Asymptomatic presentation of ovarian tumors was the least common. Most of the patients with malignant tumors presented with abdominal pain, followed by mass per abdomen.

The majority of the tumors were unilateral, accounting for 88% of all tumors, while 12% had a bilateral presentation. The majority of the tumors measured 6–10 cm in size. Fourteen percent of tumors had their largest dimension >15 cm. The largest tumor was a unilateral benign papillary serous cystadenofibroma affecting a 40-year-old female. A unilateral granulosa cell tumor was the smallest tumor in this study, found in a 45-year-old female.

The most common gross morphology was the cystic nature of tumors, accounting for 68%. Tumors presenting with gross cystic morphology were benign, especially those of the surface epithelial category. Among tumors with solid or complex morphology, the majority were malignant.

Table 1. Distribution of age, immunohistochemical expression, and basic characteristics of patients with serous ovarian tumours

Age distribution	Number	Percentage
< 30 year	14	28.0
31-40 year	17	34.0
41-50 year	13	26.0
51-60 year	6	12.0
Cardinal symptoms		
Pain abdomen	31	62
Abdominal mass	14	28
Irregular bleed	4	8
Infertility	1	2
Tumour size		
1-5 cm	13	26
6-10 cm	21	42
11-15 cm	9	18
> 15 cm	7	14
Laterality		
Left	24	48
Right	20	40
Bilateral	6	12
Tumour type		
Benign	44	88
Borderline	4	8
Malignant	2	4

Papillary serous cystadenocarcinoma was the major contributor among malignant tumors, accounting for 6% of cases. Benign serous cystadenoma was the most common histopathological pattern encountered in the present study, contributing to 44% of cases, followed by

benign papillary serous cystadenoma (24%) and benign serous cystadenofibroma (20% of tumors) (Table 2).

Increasing age, postmenopausal status, bilaterality, and complex or solid tumor morphology associated with a higher risk of malignancy. Early menarche and the tumor size did not correlate with an increased risk of malignancy.

Table 2. Histopathological category of tumour

Nature of Serous tumours	No. of cases	Percentage
A. Benign		
1.Serous cyst adenoma	22	44%
2. Papillary serous cyst adenoma	12	24%
3. Serous cystadenofibroma	10	20%
B. Borderline		
1. Serous	2	4%
C. Malignant		
1. Serous cystadenocarcinoma	1	2%
2. Papillary serous cystadenocarcinoma	3	6%

The Ki-67 labeling index was performed in both cases of borderline tumors and all four cases of malignant tumors. Diffuse intense nuclear staining was considered positive, while weak cytoplasmic staining was considered negative. There were two cases of high-grade serous carcinomas, one of which showed a Ki-67 labeling index between 26–50, and the other showed a Ki-67 labeling index above 50.

The immunostaining pattern was heterogeneous throughout the tumor, and evaluation was done in the most positively stained areas. The mean Ki-67 labeling index in borderline tumors was 26%, while in malignant tumors, it was 50%. When compared with borderline tumors, the Ki-67 labeling index was found to be statistically significant in malignant tumors ($p < 0.001$). In the malignant group of tumors, serous carcinomas showed a high index of 50%, followed by mucinous carcinomas with a mean index of 36%.

Table 3. IHC profile in serous ovarian carcinoma cases

IHC marker	Percentage of malignant cases		Pattern of staining
	Positive	Negative	
WT 1	100%	0%	Nuclear
CK 7	100%	0%	Cytoplasmic
CK 20	0%	100%	Cytoplasmic
CEA	0%	100%	Cytoplasmic/Luminal
CA 125	100%	0%	Membranous

The reported IHC profile (positivity for WT1, CK7, and CA125, along with negativity for CK20 and CEA) strongly confirms the diagnosis of serous ovarian carcinoma and holds significant value in ruling out other mimicking tumors (such as gastrointestinal metastases). These findings are entirely consistent with the well-established characteristics of serous ovarian carcinoma (Table 3).

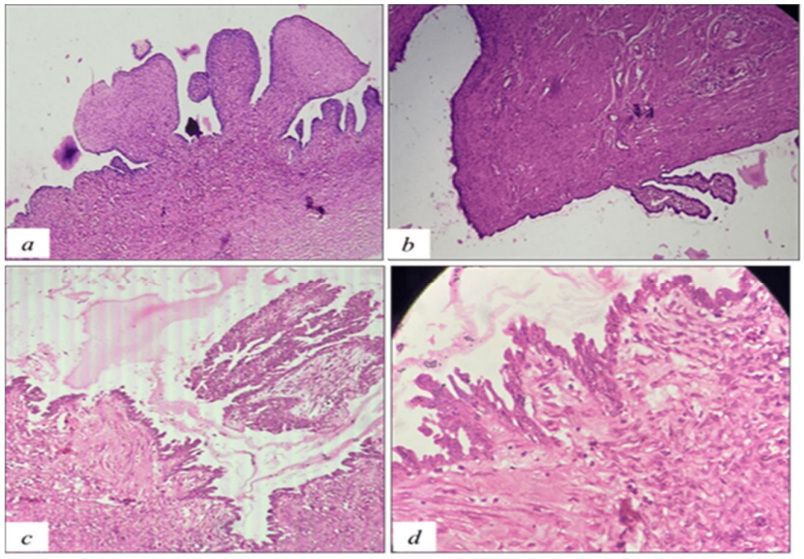

Fig. 1. Histology images (Magnification: ×100). a. Papillary serous cystadenofibroma-papillary structures with a prominent stromal component. b. Serous cystadenoma showing a cyst lined by cuboidal epithelium. c. & d. Borderline serous tumor showing hierarchical branching pattern with thick papillae, with the lining epithelium showing budding and stratification.

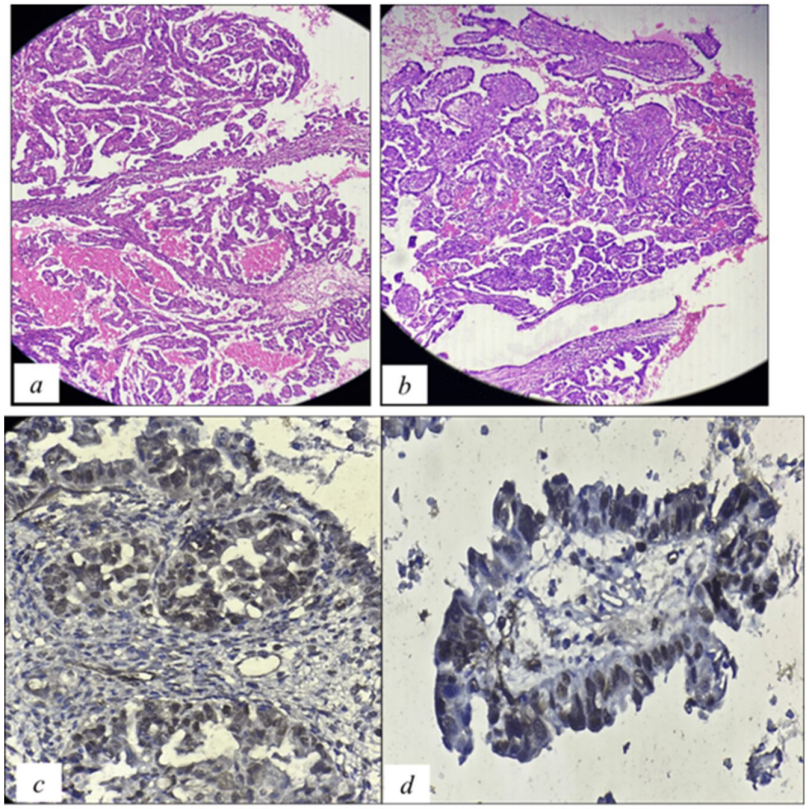

Fig. 2. a & b. Papillary serous cystadenocarcinoma showing micropapillary and complex papillary forms with effacement of the underlying stroma (×100). C & d. Diffuse, strong WT-1 nuclear positivity in papillary serous cystadenocarcinoma (×400).

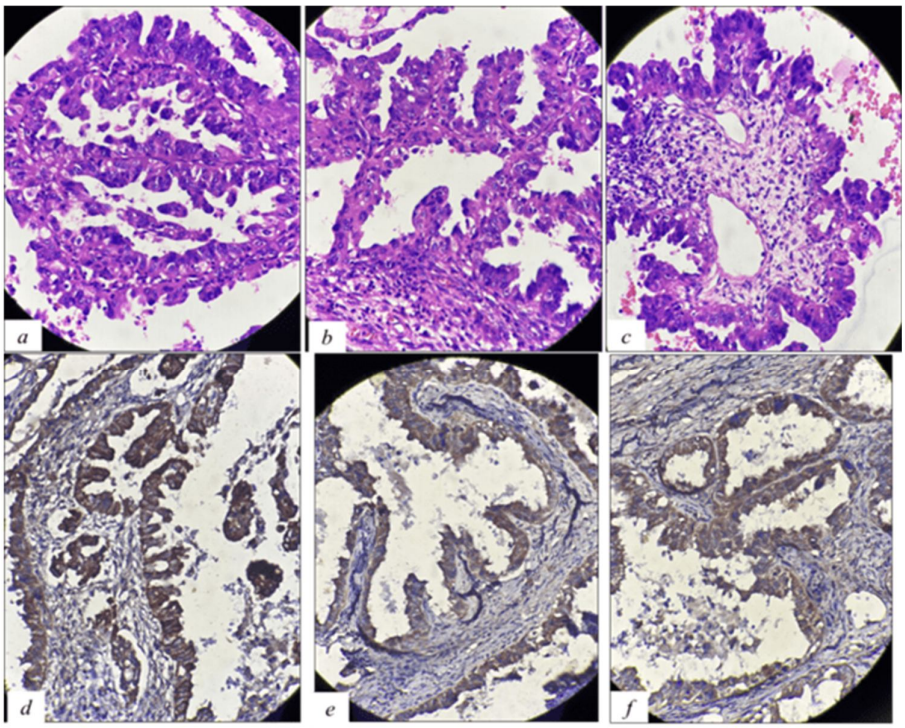

Fig. 3. a, b, c. Papillary serous cystadenocarcinoma - nuclear atypia with prominent nucleoli, mitotic figures, glandular complexity, and branching papillary fronds. d, e, f. Diffuse, strong cytokeratin 7 cytoplasmic positivity in papillary serous cystadenocarcinoma (×400)

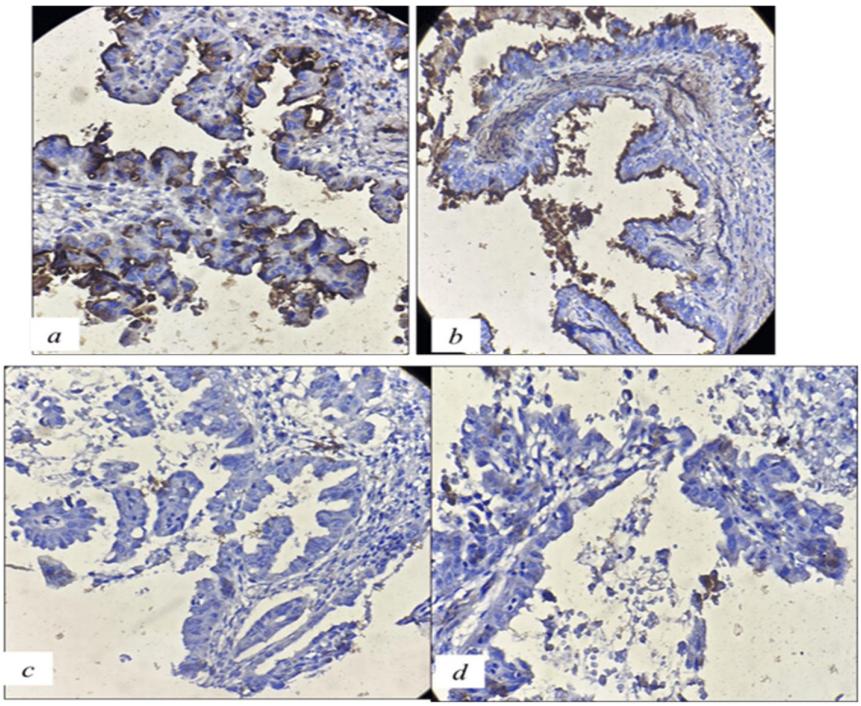

Fig. 4. a, b. Papillary serous cystadenocarcinoma demonstrating a membranous pattern of staining with CA 125. c. Papillary serous carcinoma showing negative staining with CEA. d. Papillary serous carcinoma showing negative staining with cytokeratin 20 (×400)

Discussion

The majority of tumors (34%) were found in individuals aged 31–40 years, with 62% occurring in the reproductive age group. The average age of the study population was 34.8 years. Clinically, most patients presented with abdominal pain (62%), followed by an abdominal mass, while asymptomatic tumors were the least common. These findings align with previous research indicating that two-thirds of all ovarian tumors arise in women of reproductive age (6). Due to their anatomical location, ovarian tumors often remain undetected for an extended period, with symptoms manifesting only in later stages. Doubeni et al. and Dilley et al. similarly reported that most ovarian tumors are discovered at an advanced stage, contributing to a poor prognosis (17, 18).

In this study, the majority of tumors measured 6–10 cm in size, with 14% exceeding 15 cm in their largest dimension. Benign tumors comprised 88% of cases, while 4% were malignant and 4% were borderline. The proportion of benign, borderline, and malignant tumors in this study is consistent with Modepalli et al. (7), who reported a distribution of 83.01%, 4.9%, and 12.1%, respectively. This variation in malignancy rates across studies may be due to differences in patient demographics, genetic predispositions, and diagnostic criteria.

Menarche and menopausal status have been implicated as potential risk factors for ovarian tumors. In this study, 80% of patients had menarche after the age of 12, while 20% had menarche before 12 years. This finding contrasts with Western studies by Adami et al. (8) and Hildreth et al. (9), which reported a 5% increased risk of ovarian tumors associated with early menarche. The discrepancy may be attributed to genetic and environmental factors, including nutritional differences, as Kayastha et al. (10) reported similar findings among the Indian population. Unlike previous studies, our analysis found no significant correlation between early menarche and malignancy, suggesting that additional hormonal or genetic influences may play a more significant role in tumor development.

The clinical presentation of ovarian tumors varies, with some cases detected incidentally during routine ultrasound. This study found that most patients presented with abdominal pain (62%), followed by an abdominal mass, a pattern consistent with findings from Rashid et al. (11), where 59% of patients had abdominal discomfort and 25.42% presented with a mass. These results highlight the importance of routine imaging and early symptom recognition to improve diagnostic outcomes.

Regarding tumor laterality, 88% of tumors were unilateral, while 12% were bilateral. This finding aligns with Jha et al. (12), who reported bilaterality in 6.7% of benign tumors and 42.3% of malignant tumors. Bilaterality is considered a potential marker for malignancy, as malignant tumors often exhibit a higher rate of bilateral involvement compared to benign lesions. Further radiological and histopathological assessment is essential in such cases.

Histologically, the most common malignancy was papillary serous cystadenocarcinoma (6%), while benign serous cystadenoma was the most prevalent tumor overall (44%). This distribution is in agreement with prior studies, such as Pilli et al. (13), who found that benign serous cystadenoma was the most frequently encountered ovarian tumor. In terms of gross morphology, 68% of tumors exhibited a cystic appearance, primarily among benign surface epithelial tumors, while solid or complex morphology was more frequently observed in malignant cases. This observation reinforces the role of tumor morphology in predicting malignancy.

Immunohistochemical Findings and Diagnostic Significance

The Ki-67 labeling index was analyzed in two borderline tumors and four malignant tumors. Diffuse, strong nuclear staining was considered positive, while weak cytoplasmic staining was negative. Among malignant tumors, two high-grade serous carcinomas showed Ki-67 labeling indices of 26–50% and >50%, respectively. The mean Ki-67 index was 26% in borderline tumors and 50% in malignant tumors, a difference that was statistically significant ($p < 0.001$).

These findings align with Gursan et al. (14), who reported a mean Ki-67 expression of 42.8% in malignant tumors and 22.8% in borderline tumors. While Ki-67 staining is not a definitive diagnostic tool, its strong correlation with malignancy suggests that it may serve as a useful adjunct marker in challenging cases.

The IHC profile of serous ovarian carcinoma was characterized by WT1, CK7, and CA125 positivity, along with CK20 and CEA negativity. This pattern is well-established in distinguishing primary serous ovarian carcinoma from metastatic gastrointestinal tumors (Ayadi et al. (15), Sylvia et al. (16)). The findings confirm that WT1 and CK7 positivity, along with CK20 and CEA negativity, remain key markers for diagnosing serous ovarian carcinoma.

Clinical and Research Implications

The results of this study emphasize several key clinical takeaways:

1. Most serous ovarian tumors occur in reproductive-age women and are diagnosed at a late stage, reinforcing the need for improved early detection strategies.
2. Bilateral involvement and solid morphology are potential malignancy indicators, warranting closer radiological monitoring.
3. Ki-67 labeling index is significantly higher in malignant tumors, making it a potential prognostic marker.
4. IHC profiling remains crucial for distinguishing primary ovarian malignancies from metastatic mimics.

Limitations

This study has several limitations. It is retrospective in design, which introduces potential biases due to reliance on medical records. The sample size was relatively small, with only 50 cases, including a limited number of malignant and borderline tumors, which may affect the generalizability of the findings. Additionally, the study's scope is geographically restricted to a single medical college in Telangana, and the findings may not be representative of populations outside this region. These limitations highlight the need for larger, prospective studies with follow-up data to evaluate clinical outcomes.

Conclusion

This study provides a comprehensive evaluation of serous ovarian tumors, with a focus on clinicopathological characteristics, histological subtypes, and immunohistochemical markers. The findings highlight that most tumors are benign, with malignancy being more common in postmenopausal women. Tumor bilaterality and solid morphology are strong malignancy indicators, while Ki-67 expression is significantly higher in malignant cases. The IHC profile of WT1+, CK7+, CA125+, CK20-, and CEA- confirms its diagnostic reliability for serous ovarian carcinoma. Future research should focus on molecular characterization and targeted therapies to improve diagnostic accuracy and patient outcomes.

Acknowledgments

The authors would like to thank the laboratory staff for their support.

Ethical statement

Patients' initials and personal information were kept confidential. The researchers adhered to all the principles recommended by the Helsinki Convention on Ethics in Research. The study was approved by the institutional ethics committee, SVS Medical College and Hospital, Yenugonda, Mahabubnagar.

Data availability

The data from this study are available upon request from the corresponding author.

Conflict of interest

The authors declare no conflict of interest.

Funding/support

No support was received.

Author contributions

Manoja and Shamoon were responsible for writing the paper. Florence, Jyothi, and Shamoon contributed to the conception and design of the analysis. Manoja, Jyothi, Shamoon, Priyatham, and Sirisha were involved

in data collection. Florence, Shilpa, and Jyothi handled the analysis and supervision.

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