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Evaluation of p16 Immunohistochemical Stain Expression in Cervical Cancer and Its Correlation with Clinico-Pathological Findings

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Author`s Contribution

[1,2]Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, [3,4]Drafting the work or revising it critically for important intellectual content,[5]Final approval of the version to be published

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A B S T R A C T

Objective: To evaluate p16 immunohistochemical expression in cervical squamous cell carcinoma and determine its association with demographic and clinicopathological characteristics.

Methods: This cross-sectional analytical study included 96 histopathologically confirmed cases of cervical squamous cell carcinoma evaluated at Chughtai Lab Lahore, Pakistan. Formalin-fixed paraffin-embedded tissue sections were stained for p16 using standard immunohistochemistry protocols. Associations between p16 expression and age group, menstrual status, histological grade, and clinical presentation were analyzed using the Pearson chi-square test. A p-value less than 0.05 was considered statistically significant.

Results: p16 positivity was observed in 84 of 96 cases (87.5%). There was no statistically significant association between p16 expression and menstrual status (p = 0.395), histological grade (p = 0.633), or age group distribution (p = 0.403). Clinical presentation showed a significant association with p16 expression (p = 0.015). Notably, all patients presenting with abnormal uterine bleeding were p16-positive (28 of 28, 100.0%), whereas p16-negative cases were more frequent among those presenting with postmenopausal bleeding and vaginal discharge.

Conclusion: p16 is highly expressed in cervical squamous cell carcinoma in this Pakistani cohort and demonstrates a significant association with clinical presentation, particularly abnormal uterine bleeding. These findings support the role of p16 as a useful adjunct biomarker in routine diagnostic evaluation of cervical cancer. Incorporation of p16 immunohistochemistry may enhance diagnostic accuracy in resource-limited settings where HPV testing is not widely available.

Keywords: Cervical cancer; p16I^{NK4a}; immunohistochemistry; human papillomavirus; clinicopathological correlation; Pakistan.

Introduction

Cervical cancer remains a significant public health issue globally, ranking as the fourth most frequent cancer among women and a leading cause of cancer mortality, particularly in developing countries.[1,2] The high prevalence of cervical cancer is primarily attributed to persistent infection with high-risk human papillomavirus (HPV), particularly types 16 and 18, which are implicated in the majority of cervical malignancies.[3,4] A pivotal mechanism in HPV-associated carcinogenesis involves the interaction of viral oncogenes with host cell pathways, particularly impacting the cell cycle regulatory proteins.[5,6]

p16^{INK4a}, a cyclin-dependent kinase inhibitor, has emerged as a valuable biomarker in the histopathological diagnosis and prognosis of cervical cancer.[7,8] Its overexpression is considered a surrogate marker of oncogenic HPV infection due to its role in inhibiting cyclins D and E, leading to cell cycle arrest .[9,10] The correlation between p16 expression and various clinicopathological parameters such as tumor grade, stage, and patient outcomes has been well-documented.[11,12] For instance, studies by Mahendra et al. noted a significant association between p16 positivity and higher tumor grades in cervical squamous cell carcinoma (CSCC).[3]

Recent research has demonstrated that utilizing p16 as a diagnostic adjunct not only improves the accuracy of cervical precancer and cancer detection but also serves as a critical prognostic indicator. For example, Eni et al. found that p16 expression significantly correlated with the degree of dysplasia and tumor invasion, further substantiating p16's role as a biomarker in clinical practice.[13, 14] However, the expression patterns can vary markedly across different demographics and disease stages, leading to the necessity for region-specific studies to better understand these relationships.[15,16]

In our study, we evaluated the expression of p16 in cervical cancer tissues obtained from 96 patients. Of these, p16 positivity was observed in 84 cases (87.5%), highlighting its potential utility as a reliable biomarker. Furthermore, our findings revealed no statistically significant association between p16 expression and menstrual status (p=0.395), histological grade (p=0.633), or age group distribution (p=0.403). However, the correlation of

clinical presentations with p16 expression was statistically significant, indicating that all cases of abnormal uterine bleeding (AUB) were p16 positive (p=0.015).[7, 17] These observations underscore the potential of p16 immunohistochemistry in enhancing diagnostic outcomes and guiding treatment decisions in cervical cancer management.

The rationale for our study is particularly relevant in Pakistan, where cervical cancer remains a significant health threat, largely due to limited screening and vaccination programs. The World Health Organization (WHO) estimates that approximately 70% of cervical cancer cases in Pakistan are attributable to HPV infection, with p16's role as a diagnostic adjunct increasingly relevant.[1, 18] There is an urgent need for integrated public health strategies that focus on HPV awareness, vaccination, and the incorporation of p16 as a diagnostic tool in routine cervical screening or diagnostic programs, particularly in high-risk populations. The outcome of this study aims to provide local evidence that supports these initiatives while improving patient care outcomes in the Pakistani context

Methodology

This cross-sectional analytical study was conducted at Chughtai Lab, Lahore, using histopathology and immunohistochemistry records of women evaluated for suspected cervical malignancy from January 2023 till July 2023. A total of 96 histopathologically confirmed cases of squamous cell carcinoma of the uterine cervix (Figure 1) were included in the final analysis.

All cases with a confirmed diagnosis of cervical squamous cell carcinoma and complete reporting of the key study variables were eligible. Records were excluded if essential information was missing, including age group, menstrual status, presenting complaint category, tumor grade, or p16 immunohistochemistry status, to ensure complete-case, pairwise comparisons.

A non-probability consecutive sampling approach was used, and all eligible cases available in the laboratory database during the study period were included until the required sample was achieved. Clinical information was extracted from laboratory-linked records and categorized as abnormal uterine bleeding, postmenopausal bleeding, mass per vagina, postcoital bleeding, per vaginal discharge, pain, pelvic organ prolapse, or other presentations. Menstrual status was recorded as premenopausal or postmenopausal. Age was recorded in predefined categories (21 to 30, 31 to 40, 41 to 50, 51 to 60, and 61 to 70 years).

Formalin-fixed paraffin-embedded cervical tissue blocks and corresponding hematoxylin and eosin-stained slides were reviewed to confirm the diagnosis. Tumor differentiation was recorded as well-differentiated, moderately-differentiated, or poorly-differentiated squamous cell carcinoma according to routine histopathology reporting at the laboratory.

Immunohistochemistry for p16 was performed on representative tumor sections following the laboratory's validated immunostaining workflow with appropriate positive and negative controls. p16 expression was documented as positive when there was strong diffuse nuclear expression (Figure 2) or negative, and this status was used to assess clinicopathological associations.

Data were entered and analyzed using SPSS. Categorical variables were summarized as frequencies and percentages. Associations between categorical variables were assessed using the Pearson chi-square test, including comparisons of histological grade and p16 expression by menstrual status, and correlations of p16 status with age group, clinical presentation, and histological grade. A p-value less than 0.05 was considered statistically significant

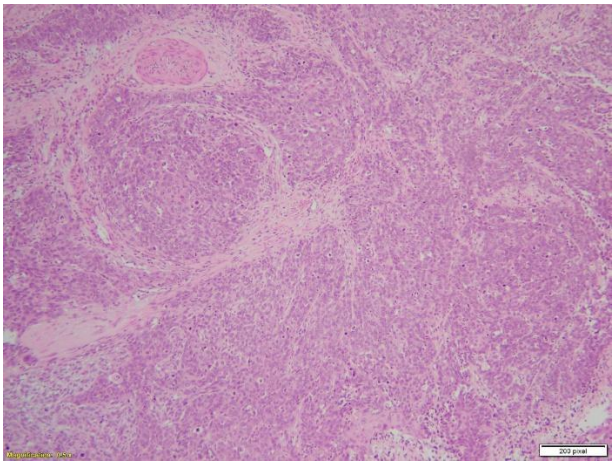

Figure 1A. Squamous Cell Carcinoma in Cervix – H&E(4x):

Section shows invasive squamous cell carcinoma arranged in nests and sheets of atypical squamous cells.

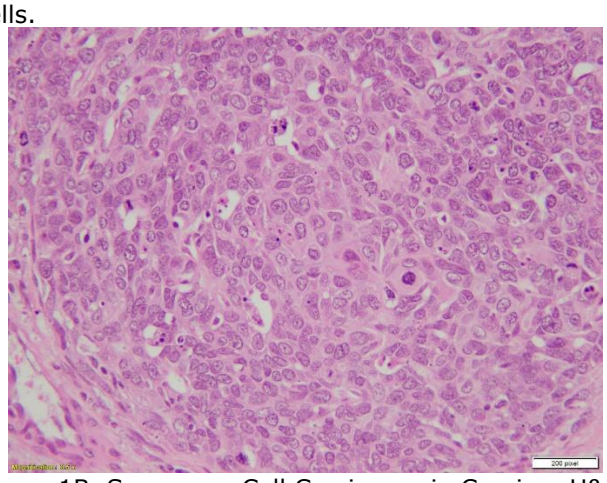

Figure 1B. Squamous Cell Carcinoma in Cervix – H&E (40x):

Section shows invasive squamous cell carcinoma arranged in nests and sheets of atypical squamous cells with nuclear pleomorphism, intercellular bridging and focal keratinization.

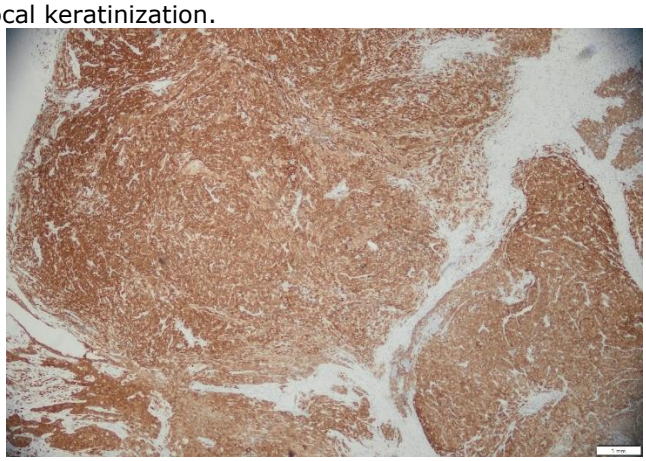

Figure 2. p16 Immunohistochemistry.

Diffuse, strong ("block-type") nuclear and cytoplasmic positivity for p16 is seen throughout the tumor, supporting HPV-associated squamous cell carcinoma in cervix.

Results

A total of 96 patients were included in the analysis. Premenopausal women accounted for 51 (53.1%), and postmenopausal women accounted for 45 (46.9%). Most participants were aged 41 to 50 years (35, 36.5%), followed by 51 to 60 years (28, 29.2%) and 31 to 40 years (21, 21.9%). (Table I)

Table I. Age group distribution. (n=96)		
Age group (years)	n	%
21 to 30	3	3.1
31 to 40	21	21.9
41 to 50	35	36.5
51 to 60	28	29.2
61 to 70	9	9.4

Overall, the most frequent presentations were AUB (28, 29.2%) and others (28, 29.2%), followed by postmenopausal bleeding (18, 18.8%) and mass per vagina (10, 10.4%). When stratified by menstrual status, AUB was more common among premenopausal women (22/51, 43.1%), whereas postmenopausal bleeding occurred only among postmenopausal women (18/45, 40.0%). (Table 2)

Most tumors were moderately differentiated (72, 75.0%), followed by poorly differentiated (15, 15.6%) and well differentiated (9, 9.4%). The distribution of histological grade did not differ significantly by menstrual status (Pearson chi-square p=0.352). (Table 3)

Overall, p16 positivity was observed in 84 cases (87.5%) and negativity in 12 cases (12.5%). p16 expression was not significantly associated with menstrual status (p=0.395). (Table 4)

Table II: Clinical presentation by menstrual status (n=96)			
Clinical presentation	Premenopausal n (%)	Postmenopausal n (%)	Total n (%)
AUB	22 (43.1)	6 (13.3)	28 (29.2)
Others	15 (29.4)	13 (28.9)	28 (29.2)
Postmenopausal bleeding	0 (0.0)	18 (40.0)	18 (18.8)
Mass per vagina	7 (13.7)	3 (6.7)	10 (10.4)
PV discharge	3 (5.9)	2 (4.4)	5 (5.2)
Postcoital bleeding	3 (5.9)	0 (0.0)	3 (3.1)
Pain	1 (2.0)	2 (4.4)	3 (3.1)
Pelvic organ prolapse	0 (0.0)	1 (2.2)	1 (1.0)

Table III. Histological grade by menstrual status (n=96)			
Histological grade	Premenopausal n (%)	Postmenopausal n (%)	Total n (%)
Well differentiated	3 (5.9)	6 (13.3)	9 (9.4)
Moderately differentiated	41 (80.4)	31 (68.9)	72 (75.0)
Poorly differentiated	7 (13.7)	8 (17.8)	15 (15.6)
Chi-square p-value			0.352

Table IV. p16 expression by menstrual status (n=96)			
p16 expression	Premenopausal n (%)	Postmenopausal n (%)	Total n (%)
Positive	46 (90.2)	38 (84.4)	84 (87.5)
Negative	5 (9.8)	7 (15.6)	12 (12.5)
Chi-square p-value			0.395

p16 expression did not show a significant association with histological grade (p=0.633). Similarly, age-group distribution was not significantly associated with p16 status (p=0.403). (Table 5, 6)

The clinical presentation showed a statistically significant association with p16 expression (Pearson chi-square, p=0.015). Notably, all AUB cases were p16-positive (28/28, 100.0%), while postmenopausal bleeding included 4 p16-negative cases (4/18, 22.2%). (Table VII)

Table V. Histological grade by p16 expression (n=96)			
Histological grade	p16 Negative n (%)	p16 Positive n (%)	Total n (%)
Well differentiated	1 (8.3)	8 (9.5)	9 (9.4)
Moderately differentiated	8 (66.7)	64 (76.2)	72 (75.0)
Poorly differentiated	3 (25.0)	12 (14.3)	15 (15.6)
Chi-square p-value			0.633

Table VI. Age group by p16 expression (n=96)			
Age group (years)	p16 Negative n (%)	p16 Positive n (%)	Total n (%)
21 to 30	0 (0.0)	3 (3.6)	3 (3.1)
31 to 40	3 (25.0)	18 (21.4)	21 (21.9)
41 to 50	2 (16.7)	33 (39.3)	35 (36.5)
51 to 60	6 (50.0)	22 (26.2)	28 (29.2)
61 to 70	1 (8.3)	8 (9.5)	9 (9.4)
Chi-square p-value			0.403

Table VII. Clinical presentation by p16 expression (n=96)			
Clinical presentation	p16 Negative n (%)	p16 Positive n (%)	Total n (%)
AUB	0 (0.0)	28 (100.0)	28 (29.2)
Others	3 (10.7)	25 (89.3)	28 (29.2)
Postmenopausal bleeding	4 (22.2)	14 (77.8)	18 (18.8)
Mass per vagina	2 (20.0)	8 (80.0)	10 (10.4)
PV discharge	2 (40.0)	3 (60.0)	5 (5.2)
Postcoital bleeding	0 (0.0)	3 (100.0)	3 (3.1)
Pain	0 (0.0)	3 (100.0)	3 (3.1)
Pelvic organ prolapse	1 (100.0)	0 (0.0)	1 (1.0)
Chi-square p-value			0.015

Discussion

The analysis of the 96 patients in our study reveals pertinent insights into menstrual status, clinical presentation, histological grading, and p16 expression. This discussion compares our findings with recent literature, focusing on key areas of interest.

The demographic breakdown of our study indicates premenopausal women accounted for 53.1%, while postmenopausal women comprised 46.9% of participants, with the majority falling within the age range of 41 to 50 years. The prominence of this age group is consistent with findings from Kusum et al., who noted a similar distribution in their cohort of women with abnormal uterine bleeding, indicating that most patients are often in their late 40s to early 50s.[19] This suggests that age is a significant risk factor for both AUB and subsequent pathologies.

The balanced composition between premenopausal and postmenopausal women in our study aligns with the conclusion drawn by Ibrahim et al., which emphasized the relevance of age in the presentation of endometrial disorders.[20] Further, a more recent study by Zhao et al. reinforced this notion by assessing the implications of advancing age on endometrial cancer risk, suggesting heightened vigilance in these age brackets.[21] This consensus across studies underscores the need for targeted screening and investigation strategies tailored to age-specific risks.

Our data highlight abnormal uterine bleeding (AUB) as the most frequent clinical presentation, observed in 29.2% of the subjects, with a disproportionate occurrence among premenopausal women. Indeed, studies by Kim et al. and Antoun et al. affirm that AUB remains a predominant symptom in women, often linked to various gynecological conditions.[22,23] The notable 43.1% incidence of AUB in premenopausal women within our analysis corroborates findings from Sangwan et al., where AUB constituted about 90% of presentations in endometrial stromal sarcoma cases, emphasizing its critical role as a clinical indicator.[24]

Furthermore, the exclusive occurrence of postmenopausal bleeding in postmenopausal women (40.0% of this group) aligns with literature focusing on the postmenopausal population's risk for serious pathologies, such as endometrial cancer.[25,26] However, while our study observed significant associations between specific presentations and menstrual status, further investigation is warranted to delineate the causal pathways.

Our findings indicated that most tumors were moderately differentiated (75.0%), with no significant differences in histological grade when stratified by menstrual status (p=0.352). This aspect mirrors the observations made by Fausto et al., which highlighted the predominance of moderately differentiated tumors across similar demographic groups.[27] Moreover, the lack of association between histological grade and menstrual status in our study reflects earlier observations by Raffaone et al., who also noted no substantial correlation in their investigations regarding endometrial cancer.[28]

The consistency between our findings and existing literature supports the hypothesis that menstrual

status may not critically affect tumor differentiation. However, the variation in tumor presentation warrants exhaustive histological examination and possible reconsideration of diagnostic criteria.

Our study demonstrated a high rate of p16 positivity (87.5%), with no significant association between p16 expression and menstrual status (p=0.395), consistent with previous literature indicating a high prevalence of p16 positivity in various endometrial neoplasms.[29, 30] Interestingly, all AUB cases were p16-positive, showcasing a potentially vital marker for understanding the underlying pathology of AUB, as suggested by Lensen et al. in their recent focus on utilizing biomarkers in gynecological malignancies.[31]

In contrast, the relationship between p16 expression and histological grade showed no significant association (p=0.633), which aligns with findings from Ghanavati et al., underscoring the complex interplay between histological features and tumor biomarkers.[26] This raises pertinent questions regarding the utility of p16 as a singular predictive biomarker in clinical settings.

Our study findings contribute to a growing body of literature highlighting the interplay between menstrual status, clinical presentation, histological grading, and biomarker expression in women experiencing abnormal uterine bleeding. The identified trends underscore the need for meticulous clinical assessments in targeted age groups and the implications of specific symptoms in guiding further diagnostic and therapeutic interventions.

The necessity for interdisciplinary collaboration is essential to enhance the understanding of these conditions and improve patient outcomes, particularly in populations at increased risk for malignancies.

Conclusion

This study shows a high prevalence of p16 positivity in women with cervical squamous cell carcinoma, particularly linked to abnormal uterine bleeding. While p16 expression was not significantly related to age, menstrual status, or histological grade, its prevalence suggests it could be a valuable diagnostic tool in histopathology. In Pakistan, where HPV screening is limited, p16 immunohistochemistry can aid in accurate diagnosis and early clinical decisions. These findings support the integration of p16 staining into cervical cancer diagnostic processes and emphasize the need for improved cervical cancer screening and prevention strategies.

References

1. Zuberi Z, Mremi A, Chilongola J, Semango G, Sauli E. Expression analysis of p16 and TOP2A protein biomarkers in cervical cancer lesions and their correlation with clinico-histopathological characteristics in a referral hospital, Tanzania. *PLoS One*.2021;16(10):e0259096. https://doi.org/10.1371/journal.pone.0259096
2. Pandey A, Chandra S, Nautiyal R, Shrivastav V. Expression of p16INK4a and human papillomavirus 16 with associated risk factors in cervical premalignant and malignant lesions. *South Asian J Cancer*.2018;7(4):236–239. https://doi.org/10.4103/sajc.sajc_118_17
3. Mahendra I, Budiana I, Putra I, Mulyana R, Winata I, Harjoto B. E6/E7 oncogenes mutation of human papillomavirus type 16 associated with p16 protein expression in cervical cancer. *Eur J Med Health Sci*. 2023;5(2):81–84. https://doi.org/10.24018/ejmed.2023.5.2.1404
4. Perera M, Perera I. Snapshot of clinical implications of p16 overexpression in carcinogenesis. *Clin Oncol Res*.2021:1–3. https://doi.org/10.31487/j.cor.2021.05.04
5. Kalyani R, VR, Sheela S. Expression of p16 biomarker in squamous cell carcinoma of uterine cervix and its association with clinico-pathological parameters: a cross-sectional study. *Biomed Res Ther*.2020;7(9):3954–3961. https://doi.org/10.15419/bmrat.v7i9.626
6. Zheng Q, Chen X, Han R, Zhu J, Wang H, Chen L, et al. HPV58 E7 protein expression profile in cervical cancer and CIN with immunohistochemistry. *J Cancer*.2021;12(6):1722–1728. https://doi.org/10.7150/jca.50816
7. Paskarani P, Winata I, Sitohang E, Felyanto F, Yuliantini S. p16 expression in patient with loop electrosurgical excision procedure (LEEP). *Maj Obstet Ginekol*. 2024;32(3):161–167. https://doi.org/10.20473/mog.v32i32024.161-167
8. Garrido F, Wild C, Jeschke U, Dannecker C, Mayr D, Cavaillès V, et al. Expression of progesterone receptor A as an independent negative prognosticator for cervical cancer. *Int J Mol Sci*. 2023;24(3):2815. https://doi.org/10.3390/ijms24032815
9. Shi Q, Xu L, Yang R, Meng Y, Qiu L. Ki-67 and p16 proteins in cervical cancer and precancerous lesions of young women and the diagnostic value for cervical cancer and precancerous lesions. *Oncol Lett*. 2019. https://doi.org/10.3892/ol.2019.10430
10. Sari N, Nizar R, Asri A. The correlation of p16 expression with degree of differentiation and tumor stage in cervical squamous cell carcinoma. *Maj Patol Indones*.2023;32(3). https://doi.org/10.55816/mpi.v32i3.653
11. Pino M, Svanholm-Barrie C, Torné A, Marimón L, Gaber J, Sagasta A, et al. mRNA biomarker detection in liquid-based cytology: a new approach in the prevention of cervical cancer. *Mod Pathol*. 2015;28(2):312–320. https://doi.org/10.1038/modpathol.2014.106

12. Vedula B, VR, Rajani M, RS, KS. Expression of p16 in cervical premalignant and malignant lesions: an IHC study. *Indian J Pathol Oncol*. 2020;7(3):404–407. https://doi.org/10.18231/j.ijpo.2020.080
13. Eni A, Ndukwe C, Olusina D, Nnakenyi N, Nzegwu M, Eluke C, et al. Spectrum, clinicopathologic profile, and p16 expression pattern of nonmalignant cervical tissues in Enugu, South-East Nigeria. *Ibnosina J Med Biomed Sci*. 2023;15(3):121–128. https://doi.org/10.1055/s-0043-1770702
14. Pérez C, Castillo M, Alemany L, Tous S, Klaustermeier J, Sanjosé S, et al. Evaluation of p16INK4a overexpression in a large series of cervical carcinomas. *Int J Gynecol Pathol*. 2014;33(1):74–82. https://doi.org/10.1097/pgp.0b013e3182774546
15. Lin S, Liang Z, Chen X, Ye X, Pang Y, Luo J, et al. Detection of complement C1q B chain overexpression and its latent molecular mechanisms in cervical cancer tissues using multiple methods. *Int J Genomics*. 2022;2022:8775330. https://doi.org/10.1155/2022/8775330
16. Devi N, Devi L, Singh L. Expression of p16 and Ki-67 in cervical intraepithelial neoplasia and carcinoma: an institute-based study. *IP J Diagn Pathol Oncol*. 2021;6(1):19–24. https://doi.org/10.18231/j.jdpo.2021.005
17. Bose M, Singh S, Selvaluxmy G, Chiwate A, Hingmire S, Rajkumar T. Development and evaluation of p16-based double antibody sandwich ELISA for detection of cervical precancer and cancer. *Asian Pac J Cancer Prev*. 2023;24(7):2337–2346. https://doi.org/10.31557/apjcp.2023.24.7.2337
18. Ghosh A, Nirupama M, Padmanabha N, Kini H. Assessment of p16 and Ki-67 immunohistochemistry expression in squamous intraepithelial lesion with cytohistomorphological correlation. *Iran J Pathol*. 2020;15(4):268–273. https://doi.org/10.30699/ijp.2020.112421.2208
19. Assessment of profile of patients with abnormal uterine bleeding. *Int J Clin Obstet Gynaecol*. 2024;8(3):9–11. https://doi.org/10.33545/gynae.2024.v8.i3a.1445
20. Ibrahim E, Sheridan T, Mandavilli S. Mesonephric-like carcinoma of the uterus with a predominant spindled morphology: a case report. *Am J Clin Pathol*. 2021;156(Suppl 1):S76. https://doi.org/10.1093/ajcp/aqab191.160
21. Zhao Q, Wang M, Chen M. Tumor polo-like kinase 4 protein expression reflects lymphovascular invasion, higher FIGO stage, and shortened survival in endometrial cancer patients who undergo surgical resection. *BMC Womens Health*. 2024;24(1). https://doi.org/10.1186/s12905-024-02911-9
22. Yadav M, Kose V, Bhalerao A. Frequency of thyroid disorder in pre- and postmenopausal women and its association with menopausal symptoms. *Cureus*. 2023. https://doi.org/10.7759/cureus.40900
23. Lu J, Li K, Zheng X, Liu R, Chen M, Xian J, et al. Prevalence of menopausal symptoms and attitudes towards menopausal hormone therapy in women aged 40–60 years: a cross-sectional study. *BMC Womens Health*. 2023;23(1). https://doi.org/10.1186/s12905-023-02621-8
24. Sangwan V, Sangwan M, Siwach S, Duhan A, Mahendroo R, Singh N. Endometrial stromal sarcoma: where only rarity prevails over obvious presentation. *Int J Case Rep Images*. 2014;5(6):435. https://doi.org/10.5348/ijcri-201483-cr-10394
25. Mahapatra M, Parija J, Sarkar A, Pattnaik S. A case of leiomyosarcoma of vaginal vault in a post-hysterectomy patient. *J South Asian Fed Obstet Gynaecol*.2024;16(3):313–314. https://doi.org/10.5005/jp-journals-10006-2032
26. Ghanavati M, Khorshidi Y, Shadnoush M, Akbari M, Ardehali S, Chávarri-Guerra Y, et al. Tamoxifen use and risk of endometrial cancer in breast cancer patients: a systematic review and dose-response meta-analysis. *Cancer Rep*. 2023;6(4). https://doi.org/10.1002/cnr2.1806
27. Fausto D, Leitão A, Silveira J, Martins J, Dominski F, Guimarães A. An umbrella systematic review of the effect of physical exercise on mental health of women in menopause. *Menopause*. 2022;30(2):225–234. https://doi.org/10.1097/gme.0000000000002105
28. Raffone A, Travaglino A, Raimondo D, Boccia D, Vetrella M, Verrazzo P, et al. Laparotomic versus robotic surgery in elderly patients with endometrial cancer: a systematic review and meta-analysis. *Int J Gynaecol Obstet*. 2021;157(1):1–10. https://doi.org/10.1002/ijgo.13766
29. Purwar R, Soni K, Shukla M, Verma A, Kumar T, Pandey M. TFE3-associated perivascular epithelioid cell tumor with complete response to mTOR inhibitor therapy: report of first case and literature review. *World J Surg Oncol*. 2022;20(1). https://doi.org/10.1186/s12957-021-02462-5
30. A p16 positive pleomorphic endometrial stromal sarcoma: an unusual case scenario. *J Med Surg Res*.2023:1214–1218. https://doi.org/10.46327/msrjg.1.000000000000243
31. Lensen S, Bell R, Carpenter J, Christmas M, Davis S, Giblin K, et al. A core outcome set for genitourinary symptoms associated with menopause: the COMMA global initiative. *Menopause*.2021;28(8):859–866. https://doi.org/10.1097/gme.0000000000001788