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Expression of B-cell Lymphoma 2 and Ki-67 in Different Endometrial Lesions: A Histopathological and Immunohistochemical Study

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Shilpa U. Vahikar [1], Ankita Gupta [1], Kanchan Shrivastava [1], Rajesh Kumar Rai [1], Raj Kishore Singh [2], Vibha Singh [1], Reeta Singh [3], Shani Vishwakarma [4]

1. Department of Pathology, Baba Raghav Das Medical College, Gorakhpur, IND 2. Department of Medicine, Baba Raghav Das Medical College, Gorakhpur, IND 3. Department of Obstetrics and Gynaecology, Baba Raghav Das Medical College, Gorakhpur, IND 4. Multi-disciplinary Research Unit, Baba Raghav Das Medical College, Gorakhpur, IND

Corresponding author: Shilpa U. Vahikar, mall.shilpa@yahoo.co.in

Abstract

Background: Endometrial lesions include physiological, hyperplastic, and malignant conditions with altered cellular proliferation and apoptosis. B-cell lymphoma 2 (BCL-2) and Ki-67 expression assess cellular survival, proliferation, and patterns across lesions relative to histopathological findings.

Methods: This prospective study included 50 endometrial biopsy or curettage specimens collected at Baba Raghav Das (BRD) Medical College, Gorakhpur, India, from December 1, 2025, to July 31, 2026. The specimens underwent histopathological examination and immunohistochemical staining for BCL-2 and Ki-67. Expression was assessed using a semiquantitative weighted scoring system. Data were analyzed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY).

Results: The patients were predominantly aged 40-49 years (23 (46%)) and postmenopausal (26 (52%)). Postmenopausal bleeding was the most common clinical presentation (23 (46%)). Histopathological diagnoses included hyperplasia without atypia (15 (30%)), disordered proliferative endometrium (13 (26%)), proliferative endometrium (11 (22%)), secretory endometrium (7 (14%)), and endometrial carcinoma (4 (8%)). The highest mean BCL-2 score was observed in hyperplasia without atypia (11.73), whereas endometrial carcinoma showed the highest mean Ki-67 score (12.00). Secretory endometrium had the lowest mean scores for BCL-2 (7.43) and Ki-67 (5.71).

Conclusion: BCL-2 and Ki-67 showed different expression patterns across endometrial lesions. These markers may provide supplementary biological information alongside histopathology; however, their diagnostic and prognostic utility has not been established.

Categories: Pathology
Keywords: bcl-2, endometrial carcinoma, endometrial hyperplasia, endometrial lesions, immunohistochemistry, ki-67

Introduction

Endometrial lesions range from physiological and benign to premalignant and malignant, with alterations in glandular structure, cell differentiation, growth, and apoptosis [1]. Endometrial carcinoma affects the female reproductive system globally and in India [2,3]. Despite early detection, histopathological evaluation is crucial for diagnosis, risk assessment, and treatment planning [4]. Endometrial sampling is often performed for abnormal uterine bleeding (AUB), which can result from hormonal imbalances, structural issues, endometrial hyperplasia, or malignancies [5]. Atypical endometrial hyperplasia is linked to endometrioid carcinoma, and previous clinicopathological research has examined this association and common risk factors [6].

The endometrium responds to hormones, undergoing cyclical structural and functional changes due to estrogen and progesterone. In the proliferative phase, estrogen promotes endometrial growth, whereas progesterone induces secretory transformation after ovulation [7]. Normal homeostasis requires balanced proliferation, differentiation, and apoptosis. Imbalances can cause disordered proliferative endometrium, hyperplasia, or malignant transformation [8]. Diagnosis relies on histopathological examination, with immunohistochemical markers providing insights into lesion biology.

B-cell lymphoma 2 (BCL-2) and Ki-67 are immunohistochemical markers of cellular apoptosis regulation and proliferation, respectively. BCL-2 is an anti-apoptotic protein in the intrinsic mitochondrial apoptotic pathway, and its endometrial expression varies with hormonal levels and menstrual phase [9]. Ki-67, a

nuclear protein, appears in active cell cycle stages, but not in resting cells, marking proliferative activity [10].

BCL-2 and Ki-67 levels in endometrial conditions may reflect differences in apoptosis and proliferation control. Earlier studies examined these markers in cyclical, disordered proliferative, hyperplastic, and cancerous endometrium, finding differing patterns [11]. However, comparisons are difficult because populations, histopathological classifications, and immunohistochemical scoring differ.

The present study aimed to evaluate and descriptively compare the immunohistochemical expression patterns of BCL-2 and Ki-67 across different endometrial histopathological categories, including proliferative-phase endometrium, secretory-phase endometrium, disordered proliferative endometrium, endometrial hyperplasia without atypia, and endometrial carcinoma. The study focused on describing variations in the expression scores of these markers in relation to the corresponding histopathological findings among specimens examined at a tertiary care teaching hospital in Gorakhpur, India. The findings were intended to characterize marker expression within the study population rather than establish population-level prevalence, diagnostic accuracy, prognostic significance, or a sequential biological progression of endometrial lesions.

Materials And Methods

Study design and setting

This prospective study was conducted at the Department of Pathology, Baba Raghav Das (BRD) Medical College, Gorakhpur, Uttar Pradesh, in collaboration with the Department of Obstetrics and Gynecology, over an eight-month period from December 1, 2025, to July 31, 2026. The study population comprised patients presenting with suspected endometrial pathology, whose endometrial biopsy or curettage specimens were submitted for histopathological examination. Relevant demographic and clinical information was recorded for each eligible participant, and specimens meeting the predefined eligibility criteria were included in the analysis. A total of 50 eligible endometrial specimens were histopathologically and immunohistochemically evaluated.

Inclusion criteria

Endometrial biopsy and curettage specimens received from the Department of Obstetrics and Gynecology for histopathological examination were included when adequate tissue was available and informed consent was obtained.

Exclusion criteria

Specimens inadequate for histopathological evaluation, autolyzed tissues unsuitable for morphological assessment, and cases in which informed consent was not obtained were excluded.

Ethical approval

The study was approved by the Institutional Human Ethics Committee of BRD Medical College, Gorakhpur, Uttar Pradesh, India (approval number: 280/IHEC/2025, approval date: November 22, 2025).

Specimen collection, processing, and histopathological examination

Endometrial tissue specimens obtained through biopsy or curettage were processed using routine histopathological techniques. Following fixation, the tissues underwent routine processing, paraffin embedding, and sectioning. The prepared sections were deparaffinized, rehydrated, and stained with Harris hematoxylin, differentiated using 1% acid alcohol, and counterstained with eosin. Subsequently, the sections were dehydrated through ascending grades of alcohol, cleared in xylene, and mounted using distyrene plasticizer xylene (DPX). Histopathological examination was performed under a light microscope to assess glandular architecture, gland-to-stroma ratio, epithelial morphology, nuclear characteristics, cytological atypia, and other relevant morphological features. Based on these morphological parameters, histopathological diagnosis and classification were established. Where applicable, histological typing and grading of endometrial carcinoma were also performed.

Immunohistochemical staining

Immunohistochemical staining was performed on representative formalin-fixed, paraffin-embedded (FFPE) tissue sections using monoclonal primary antibodies targeting BCL-2 and Ki-67. BCL-2 expression was evaluated using an anti-BCL-2 monoclonal antibody (clone EP36; catalog number: AN723-10M; BioGenex, India), whereas Ki-67 expression was assessed using a ready-to-use anti-Ki-67 monoclonal antibody (clone MKI67/2462; catalog number: AXA01-YCD; BioGenex, India). The sections were deparaffinized in xylene and rehydrated through descending grades of ethanol. Heat-induced antigen retrieval was performed using a water bath-based technique. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for approximately 10 minutes, followed by washing with phosphate-buffered saline (PBS; pH 7.4). Separate

tissue sections were incubated with ready-to-use primary antibodies against BCL-2 and Ki-67 for approximately 30 minutes at room temperature in a humidified chamber. Following incubation, the sections were washed with PBS and treated with enhancer and horseradish peroxidase (HRP)-linked polymer detection reagents according to the laboratory protocol. Immunoreactivity was visualized using a chromogenic substrate, followed by counterstaining with Mayer's hematoxylin. Finally, the sections were dehydrated, cleared in xylene, mounted using DPX, and examined under a light microscope.

Immunohistochemical evaluation and scoring

BCL-2 immunoreactivity was evaluated based on cytoplasmic staining in endometrial glandular epithelial cells, whereas Ki-67 expression was assessed by nuclear staining in endometrial cells. Immunohistochemical expression was evaluated using a semiquantitative weighted scoring system based on the percentage of positive cells (PP) and staining intensity (SI). The proportion score was graded as follows: score 0 for less than 5%, score 1 for 5%-25%, score 2 for 26%-50%, score 3 for 50%-75%, and score 4 for more than 76% positive cells. Staining intensity was graded as 0 (absent), 1 (weak), 2 (moderate), 3 (strong/intense), and 4 (very strong). The weighted score was calculated by multiplying the proportion score by the staining intensity score. For BCL-2, the proportion score was maintained at 4, while the intensity score was used as the variable component. Conversely, for Ki-67, the intensity score was maintained at 4, while the proportion score represented the variable component. Accordingly, the resulting weighted scores were categorized as 4, 8, 12, and 16. The scoring approach was based on previously published methodology. Mean expression scores were calculated separately for each marker across the different histopathological categories. Immunohistochemical evaluation was performed manually by assessing at least 100 cells across 10 high-power fields [12-14].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 27 (IBM Corp., Armonk, NY). Categorical variables, including age groups, histopathological diagnoses, menopausal status, and clinical presentations, were summarized as frequencies and percentages. BCL-2 and Ki-67 immunohistochemical expression scores were analyzed descriptively across the different histopathological categories. The distribution of individual expression scores was presented as frequencies and percentages, while mean expression scores were calculated for each histopathological category. The findings were presented in tabular form to describe the immunohistochemical expression patterns of both markers across the study groups. No inferential statistical tests or correlation analyses were performed.

Results

Clinicopathological characteristics of the study population

A total of 50 endometrial specimens were evaluated for clinicopathological characteristics and BCL-2 and Ki-67 expression. The predominant age group was 40-49 years (23 (46%)), followed by 50-59 years (16 (32%)), below 40 years (8 (16%)), and 60 years or older (3 (6%)). Postmenopausal women constituted 26 (52%), compared with perimenopausal women with 16 (32%) and premenopausal women with 8 (16%). Postmenopausal bleeding was the most common clinical presentation (23 (46%)), followed by menorrhagia (21 (42%)); infertility and polymenorrhea together accounted for 6 (12%). Histopathological examination most frequently revealed hyperplasia without atypia (15 (30%)), followed by disordered proliferative endometrium (13 (26%)), proliferative-phase endometrium (11 (22%)), secretory-phase endometrium (7 (14%)), and endometrial carcinoma (4 (8%)) (Table *1*).

Characteristics	Number of cases	Percentage
Age group		
<40 years	8	16%
40-49 years	23	46%
50-59 years	16	32%
≥60 years	3	6%
Histopathological diagnosis		
Proliferative phase	11	22%
Secretory phase	7	14%
Disordered proliferative phase	13	26%
Hyperplasia without atypia	15	30%
Endometrial carcinoma	4	08%
Menopausal status		
Postmenopausal	26	52%
Perimenopausal	16	32%
Premenopausal/reproductive	8	16%
Clinical presentation		
Postmenopausal bleeding	23	46%
Menorrhagia	21	42%
Others (infertility, polymenorrhea)	6	12%

TABLE 1: Demographic and Clinicopathological Characteristics of the Study Population

Data are presented as frequency (number of cases) and percentage (%) of the total study population (N = 50). Age is categorized into four groups, while histopathological diagnosis, menopausal status, and clinical presentation are reported according to their respective categories.

Immunohistochemical expression of BCL-2 across endometrial lesions

Endometrial hyperplasia without atypia exhibited the highest mean immunoreactivity score (11.73), with 9 (60%) and 3 (20%) specimens attaining scores of 12 and 16, respectively. Disordered proliferative endometrium yielded a mean score of 9.54, with cases represented across all four reported staining score categories. Proliferative-phase endometrium demonstrated a mean score of 8.00, with staining predominantly concentrated at scores of 8 and 12. Secretory-phase endometrium displayed the lowest mean score (7.43), with 4 (57.14%) specimens assigned a score of 8 and no cases reaching 16. Endometrial carcinoma exhibited a mean score of 9.00, with 3 (75%) tumors scoring 8 and the remaining 1 (25%) scoring 12 (Table *2*). These descriptive findings indicate the highest mean BCL-2 immunoreactivity in hyperplasia without atypia among the categories examined. Cytoplasmic BCL-2 positivity was observed in neoplastic epithelial cells (Figure *1*), while corresponding hematoxylin and eosin (H&E) sections demonstrated nuclear pleomorphism.

Endometrial lesions	Sample size	Score 4	Score 8	Score 12	Score 16	Mean score
Proliferative phase	11	3 (27.27%)	5 (45.45%)	3 (27.27%)	-	8
Secretory phase	7	2 (28.57%)	4 (57.14%)	1 (14.28%)	-	7.43
Disordered proliferative phase	13	2 (15.38%)	6 (46.15%)	3 (23.07%)	2 (15.38%)	9.54
Hyperplasia without atypia	15	1 (6.67%)	2 (13.33%)	9 (60%)	3 (20%)	11.73
Endometrial carcinoma	4	-	3 (75%)	1 (25%)	-	9

TABLE 2: Distribution of BCL-2 Immunohistochemical Expression Scores and Mean Expression Scores Across Different Histopathological Categories of Endometrial Lesions

Data are expressed as frequency (percentage) for each BCL-2 immunohistochemical expression score. Mean scores represent the average expression score within each histopathological category. A dash (-) indicates the absence of cases in the corresponding score category.

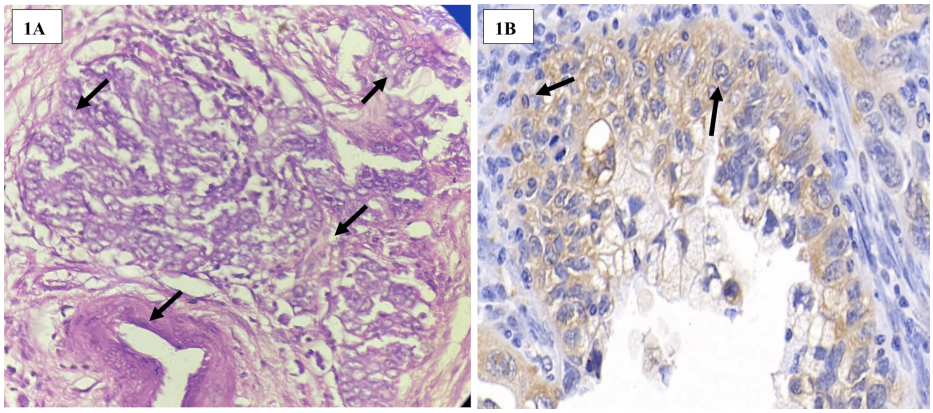


FIGURE 1: Histopathological Features and Immunohistochemical Expression of BCL-2 Proliferation Marker

(1A) High-power photomicrograph demonstrating tumor cells arranged in sheets, nests, and glandular structures exhibiting marked nuclear pleomorphism (arrow) (H&E staining, 40×). (1B) High-power immunohistochemical photomicrograph highlighting BCL-2-positive tumor cell cytoplasm (arrows), indicating anti-apoptotic activity(40×).

Immunohistochemical expression of Ki-67 across endometrial lesions

Endometrial carcinoma exhibited the highest mean Ki-67 immunoreactivity score (12.00), with 3 (75%) specimens attaining scores of 12 or 16. Hyperplasia without atypia demonstrated a mean score of 9.87, with 6 (40%) and 2 (13.33%) cases assigned scores of 12 and 16, respectively. Proliferative-phase endometrium yielded a mean score of 9.45, with 5 (45.45%) samples exhibiting scores of 12 or 16. Disordered proliferative endometrium displayed a lower mean score (7.08), with 6 (46.15%) specimens scoring 4. Secretory-phase endometrium demonstrated the lowest mean score (5.71), with staining scores restricted to 4 and 8 (Table *3*). These descriptive findings show the highest mean Ki-67 score in carcinoma and the lowest in secretory endometrium. H&E sections demonstrated pleomorphic neoplastic epithelial nests within fibrous stroma, while immunohistochemistry demonstrated nuclear Ki-67 positivity (Figure *2*).

Endometrial lesions	Sample size	Score 4	Score 8	Score 12	Score 16	Mean score
Proliferative phase	11	2 (18.18%)	4 (36.36%)	4 (36.36%)	1 (9.09%)	9.45
Secretory phase	7	4 (57.14%)	3 (42.85%)	-	-	5.71
Disordered proliferative phase	13	6 (46.15%)	4 (30.77%)	3 (23.08%)	-	7.08
Hyperplasia without atypia	15	3 (20%)	4 (26.67%)	6 (40%)	2 (13.33%)	9.87
Endometrial carcinoma	4	-	1 (25%)	2 (50%)	1 (25%)	12.00

TABLE 3: Distribution of Ki-67 Immunohistochemical Expression Scores and Mean Expression Scores Across Different Histopathological Categories of Endometrial Lesions

Data are presented as frequency (percentage) for each Ki-67 expression score. Mean scores represent the average immunohistochemical expression score within each histopathological category. A dash (-) indicates that no cases were observed in the respective score category.

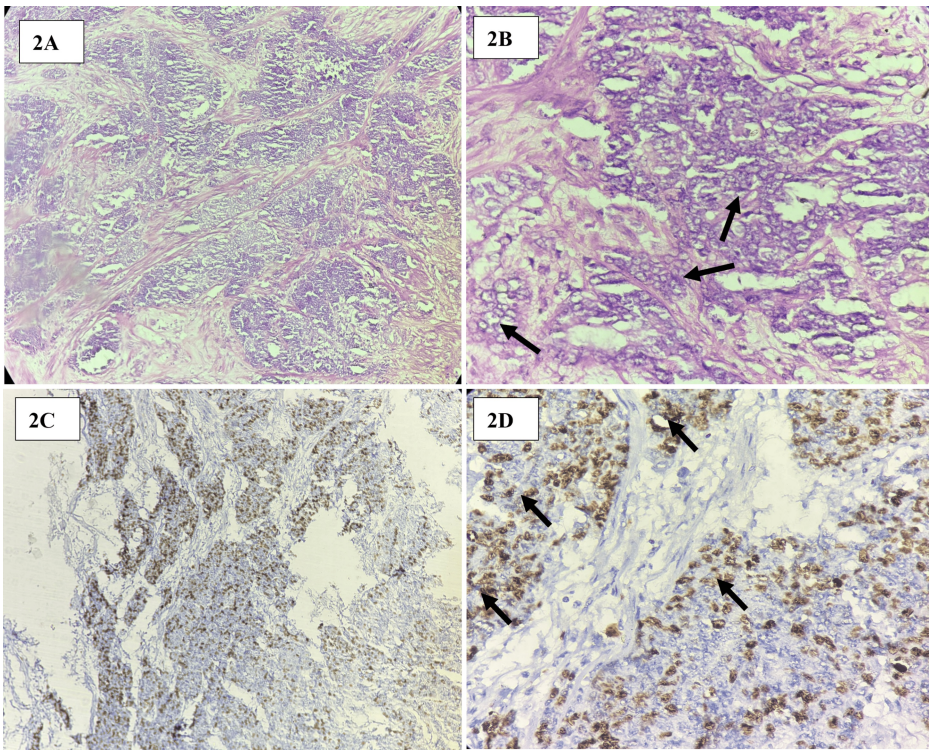


FIGURE 2: Histopathological Features and Immunohistochemical Expression of Ki-67 Proliferation Marker

(2A) Low-power photomicrograph showing the histopathological architecture of the tumor with irregularly arranged tumor cell nests and intervening fibrous stroma (H&E staining, 10×). (2B) High-power photomicrograph demonstrating tumor cell clusters with nuclear pleomorphism (arrow) (H&E staining, 40×). (2C) Low-power immunohistochemical photomicrograph showing Ki-67 expression within the tumor tissue, indicated by brown nuclear staining(10×). (2D) High-power immunohistochemical photomicrograph highlighting Ki-67-positive tumor cell nuclei (arrows), indicating proliferative activity (40×).

Comparative distribution of BCL-2 and Ki-67 expression

Comparative descriptive analysis of BCL-2 and Ki-67 demonstrated different expression profiles among the histopathological categories. BCL-2 showed the highest mean immunoreactivity score in hyperplasia without atypia, whereas Ki-67 showed the highest mean score in endometrial carcinoma. The secretory-phase endometrium displayed the lowest mean scores for both markers. Within the hyperplasia group, 12 (80%) specimens had BCL-2 scores of 12 or 16, compared with 8 (53.33%) specimens with corresponding Ki-67 scores. In carcinoma, 3 (75%) specimens had Ki-67 scores of 12 or 16, whereas 1 (25%) specimen had BCL-2 scores of 12 or 16. These are group-level descriptive comparisons and do not establish a patient-level

inverse correlation between the markers.

Discussion

Endometrial homeostasis depends on the coordinated regulation of cellular proliferation, differentiation, and programmed cell death. Cyclical hormonal fluctuations regulate endometrial growth and tissue remodeling, whereas alterations in proliferative activity and apoptotic regulation may contribute to the development of hyperplastic and neoplastic lesions. Ki-67 and BCL-2 provide complementary immunohistochemical information regarding cellular proliferation and survival, respectively [15].

BCL-2 is an anti-apoptotic protein involved in the regulation of the intrinsic mitochondrial apoptotic pathway. Its expression contributes to cellular survival by inhibiting mitochondrial apoptotic signaling [16]. Assessment of BCL-2 alongside Ki-67 may therefore provide a broader understanding of the cellular characteristics of endometrial lesions. However, immunohistochemical expression represents a surrogate marker of biological activity and does not directly quantify cellular proliferation or apoptosis [17]. Increased BCL-2 expression in endometrial hyperplasia without atypia may be consistent with enhanced anti-apoptotic signaling and prolonged epithelial cell survival. Endometrial hyperplasia is frequently associated with prolonged estrogenic stimulation inadequately opposed by progesterone, which promotes glandular proliferation and may influence the balance between cellular proliferation and apoptosis. Nevertheless, in the absence of hormonal measurements and functional apoptosis assays, these underlying mechanisms cannot be established directly.

Previous investigations have demonstrated BCL-2 expression in cyclical endometrium and endometrial hyperplasia, with variations across proliferative, secretory, and hyperplastic categories [18]. Studies evaluating BCL-2 and Ki-67 together have also reported differences in their expression across non-atypical hyperplasia, atypical hyperplasia, and malignant endometrial lesions [19,20]. In the present study, the highest mean BCL-2 expression score was observed in endometrial hyperplasia without atypia. However, the absence of atypical hyperplasia cases and the limited representation of endometrial carcinoma restrict comparisons across the spectrum of endometrial lesions. Accordingly, BCL-2 immunoreactivity in carcinoma should not be interpreted as evidence of greater anti-apoptotic activity than that observed in all benign lesions.

Ki-67 is a nuclear proliferation-associated marker that reflects the proportion of cells participating in the active phases of the cell cycle. Its expression in endometrial tissue is influenced by hormonal regulation and physiological changes that occur throughout the menstrual cycle. Relatively lower expression during the secretory phase is consistent with the transition from estrogen-associated proliferation to progesterone-mediated differentiation [21,22]. Conversely, increased Ki-67 expression in neoplastic tissue may reflect alterations in normal cell cycle regulation. Previous studies have reported higher Ki-67 immunoreactivity in endometrial carcinoma than in benign endometrial conditions [23]. A study published in 2022 also demonstrated higher Ki-67 expression in endometrial carcinoma than in proliferative endometrium and simple hyperplasia, with associations reported with tumor grade. Similarly, other investigations have described increased expression in hyperplastic and malignant lesions compared with secretory endometrium [24].

In the present study, the highest mean Ki-67 expression score was observed in endometrial carcinoma, whereas the lowest was recorded in the secretory-phase endometrium. These findings represent descriptive differences within the study population and do not establish statistically significant differences between histopathological categories. Nevertheless, Ki-67 expression should not be interpreted as continuous progression across endometrial lesions. Proliferative endometrium, disordered proliferative endometrium, and hyperplasia without atypia represent distinct histopathological conditions rather than obligatory stages of malignant transformation [25]. Their proliferative characteristics may vary according to hormonal exposure, glandular differentiation, cellular heterogeneity, and cell cycle activity. In addition, differences in immunoreactivity may be influenced by sampling variation and intralesional heterogeneity [26]. Therefore, Ki-67 expression should be interpreted as supplementary immunohistochemical information alongside conventional morphological assessment rather than as an independent determinant of histopathological diagnosis.

The expression patterns of BCL-2 and Ki-67 across the examined histopathological categories highlight the complementary biological processes represented by these markers. Previous studies investigating both markers in cyclical endometrium, hyperplasia, and carcinoma have also described variations in their respective immunohistochemical expression patterns [27,28]. In the present study, both markers were descriptively compared across different endometrial lesions. Although BCL-2 is associated with cellular survival and Ki-67 reflects proliferative activity, their patient-level relationship was not investigated through correlation analysis; therefore, an inverse association between their expression patterns cannot be established. Furthermore, the study did not evaluate the diagnostic accuracy of these markers, individually or in combination, in distinguishing endometrial hyperplasia without atypia from endometrial carcinoma, or their additional diagnostic value over routine H&E examination. Accordingly, the findings should be interpreted as descriptive immunohistochemical observations rather than evidence of a direct biological relationship or diagnostic superiority. Further studies incorporating patient-level correlation and diagnostic

performance analyses are warranted.

Study limitations and future perspectives

The interpretation of these findings has several limitations. The present study has certain limitations that should be considered while interpreting the findings. The relatively small sample size (N = 50), obtained from a single tertiary care teaching hospital, particularly the limited number of endometrial carcinoma cases (n = 4), may affect the precision and generalizability of the observed immunohistochemical expression patterns. Furthermore, the absence of atypical endometrial hyperplasia cases restricted the evaluation of BCL-2 and Ki-67 expression across the complete spectrum of endometrial lesions. Therefore, the findings should be interpreted cautiously and should not be generalized to the wider population. Larger multicentric studies with adequate representation of different histopathological categories are required to validate these observations. The absence of atypical endometrial hyperplasia prevented the assessment of immunohistochemical changes across premalignant endometrial lesions. Additionally, the results comprised semiquantitative immunoreactivity scores rather than quantitative staining indices or percentages of positive epithelial cells. The scoring rubric requires confirmation from original laboratory records. No inferential results or paired marker-level analyses were available; therefore, group differences and marker correlations could not be established. Technical details should be verified and reported to improve reproducibility.

Further investigations with multicenter cohorts, standardized immunohistochemical protocols, validated scoring systems, and histopathological subclassification would help establish reproducibility and clinical significance. Incorporating hormonal receptor status, molecular classification, and longitudinal outcomes could clarify the relationships between endometrial hormonal regulation, proliferative activity, apoptosis-associated signaling, and neoplastic transformation.

Conclusions

The present study demonstrated variations in BCL-2 and Ki-67 immunohistochemical expression across different endometrial histopathological categories. BCL-2 showed the highest mean expression score in endometrial hyperplasia without atypia, whereas Ki-67 demonstrated the highest mean expression score in endometrial carcinoma. These findings represent descriptive observations within the study population and should be interpreted in the context of the limited sample size and absence of inferential statistical analysis. Further studies involving larger cohorts, patient-level correlation analyses, and diagnostic performance assessment are required to establish the biological and potential clinical significance of these markers in endometrial lesions.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Shilpa U. Vahikar, Ankita Gupta, Kanchan Shrivastava

Acquisition, analysis, or interpretation of data: Shilpa U. Vahikar, Ankita Gupta, Kanchan Shrivastava, Rajesh Kumar Rai, Raj Kishore Singh, Vibha Singh, Reeta Singh, Shani Vishwakarma

Critical review of the manuscript for important intellectual content: Shilpa U. Vahikar, Kanchan Shrivastava, Rajesh Kumar Rai, Raj Kishore Singh, Vibha Singh, Reeta Singh, Shani Vishwakarma

Supervision: Shilpa U. Vahikar, Raj Kishore Singh

Drafting of the manuscript: Ankita Gupta, Kanchan Shrivastava, Rajesh Kumar Rai, Raj Kishore Singh, Vibha Singh, Reeta Singh, Shani Vishwakarma

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. The Institutional Human Ethics Committee of Baba Raghav Das (BRD) Medical College, Gorakhpur issued approval 280/IHEC/2025 (date: November 22, 2025). **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **AI use statement:** The authors used ChatGPT as follows: language polishing, structure or formatting in Introduction, Discussion, and manuscript presentation (language editing, grammar correction, improvement of scientific writing, and formatting). The authors carefully reviewed all AI-assisted suggestions and independently verified the scientific content, factual accuracy, statistical results, and cited references against the original study data and relevant scientific literature. All interpretations and conclusions were critically evaluated by the authors. No AI-generated data, results, or references were accepted without independent verification. The

authors retain full responsibility for the accuracy, originality, and integrity of the manuscript. The authors confirm that they have reviewed and verified all AI-assisted content and take full responsibility for the work. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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