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# Immunohistochemical expression of B-cell lymphoma 2 gene - Bcl-2 in endometrial carcinoma

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## Abstract:

**Background and objectives:** Apoptosis, a process of cell death, is inhibited by the B-cell lymphoma 2 protein, leading to the prolonged survival of cells. Participation of Bcl-2 in starting and advancement of endometrial carcinoma remains inconclusive, with varying results observed. The aims of this study were to assess the frequency of B-cell lymphoma 2 expression in endometrial carcinoma, and to investigate the connection between B-cell lymphoma 2 expression with some clinicopathological parameters.

**Methods:** A retrospective study was carried out for seventy-eight formalin fixed paraffin embedded blocks of total abdominal hysterectomy specimens diagnosed as endometrial carcinoma, which were randomly obtained from a private laboratory and Rizgary teaching hospital laboratory in Erbil city during June 2021-June 2022. In this study, endometrial carcinoma cases were subjected to the utilization of B-cell lymphoma 2 gene, which is a Mouse monoclonal antibody, and its expression was evaluated.

**Results:** The expression of Bcl-2 was observed in 61.5% of the studied cases. The majority (93.6%) of EC cases were of low grade, although Bcl-2 expression was observed at a greater frequency (64.4%) in low-grade endometrial carcinoma, but there was no significant association. Additionally, no statistically significant correlation was found between B-cell lymphoma 2 gene expression and other clinicopathological parameters like, age, myometrial invasion, lympho-vascular invasion, lymph node status and tumor stage.

**Conclusion:** Bcl-2 was expressed in 61.5% of the studied cases with no significant association with any of the variables, additional research is necessary to assess the expression of B-cell lymphoma 2 gene in relation to endometrial carcinoma invasion and metastasis.

**Keywords:** Apoptosis, B-cell lymphoma 2 gene, Endometrial carcinoma, Immunohistochemistry

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## Introduction:

Endometrial carcinoma (EC) is the leading gynecological cancer and ranks as the fourth most common malignancy in women in developed nations.[1] As per the information provided by the International Agency for Research on Cancer, the global occurrence of endometrial carcinoma is rapidly rising, with projections indicating a potential rise of over 50% by the year 2040.[2] Endometrial carcinoma ranks as the seventh most prevalent malignant condition among women in the Erbil governorate, Kurdistan region of Iraq.[3] Countries with high economic prosperity have a higher frequency of EC than low-resource countries. This could be explained by significant obesity and sedentary lifestyle rates, that are two considerable risk factors in wealthy nations, and to ageing of the community. Increased concentration of estrogen is recognized as the leading potential reason of the higher risk of EC for females in the postmenopausal phase with obesity.[4] In contrast, regular physical exercise and extended utilization of estrogen-progestin combination therapy are linked to a decreased likelihood of developing EC.[5,6] Other studies mentioned that several risk factors for EC have been found including conditions such as high blood pressure, diabetes, nulliparity, experiencing menopause at a later age, and possessing a familial background of the disease.[7-9] In most instances, EC develops from a premalignant stage known as intraepithelial endometrial neoplasia.[10] Programmed cell death, also known as apoptosis, is a recognized vital characteristic that serves as a highly effective mechanism in regulating cell numbers in various bodily organs. The B cell leukemia, lymphoma-2 gene (Bcl-2) was identified as the initial gene capable of suppressing programmed cell death in numerous cellular systems. This specific gene is located on chromosome 18. The initial discovery of this gene occurred in cases of follicular and diffuse lymphomas, but the discovery of Bcl-2 expression in different epithelial tissues, for example breast, cervix and ovary proposed a probable involvement in the emergence of several neoplasms of epithelial tissues.[11-15] The ratio between Bcl-2 and Bax proteins maintains the equilibrium of proliferation in endometrial cells. The role of Bcl-2 family proteins in modulating cell growth is significant, and it is partly affected by hormonal factors in the endometrial epithelium. Meanwhile, in the secretory phase, Bcl-2 expression disappears. Nevertheless, the clear function of this family protein in onset, differentiation and infiltration nature remains poorly comprehended.[16,17] It has been demonstrated that apoptotic mechanism takes place because of alterations in the gene family responsible for regulating apoptosis.[18-22]Targeted therapy against Bcl-2 has been applied to various cancer types, including small cell lung carcinoma, leukemia, as well as breast and ovarian cancers; therefore, the investigation of Bcl-2 expression in endometrial carcinoma, which is a highly prevalent gynecological disease, appears increasingly appealing.[23] Several research studies have investigated Bcl-2 expression in cases of EC, with variable outcomes. Some authors revealed higher Bcl-2 expression in EC, [16,24] whereas others displayed decreased expression in EC.[25-28] The aims of the ongoing study are to explore and examine for the frequency of the expression of Bcl-2 assessed through immunohistochemistry in patients diagnosed with EC, and to correlate Bcl-2 expression with Several clinicopathological factors, including age, tumor grade, extent of myometrial invasion, presence of lympho-vascular invasion, lymph node involvement, and tumor stage.


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## Material and methods:

A retrospective study was done for a total of seventy-eight endometrial carcinoma samples, which were collected from total abdominal hysterectomy specimens preserved in formalin-fixed paraffin blocks, in which they were randomly obtained from a private laboratory and Rizgary teaching hospital laboratory in Erbil city during June 2021-June 2022. Two sections were created from every individual block, one stained with Hematoxylin & Eosin to make histological analysis, at the same time the other was used for immunohistochemical evaluation of Bcl-2 expression. A dual of International Federation of Gynecology and Obstetrics (FIGO) grading system was performed, which categorizes grade 1 and 2 carcinomas as low grade, while grade 3 carcinomas are considered high grade,[29] and the American Joint Committee on Cancer (AJCC) (2017) guidelines were used to conduct the pathological staging.[30] The committee responsible for ethical considerations at the Kurdistan Higher Council of Medical Specialties granted ethical approval of the study. Sections with a thickness of four micrometers were sliced and placed on charged slides. Following one hour of drying at 60 °C, the slides underwent deparaffinization and rehydration at room temperature (20-25 °C). Afterward, the sections were placed in a xylene solution for a duration of 5 minutes, followed by immersion in ethanol for 3 minutes. Finally, immersion in distilled water was done for 30 seconds. The epitope retrieval process was conducted using a specific method in 10 mmol/L citrate buffer 1:10 ratio with distilled water. Immunohistochemical staining was carried out using Bcl-2 antibody, an antibody derived from mice that is monoclonal in nature (Clone 124; DAKO; catalog no: M0887; 0.5ml concentrated; dilution 1:100) this antibody was applied to the tissue sections. The presence of cytoplasmic staining was considered as a positive indication for Bcl-2 reactivity. The examination and analysis of Bcl-2 expression were performed by two pathologists with extensive expertise. For every staining run, slides containing positive and negative controls were included as part of the process. To establish negative controls, the primary antibody was omitted and instead, N-Universal negative control was employed. As a positive control for assessing Bcl-2 expression, human tonsil tissue was utilized. For scoring of the Bcl-2 expression, we recorded the percentage of positive cells for Bcl-2 staining. A cutoff point of 10% is selected as the threshold. Specimens were regarded positive when a threshold level of 10% or more of the malignant cells displayed conclusive proof of cytoplasmic staining for Bcl-2. In contrast, specimens were considered negative when less than 10% of the neoplastic cells showed staining of the cytoplasm for Bcl-2.[31,32] The data was subjected to analysis using the Statistical Package for the Social Sciences (SPSS, version 25). Proportions of two or more groups were compared using the Chi-square test of association as a statistical method. When the expected frequency (value) was less than 5 of more than 20% of the cells of the table, Fisher's exact test was applied. Statistical significance was defined as a p value of $\leq 0.05$.

## Results:

Seventy-eight women with endometrial carcinoma were included in the current study. Their mean age (SD) was 60.1 (11.6) years, the median was 60 years, and the age range was 34 to 85 years. Around half of the women (47.4%) were aged more than 60 years. The majority (93.6%) of the tumors were of low grade. The tumor invaded at least 50% of the myometrium in over two-thirds (69.2%) of the cases. 14.1% of the tumors had lympho-vascular invasion. Positive lymph nodes were detected in 5.1% of the patients, and 83.3%


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of the tumors were of stage T1. A positive Bcl-2 expression score was detected in 61.5% of the patients. The details are demonstrated in Table (1).

**Table (1):** Tumor characteristics.

| | No. | (%) |
|---|---|---|
| Tumor grade<br>Low | 73 | (93.6) |
| High | 5 | (6.4) |
| Myometrial invasion<br>< 50% | 24 | (30.8) |
| ≥ 50% | 54 | (69.2) |
| Lympho-vascular invasion<br>Positive | 11 | (14.1) |
| Negative | 67 | (85.9) |
| Lymph node status<br>Positive | 4 | (5.1) |
| Negative | 74 | (94.9) |
| Tumor stage<br>T1<br>T2<br>T3<br>T4 | <br>65<br>5<br>7<br>1 | |
| Bcl-2 expression score | | (83.3) |
| Positive | 48 | (6.4)<br>(9.0) |
| Negative | 30 | (1.3)<br>(61.5)<br>(38.5) |
| Total | 78 | (100.0) |

No significant association was detected between Bcl-2 expression and the clinicopathological parameters including age (p = 0.197), tumor grade (p = 0.069), myometrial invasion (p = 0.261), lympho-vascular invasion (p = 0.516), lymph node status (p = 1.000), and tumor stage (p = 0.872). The details are demonstrated in Table (2).

**Table (2):** The expression of Bcl-2 and its relationship with the studied factors.



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| | Bcl-2 expression | | | |
|---|---|---|---|---|
| | Positive | Negative | Total | p value |
| Age (years)<br>≤ 60 | 28 (68.3) | 13 (31.7) | 41 (100.0) | |
| > 60 | 20 (54.1) | 17 (45.9) | 37 (100.0) | 0.197* |
| Tumor grade<br>Low | 47 (64.4) | 26 (35.6) | 73 (100.0) | |
| High | 1 (20.0) | 4 (80.0) | 5 (100.0) | 0.069** |
| Myometrial invasion<br>< 50% | 17 (70.8) | 7 (29.2) | 24 (100.0) | |
| ≥ 50% | 31 (57.4) | 23 (42.6) | 54 (100.0) | 0.261* |
| Lympho-vascular invasion<br>Positive | 8 (72.7) | 3 (27.3) | 11 (100.0) | |
| Negative | 40 (59.7) | 27 (40.3) | 67 (100.0) | 0.516** |
| Lymph node status<br>Positive | 3 (75.0) | 1 (25.0) | 4 (100.0) | |
| Negative | 45 (60.8) | 29 (39.2) | 74 (100.0) | 1.000** |
| Tumor stage<br>T1 | 39 (60.0) | 26 (40.0) | 65(100.0) | |
| T2 | 4 (80.0) | 1 (20.0) | 5(100.0) | |
| T3 | 4 (57.1) | 3 (42.9) | 7(100.0) | |
| T4 | 1 (100.0) | 0 (0.0) | 1(100.0) | 0.872** |
| Total | 48 (61.5) | 30 (38.5) | 78 (100.0) | |

*By Chi square test. **By Fisher's exact test.

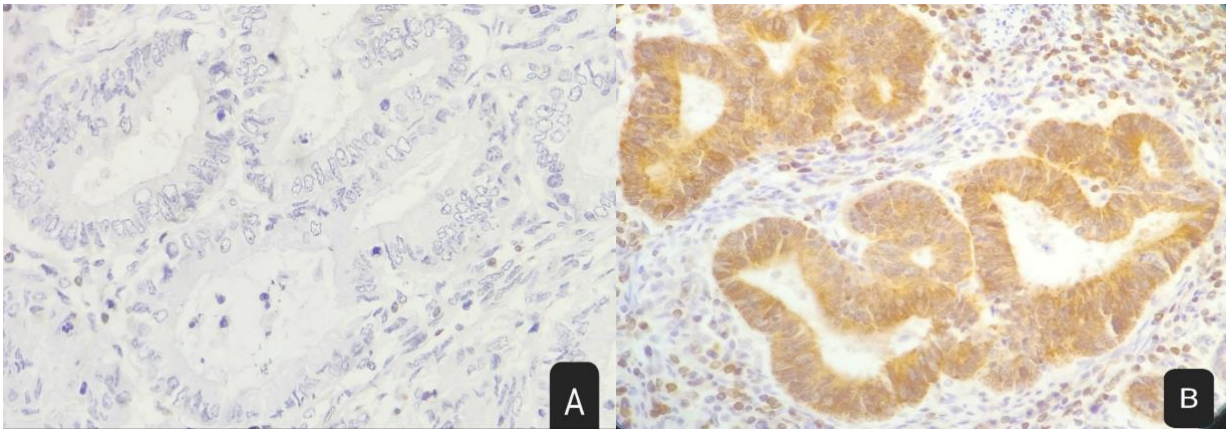


**Figure (1):** Bcl-2 expression. A. Absence of Bcl-2 expression (IHCx400). B. Presence of Bcl-2 expression (IHCx400)

## Discussion:

It has been believed that apoptosis could be a significant mechanism in the development of cancer. Apoptosis-related genes and genes involved in antiapoptotic processes produce proteins that regulate the intricate process of


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programmed cell death. The malfunction of their expression may lead to pathways involved in the development of cancer. Bcl-2 as an antiapoptotic protein prevents apoptotic cell death and its expression throughout the regular menstrual cycle is a recognized truth. There exist studies which demonstrate that the excessive expression of this protein in the tissue of endometrium might be a sign indicating that cancer cells need to validate their existence in the tissue and develop in a malignant tumor.[33,34] Within the scope of this current study, Bcl-2 revealed expressions in 61.5% of cases, which was in agreement with different studies that had variable expressions of Bcl-2 for EC ranging from 56% to up to 86%.[17,25,31,35-37] This study showed that the age distribution among the patients on an average basis (SD) was 60.1 (11.6) years, the majority (52.6%) were aged less than or equal to 60 years, this aligned with the findings of Laban et al.[38] No significant relationship was identified between Bcl-2 expression and patients' age, consistent with the findings of Erkanli et al.[25] In the context of our study, the prevalence of Bcl-2 expression was higher in low-grade EC, and although the observed difference neared statistical significance ($p = 0.069$), similar findings of Bcl-2 overexpression in low-grade EC were previously reported by Kounelis et al.[35], Deger et al.[17] and Appel et al.[31] It is believed that the expression of Bcl-2 possibly suppressed during cancer development. As a result, the expression of Bcl-2 may serve as a critical indicator for the progression and prognosis of cancer.[17]Common features of tumor advancement are invasion and metastasis. Fifty four out of seventy eight cases with EC had deep myometrial invasion (≥50%). The present study demonstrated elevated Bcl-2 expression in patients exhibiting deep myometrial invasion, although the observed difference did not reach statistical significance, the findings of this study did not align with results reported by Kalogiannidis et al.[39] and Fyallah et al.[40], who showed a lower expression of Bcl-2 in patients with deep myometrial invasion but without significant correlation. Based on this study, 67 out of 78 patients had no lympho-vascular invasion, Bcl-2 is expressed more frequently in those cases who had no lympho-vascular invasion (LVI), as more than half of the cases who had no LVI were immunoreactive for Bcl-2, although there was no significant correlation. The findings of this study was consistent with the observations reported by Kalogiannidis et al.[39] Furthermore, this study showed that the lymph nodes were not invaded in 74 out of 78 cases and in 60.8% of the cases there were Bcl-2 expression, similar to other studies which showed increased immunoreactivity of Bcl-2 in those cases with no lymph node metastasis, but without any significant association between Bcl-2 and lymph node status.[39,41]In the present study among 78 patients with EC, 65 of them were at stage T1 in which 60% of them showed Bcl-2 expression, while the expression of Bcl-2 was 80% at stage T2, 57.1% at stage T3 and 100% at stage T4, respectively. The difference in outcomes were not statistically significant in our study. Erdem et al.[41] and Kalogiannidis et al.[39] also did not find any substantial link between Bcl-2 expression and tumor stage. The discrepancies between results of this study compared with that of other studies might be influenced by the variation in the immunohistochemical techniques, duration of fixation, the application of monoclonal antibodies from different sources, different sample size, and difference in the determination of positive staining.

## Conclusion:

Our findings showed that Bcl-2 was expressed in 61.5% of the studied cases with no significant association with any of the clinicopathological variables, further studies are required to assess immunohistochemical


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expression of Bcl-2 in relation to EC invasion and metastasis.

## Conflict of interest:

The author declared no conflict of interest.

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