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IMMUNOHISTOCHEMICAL EXPRESSION OF B CELL LYMPHOMA-2 PROTEIN IN ENDOMETRIAL CARCINOMA IN IRAQI FEMALE PATIENTS, AND ITS CORRELATION WITH CLINICOPATHOLOGICAL VARIABLE

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ABSTRACT

Background: Endometrial carcinoma is a type of cancer that originates from the endometrium, it is the most common cancer of lower female genital tract in developed countries, the fourth most common cancer in women worldwide and the eighth most common of cancer of women in Iraq. Bcl-2 is an anti-apoptotic gene inhibit programmed cell death, and its expression has been observed in variety of human neoplasm including endometrial carcinoma. **Aim of the study:** The aim of this study is to investigate the expression of Bcl-2 in endometrial carcinoma and its correlation with clinicopathological variables. **The variables will include:** patient age, histopathological type, histopathological grade, the depth of myometrial invasion, FIGO stage, lower uterine segment invasion and cervical stromal invasion. **Patients and Method**: Across-sectional study done at The Medical City Teaching Complex/ The National Center for Educational Laboratories, from the first of March 2024 until the end of July 2024, The samples were collected from 50 patients' records with endometrial carcinoma and tissue blocks embedded in paraffin stored in The National Center for Educational Laboratories, Immune histochemical staining of the slides with highest percentage of tumor cells of endometrial carcinoma was carried out to identify the positivity for Bcl-2 protein. **Results:** The mean age of the study group was 57.08 years, the majority of cases were classified as grade I tumors, pT1a was the most common FIGO staging, the expression of Bcl-2 protein occur in 62 % of cases of endometrial carcinoma, 12 cases (24.0%) had weak positive, 12 cases (24.0%) moderately positive Bcl2 expression, 7 cases (14.0%) had strong positive Bcl2 expression and 19 cases (38.0%) were of negative Bcl2 expression. The majority of Bcl-2 expression was grade I and FIGO stage pT1, this association was statistically not significant (p-value > 0.05). Endometrioid adenocarcinoma constituted the predominant type in both cohorts, accounting for 84.2% in the negative group and 93.5% in the positive group. **Conclusion:** The expression of Bcl-2 protein in 62 % of cases of endometrial carcinoma, there is no significant association with any of the clinicopathological variables (age of the patient, FIGO grade, FIGO stage, histopathologic type, myometrium invasion, lower uterine segment invasion and cervical stromal invasion).

KEYWORDS: The aim of this study is to investigate the expression of Bcl-2 in endometrial carcinoma and its correlation with clinicopathological variables.

INTRODUCTION

Endometrial carcinoma is a type of cancer that originates from the endometrium (the lining of the uterus), It is the most common cancer of lower female genital tract in developed countries and the fourth most common cancer in women worldwide.[1]

It affects mainly postmenopausal women. The average age of diagnosis is 62[2], However, about 15% of endometrial carcinoma cases occur in the premenopausal period, of these 5 % occur before 40 years of age.[3]

This cancer is slightly more common in white women[2]; However, Black women have experienced an increase in incidence of aggressive, high grade, type II tumors compared to white women.[4]

Endometrial carcinomas are histologically classified according to the World Health Organization (WHO) classification system, and are divided into the following subgroups.

Type 1 endometrioid adenocarcinoma: is the most common type, associated with excess estrogen hormone, frequently preceded by complex atypical hyperplasia and occur predominantly in premenopausal, these types of cancers are usually diagnosed at an early stage and treated successfully[5] There are several types of type I endometrioid adenocarcinomas.[5,6]

- Villoglandular (papillary)
- Secretory
- Ciliated cell
- Adenocarcinoma with squamous differentiation.

While type 2 non-endometrioid carcinoma including the serous and clear cell type, these types are much less common than endometrioid cancers. It also develops from the lining of the uterus, and not associated with unopposed estrogen hormone.[6]

Other types of endometrial cancers include[7]

- Undifferentiated carcinoma.
- Mixed carcinoma.
- Gastrointestinal mucinous carcinoma.
- Carcinosarcoma - has features of both endometrial cancer and sarcoma when examined under a microscope.
- Mesonephric-like carcinoma

Around 75% of patients with endometrial cancer are diagnosed in the early stages (International Federation of Gynecology and Obstetrics [FIGO] stages I or II), and 5-year overall survival is 74–91%. For women with advanced stage III or IV disease, 5-year overall survival of 57–66% and 20–26%, respectively.[6]

B -Cell Lymphoma 2 protein (BCL-2)

A protein that control cell cycle by blocking a programmed cell death (apoptosis). The BCL2 gene is located on chromosome 18, and transfer of the BCL-2 gene to a different chromosome, causes the BCL2 protein to be synthesized in larger amounts, which protect cancer cells from death.[8]

The Bcl-2 family consists of a number of proteins that share (BH) domains of Bcl-2 homology. These proteins that either promote or inhibit apoptosis and control apoptosis by controlling the key step in the intrinsic pathway of apoptosis (mitochondrial outer membrane permeabilization) (MOMP), A 25 genes in the Bcl-2 family were identified.[9]

The BCL-2 plays an important role in cell survival by inhibit the actions of pro-apoptotic proteins(BAX and BAK), These pro-apoptotic proteins normally act on the mitochondrial membrane to promote permeabilization and release of cytochrome c and ROS, that are important signals in the apoptosis cascade. These pro-apoptotic proteins are activated by BH3-only proteins, and inhibited by the action of BCL-2 and its relative BCL-Xl.[10]

Bcl-2 targeted therapy

An effective approach for targeting the BCL-2 anti-apoptotic proteins has been concentrate on the developing BH3 mimetic, that is directly bind to the hydrophobic cleft of the pro-survival proteins.

A number of BCL-2inhibitors drug has been discovered after understanding the biology of BCL-2 proteins[11], include.

• Oblimersen: is a Bcl-2 antisense oligonucleotide was developed to treat the patients with refractory/ relapsed chronic lymphocytic leukemia.[12]

ABT-737 and navitoclax (ABT-263)

ABT-737 a novel Bcl-2 Bcl-xL and Bcl-w inhibitor, these drugs are BH3 mimetic small molecule inhibitors (SMI) that target the Bcl-2 family proteins. ABT-737 has higher affinity for Bcl-2, Bcl-xL and Bcl-w, with lower affinity to Mcl-1 or Bcl2A1.[13]

Navitoclax is well tolerated, safe drug and, but a dose-limiting thrombocytopenia is a major side effect because of BCL-XL inhibition.[14]

Venetoclax (ABT-199): is a highly selective Bcl-2 inhibitor which inhibits Bcl-2, but not Bcl-xL or Bcl-w, in the clinical trials good responses have been observed and thrombocytopenia not developed in patients with chronic lymphocytic leukemia (CLL), so that the US FDA approved that the Venetoclax (ABT-199) is a second-line treatment for CLL.[15,22]

Sonrotoclax (BGB-11417) have greater inhibition on tumor growth in hematologic tumor than venetoclax. Sonrotoclax is under clinical investigation as a monotherapy and in combination with other anticancer agents.[16]

Aim of the study

- To assess the expression of Bcl-2 in endometrial carcinoma.
- To correlate the Bcl-2 expression with the clinic pathological variables will include: patient age, histopathological type, histopathological grade, the depth of myometrial invasion, FIGO stage, lower uterine segment invasion and cervical stromal invasion.

MATERIALS AND METHODS

a cross-sectional study done at The Medical City Teaching Complex/ The National Center for Educational Laboratories, from the first of March 2024 until the end of July 2024.

The samples were collected from 50 patients' records from 2022 to 2024 with endometrial carcinoma and

tissue blocks embedded in paraffin stored in The National Center for Educational Laboratories.

inclusion criteria
patient with endometrial carcinoma who had total abdominal hysterectomy bilateral salpingo-oopherectomy.

exclusion criteria
D&C sample of endometrial tissue.

Control group include small B and T lymphocytes in mantle zone of the lymph node and germinal center B-cells were obtained and examined for expression of BCL-2 as positive control from the former and negative control from the later.

Positive Bcl-2 protein defined as any specific cytoplasmic staining was detected, the percentage of positive staining malignant cells (the number of positive malignant cells divided by the total number of malignant cells) was evaluated.[17]

- A semi quantitative assessment of staining was done as follows

- Negative (0): No Bcl-2 immunoreactive malignant cells were detected.
- Weak positive (1+): less than 33 % of malignant cells were positive for Bcl-2.
- Moderate positive (2+):33-66 % of malignant cells were positive for Bcl-2.
- Strong positive (3+): 67 -100 % of malignant cells were positive for Bcl-2.

Statistical analysis: Data input and tabulation was done using Statistical Package for Social Sciences version 24. For categorical data chi-square test was used. P-value <0.05 was considered significant throughout the study.

RESULT

Fifty patients were assessed. Their ages ranged from 40 to 80 years. The mean age of the study group was 57.08 ± 9.54. Individuals aged 50-59 comprised 34.0% of the study group, followed by 26.0% who were under 50 or aged 60-69, while those aged 70 and above represented 14.0%. As shown in table.[1]

Table 1: Distribution of the study participant according to the age group.

Age	Frequency	Percentage
Mean ± sd	57.08 ± 9.54	
40-49	13	26.0
50-59	17	34.0
60-69	13	26.0
70-80	7	14.0
Total	50	100.0

Table (2): The correlation of the tumor grade and FIGO stage with the age group.

Variable		<50	50-59	60-69	≥ 70	P- value
Tumor grade	**Grade I**	6 (46.2%)	8 (47.1%)	7 (53.8%)	2(28.6%)	0.227
	Grade II	4 (3.8%)	5 (29.4%)	2 (15.4%)	5(71.4%)	
	Grade III	3 (23.1%)	4 (23.5%)	4 (30.8%)	0 (0.0)	
FIGO stage	**pT1a**	5 (38.5%)	8 (47.1%)	6 (46.2%)	2(28.6%)	0.500
	pT1b	1 (7.7%)	2 (11.8%)	3 (23.1%)	2(28.6%)	
	Pt1c	1 (7.7%)	0 (0.0)	1 (7.7%)	0 (0.0)	
	Pt2	1 (7.7%)	3 (17.6%)	1 (7.7%)	1 (7.7%)	
	pT2b	0 (0.0%)	0 (0.0)	1 (7.7%)	0 (0.0)	
	pT3a	4 (30.8%)	4 (23.5%)	0 (0.0)	2(28.6%)	
	pT3b	1 (7.7%)	0 (0.0%)	1 (7.7%)	0 (0.0)	
Total		**13 (100.0%)**	**17 (100.0%)**	**13 (100.0%)**	**7 (100.0%)**	**50**

Table (2) illustrated the correlation between tumor grade, FIGO stage, and age group. In all age demographics, the majority of cases were classified as grade I tumors; however, among patients aged 70 years and beyond, 71.4% were classified as grade II tumors, with no cases identified as grade III in this age group. Across almost all age demographics, pT1a was the most common stage for FIGO staging, followed by pT3a, while pT1c, pT2b, and pT3b were less common. No statistically significant association was seen in tumor grade, FIGO stage, and age group (p-value > 0.05).

From the total 50 cases that were included in the study, 12 cases (24.0%) had weak positive and moderately positive Bcl2 expression, and 7 cases (14.0%) had strong positive Bcl2 expression. On the other hand, 19 cases (38.0%) were of negative Bcl2 expression. As shown in figure (1).

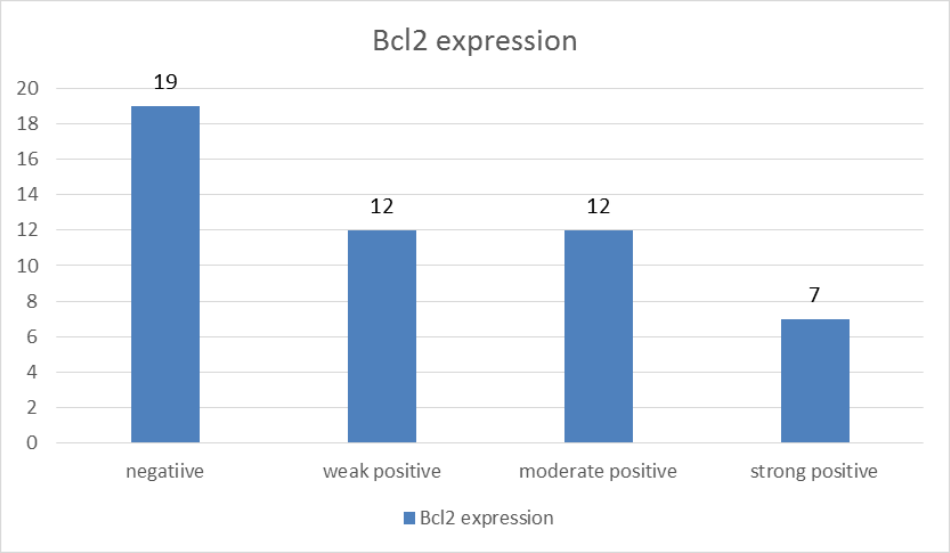
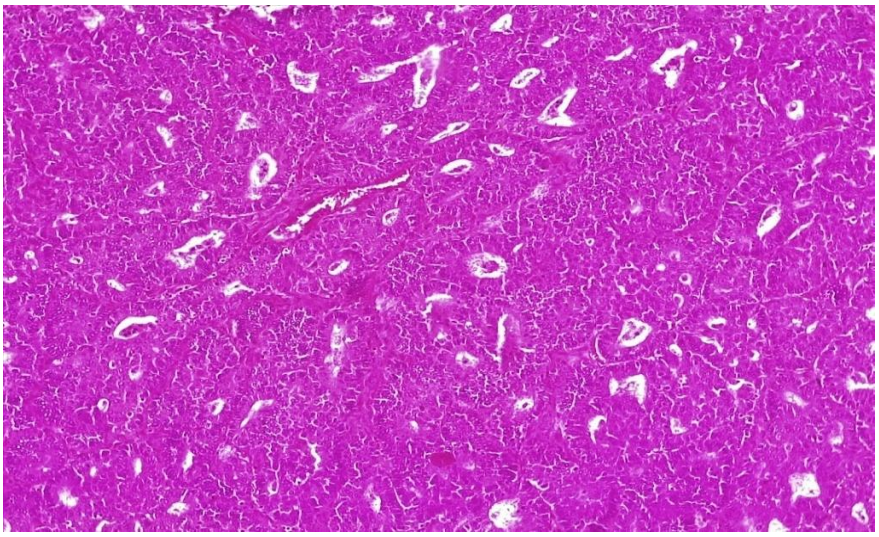


Figure (1): Distribution of cases according to Bcl2 expression.

A



B

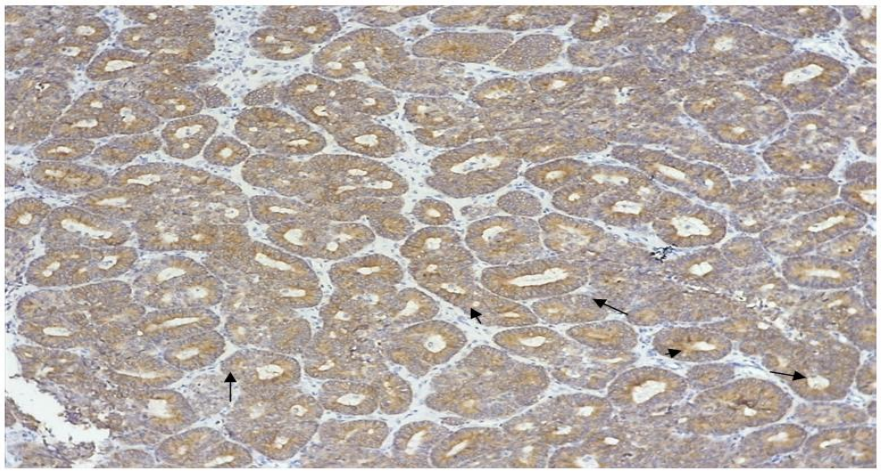


Figure 2: showing A-endometrioid type endometrial carcinoma, FIGO grade I, B- Immunohistochemical staining for endometroid endometrial carcinoma with Bcl-2 protein showing strong staining (arrow), lower power view (100x).

A

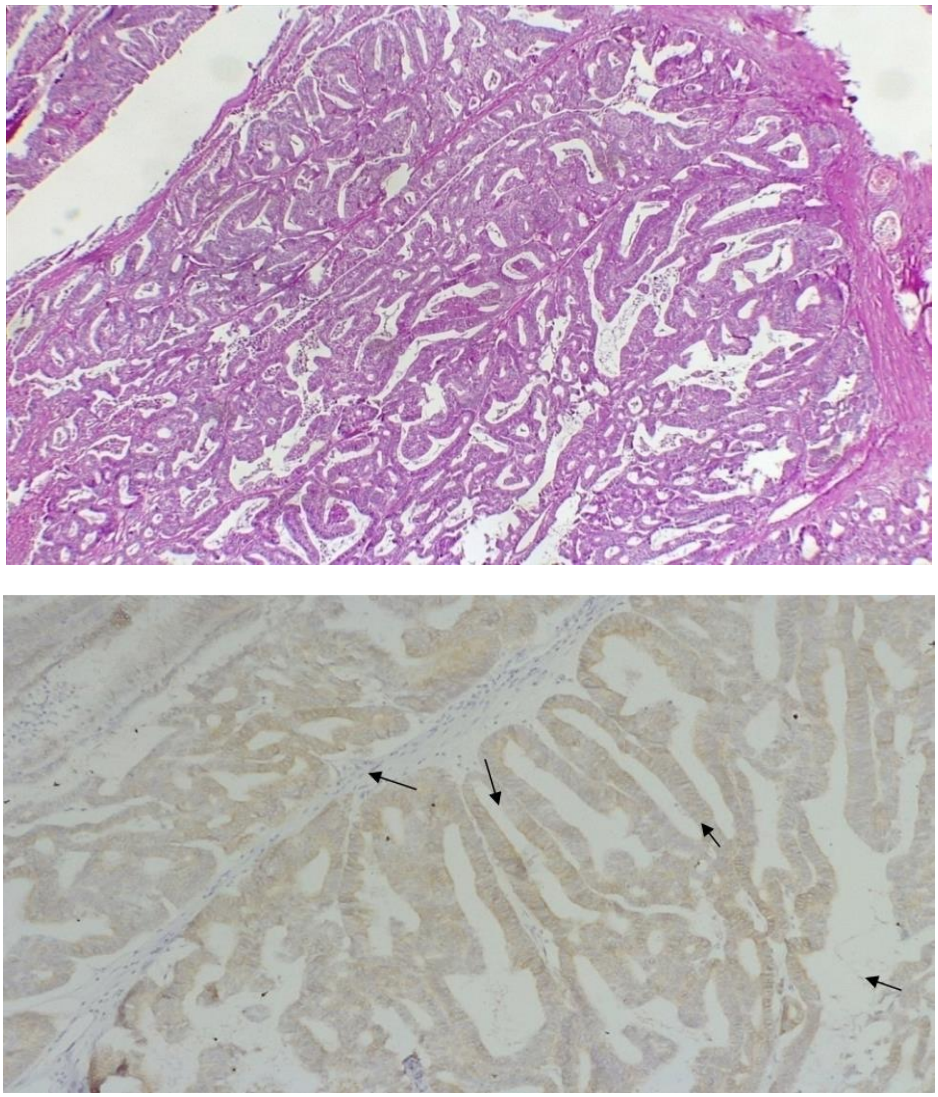
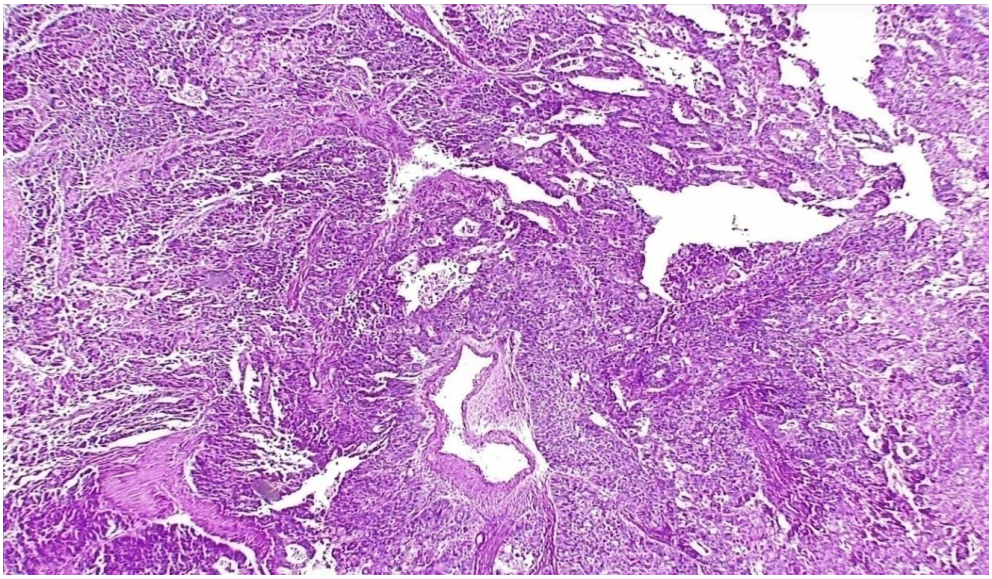


Figure 3: showing A- endometrioid endometrial carcinoma,NOS, FIGO gradeII, B- Immunohistochemical staining with Bcl-2 protein showing strong staining (arrow), lower power view (100x).

A



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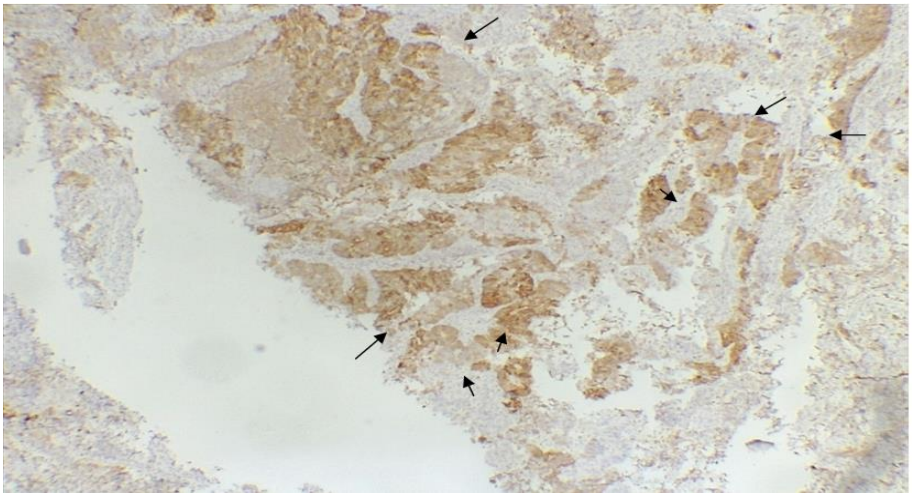
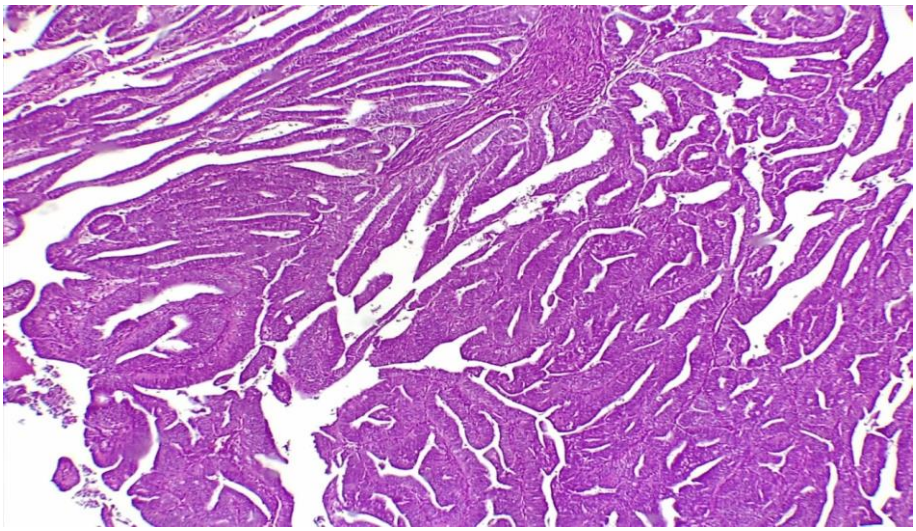


Figure – 4: showing A-mixed carcinoma (25%) serous carcinoma endometroid carcinoma, FIGO grade III, B-Immunohistochemical staining with Bcl-2 protein showing moderate staining (arrow), lower power view (100x).

A



B

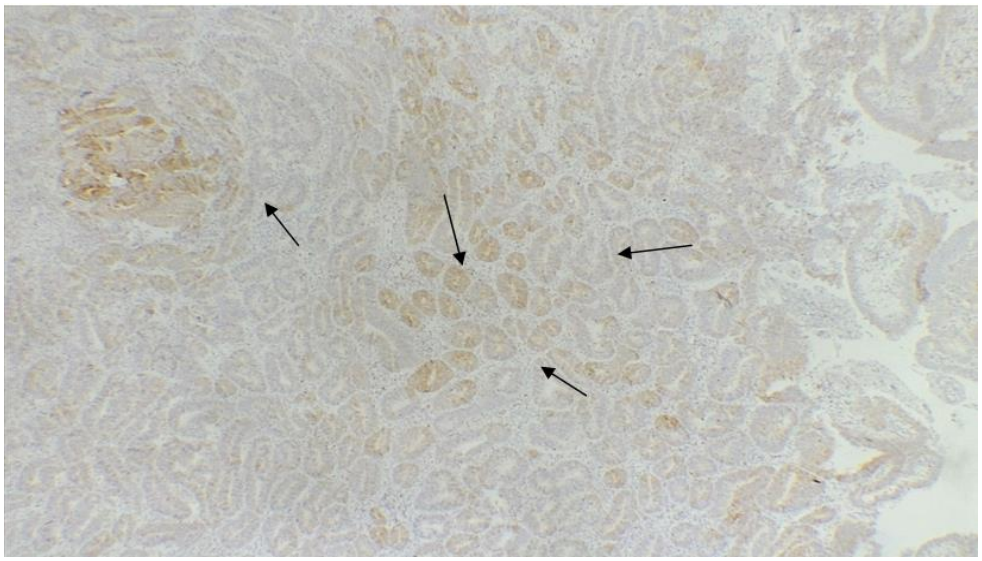
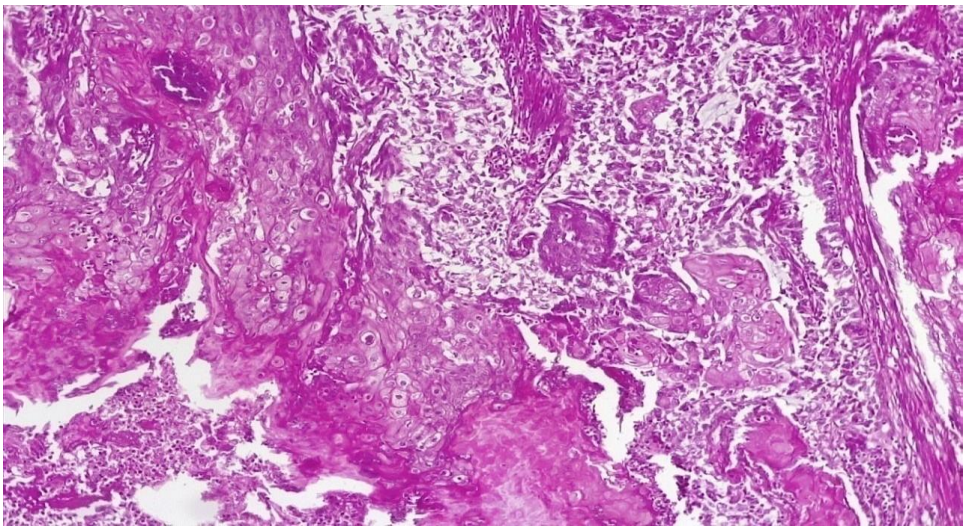


Figure 5: A-endometrioid endometrial carcinoma with, FIGO grade I, B-Immunohistochemical staining for Bcl-2 showing weak staining(arrow)(lower power view 100x).

A



B

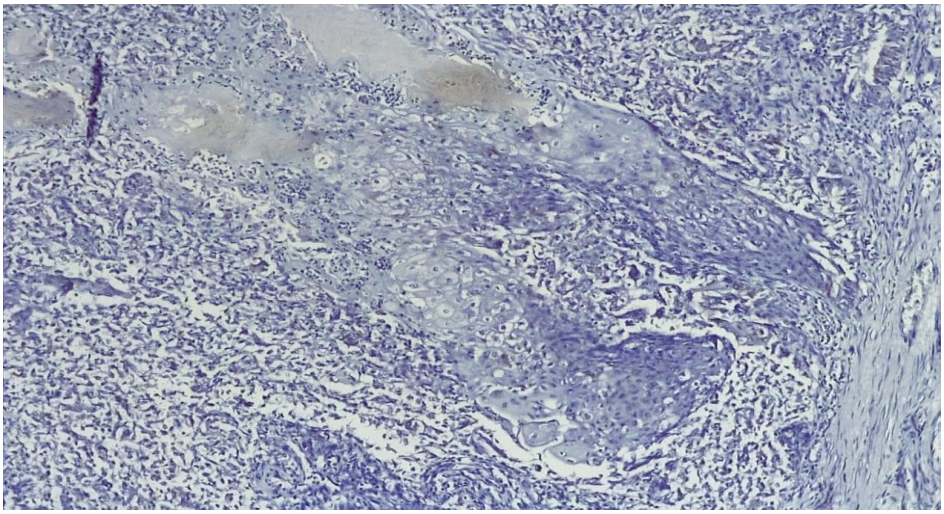


Figure 6: A- endometrial carcinoma with squamous differentiation FIGO grade III, B-Immunohistochemical staining for Bcl-2 showing negative staining (lower power view 100x).

Table 3: The correlation between tumor grade and FIGO stage and Bcl2 expression.

Variable		Negative	Positive	P- value
Tumour grade	**Grade I**	6 (31.6%)	17 (54.8%)	0.110
	Grade II	6 (31.6%)	10 (32.3%)	
	Grade III	7 (36.8%)	4 (22.0%)	
FIGO stage	**pT1a**	9 (47.4%)	12 (38.7%)	0.562
	pT1b	2 (10.5%)	6 (19.4%)	
	pT1c	1 (5.3%)	1 (3.2%)	
	pT2	3 (15.8%)	3 (9.7%)	
	pT2b	1 (5.3%)	0 (0.0%)	
	pT3a	2 (10.5%)	8 (25.8%)	
	pT3b	1 (5.3%)	1 (3.2%)	
Total		**19 (100.0%)**	**31 (100.0%)**	**50**

The correlation between tumor grade and FIGO stage and Bcl2 expression

Among the total positive instances of Bcl2 expression, 17 (54.8%) were classified as grade I, followed by 10 cases (32.3%) of grade II, and 4 cases (22.0%) of grade III; as compared to 7 cases (36.8%) of negative Bcl2 expression with grade III. This association was statistically not significant (p-value > 0.05).

In terms of FIGO stage, the majority of cases in both groups fell within pT1a, with 9 cases (47.4%) in the negative group and 12 cases (38.7%) in the positive group. Other stages showed low frequencies, with no significant disparities between the groups. The presence of more advanced stages (pT3a) in the positive group 8 cases (25.8%) compared to the negative group 2 cases (10.5%) is notable, but again, this difference did not achieve statistical significance (p- value > 0.05).

Table (4): The correlation between invasion parameters and Bcl2 expression.

Invasion parameter		Negative	Positive	P- value
Myometrial invasion	**Less than 50%**	11 (57.9%)	16 (51.6%)	0.773
	More than 50%	8 (42.1%)	15 (48.4%)	
Cervical stromal invasion	**Not identified**	14 (73.7%)	26 (83.9%)	0.474
	present	5 (26.3%)	5 (16.1%)	
Lower uterine invasion	**Not identified**	9 (47.4%)	13 (41.9%)	0.774
	present	10 (52.6%)	18 (58.1%)	
Total		**19 (100.0%)**	**31 (100.0%)**	**50**

Table (4) demonstrates the correlation between the invasion parameter and Bcl2 expression. Nearly half of the cases with positive Bcl2 expression 16 cases (51.6%) and 11 cases (57.9%) with negative Bcl2 expression showed less than 50% myometrial invasion. For the cervical stromal invasion and lower uterine invasion, the percentages of cases in both the negative and positive categories are relatively similar. The P-value (>0.05) indicates that there are no statistically significant differences in the invasion parameters assessed between the negative and positive groups.

Table 5: The correlation between histological type and Bcl2 expression.

Histological type	Negative	Positive	P- value
Endometroid adenocarcinoma	16 (84.2%)	29 (93.5%)	
Adenosequamous carcinoma	1 (5.3%)	0 (0.0%)	0.515
Endometrial mixed type adenocarcinoma (endometrial and serous carcinoma component)	1 (5.3%)	1 (3.2%)	
Endometrial serous carcinoma	1 (5.3%)	1 (3.2%)	
Total	**19 (100.0%)**	**31 (100.0%)**	**50**

The correlation between histological type and Bcl2 expression

The findings regarding histological types demonstrate that the distribution of different carcinoma types across the negative and positive groups does not exhibit significant differences, as shown by the P-values (> 0.05).

Adenosequamous carcinoma was identified in one instance within the negative group, but no cases were noted in the positive group. Endometrial mixed-type adenocarcinoma and endometrial serous carcinoma were seen at low frequency, with each group represented by one case. Endometrioid adenocarcinoma constituted the predominant type in both cohorts, accounting for 84.2% in the negative group and 93.5% in the positive group.

DISCUSSION

Endometrial carcinoma is the most common cancer of female genital tract; among women the endometrial carcinoma is the fourth most common type of cancer.[17] The prognosis of endometrial carcinoma depending on many factors, one of them is the age of the patient at time of diagnosis, and the five-year survival rate reach 100% in endometrial carcinoma of premenopausal women because it exhibits good histopathological type, low histopathologic grade and are hormone dependent. the survival rate decreases to 50 %in post-menopausal women.[18]

Other prognostic factor includes tumor stage, tumor grade and histopathological type.

BCL-2 is an anti-apoptotic proto-oncogene that inhibits programmed cell death. In the endometrium, Bcl-2 is highly expressed in the proliferative phase of menstrual cycle with decrease its expression during the secretory phase. The expression of Bcl-2 is related to good prognosis and may play a vital role in tumor progression from early to higher stages.[18]

In current study group comprising women from age of 40 to age of 80, the majority of cases occurred between the age group 50 and 59 years, with mean age group is 57 years this is similar to a study conducted by Gupta, Nidhi; et al; in india (2023), which reported that the mean age group is 57.7 years.[19]

In this study about 90% of endometrial carcinoma cases belong to type I endometrioid adenocarcinoma, while the

remaining 10% constitute the type II non endometrioid adenocarcinoma, this is similar to study conducted by Walvir, et al in India (2022) which reported (92.31%) cases were of endometrioid carcinoma.[21]

We graded the endometrial carcinoma of both type I and type II into three grading based on the percentage of solid component and nuclear changes. In current study group 23 out of 50 case (46%) were grade I, Grade II tumors account for 32% and Grade III tumors account for 22 % which is similar to data obtained from a study conducted by Walvir, et al in India (2022) which reported 46.15% of the endometrial carcinoma patients were classified as Grade I; 38.46% as Grade II; and 15.38% as Grade III.[21]

In this study the correlation between tumor grade and the age of patient revealed that the majority of cases in all age group were grade I, except in age of patient more than 70 year were 5 out of 7 (71.4 %) of tumor were grade II. There is no positive correlation between age group and tumor grade.

In current study the correlation between the age of the patient and FIGO stage revealed that the majority of cases in all age group were FIGO stage I, this is not clinically significant (p- value more than 0.05).

In current study group 31 out of 50 case (62%) were stage I, Stage II tumors account for 14% and Stage III tumors account for 24%. which is similar to data obtained from a study conducted by Gupta, et al in India (2023), which reported that percent (74.41%) of cases were stage I, (14.7 %) of cases were stage II, 8.8% were stage III and remaining 2% were stage IV.[19]

In this study group, Bcl-2 expression was seen in 31 out of 50 cases (62%), which is similar to data obtained from a study conducted by Hozan Dler Dhahir* et al in Erbil (2024) which reported that the Bcl-2 expressions in 61.5% of cases[20], and also similar to data obtained from a study conducted by Sharanya Kandaswamy, et al in India (2023) which reported 64.4 % of cases were positive for Bcl-2.[18]

In this study group the Bcl-2 was positive in 17 out of 31 case (54.8%) of grade I, And about (10) cases 32.3% of Grade II tumors, And (4) cases (22%) Grade III tumors this is similar to a study conducted by Hozan Dler Dhahir, et al, in Erbil (2024) which reported that the Bcl-2 expression was higher in low-grade Endometrial Carcinoma, compared with high grade tumor, This association was statistically not significant (p-value > 0.05).[20]

In this study group the Bcl-2 was positive in 19 out of 31 case (61.2%) for stage I, this is similar to a study conducted by Hozan Dler Dhahir, et al in Erbil (2024) which reported that the Bcl-2 expression is 60% in stage I[20], and about (3) cases 9.7 % of stage II tumors, And (9) cases (29%) stage III tumors, this is similar to a study conducted by Sharanya Kandaswamy, et al in India (2023) which reported that the Bcl-2 expression is 13 % in stage II and (15.21%) in stage III and VI.[18]

In this study the expression of Bcl-2 in relation to histopathological type is 29 out of 31 of positive cases (93.5%) were positive in endometrioid adenocarcinoma and (64.44%) 29 out of all 45 cases of Type I endometrioid adenocarcinoma were positive for Bcl-2 protein this is similar to data obtained from a study conducted by Sharanya Kandaswamy, et al in India (2023) which reported that (69.09%) 38 out of 55 of cases of Type I endometrioid Adenocarcinoma were positive for Bcl-2[18], and 1 out of 31 positive cases (3.2 %) were positive in both non endometrioid serous carcinoma and Endometrial mixed type adenocarcinoma (endometrial and serous carcinoma component, this is similar to study conducted by Sharanya Kandaswamy, et al in India (2023) which reported that the expression of Bcl-2 protein in type II non endometrioid adenocarcinoma is (0 %) zero out of four cases.[18]

In this study the expression of Bcl-2 in relation to myometrial invasion is nearly equal, about 16 out of 31 cases (51.6%) were positive in tumors with less than half of myometrial invasion, and 15 out of 31 cases (48.4%) were positive in tumors with more than half of myometrial invasion, this is disagree with a study conducted by Hozan Dler Dhahir, et al in Erbil (2024) which reported that Fifty four out of seventy eight cases with Endometrial Carcinoma (69.2%) had deep invasion of myometrium (more than half of myometrium) although this difference didn't reach statistical significant.[20]

In this study the expression of Bcl-2 in relation to lower uterine segment invasion is 13 out of 31 cases (41.9%) were positive in tumors with no invasion of lower uterine segment and 18 out of 31 cases (58.1%) were positive in tumors with lower uterine segment invasion, there is no similar study was found.

In current study the expression of Bcl-2 in relation to cervical stromal invasion is 26 out of 31 cases (83.9%) were positive in tumors with no cervical stromal invasion, and 5 out of 31 cases (16.1%) were positive in tumors with cervical stromal invasion, there is no similar study was found.

The limitation of our study includes small sample size. therefore, a large prospective study is essential to prove the utility of Bcl-2 expression as a routine prognostic tool.

CONCLUSIONS

1. The expression of Bcl-2 protein in 62 % of cases of endometrial carcinoma.

2. The expression of Bcl-2 protein occurs mainly in low grade (Grade I) and early stage (Stage I) of endometrial carcinoma.
3. There is no significant correlation with any of the clinicopathological variables (age of the patient, FIGO grade, FIGO stage, histopathologic type, myometrium invasion, lower uterine segment invasion and cervical stromal invasion.

Recommendations

1. A large prospective study is essential to prove the utility of Bcl-2 expression as a routine prognostic tool.
2. Clinical follow up of patients to confirm the prognostic significance of Bcl-2 expression in endometrial carcinoma.

Ethical considerations The study was approved by scientific committee of the Iraqi board of medical specialization.

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