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BCL-2 Protein Expression in Epithelial Ovarian Cancer: Association with Age and Histopathological Features in Uganda

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ABSTRACT

Background: Globally, ovarian cancer accounted for 314,000 new cases and 207,000 deaths in 2020. In Uganda, 626 cases were documented over 25 years, with an average incidence rate of 7.1 per 100,000 women. Epithelial ovarian carcinoma is the predominant subtype, and BCL-2, a 26-kDa anti-apoptotic protein, has been associated with chemotherapy resistance. However, no study has assessed BCL-2 expression in epithelial ovarian cancer in Uganda.

Objective: This study aimed to determine the prevalence of BCL-2 protein expression in epithelial ovarian cancer and its association with age and histopathological features in Uganda.

Methods: A retrospective cross-sectional study was conducted using randomly sampled archived tissue blocks from 113 patients diagnosed with epithelial ovarian cancer. Samples underwent hematoxylin and eosin (H&E) and immunohistochemistry (IHC) staining to evaluate BCL-2 expression.

Results: The mean patient age was 55 years, with the largest proportion (36.3%) aged 50–59 years. BCL-2 expression was observed in 36.3% of cases. There was no statistically significant association between BCL-2 expression and age ($p = 0.396$), histological subtype ($p = 0.520$), or tumor grade ($p = 0.833$). High-grade serous carcinoma was the predominant histological subtype (46%), and well-differentiated carcinoma was the most common grade (53%).

Conclusion: BCL-2 expression was prevalent in epithelial ovarian cancer in Uganda but showed no significant association with age, histological grade, or subtype. These findings underscored the need for further research to explore the prognostic and therapeutic implications of BCL-2 in ovarian cancer management.

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Introduction

Globally, ovarian cancer is the seventh most frequently diagnosed cancer and the eighth leading cause of cancer-related deaths among women [1]. In 2020, approximately 314,000 new cases and 207,000 deaths were reported worldwide [2]. Incidence rates are highest in developed regions, exceeding 7.5 per 100,000 women, while the lowest rates, below 5 per 100,000 women, are observed in sub-Saharan Africa (SSA) [3,4].

In SSA, ovarian cancer contributed to 18,000 new cases and 13,000 deaths in 2020. East Africa alone reported 7,298 new cases and 5,258 deaths [1]. In Uganda, data on ovarian cancer incidence and trends remain scarce. However, the Kampala Cancer Registry documented 626 cases over a 25-year period, with an average incidence rate of 7.1 per 100,000 women. The highest incidence rate, 8.4 per 100,000 women, was recorded between 2001 and 2005 [5,6].

Epithelial ovarian cancer (EOC), which constitutes approximately 90% of all ovarian cancers, is the most prevalent subtype [7]. Like other solid tumors, EOC demonstrates varying levels of B-cell lymphoma 2 (BCL-2) protein expression, with reported prevalence rates ranging from 9.7% to 47.4% in global studies [8,11]. BCL-2 is an anti-apoptotic protein implicated in tumorigenesis and resistance to chemotherapy. While studies from different parts of the world have shown inconsistent associations between BCL-2 expression and factors such as age, tumor grade, and histological subtype, no such studies have been conducted in Uganda [12-14].

The lack of local data creates a gap in understanding the role of BCL-2 in Ugandan patients with EOC. This cross-sectional study aimed to determine the frequency of BCL-2 protein expression in EOC and examine its association with clinicopathological features in this population

Materials and Methods

Study Design

This study employed a retrospective laboratory-based cross-sectional design.

Study Setting

The study was conducted in the Department of Pathology at Makerere University. Additional tissue blocks were retrieved from the Department of Pathology at Mulago National Referral Hospital and the Uganda Cancer Institute. These departments were selected due to their proximity at Mulago in Kampala, Uganda, and their status as major centers

providing diagnostic histopathological and cytological services for patients across the country. Beyond their clinical roles, these departments actively engage in academic and research activities, making them ideal settings for the study.

Study Duration

The study was conducted over a six-month period, from January 2024 to June 2024.

Selection Criteria

- **Inclusion Criteria:** Archived formalin-fixed and paraffin-embedded (FFPE) tissue blocks from patients histologically diagnosed with epithelial ovarian cancer between January 2013 and March 2024 at the above-mentioned institutions.
- **Exclusion Criteria:** Tissue blocks that were poorly fixed, inadequately processed, extensively damaged, or showed extensive necrosis were excluded.

Sampling Method and Sample Size Estimation

Eligible cases meeting the inclusion criteria were selected using a convenience sampling method until the desired sample size was achieved. The sample size was calculated using the Kish and Leslie formula (1965) as follows:

$$n = \frac{z^2 \times p(1-p)}{e^2}$$

Where:

- **n** = Sample size
- **z** = Standard normal deviation at a 95% confidence interval, corresponding to 1.96
- **p** = Prevalence of BCL-2 protein expression in epithelial ovarian cancer. Since the prevalence of BCL-2 protein expression in Uganda and sub-Saharan Africa is unknown, a conservative estimate of 50% was used.
- e = Margin of error accepted in this study, set at 5% (0.05).

$$n = \frac{1.96^2 \times 0.5(0.5-p)}{0.05^2}$$

$$n = \frac{0.9604}{0.0025}$$

n = **384.16**.

The total number of tissue blocks (population size) diagnosed with epithelial ovarian cancer was 160. To account for the finite population size, the sample size was adjusted using the finite population correction formula. The corrected sample size was calculated as follows:

$$N = \frac{\text{Calculated sample size} \times \text{Population size}}{\text{Calculated sample size} + (\text{Population size} - 1)}$$

$$N = \frac{384.16 \times 160}{384.16 + (160 - 1)}$$

Therefore, the minimum sample size required for the study was 113

Study Variables

- **Independent Variables:** These included patient age, histological subtypes, and tumor grade.
- **Dependent Variable:** BCL-2 protein expression.

BCL-2 Immunohistochemistry Procedure

For each tissue sample, a 3-µm-thick section was cut using a microtome, mounted on a charged slide, and baked overnight in a hot air oven at 65°C. Epitope retrieval was performed by immersing the slides in Epitope Retrieval Solution (Novocastra) and incubating them in a decloaking chamber at 95°C for 30 minutes. Tissue peroxidase activity was inhibited by incubating the slides with hydrogen peroxide for 10 minutes.

The sections were then incubated with a pre-diluted anti-BCL-2 clone (124) monoclonal mouse primary antibody, followed by Post-primary (Rabbit anti-mouse IgG) for 30 minutes at room temperature. Subsequently, they were incubated with Novolink Polymer (Anti-rabbit poly-HRP-IgG) for another 30 minutes at room temperature and rinsed in Tris buffer for 3 minutes. Detection was achieved using the chromogen 3,3′-diaminobenzidine (DAB) for 3 minutes, followed by washing with tap water. The slides were counterstained with Harris hematoxylin for 1 minute, mounted with DPX, and cover-slipped.

A human tonsil specimen was used as a positive control, while a tissue section processed without the primary antibody served as a negative control.

BCL-2 Immunohistochemistry Scoring Method

- **Intensity Score:** 0 (negative), 1 (weak), 2 (moderate), or 3 (strong).
- **Percentage of Positive Tumor Cells:** 0 (none), 1 (<10%), 2 (11–50%), 3 (51–80%), or 4 (>80%).
- The intensity and percentage scores were multiplied to calculate a semi-quantitative Immunoreactive Score (IRS), ranging from 0 to 12. An IRS of ≥2 was considered positive, while a score <2 was considered negative.

Data Management and Analysis

Data were entered into Microsoft Excel, cross-checked, cleaned, and edited to ensure accuracy. Statistical analysis was performed using STATA version 17. The association between BCL-2 protein expression and clinicopathological features was assessed using Pearson's Chi-square test. A 95% confidence interval was used, and a p-value ≤0.05 was considered statistically significant.

Results

Demographic and Histological Characteristics

Table 1 presents the distribution of epithelial ovarian cancers (EOCs) by age, histological subtype, and tumor grade. A total of 113 formalin-fixed paraffin-embedded (FFPE) tissue blocks from patients diagnosed with EOCs were analyzed for histological subtype, tumor grade, and BCL-2 protein expression. The mean age of the patients was 55 ± 11 years (range: 20–78 years). The majority of cases, 41 out of 113 (36.3%), were within the 50–59 age group, and over two-thirds (70.8%; 80/113) of the patients were aged 50 years and above.

Histologically, high-grade serous carcinoma was the most prevalent subtype, representing 46.0% (52/113) of the cases. In terms of tumor grade, well-differentiated carcinomas were the most common, accounting for 53.1% (60/113) of the cases.

Immunohistochemistry (IHC) Staining for BCL-2 Protein

A total of 113 cases were included for immunohistochemical (IHC) staining of BCL-2. The prevalence of BCL-2 protein expression among epithelial ovarian carcinoma (EOC) cases was 36.3% (41/113), as detailed in Table 1. Figure 2 illustrates the intensity of BCL-2 cytoplasmic staining. Among the BCL-2-positive cases, 24.4% (10/41) exhibited strong cytoplasmic staining (Figure 2), 36.6% (15/41) showed moderate staining intensity (Figure 3), and 39.0% (16/41) demonstrated weak staining intensity. Negative BCL-2 cytoplasmic staining is shown in Figure 4. No statistically significant differences were observed in BCL-2 expression concerning patient age (P = 0.396), histological

subtypes (P = 0.520), or tumor grade (P = 0.833), as presented in Table 2.

Table 1: Demographic Characteristics of Patients with EOC in Uganda (N = 113)

Characteristic Age (mean±SD)	Frequency 55(±11)	Proportion (%)
Age categories		
20-29	01	0.8
30-39	09	8.0
40-49	23	20.4
50-59	41	36.3
60-69	28	24.8
70-79	11	9.7
Histological subtype		
SEROUS		
High-grade serous carcinoma	52	46.0
Low-grade serous carcinoma	47	41.6
NON -SEROUS		
Endometroid ovarian carcinoma	06	5.30
Mucinous ovarian carcinoma	07	6.20
Brenner tumor	01	0.90
Tumor grade		
Well differentiated (Grade 1)	60	53.1
Moderately differentiated (Grade 2)	33	29.2
Poorly Differentiated (Grade 3)	20	17.7
Bcl-2 status		
Positive	41	36.3
Negative	72	63.7

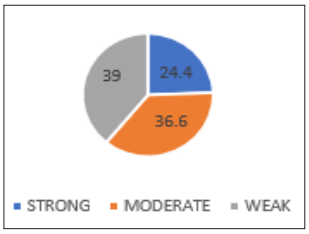

Figure 1: BCL-2 cytoplasmic staining intensity

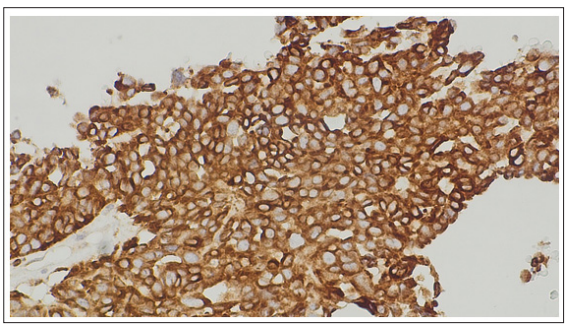

Figure 2: Photomicrograph Showing strong Bcl-2 cytoplasmic Staining in high-grade serous carcinoma (X200)

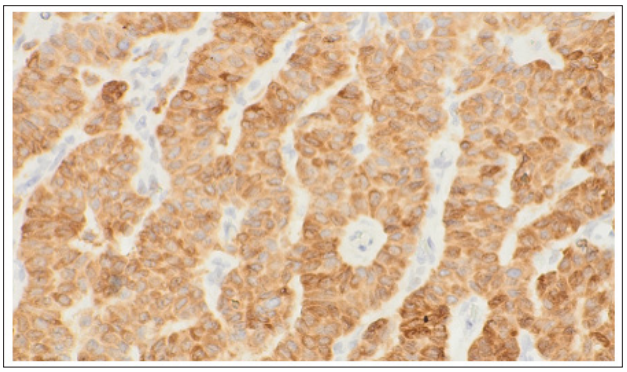

Figure 3: Photomicrograph Showing Moderate Staining for BCL-2 in low-grade Serous Carcinoma (X200).

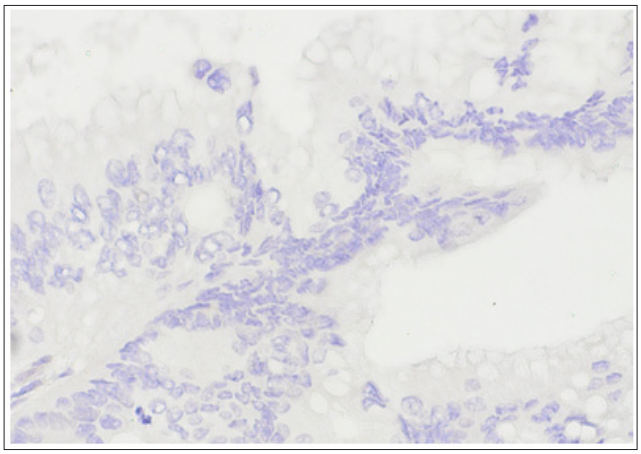

Table 2: Association Between BCL-2 Protein Expression with age, Histological Subtypes, and Tumour Grade (N= 113)

Characteristic	BCL2 status		P-value
	Positive (%)	Negative (%)	
Age (mean±SD)	55±10	54 ±12	0.396
<50years	10 (30.3)	23 (69.7)	
≥50years	31 (38.7)	49 (61.3)	
Histological subtype			0.520
SEROUS			
High grade serous	19 (46.3)	33(45.8)	
low grade serous	16(39.0)	31(43.1)	
NON-SEROUS	6(14.6)	8(11.1)	
Tumour grade			0.833
Grade 1	21 (51.2)	39 (54.2)	
Grade 2	12(29.3)	21 (29.2)	
Grade 3	8(19.5)	12 (16.6)	

Discussion

This study aimed to determine the prevalence of BCL-2 protein expression and its association with age and histopathological features in epithelial ovarian cancer (EOC) in Uganda. The mean age of the patients in this study was consistent with reports from other African countries [9,15]. In contrast, studies from Europe reported a slightly higher mean age of EOC diagnosis at 62 years,

while a study from India reported a lower mean age of 50.6 years [12,16]. These variations may reflect regional differences in the age of menopause onset, which affects lifetime estrogen exposure, a factor that influences EOC risk.

The study found that serous carcinoma, particularly high-grade serous carcinoma, was the most common histological subtype of EOC in Uganda. This aligns with findings from studies conducted in Africa and globally [17,18]. Mucinous ovarian carcinoma was the most common non-serous subtype in this study, consistent with other African studies [15]. However, studies conducted in both European and African countries have reported endometrioid ovarian carcinoma as the second most prevalent subtype [9,19]. These differences highlight the heterogeneity of EOC and its variable distribution across populations.

The majority of tumors in this study were classified as Grade I, consistent with some prior research [12]. However, this contrasts with findings from other studies, particularly in Africa and other continents, where Grade III tumors were more prevalent [16,20]. Sagarra et al. (2002) also reported Grade II as the most common. These discrepancies may reflect variations in tumor biology across regions, despite the use of standardized grading systems.

The prevalence of BCL-2 protein expression in this study was 36.3%, comparable to rates reported in Poland (32%), Atlanta (34%), and Norway (39%) [21-23]. However, this prevalence was lower than those reported in Tunisia (47.4%), France (47.56%), China (62.7%), Greece (69%), Japan (42%), and India (74%) (10, 14, 20, 24, 25). Conversely, it was higher than rates observed in Austria (23.8%), China (20%), and Brazil (9.7%) [11,26,27]. These variations may be attributed to differences in sample size, immunohistochemistry (IHC) techniques, scoring criteria, tumor biology, disease stage, and treatment protocols across regions.
There was no statistically significant association between BCL-2 protein expression and age. This finding is consistent with studies conducted in Austria and Greece, likely due to comparable mean patient ages (55 years), which may result in similar patterns of BCL-2 expression [25,26]. Most patients in this study were aged 50–59 years, contributing to the observed consistency. However, a study from China found a significant association between age and BCL-2 expression, with higher expression observed in post-menopausal women compared to pre-menopausal women [10]. These discrepancies may be explained by regional differences in genetic factors, environmental exposures, and the timing of menopause, a key risk factor for EOC.

No association was observed between histological subtypes of EOC and BCL-2 protein expression, a finding consistent with studies conducted in Austria, Greece, Tunisia, and Georgia [8,9,23,28]. This similarity may stem from shared molecular pathways regulating BCL-2 expression across EOC subtypes, despite histological differences. In contrast, Mishra and Crasta (2010) reported a significant association, with higher BCL-2 expression in high-grade serous carcinoma compared to low-grade serous carcinoma [29]. This discrepancy may be attributed to Mishra et al.'s exclusive focus on serous carcinoma, as well as differences in sample size and sampling methodologies.

Similarly, no statistically significant association was found between BCL-2 protein expression and tumor grade, aligning with findings by Arik & Kulacoglu (2011) and Kupryjańczyk et al [30]. (2003) [22]. However, other studies have shown that BCL-2 expression decreases with increasing tumor grade [12,13,27,31]. Despite comparable sample sizes and mean ages, BCL-2 expression may not be strongly influenced by histological grade in certain populations, suggesting that other molecular or genetic mechanisms could play a more critical role in regulating its expression, regardless of grade.

Limitations

- Poor storage of the tissue blocks hindered the availability of the tissue blocks from the archives despite the availability of the request forms which could create a selection bias.
- Some request forms had incomplete information pertaining to important variables like age.
- Inappropriate fixation could have affected antigen retrieval during IHC since the FFPE blocks are being used.

Conclusion

The prevalence of BCL-2 protein expression in epithelial ovarian tumors in Uganda is 36.3%. There is no statistically significant association between BCL-2 protein expression and age, histological subtype, or tumor grade in this population.

Recommendations

- Future studies with larger sample sizes are recommended to further elucidate the association between BCL-2 protein expression and the clinicopathological characteristics of epithelial ovarian cancer (EOC).
- A prospective study is recommended to evaluate the relationship between BCL-2 protein expression and clinical outcomes, including overall survival and response to different chemotherapy regimens in Ugandan patients with ovarian cancer.

Ethical Considerations

Ethical approval for the study was obtained from the School of Biomedical Sciences Research and Ethics Committee (SBSREC) and the Uganda National Council for Science and Technology. A waiver of patient consent to use archived biopsy specimens was granted by SBSREC (Reference Number SBS 2023-492). To maintain confidentiality, patient names and biopsy numbers were replaced with unique identification codes for each specimen.

Data Availability

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

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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This study received no external funding.

Authors' Contributions

G.A. conceptualized and designed the study, collected and managed the data, performed the analysis, and contributed to manuscript development and revisions. T.O., A.M., A.W., N.V., K.M., M.R., O.J.K., N.G., O.P.B., M.S contributed to the study's conceptualization, design, data collection, analysis, and manuscript revisions. M.B. provided critical proofreading and editing of the final manuscript. A.L.O., K.S., and B.P. supervised the project. All authors reviewed and approved the final manuscript.

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