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Original Article

# Immunohistochemical Expression of BCL-2 Across Histopathological Types of Benign and Malignant Salivary Gland Tumours: A Cross-Sectional Study

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## ABSTRACT

**Background:** Salivary gland tumours comprise a heterogeneous group of neoplasms with considerable variation in histopathological features and biological behaviour. B-cell lymphoma-2 (BCL-2) is an anti-apoptotic protein that has shown variable expression across different salivary gland tumour types. **Objective:** The study was conducted to evaluate BCL-2 immunohistochemical expression across histopathological types of benign and malignant salivary gland tumours and to compare its expression between the two biological groups. **Methods & Materials:** This prospective cross-sectional analytical study was conducted from January 2019 to December 2020 at Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh. A total of 55 histopathologically diagnosed salivary gland tumours, comprising 33 benign and 22 malignant cases, were included. BCL-2 immunohistochemistry was performed using monoclonal mouse anti-human BCL-2 antibody, clone 124. Expression was assessed as the percentage of immunoreactive neoplastic cells, and a 5% cut-off was used to categorize positive expression. Data were analysed using SPSS version 22, with a p value <.05 considered statistically significant. **Results:** Positive BCL-2 expression was observed in 29 (52.7%) tumours. Positivity was detected in 12 of 33 benign tumours (36.4%) and 17 of 22 malignant tumours (77.3%). Mean BCL-2 expression was significantly higher in malignant tumours than in benign tumours (34.00 ± 30.02% vs. 4.48 ± 5.29%; p = .001). Among malignant tumours, adenoid cystic carcinoma showed the highest mean expression (67.57 ± 15.38%) with positivity in all 7 cases, followed by mucoepidermoid carcinoma (21.15 ± 20.74%), with 10 of 13 cases (76.9%) positive. Both salivary duct carcinomas were negative. Mean BCL-2 expression differed significantly among malignant histopathological subtypes (p = .001). No significant difference was observed across low-, intermediate-, and high-grade mucoepidermoid carcinomas (p = .897). **Conclusion:** BCL-2 expression was higher in malignant than benign salivary gland tumours and varied substantially across histopathological types. The highest expression was observed in adenoid cystic carcinoma, while no significant association was found with mucoepidermoid carcinoma grade.

***Keywords:*** *BCL-2, Immunohistochemistry, Salivary gland tumours, Adenoid cystic carcinoma, Mucoepidermoid carcinoma*

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## INTRODUCTION

Salivary gland tumours comprise a relatively uncommon, but histopathologically heterogeneous group of neoplasms with marked variation in morphology and biological behaviour. In a recent global population-based analysis by Huang et al., 53,583 new cases of salivary gland cancer were estimated, with an age-standardized incidence rate of 0.57 per 100,000 population. Considerable geographical variation in disease burden was also demonstrated [1]. Across institutional histopathological series, benign tumours generally predominate, although the proportions vary according to population and referral setting. In the Hiroshima Tumor Tissue Registry, 3,998 (80.0%) of 5,015 salivary gland neoplasms were benign and 1,017 (20.0%) were malignant [2]. Pleomorphic adenoma accounted for 68% of benign tumours, while adenoid cystic carcinoma and mucoepidermoid carcinoma represented 27% and 26% of malignant tumours, respectively. Similar predominance of benign disease was reported in Brazilian and Sudanese series, although differences in the relative distribution of individual malignant types were observed [3,4]. Marked histological diversity remains an important feature of salivary gland pathology. Overlapping architectural and cytological patterns may occur between different tumour entities, and the classification has continued to evolve with advances in immunohistochemistry and molecular pathology [5,6]. Molecular heterogeneity has also been demonstrated across major tumour types, including PLAG1 and HMGA2 alterations in pleomorphic adenoma, CRTC1/3-MAML2 fusions in mucoepidermoid carcinoma, and MYB-related alterations in adenoid cystic carcinoma [7]. In a Brazilian series, seven of 174 salivary gland tumours were reclassified after morphological review and supplementary immunohistochemical assessment according to the updated WHO classification [3]. Therefore, evaluation of biological markers according to individual histopathological type may provide additional information beyond a simple benign-versus-malignant categorization. Apoptosis is a regulated process required for normal cellular homeostasis, and disruption of apoptotic signalling contributes to neoplastic cell survival. The B-cell lymphoma-2 (BCL-2) family contains both pro-apoptotic and anti-apoptotic proteins that regulate the mitochondrial pathway of apoptosis [8]. In salivary gland neoplasms, an anti-apoptotic transcriptional profile has been demonstrated. In the study by Gomes et al., BCL-2 mRNA overexpression was observed in 21 of 27 salivary gland neoplasms, although no significant difference in BCL-2 mRNA expression was found between benign and malignant groups [9]. These findings suggest that BCL-2-related alterations may occur across different biological categories and may vary according to histopathological context. Previous immunohistochemical studies have shown inconsistent patterns of BCL-2 expression. In the study by Manjunatha et al., BCL-2 positivity was observed in 36 of 50 salivary gland tumours, including 8 of 14

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benign and 28 of 36 malignant neoplasms [10]. In contrast, greater BCL-2 expression was demonstrated in pleomorphic adenoma than in mucoepidermoid carcinoma in the comparative study by Atarbashi et al., in which 13 of 18 pleomorphic adenomas and 3 of 10 mucoepidermoid carcinomas were positive [11]. Variation has also been demonstrated within specific malignant histologies. In adenoid cystic carcinoma, BCL-2 expression was documented in immunohistochemical studies by Jiang et al. and Goulart-Filho et al., although different relationships with Beclin-1 and other clinicopathological variables were reported [12,13]. Thus, existing evidence indicates that BCL-2 expression in salivary gland tumours is heterogeneous and may differ according to histopathological type rather than following a uniform benign-to-malignant pattern. Differences in study populations, tumour composition, staining methods, scoring systems, and positivity thresholds further limit direct comparison between published studies. The present study was therefore conducted to evaluate the immunohistochemical expression of BCL-2 across histopathological types of benign and malignant salivary gland tumours, and to compare its expression between the two biological groups. BCL-2 expression according to histopathological grade of mucoepidermoid carcinoma was also assessed.

## METHODS & MATERIALS

This prospective cross-sectional analytical study was conducted in the Department of Pathology, Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh, in collaboration with other teaching hospitals in Dhaka, from January 2019 to December 2020. A total of 55 histopathologically diagnosed salivary gland tumours, comprising 33 benign and 22 malignant cases, were included using purposive and convenience sampling. Cases with confirmed histopathological diagnoses and adequate tissue specimens were eligible for inclusion. Patients who declined consent, those who had received prior chemotherapy or radiotherapy, and specimens showing extensive necrosis or haemorrhage were excluded. Relevant demographic and histopathological information was collected using a structured data collection sheet. Following surgical excision, tissue specimens were fixed in 10% neutral buffered formalin, routinely processed and embedded in paraffin. Sections measuring approximately 4 µm were prepared for haematoxylin and eosin staining and subsequent immunohistochemical examination. Tumours were classified as benign or malignant according to their histopathological characteristics, and mucoepidermoid carcinomas were further categorised into low, intermediate and high grades. For BCL-2 immunohistochemistry, formalin-fixed, paraffin-embedded sections underwent deparaffinisation, rehydration and heat-induced antigen retrieval using EnVision FLEX Target Retrieval Solution. Immunostaining was performed using monoclonal mouse anti-human BCL-2 antibody (clone 124, Dako) with the EnVision FLEX detection system on a Dako Autostainer/Autostainer Plus. Diaminobenzidine was used as the chromogen, followed by haematoxylin counterstaining. Immunohistochemical expression of BCL-2 was evaluated semi-quantitatively by examining at least 1,000 neoplastic cells under light microscopy at ×40 objective magnification. The percentage of immunoreactive tumour cells was calculated relative to the total number of neoplastic cells examined in the selected area. A 5% cut-off was applied to categorise BCL-2 expression as positive or negative. The percentage of positively stained tumour cells was also recorded as a continuous variable for comparison across benign and malignant tumours, individual histopathological subtypes, and histological grades of mucoepidermoid carcinoma. Staining intensity was not considered in the quantitative evaluation. Data were analysed using the Statistical Package for the Social Sciences (SPSS), version 22. Categorical variables were expressed as frequencies and percentages, while continuous variables were summarised using means, standard deviations (SD) and ranges. The independent-samples t test was used to compare mean age and BCL-2 percentage expression between benign and malignant tumours, whereas the chi-square test was applied to assess the association between sex and tumour status. Differences in mean BCL-2 expression across malignant histopathological subtypes and grades of mucoepidermoid carcinoma were assessed using one-way analysis of variance (ANOVA), with Bonferroni-adjusted pairwise comparisons reported for mucoepidermoid carcinoma grades. A p value below .05 was considered statistically significant. Ethical approval was obtained from the Ethical Committee of Sir Salimullah Medical College, Dhaka. Written informed consent was obtained from all participants following an explanation of the study objectives and procedures in Bengali. Participant confidentiality was maintained throughout data collection and analysis.

## RESULTS

A total of 55 histopathologically diagnosed salivary gland tumours were included in this cross-sectional study conducted between January 2019 and December 2020. Of these, 33 (60.0%) were benign and 22 (40.0%) were malignant. The findings are presented according to clinicodemographic and histopathological characteristics, overall BCL-2 immunohistochemical expression, expression across individual histopathological tumour types, and its association with histopathological grading of mucoepidermoid carcinoma. Among the study participants, the largest proportion belonged to the 41–50-year age group (27.3%). The mean age was significantly higher among patients with malignant tumours (45.36 ± 10.50 years) than among those with benign tumours (34.12 ± 11.63 years; p = .001). Overall, 28 (50.9%) patients were female and 27 (49.1%) were male, with no statistically significant association between sex and tumour status (p = .225). Of the benign tumours, pleomorphic adenoma was the predominant histopathological type (75.8%), followed by Warthin tumour (18.2%). Among malignant tumours, mucoepidermoid carcinoma was the most frequent diagnosis (59.1%), followed by adenoid cystic carcinoma (31.8%) and salivary duct carcinoma (9.1%) (*Table I*).

**Table I**
Clinicodemographic and Histopathological Characteristics of Patients with Benign and Malignant Salivary Gland Tumours (*n* = 55).

| Characteristics | Benign (n = 33) | Malignant (n = 22) | Total (N = 55) | p |
|---|---|---|---|---|
| Age group (years) | | | | |
| ≤20 | 1 (3.0) | 1 (4.5) | 2 (3.6) | |
| 21–30 | 14 (42.4) | 0 (0.0) | 14 (25.5) | |
| 31–40 | 9 (27.3) | 5 (22.7) | 14 (25.5) | |
| 41–50 | 6 (18.2) | 9 (40.9) | 15 (27.3) | |
| >50 | 3 (9.1) | 7 (31.8) | 10 (18.2) | |
| Mean age ± SD (years) | 34.12 ± 11.63 | 45.36 ± 10.50 | | .001 |
| Sex | | | | |
| Male | 14 (42.4) | 13 (59.1) | 27 (49.1) | .225 |
| Female | 19 (57.6) | 9 (40.9) | 28 (50.9) | |
| Histopathological diagnosis | | | | |
| Pleomorphic adenoma | 25 (75.8) | — | 25 (45.5) | NA |
| Warthin tumour | 6 (18.2) | — | 6 (10.9) | NA |
| Oncocytoma | 1 (3.0) | — | 1 (1.8) | NA |
| Basal cell adenoma | 1 (3.0) | — | 1 (1.8) | NA |
| Mucoepidermoid carcinoma | — | 13 (59.1) | 13 (23.6) | NA |
| Adenoid cystic carcinoma | — | 7 (31.8) | 7 (12.7) | NA |
| Salivary duct carcinoma | — | 2 (9.1) | 2 (3.6) | NA |

*Note. Values are presented as frequency (%) unless otherwise specified. Percentages were calculated using the corresponding column totals. The p values for age and sex were obtained using the independent-samples t test and chi-square test, respectively. SD = standard deviation.*

Overall, positive BCL-2 immunohistochemical expression was observed in 29 (52.7%) of the 55 salivary gland tumours. A higher proportion of malignant tumours demonstrated BCL-2 positivity compared with benign tumours (77.3% vs. 36.4%). Similarly, the mean percentage of BCL-2-positive tumour cells was significantly higher in malignant tumours (34.00 ± 30.02%) than in benign tumours (4.48 ± 5.29%; p = .001). The observed expression ranged from 0% to 95% in malignant tumours, compared with 0% to 20% in benign tumours (*Table II*).

**Table II**
Comparison of BCL-2 Immunohistochemical Expression Between Benign and Malignant Salivary Gland Tumours (*n* = 55).

| BCL-2 expression parameters | Benign (n = 33) | Malignant (n = 22) | Total (N = 55) | p |
|---|---|---|---|---|
| Mean expression ± SD (%) | 4.48 ± 5.29 | 34.00 ± 30.02 | — | .001 |
| Range (%) | 0–20 | 0–95 | 0–95 | |
| Positive expression, n (%) | 12 (36.4) | 17 (77.3) | 29 (52.7) | |
| Negative expression, n (%) | 21 (63.6) | 5 (22.7) | 26 (47.3) | |

*Note. BCL-2 expression represents the percentage of immunoreactive tumour cells, with a 5% cut-off applied to categorise positive expression. The p value refers to the comparison of mean percentage expression between benign and malignant tumours using the independent-samples t test. SD = standard deviation.*

Considerable variation in BCL-2 immunohistochemical expression was observed across the histopathological tumour types. Among benign tumours, BCL-2 positivity was detected in 9 of 25 pleomorphic adenomas (36.0%) and 2 of 6 Warthin tumours (33.3%), with mean expression levels of 5.00 ± 6.00% and 4.00 ± 4.20%, respectively. The single oncocytoma demonstrated positive expression (10.0%), whereas basal cell adenoma showed no BCL-2 expression. Among malignant tumours, adenoid cystic carcinoma demonstrated the highest mean expression (67.57 ± 15.38%), with positivity in all seven cases (100.0%). In comparison, 10 of 13 mucoepidermoid carcinomas (76.9%) were positive, with a mean expression of 21.15 ± 20.74%, whereas both salivary duct carcinomas were negative. The difference in mean BCL-2 expression among the malignant histopathological subtypes was statistically significant (p = .001) (*Table III*).

**Table III**
Distribution and Extent of BCL-2 Immunohistochemical Expression Across Histopathological Types of Benign and Malignant Salivary Gland Tumours (*n* = 55).

| Histopathological diagnosis | n | BCL-2 positive, n (%) | BCL-2 negative, n (%) | Mean expression ± SD (%) | Range (%) |
|---|---|---|---|---|---|
| Benign tumours | | | | | |
| Pleomorphic adenoma | 25 | 9 (36.0) | 16 (64.0) | 5.00 ± 6.00 | 0–20 |
| Warthin tumour | 6 | 2 (33.3) | 4 (66.7) | 4.00 ± 4.20 | 0–10 |
| Oncocytoma | 1 | 1 (100.0) | 0 (0.0) | 10.00 (NA) | 10–10 |
| Basal cell adenoma | 1 | 0 (0.0) | 1 (100.0) | 0.00 (NA) | 0–0 |
| Malignant tumours | | | | | |
| Mucoepidermoid carcinoma | 13 | 10 (76.9) | 3 (23.1) | 21.15 ± 20.74 | 0–66 |
| Adenoid cystic carcinoma | 7 | 7 (100.0) | 0 (0.0) | 67.57 ± 15.38 | 50–95 |
| Salivary duct carcinoma | 2 | 0 (0.0) | 2 (100.0) | 0.00 ± 0.00 | 0–0 |

*Note. Positive and negative expression values represent the proportion of cases within each histopathological subtype. Mean expression represents the percentage of BCL-2-immunoreactive tumour cells. NA = not applicable, as the standard deviation cannot be estimated for a single observation; SD = standard deviation. The comparison of mean BCL-2 expression across the three malignant histopathological subtypes was performed using one-way analysis of variance (ANOVA), p = .001.*

Of the 13 histopathologically diagnosed mucoepidermoid carcinomas, 2 (15.4%) were low grade, 3 (23.1%) were intermediate grade and 8 (61.5%) were high grade. The highest mean BCL-2 expression was observed in intermediate-grade tumours (24.67 ± 28.94%), followed by high-grade (21.00 ± 22.00%) and low-grade tumours (15.00 ± 7.07%). However, the difference in mean BCL-2 expression across the three histopathological grades was not statistically significant (p = .897). Similarly, none of the pairwise comparisons demonstrated a statistically significant difference (all p values greater than .05) (*Table IV*).

**Table IV**
Association Between BCL-2 Immunohistochemical Expression and Histopathological Grades of Mucoepidermoid Carcinoma (*n* = 13).

| Histopathological grade | n (%) | Mean BCL-2 expression ± SD (%) |
|---|---|---|
| Low grade | 2 (15.4) | 15.00 ± 7.07 |
| Intermediate grade | 3 (23.1) | 24.67 ± 28.94 |
| High grade | 8 (61.5) | 21.00 ± 22.00 |

*Note. SD = standard deviation. The overall comparison was performed using one-way ANOVA, p = .897. Bonferroni post hoc comparisons yielded the following results: low versus intermediate grade, p = .688; intermediate versus high grade, p = .824; and low versus high grade, p = .732.*

## DISCUSSION

The present study demonstrated marked heterogeneity of BCL-2 immunohistochemical expression across benign and malignant salivary gland tumours. Overall positivity was observed in 29 of 55 tumours (52.7%), comprising 12 of 33 benign tumours (36.4%) and 17 of 22 malignant tumours (77.3%). The mean percentage of BCL-2-positive tumour cells was significantly higher in malignant tumours than in benign tumours, 34.00 ± 30.02% and 4.48 ± 5.29%, respectively (*p* = .001). A similar descriptive pattern was reported by Manjunatha et al., in which 28 of 36 malignant tumours (77.8%) and 8 of 14 benign tumours (57.1%) were BCL-2 positive [10]. However, a significant aggregate difference in staining intensity between benign and malignant groups was not demonstrated in that study. So, higher overall BCL-2 expression was demonstrated in malignant tumours in the present study, without indicating uniform expression across malignant histologies. Among benign tumours, positivity was detected in 9 of 25 pleomorphic adenomas (36.0%), with a mean expression of 5.00 ± 6.00%. Higher expression was reported in previous series. Positivity was observed in 5 of 9 pleomorphic adenomas by Manjunatha et al. and in 13 of 18 cases by Atarbashi et al [10,11]. A mean percentage staining of 47.78 ± 40.56% was also reported by Atarbashi et al., although an H-score incorporating staining intensity was used [11]. For Warthin tumour, positivity was present in 2 of 6 cases (33.3%) in the present study, whereas 18 of 20 cases (90.0%) were reported positive by Abd-Elhamid and Elshafei [14]. Differences in positivity thresholds and staining assessment may partly explain these variations. The single oncocytoma showed BCL-2 positivity, whereas the single basal cell adenoma was negative. These observations remain descriptive because only one case of each type was included. In comparison, BCL-2 expression was retained in 32 of 36 evaluable basal cell adenomas in the study by Wilson and Robinson [15]. Therefore, the negative basal cell adenoma in the present series should not be interpreted as a characteristic immunophenotype. The most prominent malignant-tumour expression was observed in adenoid cystic carcinoma. All 7 cases (100.0%) were positive, with a mean expression of 67.57 ± 15.38% and a range of 50–95%. Universal BCL-2 expression was reported in 21 of 21 adenoid cystic carcinomas by Manjunatha et al. and in all 31 cases evaluated by Xie et al [10,16]. Similarly, 23 of 25 adenoid cystic carcinomas showed at least 5% BCL-2-positive cells in the study by Goulart-Filho et al., while 19 cases (76.0%) showed expression in more than 50% of tumour cells [13]. A lower positivity rate of 21 of 35 cases (60.0%) was reported by Jiang et al., but a substantially higher cut-off of at least 30% positive cells was applied [12]. Thus, prominent BCL-2 expression in adenoid cystic carcinoma was reproduced across several independent series. Mucoepidermoid carcinoma showed positivity in 10 of 13 cases (76.9%), with a mean expression of 21.15 ± 20.74%. Considerable variation has been reported previously. Positivity was documented in 5 of 11 cases by Manjunatha et al., 3 of 10 cases by Atarbashi et al., and 24 of 40 cases by Janjua et al [10,11,17]. Despite the lower categorical positivity in the study by Atarbashi et al. (2014), a mean percentage staining of 19.5 ± 36.55% was reported, which was close to the present mean. In contrast, BCL-2 staining was present in all 21 mucoepidermoid carcinomas assessed by Rasul et al. (2021). These findings show substantial between-study variation in categorical positivity. Both salivary duct carcinomas in the present study were BCL-2 negative. A concordant result was reported by Etges et al., in which all 5 salivary duct carcinomas examined were negative for BCL-2. Across malignant histopathological types, mean BCL-2 expression differed significantly in the present study (*p* = .001) [18]. A significant association between BCL-2 staining category and malignant histopathological type was also reported by Rasul et al. (*p* = .001) [19]. However, no significant difference in BCL-2 scores among pleomorphic adenoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma was reported by Atlı et al. (*p* = .219) [20]. Therefore, histotype-related heterogeneity has been demonstrated in some studies, but not consistently. No significant difference in mean BCL-2 expression was observed among low-, intermediate-, and high-grade mucoepidermoid carcinomas, with values of 15.00 ± 7.07%, 24.67 ± 28.94%, and 21.00 ± 22.00%, respectively (*p* = .897). This differed from the findings reported by Janjua et al., where positivity was present in 19 of 22 low-grade cases, 5 of 7 intermediate-grade cases, and none of 11 high-grade cases, with a significant association between BCL-2 expression and grade [17]. The present study therefore did not reproduce a progressive reduction of BCL-2 expression with increasing grade. Interpretation should remain cautious because only 13 mucoepidermoid carcinomas were included. Overall, the present pattern was characterized by higher BCL-2 expression in malignant tumours and substantial variation among histopathological types. The strongest agreement with previous evidence was observed for adenoid cystic carcinoma and salivary duct carcinoma. Lower expression in pleomorphic adenoma and Warthin tumour differed from several earlier reports, while mucoepidermoid carcinoma showed heterogeneous findings across studies. Differences in cut-offs, percentage-based scoring, intensity-based scoring, and tumour composition should be considered when these results are compared.

## LIMITATIONS

The study was limited by its relatively small sample size and the very small numbers within several histopathological subtypes, which restricted the precision of subtype-specific comparisons. Purposive and convenience sampling, together with the cross-sectional design and absence of clinical follow-up, also limited the generalizability of the findings and prevented assessment of the prognostic significance of BCL-2 expression.

## CONCLUSION

The present study showed that BCL-2 immunohistochemical expression was significantly higher in malignant salivary gland tumours than in benign tumours. Considerable variation was observed across individual histopathological types, with the highest expression demonstrated in adenoid cystic carcinoma, frequent expression in mucoepidermoid carcinoma, and no expression in the two salivary duct carcinomas. BCL-2 expression did not differ significantly across histopathological grades of mucoepidermoid carcinoma. These findings indicate that BCL-2 expression in salivary gland tumours is heterogeneous and appears to be more closely related to histopathological type than to a uniform benign-versus-malignant pattern or mucoepidermoid carcinoma grade.

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## CONFLICT OF INTEREST

None declared.

## ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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