The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 51, May 2026
ISSN No. 2078-2101



Special Issue Featuring Original Articles and Conference Proceedings

Regional Oncology Conference | 13th GFFCC Annual Conference | Cancer: Reality and Challenges

Scientific Abstracts, Poster Presentations, Conference Recommendations and Highlights

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

Immunohistochemical Expression of BCL2 (B cell lymphoma 2) in Invasive Breast Carcinoma and its Correlation with Clinicopathological Parameters

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Abstract

Introduction: Breast cancer (BC) is the most common cancer and foremost cause of death in women.

Aim: This study was conducted to study the BCL2 expression in BC and its correlation with other clinicopathological parameters such as histological grade, tumor size, lymph node status, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2/neu), Ki67 status and molecular subtypes in Indian setting.

Materials and methods: Fifty cases of BC diagnosed between 2015 and 2020 were included in the study. A technique of manual tissue microarray was employed for the analysis of expression of IHC markers such as BCL2, ER, PR, Her2/neu, Ki67, CK5/6 and EGFR in all cases. Results were subjected to statistical analysis.

Results: BCL2 positivity was seen in 36% cases of BC of which 22.22% were HER2 enriched, 33.33% were hormone receptor positive, 38.89% were triple negative (TNBC) non–classifiable, and 5.56% were of basal like BC (BLBC) molecular subtype. Maximum cases of BC showing loss of BCL2 expression showed a statistically insignificant association with higher tumor grade and stage, lymph node positivity, presence of lymphovascular invasion, absence of ER/PR and HER2/neu expression, and Ki67 positivity.

34% cases were of hormone receptor positive BC cases. BCL2 was found positive in 35.29% of hormone receptor positive BC cases. 44% cases were TNBC. BCL2 was found positive in 36.36% of TNBC cases. 20% cases were BLBC. BCL2 was found positive in 10% of BLBC cases. Maximum cases of hormone receptor positive BC, TNBC and BLBC showing loss of BCL2 expression showed a statistically insignificant association with higher grade and stage, lymph node positivity, lymphovascular invasion, and Ki67 expression.

BCL2 can serve as a useful prognostic marker and merits inclusion in the routine IHC panel for breast cancer, as it may contribute to the development of individualized, tailored therapeutic strategies.

Keywords: BCL2, breast carcinoma, prognosis, hormone receptor positive, TNBC, BLBC

Introduction

Breast cancer (BC) is the most common malignancy among women worldwide. In 2020, it surpassed lung cancer to become the leading cause of global cancer incidence, with an estimated 2.3 million new cases, accounting for 11.7% of all cancers. In India, the age–standardized incidence rate of BC in women increased by 39.1% between 1990 and 2016. According to Globocan 2020 data, BC constituted 13.5% of all cancer cases and 10.6% of cancer–related deaths in the country, with a cumulative risk of 2.81. Notably, current trends indicate that a higher proportion of Indian women are affected at a younger age compared to their Western counterparts.[1]

BC is a heterogeneous disease comprising multiple pathological and molecular subtypes, each associated

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with distinct prognoses and therapeutic responses. Standard prognostic factors currently utilized in BC include histological subtype, tumor grade (assessed using the Nottingham modification of the Bloom–Richardson system), tumor size, axillary lymph node (LN) status, , hormone receptor status, human epidermal growth factor receptor 2 (HER2/neu) status, and proliferation indices such as the Ki67 labeling index (Ki67LI). Gene expression profiling has further stratified BC into intrinsic molecular subgroups: luminal A, luminal B, HER2 enriched, and triple negative BC (TNBC). Advances in understanding the molecular mechanisms underlying BC, coupled with the development of targeted therapies, have contributed to improved clinical outcomes.[2]

The present study was conducted to evaluate and document the BCL2 expression in BC cases and its correlation with other clinicopathological parameters in the Indian literature.

Materials And Methods

This cross–sectional pilot study was conducted in the Department of Pathology in a tertiary care hospital. Ethical clearance was obtained from Institute's Ethical Committee. Fifty cases of BC cases operated upon and diagnosed from 2015 to 2020 were included in the study. The available data for all the patients as regards with age, location of tumor, grade, stage, and LN status was collected from the records of histopathology section of the Department of Pathology.

All the slides were evaluated by two senior histopathologists. The Modified Bloom–Richardson (MBR) system of cancer grading system was used in this study. TNM classification and staging of the cases was done as per American Joint Committee on Cancer (AJCC) guidelines.[6] The most suitable tissue block of BC cases was selected for immunohistochemical (IHC) evaluation. A technique of manual tissue microarray was employed for the study of B cell lymphoma 2 (BCL2), estrogen receptor (ER), progesterone receptor (PR), HER2/neu, Ki67, cytokeratin (CK)5/6 and epidermal growth factor receptor (EGFR) in all cases with one tissue core taken from each selected BC block.[3] Antigen retrieval was done using Citrate Buffer Antigen Retrieval Protocol. Pressure cooker was used as heating source.

The primary antibodies used were BCL2 (Clone 124, Dako), ER (Clone 6F 11, Novacastra), PR (Clone PGR312, Novacastra), HER2/neu (Clone CB11, Novacastra), Ki67 (Clone MM1, Novacastra), EGFR (Clone EP22, BioGenex) and CK5/6 (Clone D5/16 B4, Dako). Negative control (without adding primary antibody) was included in all batches.

Section from normal breast was used as positive control for BCL2 and CK5/6 expression.[4,5] Section from endometrial tissue was used as positive control for ER and PR.[6] Section from BC, which previously showed unequivocal strong immunoreactivity for HER2/neu, was used as positive control for HER2/neu.[7] Section from skin was used as positive control for Ki67 and EGFR.[7,8] Negative control (without adding primary antibody) was included in all batches. Sections were examined under High Power Field (HPF) to observe the immunoreactivity.

BCL2 expression was defined as positive when more than 10% of tumor cells expressed nuclear with or without cytoplasmic immunoreactivity. This cutoff was adopted in accordance with previously reported statistical guidelines for prognostic factors.[9]

Allred score was used to evaluate the ER and PR, and a score of 3 to 8 was considered positive. Immunoreactivity for ER and PR was assessed by estimating the percentage of tumor cells showing nuclear staining. More than 10% of the tumor cells showing immunoreactivity was considered as positive.[10] HER2/neu staining was scored according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. Moderate to strong complete membrane staining of 10% or more of the tumor cells was considered to be positive (2+ and 3+) [10] Ki67LI of equal to or more than 14% was considered to be positive.[10] EGFR stain was considered positive if any (weak or strong) membranous expression in tumor cell was observed. CK5/6 stain was scored positive if any (weak or strong) cytoplasmic and/or membranous staining was detected in the tumor cells. EGFR and CK5/6 were only used for classification of BC into molecular subtypes.[11,12]

The Primer of Biostatistics 7.0 program was used for calculation of interrelationships between the analyzed Calretinin expression and clinicopathological variables by Pearson's Chi–square test. Quantitative data was presented with the help of mean. Qualitative data was presented with the help of frequency and percentage table. The results were statistically significant when the *p value* was < 0.05 and highly statistically significant when *p value* was < 0.01.

Results

The various clinicopathological features of BC are presented in **Table 1**. The age of patients ranged from 33 to 79 years, with a mean value of 53.38 years. The highest number of cases (15/50, 30%) was seen in the age group of 41–50 years.

BCL2 expression in BC and its correlation with various clinicopathological parameters is shown in **Table 2 (Figure 1)**. BCL2 positivity was seen in 18/50

Clinicopathological characteristics	Number of tumours 50 BC cases (%)	Number of tumours 22 TNBC cases (%)
Laterality		
Right	17 (34)	07 (31.82)
Left	33 (66)	15 (68.18)
Menopausal status (48)		
Premenopausal	11 (22)	06 (27.27)
Post–menopausal	39 (78)	16 (72.73)
Histopathological types		
IDC (NST)	34 (68)	11 (50.00)
IDC (NST) with Medullary pattern	8 (16)	08 (36.36)
Mucinous carcinoma	3 (6)	–
Metaplastic carcinoma	2 (4)	02 (09.09)
Invasive Cribriform carcinoma	1 (2)	–
Secretory carcinoma	1 (2)	01 (04.54)
Encapsulated papillary carcinoma	1 (2)	–
Status of lymphovascular invasion		
Present	30 (60)	12 (54.55)
Absent	20 (40)	10 (45.45)
Tumour Size (pT)		
pT1	7 (14)	03 (13.64)
pT2	28 (56)	12 (54.54)
pT3	12 (24)	07 (31.82)
pT4	3 (6)	–
ALN metastasis		
N0	14 (28)	07 (31.82)
N1	18 (36)	07 (31.82)
N2	10 (20)	05 (22.72)
N3	8 (16)	03 (13.64)
MBR Grade		
Grade I	06 (12)	01 (4.54)
Grade II	14 (28)	3 (13.64)
Grade III	30 (60)	18 (81.82)
Stage		
I	3 (6)	01 (4.54)
II	20 (40)	10 (45.45)
III	27 (54)	11 (50.00)
IHC markers		
BCL2	18 (36)	–
ER	17 (34)	–
PR	13 (26)	–
HER2/neu	21 (42)	–
Ki67	46 (92)	–
Molecular subtype		
Luminal A	7 (14)	–
Luminal B	10 (20)	–
Her2 enriched	11 (22)	–
TNBC	22 (44)	–
BLBC	10 (20)	–
NCBC	12 (24)	–

Table 1: Clinicopathological characteristics of Breast carcinoma cases

BC=breast carcinoma, TNBC=triple negative breast carcinoma, IDC–NOS=infiltrating duct carcinoma, not otherwise specified, NEC=neuroendocrine carcinoma, MBR=modified Bloom Richardson grading, IHC=immunohistochemistry, BLBC=basal like subtype, NCBC=non–classified subtype.

*2 cases are males

Variables		BCL2		Chi–square Value	P Value
		Positive (n=18, 36%)	Negative (n=32, 64%)		
Age (Yrs)	≤50 (25)	9 (18)	16 (32)	0.087	0.768
	>50 (25)	9 (18)	16 (32)		
Side	Right (17)	5 (10)	12 (24)	0.149	0.700
	Left (33)	13 (26)	20 (40)		
Menopause status	Pre–menopausal (11)	6 (12)	5 (10)	0.278	0.598
	Post–menopausal (39)	12 (24)	27 (54)		
Tumor size (cm)	T1 (≤2) (7)	4 (8)	3 (6)	2.654	0.610
	T2 (>2 to ≤5) (28)	9 (18)	19 (38)		
	T3 (>5) (12)	4 (8)	8 (16)		
	T4 (3)	1 (2)	2 (4)		
Lymph node status	Positive (36)	11 (22)	25 (50)	0.918	0.338
	Negative (14)	7 (14)	7 (14)		
Lympho Vascular Invasion	Present (30)	11 (22)	19 (38)	0.033	0.857
	Absent (20)	7 (14)	13 (26)		
Grade	I (6)	3 (6)	3 (6)	1.265	0.531
	II (14)	6 (12)	8 (16)		
	III (30)	9 (18)	21 (42)		
Stage	I (3)	2 (4)	1 (2)	2.471	0.291
	II (20)	6 (12)	14 (28)		
	III (27)	10 (20)	17 (34)		
Estrogen receptor	Positive (17)	6 (12)	11 (22)	0.056	0.813
	Negative (33)	12 (24)	21 (42)		
Progesterone receptor	Positive (13)	5 (10)	08 (16)	0.015	0.904
	Negative (37)	13 (26)	24 (48)		
HER2/neu	Positive (21)	07 (14)	14 (28)	0.001	0.917
	Negative (29)	11 (22)	18 (36)		
Ki67	Positive (46)	17 (34)	29 (58)	0.004	0.948
	Negative (4)	1 (2)	3 (6)		
EGFR	Positive (20)	5 (10)	15 (30)	1.045	0.307
	Negative (30)	13 (26)	17 (34)		
CK5/6	Positive (18)	4 (8)	14 (28)	1.477	0.224
	Negative (32)	14 (28)	18 (36)		
Molecular subtypes	Luminal A (7)	3 (6)	4 (8)	5.832	0.212
	Luminal B (10)	3 (6)	7 (14)		
	Her2 enriched (11)	4 (8)	7 (14)		
	TNBC (22)				
	BLBC (10)	1 (2)	9 (18)		
	NCBC (12)	7 (14)	5 (10)		

Table 2: BCL2 expression and clinico–pathological parameters of breast carcinoma cases

TNBC= triple negative breast carcinoma cases, BLBC=basal like subtype, NCBC=non–classified subtype, EGFR=epidermal growth factor receptor, CK=cytokeratin.

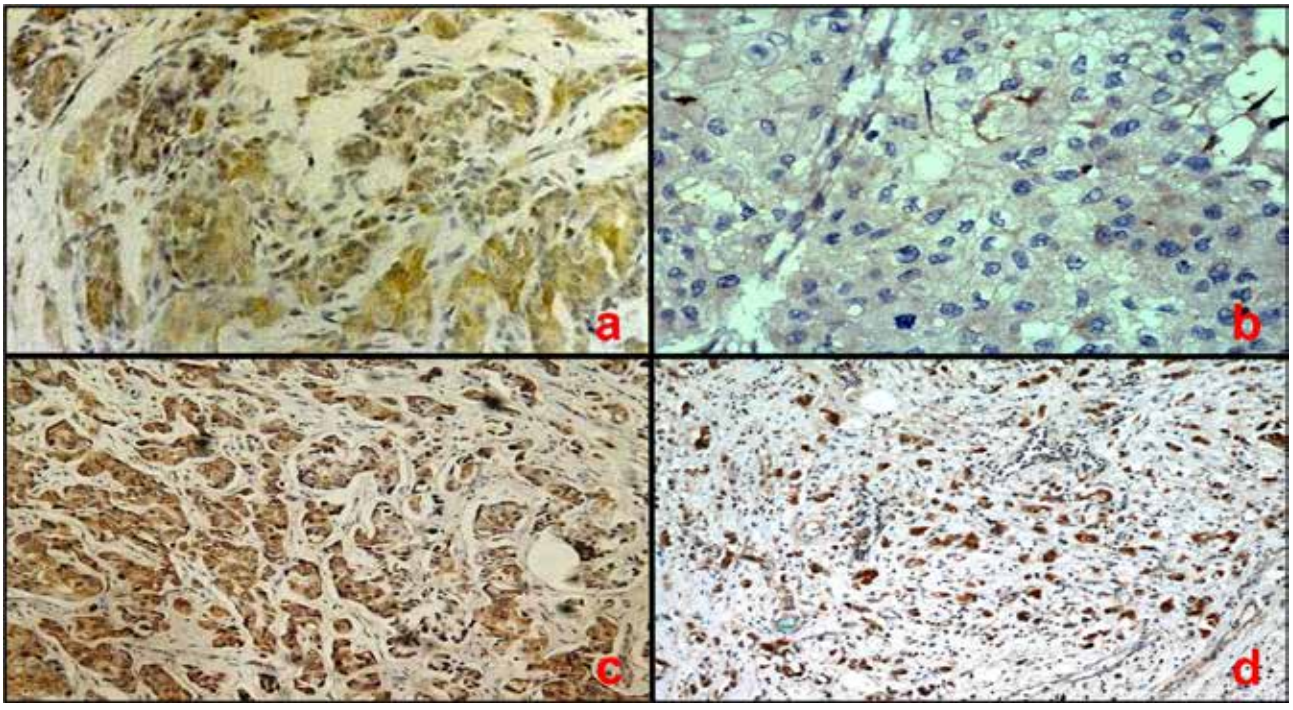


Figure 1: Photomicrograph showing a) BCL2 positivity in normal breast tisssue (IHC,400X), and b) negative BCL2 nuclear/ cytoplasmic immunoreactivity (IHC,400X), c) 80% BCL2 positivity (IHC,400X), and d) 25% BCL2 positivity (IHC,100X) in invasive breast carcinoma no special type

(36%) cases of invasive BC. Maximum cases showing absence of BCL2 expression belonged to higher grade (21/50, 42%) (χ^2=0.531), higher stage (17/50, 34%) (χ^2=0.291), positive lymph node status (25/50, 50%) (χ^2=0.338), presence of lymphovascular invasion (LVI) (19/50,38%) (χ^2=0.857), positive Ki67 expression (29/50, 58%) (χ^2=0.948), negative ER (21/50, 42%) (χ^2=0.813), PR (24/50, 48%) (χ^2=0.904) and HER2/neu expression (18/50, 36%) (χ^2=0.917). This was however statistically insignificant.

The commonest molecular subtype included in this study was triple negative BC (TNBC) (22/50, 44%), followed by HER2 enriched (11/50, 22%), luminal B (10/50, 20%) and luminal A (7/50, 14%). TNBC cases included 10/50 (20%) cases of basal like BC (BLBC) and 12/50 (24%) cases of non–classifiable BC (NCBC) subtype.

BCL2 was found positive in 6/17 (35.29%) of hormone receptor positive (HRP) BC cases. Maximum cases showing loss of BCL2 expression was seen in HRPBC cases of higher grade (Grade III, 5/17, 29.41%) and higher stage (Stage II+III, 10/17, 58.82%) with positive lymph node status (10/17,58.82%), presence of lymphovascular invasion (LVI) (9/17, 52.94%), and Ki67 positivity (10/17,58.82%). This was however statistically insignificant.

BCL2 was found positive in 8/22 (36.36%) of TNBC cases. Maximum cases showing absence of BCL2 expression was seen in TNBC cases of higher grade (Grade III, 13/22,59.09%) and higher stage (Stage II+III, 14/22, 63.64%) with positive lymph node status (9/22,40.91%) and Ki67 positivity (12/22, 54.54%). This was however statistically insignificant.

BCL2 was found positive in 1/10 (10%) BLBC cases. Maximum cases showing absence of BCL2 expression was seen in BLBC cases of higher grade (Grade III, 8/10,80%) and higher stage (Stage III, 5/10,50%) with positive lymph node status (6/10,60%) and positive Ki67 immunoreactivity (8/10, 80%). This was however statistically insignificant. Maximum cases of BLBC showing LVI showed loss of BCL2 expression (3/10, 30%) though statistically insignificant.

Discussion

The BCL2 family of proteins include proapoptotic members like BAX (BCL–2–associated X protein) and BAK, and antiapoptotic members like BCL–2 (B–cell leukemia/ lymphoma 2) and BCL–xL. BCL2 is regarded to be an oncogene in various malignancies, especially in leukemia and lymphoma, and is a key factor for the regulation of cellular apoptosis. BCL2 is located on chromosome 18q21 comprises of three exons and two promoters, both having different functions. BCL2 encodes an integral outer mitochondrial membrane protein that blocks the apoptotic death of cells. Dysregulation in the BCL–2 and

BAX genes expression may cause disruption of cellular homeostasis and origin of malignancy. The functional promoter polymorphisms in BCL–2 and BAX genes are found to change the protein expression or function that may influence the delicate balance in mechanisms which regulate apoptosis. BCL2 overexpression inhibits apoptotic cell death and activates cellular proliferation and tumor progression. Although BCL2 is well–known as an anti–apoptotic oncogene in lymphoma, the paradoxical function of the tumor suppressor gene has been reported in many solid tumors, including BC. BCL2 is upregulated by estrogens in breast cancer, through a direct consequence of transcriptional induction.[13]

Varying results have been reported with regards BCL2 expression in BC cases. Most previous studies have reported a favorable prognostic effect of BCL2 expression.[14] However, some studies have reported no association between BCL2 expression and survival, and several studies reported that BCL2 is an adverse prognostic indicator.[14] In this study BCL2 expression was seen in 36% (18/50) of cases which is much lower than (53% to 68%) documented in literature. **(Table 3)** Our patients had tumors with higher stage and grade, accounting for the possible lower percentage of cases exhibiting BCL2 expression. Our hospital is a charitable one and caters to the rural population. Due to low socioeconomic status of these patients, BC cases are usually diagnosed in advanced stages.

Here we considered BCL2 positivity when more than 10% of tumor cells expressed nuclear positivity with or without cytoplasmic expression.[9] Negative BCL2 expression was statistically insignificantly associated with absent ER and PR expression in this study. Possibly due to higher percentage of ER and PR negative cases in this study such association was documented. This finding could possibly support the inverse observation that BCL2 expressing tumors were more frequently HR positive as documented in studies in the literature.[17] BCL2 is expressed in normal breast glandular epithelium and is known to be upregulated by estrogen, possibly as a direct result of transcriptional induction.[17]

Study name	BCL2 positivity % (no. of cases)
Ki–Tae Hwang et.al [15]	68.2% (4932/7230)
Yong Hwa Eom et.al [9]	53.8% (605/1124)
Hee Ju Kim[16]	62.5% (1373/2198)
Present study	**36% (18/50)**

Table 3: Percentage positivity of BCL2 expression in other studies

Maximum HER2/neu expressing tumors in this study exhibited BCL2 negativity (14/21,66.67%) though statistically insignificant. This was in line with previous studies where statistically significant inverse association was observed between BCL2 and HER2/neu expression.[9,18]

A recent study found that BC patients with Ki67 levels exceeding 10%–14% fall into a high–risk category, making them suitable candidates for neoadjuvant therapy. Considering 14% cut off, maximum cases showing negative BCL2 expression exhibited statistically insignificant Ki67 immunopositivity in this study.[19] A study by Eom et al demonstrated statistically significant association between BCL2 expression and lower Ki67 indices. [9] Cheng et al has documented that combined Ki67/BCL2 phenotyping is useful in luminal cancers prognostication.[20]

Maximum cases showing absence of BCL2 expression belonged to higher grade (21/50, 42%), higher stage (17/50, 34%), positive lymph node status (25/50, 50%), presence of lymphovascular invasion (LVI) (19/50,38%) in this study. An association of BCL2 expression with lower grade, lower stage, negative lymph node status and absence of lymphovascular invasion is documented in literature.[9,17,21]

Molecular classification in this study showed maximum of TNBC (22/50, 44%) which included 10 cases of BLBC and 12 cases of NCBC followed by HER2 enriched cases (11/50; 22%). Luminal B and luminal A constituted 10 (20%) and 7 (14%) cases respectively. Jonnada et al. conducted a systematic review of observational studies from Indian literature and reported that, among the molecular subtypes of breast cancer, luminal A was the most common, followed by TNBC, luminal B, and HER2–enriched subtypes.[22] Our hospital, being a charitable institution serving a predominantly rural population, encounters patients who often present at advanced stages of breast cancer due to their low socioeconomic background. Consequently, the higher stage and grade of tumors in our cohort likely contributed to the increased proportion of TNBC and HER2/neu enriched BC cases. Additionally, the inclusion of equivocal (+2) cases as positive in our study may have further accounted for the higher percentage observed.

Different molecular subtypes of BC show varied BCL2 expression. 42.86% (3/7) of luminal A, 36.36% (4/11) of Her2 enriched cases and 36.36% (8/22) of TNBC expressed BCL2 in this study followed by 30% (3/10) of luminal B cases. Most studies document high BCL2 expression in luminal BC cases when compared with other molecular subtypes.[9] Seong et al. suggested that BCL2 expression is an independent, favorable prognostic factor in patients

with luminal BC.[23] It is further documented in literature that luminal BC with high BCL2 expression demonstrated more favorable outcomes compared to patients with other breast cancer subtypes.[24]

BCL2 expression was seen in 38.24% (13/34) of invasive BC no special type (IBC NST), 25% (2/6) of IBC with medullary pattern, both cases (100%, 2/2) of mucinous carcinoma and in a single case of encapsulated papillary carcinoma (100%, 1/1). Metaplastic carcinoma (2 cases), invasive cribriform carcinoma (1 case), mixed IBC with NST and mucinous features (1 case) and secretory carcinoma (1 case) were negative for BCL2 expression. This can be explained by the fact that medullary, metaplastic, and secretory carcinoma subtypes are frequently triple negative and express frequently basal like phenotype.[25,26] In this study, both cases of metaplastic and a single case of secretory carcinoma expressed basal like phenotype. One case of medullary carcinoma expressed basal like phenotype and the rest were unclassifiable. Jensen et al. reported that 13 cases of typical medullary carcinoma lacked BCL2 expression and suggested that enhanced apoptosis, counterbalancing the high proliferative activity, may partly explain the more favorable prognosis observed in this histopathological subtype.[24] In contrast, mucinous, and encapsulated papillary carcinoma exhibit hormone receptor positivity as seen in present study.[27,28] BCL2 is regarded as estrogen related protein. In this study, invasive cribriform carcinoma showed ER and PR positivity but lacked BCL2 expression. This suggests that factors other than ER expression may influence BCL2 status. Further studies with larger sample sizes are required to clarify this observation.

The authors anticipate that these findings may highlight BCL2 as a promising therapeutic target for breast cancer in the Indian context. However, additional evidence from molecular studies is required to further substantiate this possibility.

Limitations:

TMA technique was used for BCL2, ER, PR, Her2, Ki67, CK5/6 and EGFR. Whole sections were not used for their IHC evaluation. However, utmost care was taken to sample the most **representative** area from the original whole section blocks for TMA. HER2/neu was assessed only by IHC. Evaluation by FISH was not available, especially for the equivocal cases with HER2 expression 2+. Follow–up time for the patients was limited.

Conclusion

In BC cases, loss of BCL2 expression showed a statistically insignificant association with higher tumor grade and stage, lymph node positivity, presence of lymphovascular invasion, absence of ER/PR and HER2/neu expression, and Ki67 positivity. Similarly, in HRPBC, TNBC and BLBC cases, negative BCL2 expression was statistically insignificantly associated with higher grade and stage, lymph node positivity, and Ki67 expression. Overall, absence of BCL2 expression correlated predominantly with established poor prognostic factors. However, a study will larger sample size will elucidate the matter further. Nevertheless, BCL2 can serve as a useful prognostic marker and merits inclusion in the routine IHC panel for breast cancer, as it may contribute to the development of individualized, tailored therapeutic strategies.

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KFAS
مؤسسة الكويت للتقدم العلمي
Kuwait Foundation for the Advancement of Sciences

The Gulf Journal of Oncology is published with the financial support from the Kuwait Foundation for the Advancement of Sciences



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