TPM Vol. 32, No. S3, 2025
ISSN: 1972-6325
https://www.tpmap.org/

Open Access

BCL-2 EXPRESSION WITH RESPECT TO ITS PROGNOSIS IN AMONGST BREAST CARCINOMA

PRABAKARAN B[2], AKSHAYA VISWANATHAN[1], NEHA BRAHMA[1], VIMAL S[1]*, [3]DR. T. MANIGANDAN

[1]DEPARTMENT OF BIOCHEMISTRY, SAVEETHA MEDICAL COLLEGE, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICAL SCIENCES, SAVEETHA UNIVERSITY, CHENNAI, TAMIL NADU, INDIA.
[2]DEPARTMENT OF PATHOLOGY, SAVEETHA MEDICAL COLLEGE, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICAL SCIENCES, SAVEETHA UNIVERSITY, CHENNAI, TAMIL NADU, INDIA.
[3]PROFESSOR, DEPARTMENT OF ORAL MEDICINE & RADIOLOGY, SREE BALAJI DENTAL COLLEGE & HOSPITAL, CHENNAI, INDIA
CORRESPONDING AUTHOR *
DEPARTMENT OF BIOCHEMISTRY, SAVEETHA MEDICAL COLLEGE & HOSPITAL, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICAL SCIENCES (SIMATS), THANDALAM, CHENNAI - 602105, TAMIL NADU, INDIA.

Abstract

Breast cancer is the most common cancer among women worldwide, with the B-cell lymphoma 2 gene (BCL-2) gene being linked to favorable clinical outcomes. BCL-2 expression correlates with hormone receptor positivity, particularly estrogen receptor (ER) expression, and is more prevalent in luminal A and luminal B subtypes. Its prognostic value is most pronounced in ER-positive disease but may extend to certain triple-negative breast cancers. Understanding BCL-2's context-dependent behavior can enhance prognostic accuracy and inform therapeutic decision-making. Future research may integrate BCL-2 assessment with genomic profiling and multi-parametric risk models.

Keywords

Breast carcinoma, prognosis, estrogen receptor, hormone receptor-positive breast cancer, luminal subtype.

INTRODUCTION

Breast carcinoma is the most common malignancy in women globally and remains a leading cause of cancer-related mortality despite advances in early detection, molecular classification, and targeted therapeutics (1). Its biological diversity poses a challenge for accurate prognostication and individualized treatment planning. Over the past few decades, the identification and validation of molecular biomarkers have revolutionized breast cancer classification, allowing clinicians to predict outcomes and select optimal therapeutic strategies with greater precision (2). Among these biomarkers, B-cell lymphoma 2 (BCL-2) has attracted considerable attention because of its paradoxical role in tumor biology and prognosis. The protein inhibits apoptosis by binding to pro-apoptotic members of the BCL-2 family, such as BAX and BAK, thereby preventing mitochondrial outer membrane permeabilization and cytochrome c release (3). This anti-apoptotic function allows cells to evade programmed cell death, a hallmark of cancer progression. In most malignancies, including lymphomas and certain solid tumors, overexpression of BCL-2 promotes tumor survival, treatment resistance, and adverse prognosis (4).

The explanation for this paradox lies partly in the molecular and hormonal context of breast tumors. BCL-2 expression is strongly correlated with estrogen receptor (ER) positivity and, to a lesser extent, progesterone receptor (PR) expression. This association reflects the regulatory influence of estrogen signaling on BCL-2 transcription, whereby ER activation can upregulate BCL-2 expression in breast epithelial cells (5). This histological depiction contrasts normal breast tissue with pathological changes, showing a healthy lobe and duct alongside areas affected by ductal carcinoma in situ, a non-invasive form of breast cancer confined to the ductal system. Surrounding adipose tissue is also evident, reflecting the structural composition of the breast and emphasizing the distinction between healthy and malignant regions (6) (Figure 1).

Multiple immunohistochemical studies and large-scale meta-analyses have demonstrated that BCL-2 expression in breast carcinoma is associated with improved overall survival (OS) and disease-free survival (DFS). For example, in a pooled analysis of over 17,000 breast cancer cases, patients with BCL-2-positive tumors had significantly lower risks of recurrence and mortality compared to those with BCL-2-negative tumors, even after adjusting for nodal status, tumor size, and histological grade (6). The prognostic benefit appears to be strongest in ER-positive tumors, where BCL-2 status may further stratify patients into distinct risk categories beyond what traditional histopathological variables can predict. Interestingly, even in triple-negative breast cancer (TNBC), a subtype characterized by poor prognosis and limited treatment options, the minority of tumors that are BCL-2-positive tend to have better survival outcomes compared to their BCL-2-negative counterparts (7) (8).

The interplay between BCL-2 and other biomarkers further enhances its clinical relevance. HER2-positive tumors, which are generally more aggressive, tend to show lower BCL-2 expression, suggesting an inverse relationship between HER2 signaling and BCL-2 transcription (9). The biological paradox of BCL-2 in breast carcinoma that an anti-apoptotic protein can predict better outcomes underscores the importance of interpreting biomarkers in the context of tumor biology rather than in isolation. In hormone receptor-positive tumors, high BCL-2 expression may reflect a dependence on estrogen signaling and a lack of alternative survival pathways, resulting in a more predictable and therapeutically targetable disease course. In contrast, in other cancers where BCL-2 overexpression is driven by oncogenic mutations or chromosomal translocations, its role is more directly linked to treatment resistance and aggressive progression (10). This context-dependent behavior highlights the need for integrated biomarker panels and multi-omics approaches to fully capture the prognostic and predictive landscape of breast carcinoma (11) (12).

Future studies using standardized immunohistochemistry protocols and scoring criteria are needed to validate the independent prognostic utility of BCL-2 in different molecular subtypes of breast cancer (13). Second, integrating BCL-2 expression data with genomic and transcriptomic analyses may help identify co-expressed gene networks and signaling pathways that influence its prognostic behavior (14). Third, exploring the interaction between BCL-2 expressions and emerging treatment modalities, including CDK4/6 inhibitors, PI3K/AKT/mTOR pathway inhibitors, and immunotherapies, may reveal novel therapeutic combinations that leverage the prognostic advantage conferred by BCL-2 positivity. Lastly, the development of risk prediction models that incorporate BCL-2 alongside other validated biomarkers could improve patient stratification and optimize treatment selection, particularly in early-stage, hormone receptor-positive breast cancer where overtreatment remains a concern (15) (16).

In conclusion, BCL-2 expression in breast cancer is an intriguing illustration of how a biomarker's prognostic significance can vary significantly based on the tumor's molecular and hormonal environment. While BCL-2's anti-apoptotic function might intuitively suggest a role in promoting tumor aggressiveness, in breast cancer it is consistently associated with favorable clinic pathological features, hormone receptor positivity, and improved survival outcomes. Its utility as a prognostic marker lies not only in its independent predictive potential but also in its ability to complement and refine risk assessment when combined with established markers such as ER, PR, HER2, and Ki-67 (Table 1). As precision oncology continues to evolve, the integration of BCL-2 status into multi-parametric prognostic frameworks holds promise for improving patient stratification, minimizing overtreatment, and guiding the rational design of future therapeutic strategies.

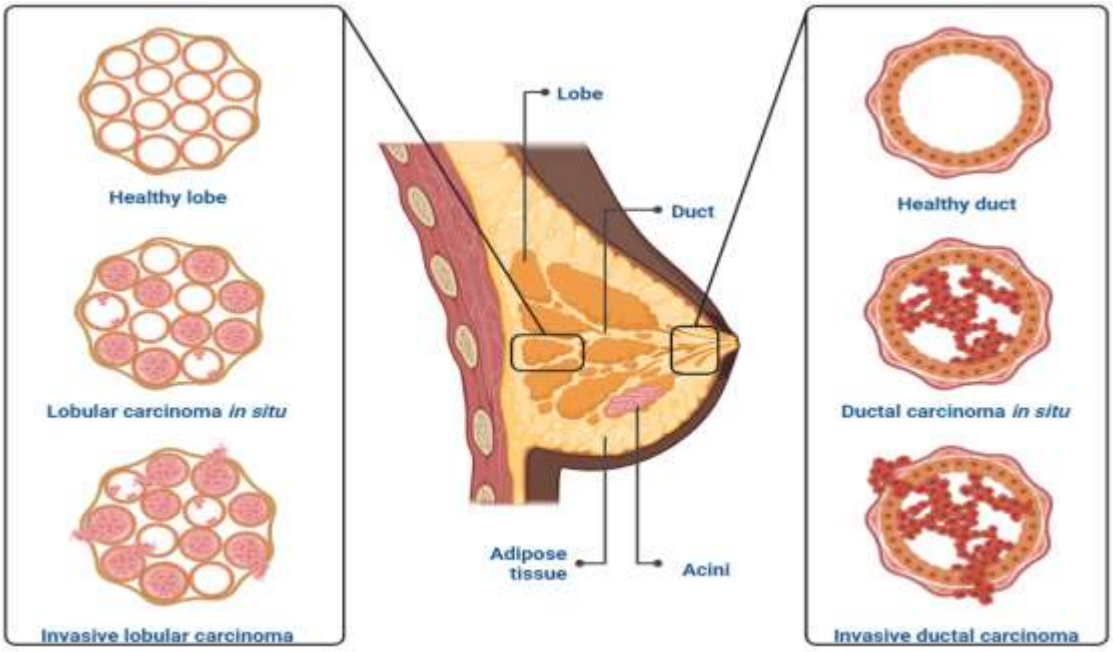

Figure 1. The image illustrates normal and cancerous changes in breast lobes and ducts. On the left, healthy lobes, lobular carcinoma *in situ*, and invasive lobular carcinoma are shown, while on the right, healthy ducts, ductal carcinoma *in situ*, and invasive ductal carcinoma are depicted, with the central diagram highlighting their anatomical locations within the breast.

Feature / Aspect	Findings	Clinical Implication	References
Prevalence in Breast Cancer	Higher expression in ER-positive and luminal A/B subtypes; less frequent in HER2-positive and basal-like tumors.	Suggests hormone receptor-driven regulation of BCL-2 transcription.	(5, 9, 13)
Association with Prognosis	Strongly linked to improved overall survival (OS) and disease-free survival (DFS) in ER-positive breast cancer.	Can be used as a positive prognostic biomarker.	(6, 13)
Triple-Negative Breast Cancer (TNBC)	Minority of TNBC cases express BCL-2; these show better outcomes compared to BCL-2-negative TNBC.	Potential prognostic subgroup within TNBC.	(7, 10)
Molecular Context	BCL-2 expression inversely related to HER2 overexpression; correlated with estrogen signaling pathways.	May reflect reduced tumor aggressiveness in hormone receptor-positive settings.	(5, 9)
Biological Role	Anti-apoptotic protein that paradoxically predicts better prognosis in breast carcinoma.	Importance of context-dependent interpretation of biomarkers.	(3, 4, 10)
Predictive Utility	Adds value when combined with ER, PR, HER2, and Ki-67 in prognostic models.	Improves risk stratification and avoids overtreatment.	(2, 11, 15)
Future Research Directions	Standardization of IHC scoring; integration with genomic/transcriptomic data; evaluation with novel therapies (CDK4/6, PI3K/AKT/mTOR inhibitors, immunotherapy).	Could refine precision oncology strategies.	(14, 15, 16)

Table 1. These table summarizes the prevalence, molecular associations, prognostic relevance, and future research directions of BCL-2 expression in breast carcinoma, highlighting its context-dependent behavior. References correspond to studies demonstrating its clinical significance across different molecular subtypes and treatment settings.

REFERENCES

1. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. Cancers (Basel). 2021;13(17).
2. Passaro A, Al Bakir M, Hamilton EG, Diehn M, André F, Roy-Chowdhuri S, et al. Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. Cell. 2024;187(7):1617-35.
3. Vogler M, Braun Y, Smith VM, Westhoff MA, Pereira RS, Pieper NM, et al. The BCL2 family: from apoptosis mechanisms to new advances in targeted therapy. Signal Transduct Target Ther. 2025;10(1):91.
4. Kaloni D, Diepstraten ST, Strasser A, Kelly GL. BCL-2 protein family: attractive targets for cancer therapy. Apoptosis. 2023;28(1-2):20-38.
5. Kawiak A, Kostecka A. Regulation of Bcl-2 Family Proteins in Estrogen Receptor-Positive Breast Cancer and Their Implications in Endocrine Therapy. Cancers (Basel). 2022;14(2).
6. Shehata M, Grimm L, Ballantyne N, Lourenco A, Demello LR, Kilgore MR, et al. Ductal Carcinoma in Situ: Current Concepts in Biology, Imaging, and Treatment. J Breast Imaging. 2019;1(3):166-76.
7. Kanagaraj S, Arumugam P, Sundaravadivelu S, Chigurupati S, Alyamani N, Felemban S, et al. Rutin induces endoplasmic reticulum stress-associated apoptosis in human triple-negative breast carcinoma MDA-MB-231 cells – In vitro and in silico docking studies. Arabian Journal of Chemistry. 2022;15:104021.
8. Zubair M, Wang S, Ali N. Advanced Approaches to Breast Cancer Classification and Diagnosis. Front Pharmacol. 2020;11:632079.
9. Sofi S, Mehraj U, Jan N, Almilaibary A, Ahmad I, Ahmad F, et al. Clinicopathological Significance and Expression Pattern of Bcl2 in Breast Cancer: A Comprehensive in silico and in vitro Study. Saudi J Biol Sci. 2024;31(2):103916.
10. Török M, Nagy Á, Cserni G, Karancsi Z, Gregus B, Nagy DH, et al. Prognostic Potential of Apoptosis-Related Biomarker Expression in Triple-Negative Breast Cancers. International Journal of Molecular Sciences. 2025;26(15):7227.
11. Wu Q, Cao H, Jin J, Ma D, Niu Y, Yu Y, et al. Integrated multi-omics analysis reveals the functional and prognostic significance of lactylation-related gene PRDX1 in breast cancer. Front Mol Biosci. 2025;12:1580622.
12. Khan F, Alam MW, Ramniwas S, Rautela I, Lakhanpal S, Pandey P. An Updated Review Deciphering Apigenin Nanostructures as Promising Therapeutic Efficiency in Human Carcinomas. Current medicinal chemistry. 2024;32.
13. Dawson SJ, Makretsov N, Blows FM, Driver KE, Provenzano E, Le Quesne J, et al. BCL2 in breast cancer: a favourable prognostic marker across molecular subtypes and independent of adjuvant therapy received. Br J Cancer. 2010;103(5):668-75.
14. Ma M, Chen Y, Chong X, Jiang F, Gao J, Shen L, et al. Integrative analysis of genomic, epigenomic and transcriptomic data identified molecular subtypes of esophageal carcinoma. Aging (Albany NY). 2021;13(5):6999-7019.
15. Garg P, Malhotra J, Kulkarni P, Horne D, Salgia R, Singhal SS. Emerging Therapeutic Strategies to Overcome Drug Resistance in Cancer Cells. Cancers (Basel). 2024;16(13).
16. Uppu JL, Challa VS, Syamprasad NP, Manepalli P, Naidu V, Syed A, et al. Apoptosis-driven synergistic anti-cancer efficacy of ethyl acetate extract of Memecylon sisparense Gamble leaves and doxorubicin in in-vitro and in-vivo models of triple-negative breast cancer. Pathol Res Pract. 2024;253:155032.