Since 1987
REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS, INTERNATIONAL EDITION | 39(2): 85-94 (2025) Rcpp

Received: 01 June 2025 | **Revised:** 22 July 2025 | **Accepted**: 23 July 2025 | **Published**: 30 August 2025

Open Access | RESEARCH REPORT

Association of Bcl-2 expression with prognostic indicators in breast cancer

Paraskevi Konstantinidi[1,2,*], Petros Papagiorgis[2], Nikolaos Thalassinos[2], Olympia Tzaida[1], Fragkiski Anthouli-Anagnostopoulou[2]

[1]Pathological Anatomy Laboratory, Metaxa Cancer Hospital, Piraeus, Greece
[2]Department of Biomedical Sciences, Faculty of Health and Caring Sciences, University of West Attica, Athens, Greece

***Corresponding author:** Paraskevi Konstantinidi, 17 Levadias Str., Piraeus GR-18542, Attica, Greece. Tel.: +30-6958418855; e-mail: pkonstantinidi@uniwa.gr

ABSTRACT

Background: The Bcl-2 protein is a member of the bcl family of proteins, which play a key role in the cell apoptosis process. Its tumorigenic potential has been established long ago in animal experimental models, and was subsequently supported by the finding of its overexpression in a variety of human tumors. Bcl-2 has been suggested as a prognostic marker for the neoplastic diseases; new evidence keeps arising providing further support to this finding. *Aim*: This study investigated the association of Bcl-2 expression with prognostically important clinicopathological features in breast carcinoma in the Greek population. *Methodology*: Immunohistochemical assessment of Bcl-2 was conducted in a case series of 100 surgically resected primary breast carcinomas from November 2022 to July 2023 and the association of Bcl-2 with the grade of histological differentiation and Lymph nodes pN was statistically investigated. *Results*: The histological grade profile of the studied samples was: Grade III (24%), Grade II (62%), Grade I (14%). High (score 3+) Bcl-2 expression was found in 65% of cases, moderate (score 2+) expression in 12%, low (score 1+) in 4%, while negative expression was shown in 19% of the samples. A statistically significant inverse association between Bcl-2 expression and the grade of histological differentiation was detected (Phi=-0.850, p=< 0.0001). Bcl-2 expression was also inversely associated with Lymph nodes pN stage (p=0.001). *Conclusion*: The observed association of immunohistochemical Bcl-2 expression with clinicopathological characteristics which are known prognositc indicators for breast cancer (grade and pN stage) provides confirmatory evidence to the potential important prognostic value of this marker in breast cancer. Future investigations should incorporate Bcl-2 expression in multivariate prediction models to weigh its value in the clinical management of breast cancer.

KEYWORDS

breast cancer, *Bcl-2* oncogene, immunohistochemistry, grade, prognosis

How to cite this article: Konstantinidi P., Papagiorgis P., Thalassinos N., Tzaida O., Anthouli- Anagnostopoulou F.: Association of Bcl-2 expression with prognostic indicators in breast cancer. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed*. 39(2): 85-94 (2025).
DOI: 10.61873/OBAR5597

Publisher note: PHARMAKON-Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. INTRODUCTION

Breast carcinoma is a pathologic condition in which non-physiological cells of the mammary gland begin to grow and multiply uncontrollably, forming tumors, which if left untreated can spread throughout the body of the patients and eventually become fatal to them [1]. The disease predominantly affects middle-aged and older women. The average age of U.S.

women diagnosed with breast cancer is 62 years old. 1 in 8 women in the United States will be diagnosed with breast cancer in her lifetime. About 9% of all new breast cancer cases in the U.S. are diagnosed in women younger than 45 years old. Younger people, particularly those under age 35 at the time of their original breast cancer diagnosis, face a higher risk of breast cancer recurrence [2].

The *Bcl*-2 oncogene is involved in a number of malignant neoplasms, including lymphoma and leukemia, with the main path of its action being the regulation of the cell apoptosis process [3].There are two main subclasses of Bcl-2 proteins: the anti-apoptotic (Bcl-2-A1, Bcl-2, Bcl-Xl, Bcl-w and Mcl-1), and the pro-apoptotic (Bad, Bak, Bax, Bid, Bik, Bim, Hrk, Noxa and Puma) [4]. Anti-apoptotic proteins of the Bcl-2 family were already identified as oncogenes in 1984 after the discovery of their role in the development of B-cell leukaemia [5]. There are studies demonstrating that overexpression of Bcl-2 and Bcl-Xl, in combination with the increased cell proliferation induced by these oncogenes, results in increased lumen filling, a characteristic morphological feature of in situ endoporotic carcinoma, an early, premalignant state [6]. Those findings demonstrate that pro-proliferative and anti-apoptotic signals cooperate with each other in early mammary epithelial cell (MEC) transformation, with the anti-apoptotic Bcl-2 proteins having an active role in this process.

In one of the largest relevant studies, involving 1081 breast cancer cases it was shown that Bcl-2 expression is an independent poor prognostic factor in patients with HER (-) or triple-negative tumor, especially for those not receiving adjuvant treatment [7]. while, in another study, the authors showed that the high Bcl-2 expression displayed superior disease-free survival compared with the low Bcl-2 expression, especially regarding local recurrence and systemic recurrence [8]. This study investigated the association of Bcl-2 expression with prognostically important clinicopathological features (pT and pN stage, grade of differentiation and histological type) in breast carcinoma in the Greek population.

2. METHODOLOGY

2.1. Study design and sample collection

The current study was conducted on 100 patients with primary breast carcinoma were collected in Histopathological Laboratory Metaxa Cancer Hospital of Piraeus. The patients were women who underwent mastectomy from November 2022 to July 2023. Ethical approval for the study was obtained from University of West Attica and Metaxa Cancer Hospital ethics committee. Voluntary written informed consent for participation in the study or the use of their biopsy was provided by all participants.

Surgical tissues were fixed in 10% neutral formalin and were followed by preparative processing according to international guidelines. Sections (3 μm) were obtained from paraffin-embedded tissue blocks of primary tumor specimens. Tumor sections stained with hematoxylin and eosin (H&E) were used to define the tumor histological type and histological grade of malignancy.

Immunohistochemistry (IHC) for all 100 cases for Bcl-2 was undertaken with polymer peroxidase method on the Auto stainer link 48 DAKO analyzer. The antibody used was Monoclonal Mouse Anti-Human Bcl-2 Oncoprotein Clone 124 (DAKO).

The DAKO EnVision System, HRP is a two-step immunohistochemical staining technique. This system is based on an HRP labeled polymer that is conjugated to secondary antibodies. The labeled polymer does not contain avidin or biotin. First quench endogenous peroxidase activity by incubating the specimen for 5 min with DAKO Peroxidase Block. Then incubate the specimen with primary Mouse Anti-Human Bcl-2 Oncoprotein Clone 124 (dilution 1:600; Dako), followed by incubation with the labeled polymer, using two sequential 30-minute incubations. Staining is completed by a 5-10 minute incubation with 3,3'-diaminobenzidine (DAB)+ substrate-chromogen which results in a brown-colored precipitate at the antigen site. Counterstaining was used EnVision FLEX Hematoxylin Mayer's for 10 min.

The slides were studied with a microscope from the German company Leica (model: DM 1000).

Based on the staining values (% stained cells) and the intensity, the results were classified by a pathologist into the four staining categories: Bcl-2 negative expression (0%), score 1+ (>0% - <30%), score 2+ (≥ 30% - <90%) and score 3+ (≥90%) [9].

2.2. Statistical analysis

Statistical analysis of the study data was performed using the SPSS v29.0 statistical software package (IBM®). The original database was created with the help with Microsoft Office Excel, those data was encoded and the new data base produced in the SPSS, with the data of the 100 women with breast cancer. The research process included the analysis of the following parameters: 1) Bcl-2 expression 2) histological types, 3) tumor pT stage, 4) lymph nodes pN stage, 5) grade of

histological differentiation and 6) association of *Bcl*-2 oncogene with tumor pT stage, grade of histological differentiation, lymph nodes pN stage and histological types. The analysis of the results was performed by using Frequencies and Descriptive Statistics. To examine the association of *Bcl*-2 oncogene with tumor pT stage, grade of histological differentiation, lymph nodes pN stage and histological types, the Fisher's exact test or ordinal regression and odds ratio statistic test was performed where appropriate.

3. RESULTS

Bcl-2 oncogene was found score 3+ in 65% of cases, negative expression in 19%, score 2+ in 12% and score 1+ in the rest 4% (Table 1) (Figures 1,2,3).

Table 1. Distribution of Bcl-2 expression.

BCL-2 Staining category	N (number of cases)	%
Negative 0%	19	19.0
Score 1+ (>0% - <30%)	4	4.0
Score 2+ (≥ 30% - < 90%)	12	12.0
Score 3+ (≥90%)	65	65.0
Total	100	100.0

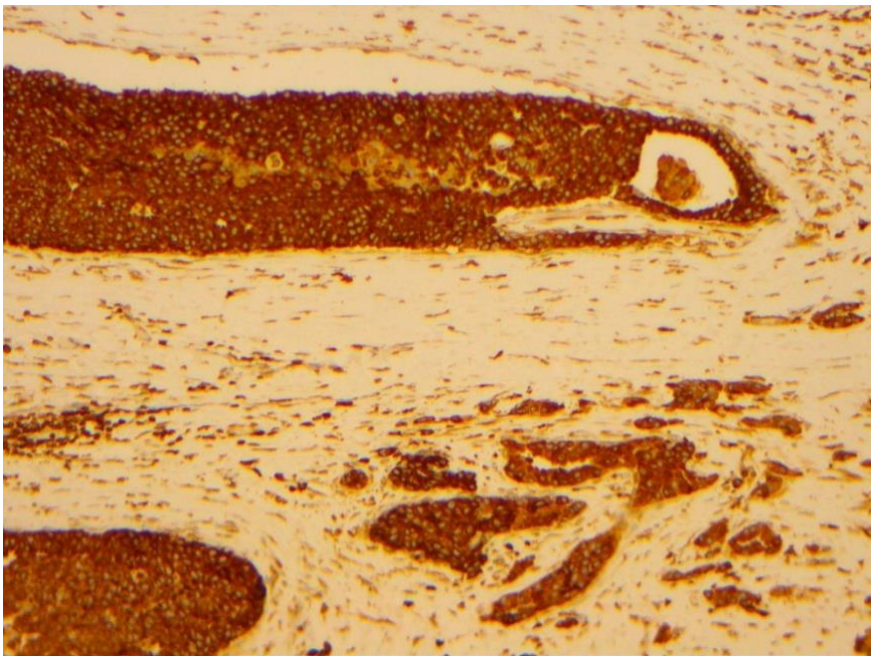

Figure 1. Ductal carcinoma in situ (DCIS). Moderately differentiated, grade II. Immunohistochemical (IHC) high expression (score 3+) Bcl-2 in ≈ 100% of neoplastic cells, both in situ and in the invasive element, membranous and cytoplasmic expression (10x).

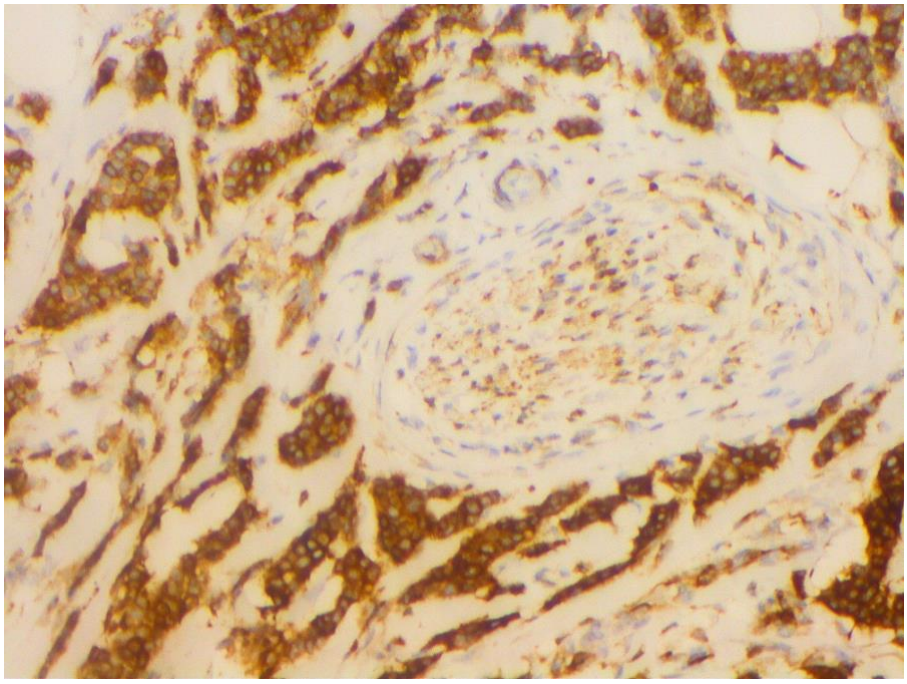

Figure 2. Invasive lobular breast carcinoma (ILC). Moderately differentiated, grade II. Immunohistochemical (IHC) moderately expression (score 2+) Bcl-2 in 90-95% of neoplastic cells. Negative normal mass parenchyma (20x).

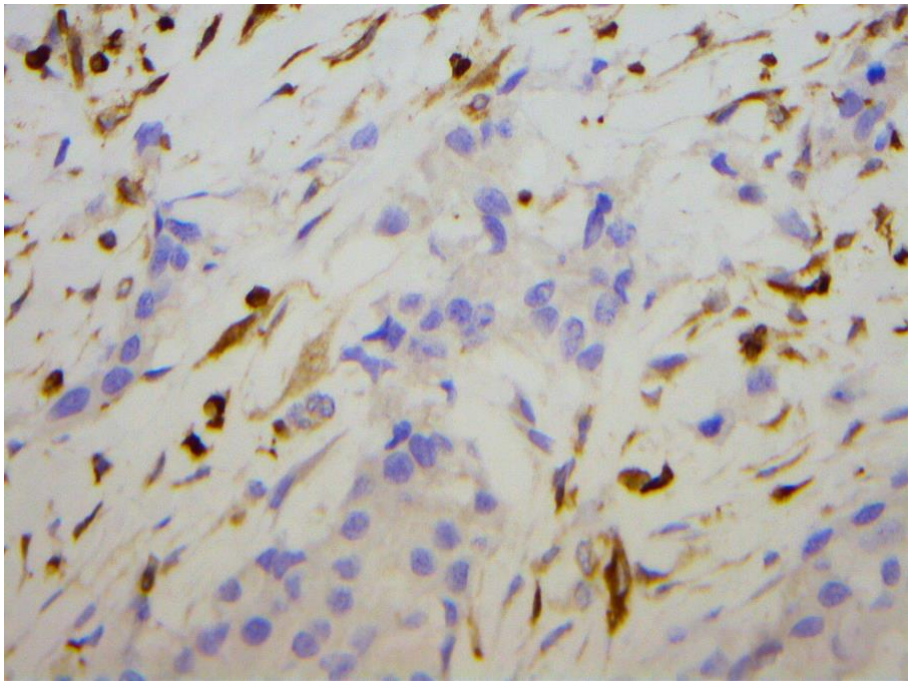

Figure 3. Invasive breast carcinoma no special type (NST). Poorly differentiated, grade III. Immunohistochemical (IHC) negative expression (-) Bcl-2 with positive endogenous control lymphocytes (40x).

Invasive ductal carcinoma no special type (NST) was detected in 60 cases (60%), followed by Invasive lobular carcinoma (15%), while the rest 25% included other histological types (Table 2). Tumor pathology stage (pT stage) was assessed for all cases and pT2 was identified in the majority 38%, followed by pT1c 34% (Table 3). Lymph nodes infiltration were absent in 63% of all the cases (Table 4).

Table 2. Distribution of histological types.

		N (number of cases)	%
Histological types	DCIS Micropapillary type	1	1.0
	DCIS multifocal with apocrine features	1	1.0
	IBC – Metaplastic breast carcinoma	1	1.0
	IBC Micropapillary type	2	2.0
	IBC Mucinous type	4	4.0
	IBC multifocal with apocrine features	4	4.0
	IBC Papillary type	4	4.0
	IDC – Invasive ductal carcinoma	4	4.0
	IDC no special type (NST)	60	60.0
	IDC with squamous differentiation	1	1.0
	ILC – Invasive lobular carcinoma	15	15.0
	IMPC – Invasive micropapillary carcinoma	1	1.0
	LCIS – Lobular carcinoma in situ	1	1.0
	MBC – Metaplastic breast carcinoma	1	1.0
	Total	100	100.0

Table 3. Distribution of tumor pT stage.

		N (number of cases)	%
Tumor pT stage	**pT1a**	4	4.0
	pT1b	15	15.0
	pT1c	34	34.0
	pT2	38	38.0
	pT3	3	3.0
	pT4a	3	3.0
	pT4b	3	3.0
	Total	100	100.0

*pT1a: > 0.1 cm and ≤ 0.5 cm
pT1b: > 0.5 cm and ≤ 1 cm
pT1c: > 1 cm and ≤ 2 cm
pT2: > 2 cm and ≤ 5 cm
pT3: > 5 cm
pT4a: cancer has spread into the chest wall
pT4b: cancer has spread into the skin and the breast might be swollen [10].

Table 4. Distribution of lymph nodes pN stage.

		N (number of cases)	%
Lymph nodes pN stage	**pN0**	63	63.0
	pN1mi	2	2.0
	pN1a	24	24.0
	pN2a	10	10.0
	pN3a	1	1.0
	Total	100	100.0

*pN0: no lymph node infiltration, or infiltration ≤ 0.2 mm
pN1mi: infiltration > 0.2 mm and ≤ 2 mm.
pN1a: infiltration in 1 to 3 lymph nodes and at least one is > 2 mm. pN2a: infiltration in 4 to 9 lymph nodes and at least one is > 2 mm.
pN3a: infiltration in 10 or more lymph nodes and at least one > 2 mm, or infiltration in the nodes below the collarbone. [10].

The most common Grade was Grade II (62%), followed by Grade III (24%), and Grade I (14%) (Table 5). The association of Bcl-2 with pT stage, Grade and pN stage, was examined using ordinal regression and odds ratio statistic test. Bcl-2 was negatively associated with tumor grade Phi=-0.850 & *p*=< 0.0001 (Table 6). The odds of negative Bcl-2 indicating higher lymph node pN stage was 4.919 (95% CIs: 1.858-13.018) times that of positive Bcl-2, with a statistical significance of *p*=0.001 (Table 7) (Figure 4). Bcl-2 was not associated with Tumor pT stage (*p*=0.749) (Table 8). With regard to the association of Bcl-2 expression and breast histological types, Bcl-2 was negatively correlated with the specific histological type IBC multifocal with apocrine features as Phi= -0.421 & *p*=< 0.0001 (Table 9).

Table 5. Distribution of tumor grade.

Grade	N (number of cases)	%
I (well differentiation)	14	14.0
II (moderate differentiation)	62	62.0
III (poor differentiation or high grade)	24	24.0
Total	100	100.0

Table 6. Association of Bcl-2 with grade.

		BCL-2		Total
Grade		**Negative**	**Positive**	
	I and II	1 5.3%	75 92.6%	76 76.0%
	III	18 94.7%	6 7.4%	24 24.0%
Total		19 100.0%	81 100.0%	100 100.0%

	Value	*p*-value
Phi	-0.850	< 0.0001
Cramer's V	0.850	< 0.0001

Table 7. Association of Bcl-2 with lymph nodes pN stage.

		BCL-2		Total	*p*-value
PN Stage		**Negative**	**Positive**		
	pN0	7 36.8%	56 69.1%	63 63.0%	0.001
	pN1mi	0 0.0%	2 2.5%	2 2.0%	
	pN1a	6 31.6%	18 22.2%	24 24.0%	
	pN2a	5 26.3%	5 6.2%	10 10.0%	
	pN3a	1 5.3%	0 0.0%	1 1.0%	
Total		19 100.0%	81 100.0%	100 100.0%	

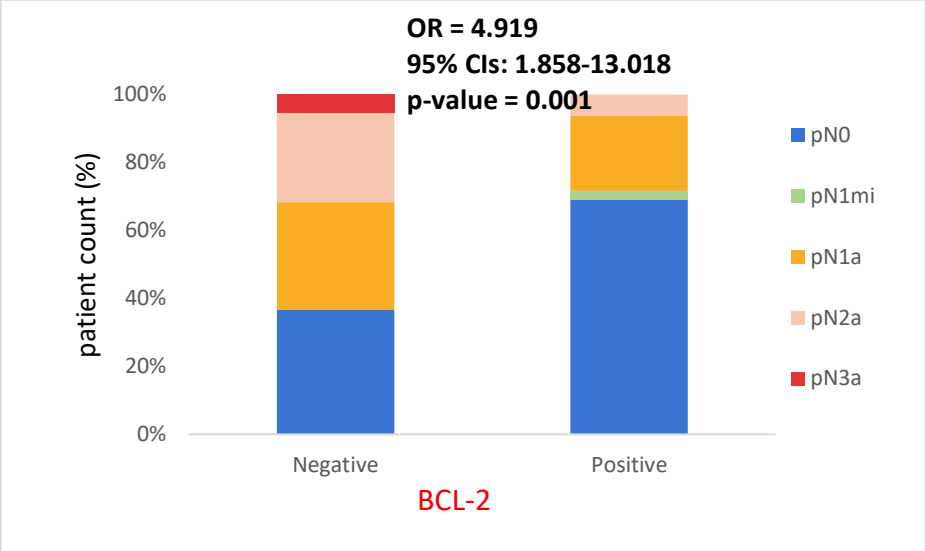

Figure 4. Association of Bcl-2 with lymph nodes pN stage.

Table 8. Association of Bcl-2 with tumor pT stage.

		BCL-2		Total	*p*-value
		Negative	**Positive**		
PT Stage	**pT1a**	2 10.5%	2 2.5%	4 4.0%	0.749
	pT1b	2 10.5%	13 16.0%	15 15.0%	
	pT1c	4 21.1%	30 37.0%	34 34.0%	
	pT2	10 52.6%	28 34.6%	38 38.0%	
	pT3	1 5.3%	2 2.5%	3 3.0%	
	pT4a	0 0.0%	3 3.7%	3 3.0%	
	pT4b	0 0.0%	3 3.7%	3 3.0%	
Total		19 100.0%	81 100.0%	100 100.0%	

Table 9. Association of Bcl-2 negative expression (-) with a specific type category (IBC multifocal with apocrine features).

		BCL-2		Total
		Negative	**Positive**	
IBC	**no**	15 78.9%	81 100.0%	96 96.0%
	yes	4 21.2%	0 0.0%	4 4.0%
Total		19 100.0%	81 100.0%	100 100.0%

	Value	***p*-value**
Phi	-0.421	< 0.0001
Cramer's V	0.421	< 0.0001

4. DISCUSSION

The Bcl-2 protein is a member of the bcl family of proteins, which play a key role in the cell apoptosis process [11]. Its oncogenic (carcinogenic) potential was established relatively early in animal experimental models, and was subsequently supported by the finding of its overexpression in a variety of tumors and lymphomas, in which Bcl-2 has oncogenic activity [12,13]. The present study investigated the role of Bcl-2 as a potential prognostic marker in patients with primary breast carcinoma in the Greek population.

The main finding of the study was that Bcl-2 expression exhibited a significant negative association with the grade of histological differentiation as Phi=-0.850 & p=< 0.0001. In addition, Bcl-2-expression showed a significant association with pN stage (p=0.001). Therefore, Bcl-2 (+) cases were more commonly detected in tumors with a better differentiation and a more favorable pN stage.

In a retrospective study involving 582 primary breast carcinomas reported that, 1) In non-triple (-) tumors, positive expression of Bcl-2 was correlated with less aggressive tumors (94% of Grade I was Bcl-2 (+) vs 62% of Grade III, p<0.011) whereas, 2) In triple negative tumors a statistically significant association was found between Bcl-2 positivity and lower incidence of lymph node metastasis [14].

Investigated the prognostic value of Bcl-2 in 83 patients with metastatic breast carcinoma and found that high Bcl-2 expression in circulating cancer cells was associated with better disease outcome. According to the authors, Bcl-2 expression in patients with metastatic breast carcinoma is likely to have predictive value for both the biological and clinical course of the disease [15]. In another investigation, showed that Bcl-2 (+) was significantly correlated with smaller tumor size and lower tumor grade, whereas there was no correlation between the expression of Bcl-2 and the nodal status of the tumor [7]. After the histological procession of 158 breast cancer cases concluded that 1) Low Bcl-2 expression was related to an increased likelihood of recurrence of the disease and 2) The probably most valuable combination of marker for the assessment of disease recurrence was that of Bcl-2 with PR [8]. While, in 76 women with breast carcinoma, found no statistically significant correlation between the expression of Bcl-2, Ki-67 and p53 and the clinicopathological features of the disease [16]. Recent research reported that Bcl-2 expression was inversely correlated with the histological differentiation of the disease [17]. Furthermore, in a series of 42 cases reported an inverse statistically significant relationship between the expression of Bcl-2 and the Grade of breast tumors, a finding consistent with the results of the present study and other previously published studies [18].

In one of the most recently published original clinical studies, in a series of 312 women of different ethnic backgrounds, concluded that 1) Positive Bcl-2 expression is associated with increased survival of breast cancer patients in age- and race-adjusted models and, 2) Bcl-2 expression has a strong statistical association with protection of breast cancer patients from death with additional adjustments for ER/PR status; such findings are indicative of a potentially important prognostic biological role of Bcl-2 in breast cancer [19]. In a clinicopathological study reported that Bcl-2 is expressed more in primary, compared-to metastatic tumors, displaying diversity in its expression profile across the primary tumor cell population [20].

Another interesting finding of the present study was the statistically significant negative correlation of the Bcl-2 expression with the lymph nodes pN stage (Table 7). Again there were contradictory findings of relevant studies: In a case series of 42 women with Invasive ductal carcinoma – No special type, did not find a statistically significant correlation between lymph nodes harboring malignant cells and Bcl-2 expression (p>0.05) [21]. On the other hand, in triple-negative breast cancer, both the expression of Bcl-2 and the LN stage have been identified as independent prognostic factors of the disease, however without the existence of a direct correlation between them [22]. Finally, in an older study, in 142 patients with T1 breast carcinoma, stated that the expression of Bcl-2 was associated with lymph node metastasis, especially when there was a co-expression of the c-Myc oncogene [23].

The main limitation of this study was the relatively small size (compared to other relevant studies) of the examined sample of patients. Nonetheless, the results were similar (for the most part) to those reported in the literature, pointing out that Bcl-2 prognostic involvement has universal application.

Another limitation was the lack of survival analysis due to the long time interval required for the follow up (approximately ten years) along with the already mentioned small sample size (inadequate to provide concrete evidence regarding the prognostic value of Bcl-2 in breast cancer). Such investigation could be conducted using a larger sample (with the appropriate power) combined with a concomitant examination of other molecular markers (with established or promising prognostic significance in breast cancer such as ER, PR, HER2 and Ki-67) and accompanied by a thorough analysis of

the main relevant studies on the issue. Hormone receptors play a key role as primary biomarkers in luminal breast cancer. There are two major forms of the estrogen receptor (ER), ERα and ERβ. However, only ERα has a validated clinical role, as it is expressed in 70-75% of breast cancers. Similarly, the progesterone receptor (PR) exists in two forms, PRA and PRB [24]. HER2 is overexpressed in 15–30% of invasive breast cancers, which has both prognostic and predictive implications. *HER2* gene overexpression is a strong predictive biomarker for the response of breast carcinomas to anti-HER2 therapies; those therapies include human monoclonal antibodies that bind to the extracellular portion of the HER2 receptor (pertuzumab and trastuzumab treatment) [25]. Finally, the molecular biomarker Ki67 is a cell proliferation marker that is expressed at all stages of the cell cycle, except for the G0 stage. Scientific research in recent years has shown that, in general, breast carcinomas in which high Ki67 expression is found are associated with a worse final prognosis [26].

5. CONCLUSION

The findings of this study revealed a connection of Bcl-2 expression with particular favorable clinicopathological characteristics of breast cancer (i.e. lower grade end pN stage) in a Greek population sample. These results in agreement with corresponding findings in the literature, support the state that the expression of the *Bcl*-2 oncogene may be a particularly useful biomarker for the prediction of disease outcome. However, further, appropriately designed prospective studies with large sample size and appropriate statistical methodology, including multivariate analysis, are needed in the near future to confirm these findings.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to the patients who consented into the study and the Metaxa hospital staff involved in the sample banking and process. We also thank Dr Triantafillos Liloglou for his critical and constructive views on this manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

REFERENCES

1. Breast cancer [Internet]. [cited 2025 Jan 2]. website:https://www.who.int/news-room/fact-sheets/detail/breast-cancer

2. National Breast Cancer Foundation, INC [Internet]. [cited 2025 Jun 12]. website:https://www.nationalbreastcancer.org/breast-cancer-facts/

3. Hwang K. T., Kim Y. A., Kim J., Oh H. J., Park J. H., Choi I. S., *et al*: Prognostic influences of BCL1 and BCL2 expression on disease-free survival in breast cancer. *Sci Rep*. 11(1): 11942 (2021). DOI: 10.1038/s41598-021-90506-x

4. Merino D., Lok S., Visvader J., Lindeman G.: Targeting BCL-2 to enhance vulnerability to therapy in estrogen receptor-positive breast cancer. *Oncogene*. 35(15): 1877–87 (2016). DOI: 10.1038/onc.2015.287

5. Tsujimoto Y., Finger L. R., Yunis J., Nowell P. C., Croce C. M.: Cloning of the chromosome breakpoint of neoplastic B cells with the t (14; 18) chromosome translocation. *Science*. 226(4678): 1097–9 (1984). DOI: 10.1126/science.6093263

6. Williams M. M., Cook R. S.: Bcl-2 family proteins in breast development and cancer: could Mcl-1 targeting overcome therapeutic resistance? *Oncotarget*. 6(6): 3519 (2015). DOI: 10.18632/oncotarget.2792

7. Honma N., Horii R., Ito Y., Saji S., Younes M., Iwase T., *et al*: Differences in clinical importance of Bcl-2 in breast cancer according to hormone receptors status or adjuvant endocrine therapy. *BMC Cancer*. 15(15): 698 (2015). DOI: 10.1186/s12885-015-1686-y

8. Ki-Tae Hwang, Young A Kim, Jongjin Kim, Hyeon Jeong Oh, Jeong Hwan Park, In Sil Choi, *et al*: Prognostic influences of BCL1 and BCL2 expression on disease-free survival in breast cancer. *Scientific Reports*. 11(1): 11942 (2021). DOI: 10.1038/s41598-021-90506-x

9. Tsuyama N., Sakata S., Baba S., Mishima Y., Nishimura N., Ueda K., *et al*: BCL2 expression in DLBCL: reappraisal of immunohistochemistry with new criteria for therapeutic biomarker evaluation. Blood. *The Journal of the American Society of Hematology*. 130(4): 489–500 (2017). DOI: 10.1182/blood-2016-12-759621

10. TNM staging for breast cancer. website:https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-grades/tnm-staging

11. Callagy G. M., Pharoah P. D., Pinder S. E., Hsu F. D., Nielsen T. O., Ragaz J., *et al*: Bcl-2 is a prognostic marker in breast cancer independently of the Nottingham Prognostic Index. *Clinical cancer research*. 12(8): 2468–75 (2016). DOI: 10.1158/1078-0432.CCR-05-2719

12. Yang D., Chen M. B, Wang L. Q, Yang L., Liu C. Y., Lu P. H.: Bcl-2 expression predicts sensitivity to

chemotherapy in breast cancer: a systematic review and meta-analysis. *Journal of Experimental & Clinical Cancer Research*. 32(1): 11 (2013).
DOI: 10.1186/1756-9966-32-105

13.Pietenpol J. A,. Papadopoulos N., Markowitz S., Willson J. K., Kinzler K. W., Vogelstein B.: Paradoxical inhibition of solid tumor cell growth by bcl2. *Cancer research*. 54(14): 3714–7 (1994).

14.Tawfik K., Kimler B. F., Davis M. K., Fan F., Tawfik O.: Prognostic significance of Bcl-2 in invasive mammary carcinomas: a comparative clinicopathologic study between 'triple-negative' and non-"triple-negative" tumors. *Hum Pathol*. 43(1): 23–30 (2012).
DOI: 10.1016/j.humpath.2011.04.011

15.Smerage J. B., Budd G. T., Doyle G. V., Brown M., Paoletti C., Muniz M., *et al*: Monitoring apoptosis and Bcl-2 on circulating tumor cells in patients with metastatic breast cancer. *Molecular oncology*. 7(3): 680–92 (2013).
DOI: 10.1016/j.molonc.2013.02.013

16.Mansouri H., Mnango L. F., Magorosa E. P., Sauli E., Mpolya E. A.: Ki-67, p53 and BCL-2 expressions and their association with clinical histopathology of breast cancer among women in Tanzania. *Scientific Reports*. 9(1): 9918 (2019).
DOI: 10.1038/s41598-019-46184-x

17.Ameh-Mensah C., Duduyemi B. M., Bedu-Addo K., Atta Manu E., Opoku F., Titiloye N.: The Analysis of bcl-2 in Association with p53 and Ki-67 in Triple Negative Breast Cancer and Other Molecular Subtypes in Ghana. *Journal of Oncology*. 2021: 1-10 (2021).
DOI: 10.1155/2021/7054134

18.Kumari N., Suresh N.: Significance of Bcl-2 expression in breast cancer. *Biomedicine*. 42(4): 775–7 (2022).
DOI: 10.51248/.v42i4.1578

19.Al-Alem U., Rauscher G. H., Alem Q.A., Kajdacsy-Balla A., Mahmoud A.M: Prognostic value of SGK1 and Bcl-2 in invasive breast cancer. *Cancers*. 15(12): 3151 (2023).
DOI: 10.3390/cancers15123151

20.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*. 31(2): 103916 (2024).
DOI: 10.1016/j.sjbs.2023.103916

21.Kumari N., Suresh N.: Significance of Bcl-2 expression in breast cancer. *Biomedicine*. 42(4): 775–7 (2022).
DOI: 10.51248/.v42i4.1578

22.Abdel-Fatah T. M. A., Perry C., Dickinson P., Ball G., Moseley P., Madhusudan S., *et al*: Bcl2 is an independent prognostic marker of triple negative breast cancer (TNBC) and predicts response to anthracycline combination (ATC) chemotherapy (CT) in adjuvant and neoadjuvant settings. *Ann Oncol*. 24(11): 2801–7 (2013).
DOI: 10.1093/annonc/mdt277

23.Sierra A., Castellsague X., Escobedo A., Moreno A., Drudis T., Fabra A.: Synergistic cooperation between c-Myc and Bcl-2 in lymph node progression of T1 human breast carcinomas. *Breast Cancer Res Treat*. 54(1): 39–45 (1999).
DOI: 10.1023/a:1006120006471

24.Li Z., Wei H., Li S., Wu P., Mao X.: The Role of Progesterone Receptors in Breast Cancer. *Drug Design, Development and Therapy*. 16(16): 305–14 (2022).
DOI: 10.2147/DDDT.S336643

25.Qbal N., Iqbal N.: Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. *Molecular Biology International*. (1): 1–9 (2014).
DOI: 10.1155/2014/852748

26.Yip C., Bhoo-Pathy N., Daniel J., Foo Y., Mohamed A., Abdullah M., *et al*.: Roles of Ki67 in Breast Cancer - Important for Management? *Asian Pacific Journal of Cancer Prevention*. 11;17(3): 1077–82 (2016).
DOI: 10.7314/apjcp.2016.17.3.1077