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Association of immunohistochemical expression of Bcl-2 with estrogen ER-PR receptors and HER2 and Ki67 in breast cancer

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ABSTRACT

Background: Breast carcinoma is among the three most common types of cancer worldwide, including lung cancer and colon cancer, regardless of gender. The *Bcl-2* oncogene is involved in a number of malignant neoplasms, including leukaemia and lymphoma, through the regulation of the cell apoptosis process. **Aim:** The main purpose of the present study is to investigate the association of Bcl-2 with other molecular parameters of significant prognostic and predictive value for disease and more specifically the ER and PR receptors, along with HER-2 and Ki-67 (MIB-1). **Methodology:** Immunohistochemical assessment of Bcl-2, ER and PR receptors, HER-2 and Ki-67 was conducted in a case series of 100 surgically resected primary breast carcinomas and the association of Bcl-2 with the other biomarkers was statistically investigated. **Results:** High (3+) Bcl-2 expression was observed in 65% of cases, moderate (2+) in 12%, low (1+) in 4% and negative expression in 19%. Association of Bcl-2 with ER-PR receptors and HER2 and Ki67 was conducted with Fisher's exact and Chi square (χ^2) test of Cramer's V statistics tests were performed where appropriate. *Bcl-2* oncogene was positively and highly associated with estrogen ER receptors ($\Phi=0.760$, $p<0.0001$); the findings of the association of *Bcl-2* oncogene with PR progesterone receptors were similar: a positive association was found between the two specific biomarkers ($\Phi=0.626$, $p<0.0001$). Finally, negative association of Bcl-2 with HER2 ($\Phi=-0.350$, $p<0.0001$). **Conclusion:** Considering the association of Bcl-2 expression with the expression of genes that are related to therapy prediction (ER and PR) it remains to be ascertained whether Bcl-2 could be used as a potential predictive marker. Moreover, the negative association of Bcl-2 with Ki67 and HER2 should be further investigated for its association with disease outcome and response to targeted therapy. Overall, this study suggests that Bcl-2 should be further tested for its incorporation into a multivariate prediction model for breast cancer therapy. In addition, more investigations are required into targeted anti-Bcl-2 therapy may be used to modify responses to current breast cancer therapy, in order to reduce resistance.

KEYWORDS

breast cancer, *Bcl-2* oncogene, ER - PR receptors, HER2, immunohistochemistry

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1. INTRODUCTION

Breast carcinoma is among the three most common types of cancer worldwide, including lung cancer and colon cancer, regardless of gender [1]. Every year, around one million new cases of the disease are diagnosed, with 50% of the cases and 60% of deaths occurring in the developing countries. Characteristic is the imbalance of the outcome of the disease where in the developed countries the five-year survival rates of women diagnosed with breast carcinoma reach 80%, whereas in the developing countries, the rates are only 40% [2].

The *Bcl-2* oncogene is involved in a number of malignant neoplasms, including leukaemia and lymphoma, through the regulation of the cell apoptosis process [3]. It is located on chromosome 18q21 and its main role is the encoding of a 26 kDa protein, which is embedded in the outer membrane of mitochondria and whose main function is the inhibition of cell apoptosis. This means that the overexpression of the *Bcl-2* protein, through the inhibition of cell apoptosis, promotes uncontrolled cell proliferation and thus the growth of the malignant tumor. Recent research in relation to the role of the *Bcl-2* oncogene has shown conflicting results regarding tumor progression and patient survival [3]. An additional, recent research finding is the interaction of *Bcl-2* with the estrogen receptor (ER), which appears to modulate oncogene expression in relation to the various molecular subtypes of the ER receptor [4,5].

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*) class. Complex interactions take place between pro- and anti-apoptotic proteins that incorporate signaling information related to the process of cell death. Because of the dynamic nature of the mammary gland, which is characterized by successive cycles of cell growth and cell death, *Bcl-2* proteins are considered essential for normal growth and homeostasis of the gland, with disruption of their function inhibiting breast development at various important stages. It appears that the persistent dysfunction of *Bcl-2* proteins contributes to the inhibition of cell death, an event of pivotal importance for neoplasm development; thus, in breast cancer, *Bcl-2* dysfunction promotes innate and/or acquired resistance to the therapeutic interventions applied for the disease [6,7].

Since the last few years, the treatment of serious human diseases is largely carried out by non-individualized therapeutic interventions and, it has

become evident that the already used biomarkers as well as the TMN staging are not sufficient for the effective management of early diagnosed breast carcinomas. Therefore, researchers have attempted to discover and validate novel molecular biomarkers that can be used to predict disease progression. These are multi-factorial, multi-analytical approaches using multiple gene assays, with several of them now being successfully used in clinical practice [8].

A number of biomarkers with established or promising clinical value in breast cancer are briefly described below.

For quite a long time it has been known that estrogens play an important stimulatory role, both in the normal female breast and in the development and progression of breast carcinoma. Today, ER is one of the most important prognostic molecular biomarkers for the disease; ER belongs to a group of hormone receptors in the cell nucleus that act as transcription factors. There are two main isoforms of ER: ER α , which is the clinically measured isoform, and ER β . Patients whose breast carcinoma is ER positive (+) have significant clinical benefit from endocrine therapeutic interventions that target these receptors treatment with tamoxifen, an aromatase inhibitor, with these therapies achieving significant decrease in local and distant tumor recurrence, as well as overall disease mortality [9]. On the other hand, ER(+) breast tumors do not respond well to cytotoxic chemotherapies, while at the same time they are significantly less likely to achieve pathologic complete response (pCR), compared to ER (-) patients undergoing neoadjuvant chemotherapy [10].

PRs, just like ERs, are expressed with two major isoforms, PR-A and PR-B, having an important role in inhibiting ER signalling. Specifically, it is likely that PRs act as the driving force for breast cancer development, especially in postmenopausal women. ER seems to regulate PR expression and the presence of PR expression is considered indicative of a functional estrogen-ER axis [11]. In most of the cases PR expression is combined with that of ER and from a practical point of view, in those cases in which strong PR expression isn't followed with related ER expression, a repeat laboratory test is needed. The early presence of ER(+) breast carcinoma has significant prognostic significance, with tumors that are both PR(+) and ER(+) having a more favorable prognosis [12].

HER2 is a transmembrane receptor of tyrosine kinase that plays an important role in cell growth, development and proliferation through several different signaling pathways, which include the mTOR and RAS/RAF/MEK/ERK pathways. The presence of *HER2* gene amplification is found in 15%-30% of breast carcinomas and is a strong

prognostic biomarker for adverse disease progression [13].

It is of particular importance to emphasize that *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), small molecule inhibitors of the tyrosine kinase receptor (lapatinib), as well as antigen-coupling with trastuzumab (ado-trastuzumab emtansine - T-DM1). Nowadays, immunohistochemical testing for *HER2* protein overexpression has been developed and is widely used in clinical practice, and is performed in all cases of invasive breast carcinomas, whether primary or metastatic [14].

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. Systematic reviews and meta-analyses showed that Ki67 expression has a direct correlation with worse prognosis, shorter patient survival without the presence of active disease and worse overall patient survival [15,16].

Notably, despite the intensive scientific research of the last decades to find reliable tools that would achieve an accurate prediction of the outcome of the disease, only the steroid hormone receptors and *HER2* are widely used in clinical practice. This is mainly due to the lack of reliable and strong evidence-based studies, which are characterized by a small sample of patients, false positive results, low statistical power and increased publication bias rates; furthermore, many of these prognostic biomarkers are interrelated, resulting in studies with small patient samples having limited power to demonstrate the independence of the effect of the novel biomarkers after multivariate analyses [17].

Moreover, despite the improvements in early diagnosis and treatment, the survival rate for breast carcinoma is modest. Therefore, evaluation of prognostic biological markers remains an important goal.

The main purpose of the present study is to investigate the association of Bcl-2 with other molecular markers of significant prognostic and predictive value for disease, including the status of the hormonal receptors ER (estrogen) and PR (progesterone), along with *HER2* (human epidermal growth factor receptor) and finally, the levels of the cell proliferation marker Ki67 (MIB-1).

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 of 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. Tumour 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, ER, PR, *HER2*, Ki67 was studied with polymer peroxidase method by the Auto stainer link 48 DAKO analyzer. The antibodies used were:

1. Monoclonal Mouse Anti-Human Bcl-2 Oncoprotein Clone 124.
2. Monoclonal Rabbit Anti-Human Estrogen Receptor Clone EP1.
3. Monoclonal Mouse Anti-Human Progesterone Receptor Clone PgR 636.
4. NCL-L-CB11.
5. Monoclonal Mouse Anti-Human Ki-67 Antigen Clone MIB-1.

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 staining protocols followed for the four immunostains (ER, PR, *HER2* and Ki67) were in

accordance with standard staining protocols of Auto stainer link 48 DAKO analyzer for each antibody.

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 into the four staining categories: Bcl-2 negative expression (0%), score 1+ (>0% - <30%), score 2+ ($\geq 30\%$ - <90%) and score 3+ ($\geq 90\%$) [18].

Any lesion with $\geq 1\%$ cells showing distinctly visible staining nuclear for ER - PR receptors was considered positive [19], while the corresponding threshold for positivity for Ki67 was $\geq 5\%$ (intermediate 6% - 29% and high $\geq 30\%$) [20]. HER2 was considered positive when $\geq 10\%$ of neoplastic cells show whole-membrane intense immunostaining, a result recorded as 3+ score while weak to moderate complete membrane staining in >10% of tumor cells was scored 2+ (equivocal) and incomplete membrane staining that is faint/barely perceptible and in >10% of tumor cells was scored 1+ (negative). Finally, as negative (0) considered staining <10% tumor cells [21].

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 database 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) ER receptors status, 3) PR receptors status, 4) Ki67 expression, 5) HER2 status and, 6) correlation of *Bcl-2* oncogene with ER-PR receptors, HER2 and Ki67 biomarkers. The analysis of the results was performed by using Frequencies and Descriptive Statistics. To examine the association of *Bcl-2* oncogene with the status of the hormonal receptors ER (estrogen) and PR (progesterone), HER2 and the levels of the cell proliferation marker Ki67, the Fisher's exact and Chi square (χ^2) test of Cramer's V statistics tests were performed where appropriate.

3. RESULTS

The mean age of the patients was 62.36 years (range 34-90). The main clinicopathological characteristics of the examining tumors (size, grade and infiltrated lymph nodes) are described in Table 1. *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 2) (Figure 1).

Table 1. Clinicopathological characteristics.

Characteristic	N (number of cases)	%
Tumor size		
≤1cm	15	15.0
1,1-1,9 cm	40	40.0
2-2,9 cm	24	24.0
3-3,9 cm	14	14.0
≥4 cm	7	7.0
Tumor grade		
I	14	14.0
II	62	62.0
III	24	24.0
Infiltrated lymph nodes (number)		
0	61	61.0
1	18	18.0
2	9	9.0
3-12	12	12.0

Table 2. 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

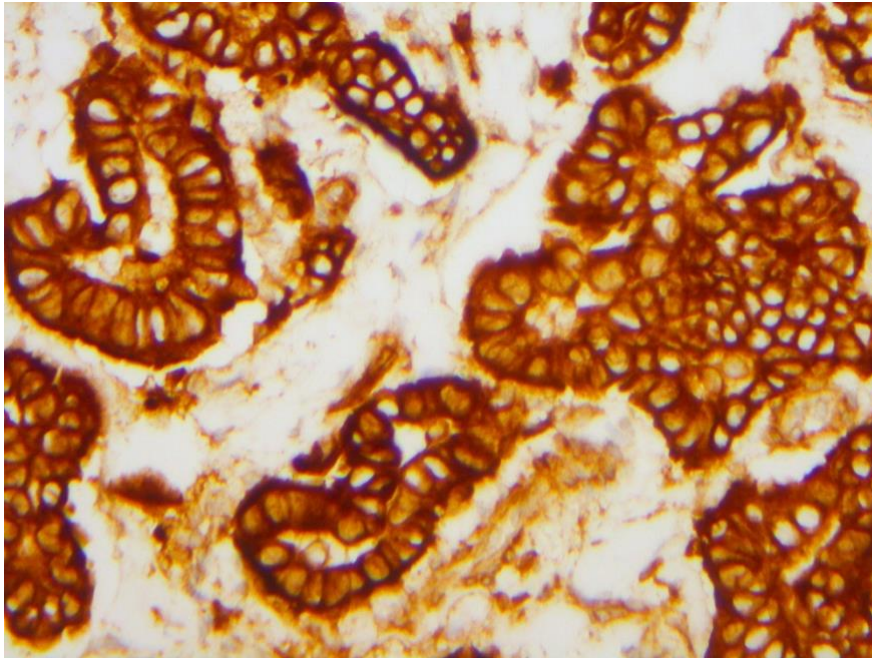


Figure 1. Invasive carcinoma no special type (NST). Well differentiated, grade I. Immunohistochemical (IHC) high expression (score 3+) Bcl-2 in 100% of neoplastic cells (40x).

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). Tu-

mor 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 3. ER receptors.

ER Staining category	N (number of cases)	%
Negative <1%	14	14.0
Positive ≥1%	86	86.0
Total	100	100.0

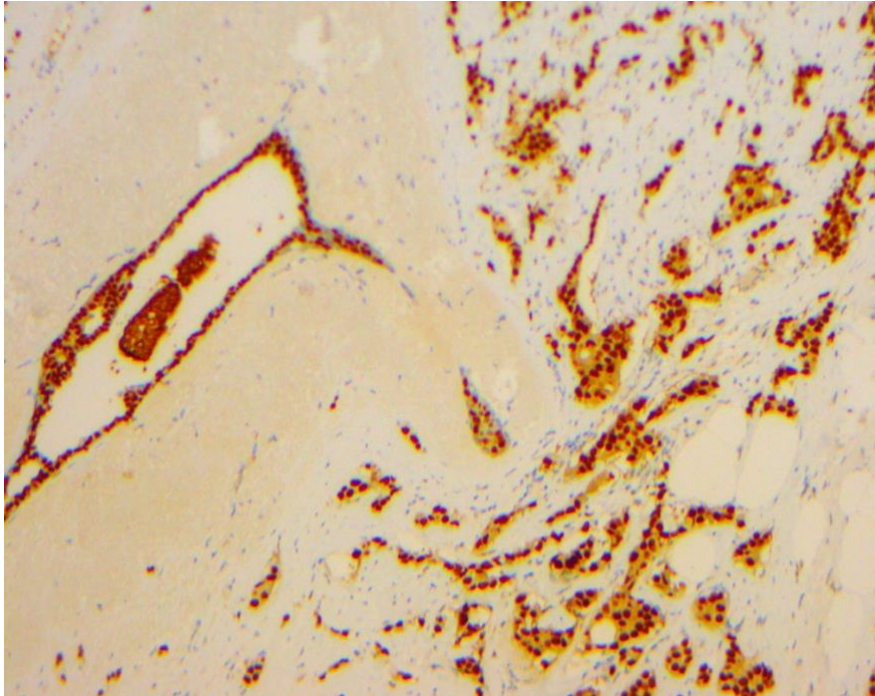


Figure 2. Ductal carcinoma in situ (DCIS). Well differentiated, grade I. Immunohistochemical (IHC) positive ER expression in $\approx 100\%$ of neoplastic cells (10x).

ER receptor expression was detected positive $\geq 1\%$ in 86% of cases and negative $< 1\%$ in the rest 14% (Table 3) (Figure 2). While PR receptor expression was detected positive $\geq 1\%$ in 79% and negative $< 1\%$ in 21% of cases (Table 4) (Figure 3). *HER2* oncogene was expressed 1+ in 46% of cases, 2+ in 26%, 0 in 24%, and 3+ in the rest 4% (Table 5) (Figure 4). The cell proliferation biomarker Ki67 was expressed 6-29% in 52% of cases, $\geq 30\%$ in 41% and $\leq 5\%$ in 7% (Table 6) (Figure 5). To examine the association of *Bcl-2* oncogene with the status of the hormonal receptors ER (estrogen) and PR (progesterone), *HER2* and the levels of the cell proliferation marker Ki67, the Fisher's exact and Chi square (χ^2) test or Cramer's V statistics tests were performed where

appropriate. *Bcl-2* oncogene is positively and highly associated with estrogen ER receptors as $\text{Phi}=0.760$, $p<0.0001$ (Table 7). This practically means that *Bcl-2* high staining values are usually observed in ER(+) tumors. A similar pattern was also found between *Bcl-2* oncogene with PR progesterone receptors ($\text{Phi}=0.626$, $p<0.0001$) (Table 8). Regarding the association of *Bcl-2* oncogene with *HER2*, a negative correlation was recorded ($\text{Phi}=-0.350$, $p<0.0001$) (Table 9). In terms of the association of *Bcl-2* oncogene with the levels of Ki67 cell proliferation marker, was not found statistically significant ($p=0.341$) (Table 10). Therefore, high *Bcl-2* expression was usually observed in tumors with lower (or negative) staining values of the above mentioned markers.

Table 4. PR receptors.

PR staining category	N (number of cases)	%
Negative $< 1\%$	21	21.0
Positive $\geq 1\%$	79	79.0
Total	100	100.00

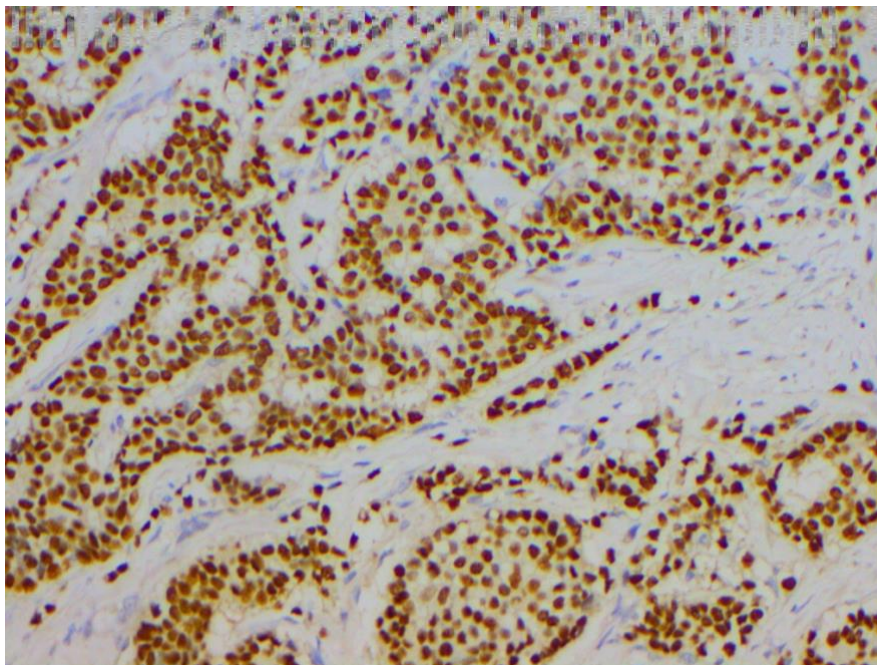


Figure 3. Invasive ductal carcinoma (NOS). Moderately differentiated, grade II. Immunohistochemical (IHC) positive PR expression in \approx 100% of neoplastic cells (20x).

Table 5. HER2 expression.

HER2 Staining category	N (number of cases)	%
0 (negative) ($<10\%$)	24	24.0
1+ (negative) (incomplete membrane staining in $>10\%$)	46	46.0
2+ (equivocal) (weak to moderate complete membrane staining in $>10\%$)	26	26.0
3+ (positive) (whole-membrane intense immunostaining in $\geq 10\%$)	4	4.0
Total	100	100.00

Table 6. Ki67 expression.

Ki67 Staining category	N (number of cases)	%
Negative $\leq 5\%$	7	7.0
Intermediate $6\% - 29\%$	52	52.0
High $\geq 30\%$	41	41.0
Total	100	100.00

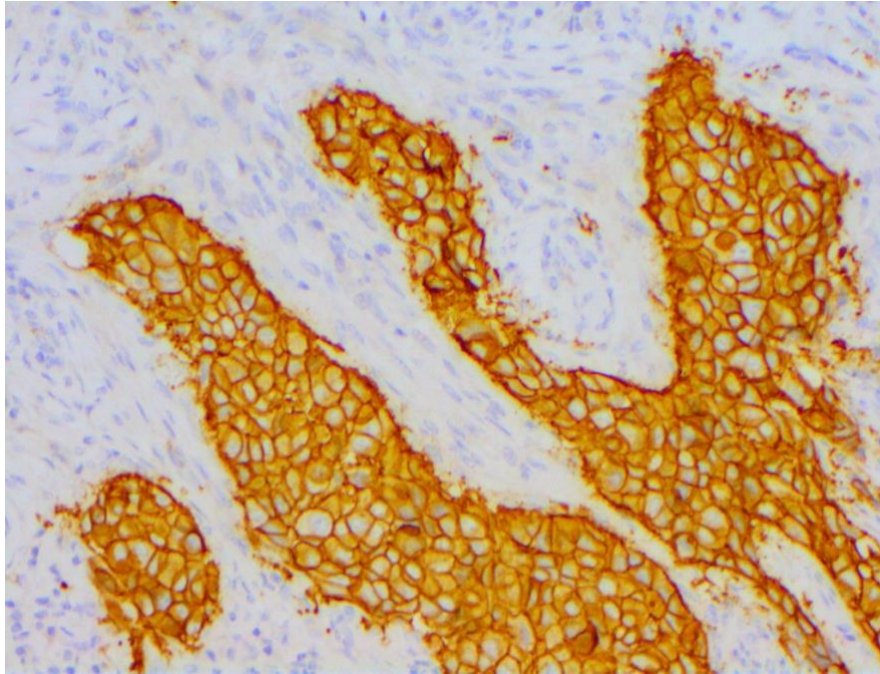


Figure 4. Invasive ductal carcinoma (IDC). Poorly differentiated, grade III. Immunohistochemical (IHC) HER2 expression score 3+ (20x).

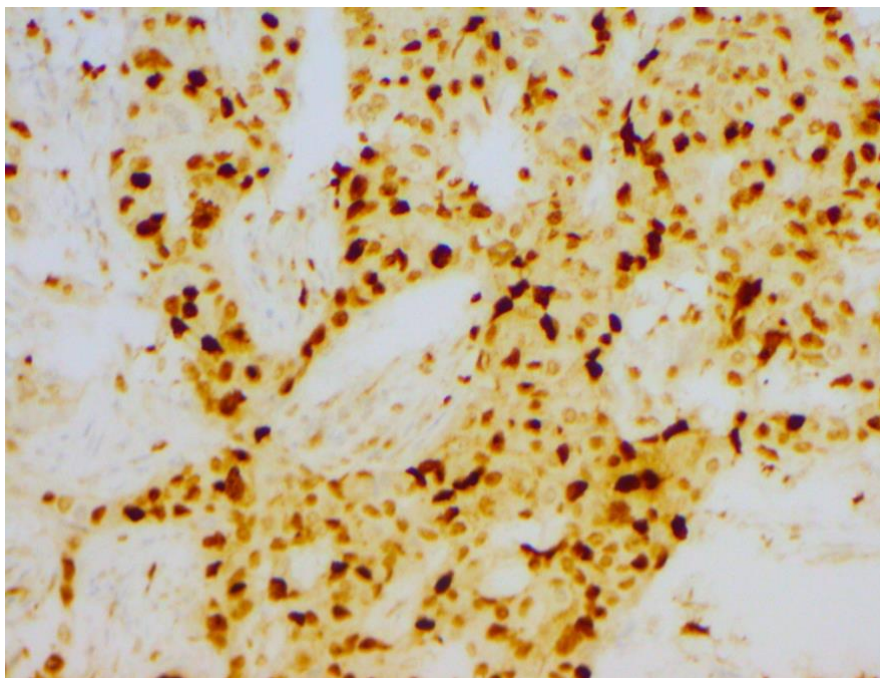


Figure 5. Invasive ductal carcinoma (IDC). Poorly differentiated, grade III. Immunohistochemical (IHC) positive Ki67 expression in \approx 80% of neoplastic cells (20x).

Table 7. Association of Bcl-2 with ER.

		BCL-2		Total
ER		Negative	Positive	
	Negative	13 68.4%	1 1.2%	14 14.0%
	Positive	6 31.6%	80 98.8%	86 86.0%
Total		19 100.0%	81 100.0%	100 100.0%
		Value		p-value
Phi		0.760		< 0.0001
Cramer's V		0.760		< 0.0001

Table 8. Association of Bcl-2 with PR.

		BCL-2		Total
PR		Negative	Positive	
	Negative	14 73.7%	7 8.6%	21 21.0%
	Positive	5 26.3%	74 91.4%	79 79.0%
Total		19 100.0%	81 100.0%	100 100.0%
		Value		p-value
Phi		0.626		< 0.0001
Cramer's V		0.626		< 0.0001

Table 9. Association of Bcl-2 with HER2.

		BCL-2		Total
HER2		Negative	Positive	
	Negative	7 36.8%	63 77.8%	70 70.0%
	Positive	12 63.2%	18 22.2%	30 30.0%
Total		19 100.0%	81 100.0%	100 100.0%
		Value		p-value
Phi		-0.350		< 0.0001
Cramer's V		0.350		< 0.0001

Table 10. Association of Bcl-2 with Ki67.

		BCL-2		Total
Ki67		Negative	Positive	
	Negative	0 0.0%	7 8.6%	7 7.0%
	Positive	19 100.0%	74 91.4%	93 93.0%
Total		19 100.0%	81 100.0%	100 100.0%
p-value				0.341

4. DISCUSSION

The Bcl-2 protein is a member of the Bcl family of proteins, which plays a key role in the cell apoptosis process. Its oncogenic (carcinogenic) potential was established relatively early in animal experimental models and was subsequently supported by the finding of overexpression in a variety of tumors and lymphomas, in which Bcl-2 has oncogene activity [22]. On the other hand, paradoxically, in several malignant solid organ neoplasms of the human body, including breast cancer, Bcl-2 appears to have a tumor-suppressive activity, with its expression being associated with favorable tumor prognostic features, such as for example low tumor grade, estrogen ER receptor positivity and ultimately more favorable patient outcome [23]. This finding was consistent in most published clinical studies, but its association with disease outcome was limited in univariate analysis in many of them [24].

The main finding of the present study regarding the association of Bcl-2 with estrogen ER receptors, was that *Bcl-2* oncogene was positively and highly associated with estrogen ER receptors ($\Phi=0.760$, $p<0.0001$). Moreover, a positive association was found between Bcl-2 and PR ($\Phi=0.626$, $p<0.0001$). Finally, inverse association of Bcl-2 with HER2, were noted.

The positive correlation of *Bcl-2* oncogene expression, with estrogen ER receptor expression - is consistent with current literature findings. In one of the first, relevant, published clinical studies, after analyzing the histopathologic findings of 293 node-negative resected breast cancer specimens showed a significantly higher number of Bcl-2 (+) cells in small, ER (+) slowly proliferating tumors, in comparison to ER (-), rapidly proliferating tumors [25].

Five years later, it was stated that the expression of Bcl-2, surprisingly, was correlated with a positive relation with the expression of ERs and with a favorable outcome after the endocrine treatment of those patients, having limited disease [26]. The following year, in a series of 114 patients of the European Organization for Research and Treatment of Cancer 10923 trial, showed that Bcl-2, HER2 and p53 had no statistically significant correlation with the clinical response of patients to treatment with doxorubicin and paclitaxel; in this particular series of patients, Bcl-2 expression was found positive in 49% of cases [27].

In an attempt to investigate whether a panel of biomarkers (HER2, Ki-67, p53 and Bcl-2) could independently and reliably predict pathologic response after preoperative chemotherapy in patients with surgical breast carcinoma a study of

248 patients found that such reliable prediction based on specific biomarkers tested before the beginning of treatment was not feasible [28]. Contrary to this were the results of a contemporary study, who investigated a large series of 1000 patients with high-risk breast carcinoma to ascertain the predictive value of Bcl-2 and p53 on response to post-operative radiotherapy. The results of the study showed that 1) Negative expression of Bcl-2 had a statistically significant association with increased overall mortality, occurrence of distant metastases and local disease recurrence, 2) A statistically significant improvement in survival was found in patients who had positive expression of Bcl-2 and finally, 3) No correlation was found regarding p53 [29].

In another study, investigating the prognostic value of a number of parameters and biomarkers in relation to the response to neoadjuvant chemotherapy in 50 patients with locally extensive breast carcinoma. These included the histopathological picture, tumor grade, expression of estrogen and progesterone receptors as well as HER2, Ki-67, p53, Bcl-2, and Bax. The results of the study showed that only apoptosis-related genes (*Bcl-2* and *Bax*) appeared to have some association with response to neoadjuvant chemotherapy [30]. A more recent study, after analyzing 1081 breast cancer cases with a long follow-up, from whom 634 did not receive any kind of adjuvant therapy and 447 with tamoxifen monotherapy, reported a strong correlation of the expression of *Bcl-2* oncogene with 1) Positive ER status, 2) Positive PR status, 3) Low grade, negative HER2 status and 4) Small tumor size [31].

The combination of ABT-199/venetoclax with tamoxifen, the standard endocrine therapy for estrogen receptor-positive breast cancers, 85% of which have Bcl-2 expression, represents a novel strategy to prime cancer cells for apoptosis and induce better responses to cancer cell death [32]. While a new opportunity for the treatment of diseases is the development of Bcl-2 protein inhibitors (BH3 mimetics). The FDA approved authentic BH3 mimetics for cancer therapy as they were proven to kill cancer cells and prevent recurrence or drug resistance [33].

In accordance with other above mentioned reports the detected in the current study correlation of Bcl-2 with the expression of genes that are associated with therapy prediction (ER(+)-mostly and PR(+)-to a lesser extend) could be considered indicative that Bcl-2 may also considered as a potential predictive marker. Moreover, the negative association of Bcl-2 with Ki-67 and HER2 could be suggestive of a connection with disease outcome and response to targeted therapy in patients with

breast cancer. The confirmation of these findings could be clinically useful, potentially leading to a more individualized approach in the prediction of the outcome and treatment response in breast cancer based on a specific panel of particular biomarkers (including those investigated here).

An apparent 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. 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) accompanied by a multivariate analysis of the examined biomarkers and other prediction factors influencing response to breast cancer therapy.

5. CONCLUSION

The results of the present study demonstrate a strong positive association between Bcl-2 and the expression of genes that are associated with hormonal therapy prediction (ER-PR) in breast cancer. Apparently, the verification of a potential prognostic or predictive role for Bcl-2 (and the other markers examined in this research) in ER (+) hormone responsive breast cancers (and –potentially– in other disease categories currently treated with the established therapies) requires further investigation in (appropriately designed) larger clinical studies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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