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Breast Cancer Prognosis: A Study on Mortality Indicators

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Rezumat

Factori de prognostic pentru mortalitatea prin cancerul mamar

Context: Prognosticul pacienților cu cancer de sân este un element esențial pentru adaptarea opțiunilor terapeutice. Deşi studiile observaționale anterioare au identificat diferiți markeri de prognostic, un consens în aplicarea lor clinică lipseşte. Acest studiu retrospectiv, unicentric şi-a propus să valideze cei mai frecventi factori de risc asociați cu o mortalitate crescută la pacienții cu cancer de sân.
Metode: Acest studiu a fost efectuat pe un interval de 8 ani (2014-2020) şi a inclus 213 de femei diagnosticate cu cancer mamar stadiul IIA-IIIB. Variabile cheie, precum vârsta, stadiul bolii şi tipul de tratament au fost analizate în raport cu supraviețuirea la un an.
Rezultate: Niveluri preoperatorii crescute ale markerilor tumorali ACE şi CA 15-3, tumorile de dimensiuni mari şi invazia avansată a ganglionilor limfatici au fost asociate semnificativ cu o mortalitate crescută. Imunohistochimia a indicat că prezența receptorilor de estrogen şi progesteron (ER şi PR) au fost factori de protecție, în timp ce receptorul 2 al factorului de creştere epidermică umană (HER2) a fost un indicator de prognostic negativ. Printre subtipurile moleculare, Luminal A a demonstrat efecte protectoare, în timp ce subtipurile HER2-pozitive şi triplu negative au fost identificate ca factori de risc.
Concluzie: Acest studiu confirmă rolul semnificativ al dimensiunii tumorii, al stadiului ganglionilor limfatici şi al markerilor moleculari specifici în prezicerea mortalității prin cancer de sân. Aceste constatări contribuie la înțelegerea nuanțată a prognosticului bolii şi oferă perspective cruciale pentru clinicieni în stabilirea planului de tratament.

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Cuvinte cheie: cancer mamar, prognostic, mortalitate, markeri tumorali, stadiul ganglionilor limfatici, imunohistochimie

Abstract

Background: The prognosis of breast cancer patients is critical for tailored treatment options. While previous observational studies have identified various prognostic markers, a consensus in their clinical application is lacking. This single-center retrospective study aimed to validate the most frequent risk factors associated with increased mortality in breast cancer patients.

Methods: Our study spanned an 8-year interval (2014-2020) and included 213 female patients with stage IIA-IIIB breast cancer. Key variables such as age, disease stage, and type of treatment were analyzed in relation to one-year survival as the primary outcome measure.

Results: Elevated preoperative levels of tumor markers ACE and CA 15-3, larger tumor size, and advanced lymph nodal invasion were significantly associated with increased mortality. Immunohistochemistry indicated that the presence of Estrogen and Progesterone Receptors (ER and PR) were protective factors, whereas Human Epidermal Growth Factor Receptor 2 (HER2) was a negative prognostic indicator. Among molecular subtypes, Luminal A demonstrated protective effects, whereas HER2-positive and Triple-negative subtypes were identified as risk factors.

Conclusion: This study confirms the significant role of tumor size, lymph node stage, and specific molecular markers in predicting breast cancer mortality. These findings contribute to a nuanced understanding of disease prognosis and offer crucial insights for clinicians in managing treatment plans.

Key words: breast cancer, prognosis, mortality, tumor markers, lymph node stage, immunohistochemistry

Introduction

Breast cancer is an extremely diverse illness with a wide range of prognoses. Giving breast cancer patients a clear prognosis is crucial in order to tell them properly about the course of the disease and place them in the appropriate therapy. Numerous observational studies have assessed the relationship between various patient characteristics and risk variables related to lifestyle and breast cancer risk and survival. The observational nature of these investigations makes it challenging to demonstrate causality, though (1), (2).

An extensive industry has developed around the study of several potential parameters, all of varying degrees of relevance, in the quest for therapeutically useful prognostic and predictive data. The usefulness of conventional histology in this field has been overshadowed by the present push towards high technology, despite the fact that the relationship between tumour form and degree of malignancy was first established more than a century ago. Unfortunately, the vast majority of prognostic data necessary for treatment classification is provided by meticulous histological evaluation of breast cancer tissues.

The majority of prognostic markers now in use are related to tumour features and the severity of the condition at the time of diagnosis.

Despite the data provided by the literature, there is an astounding variety of findings and

conclusions, and there is little consensus on which characteristics should be employed regularly in clinical practise. Lymph node stage has been the sole variable consistently utilised in practise to direct therapy, and this has also been true for patient classification in clinical studies.

We designed a study to evaluate the most frequent risk factors associated with increased mortality, repeated in the specialized literature, in order to observe the retrospective capacity of data replicability in a single-center.

Our hypothesis aimed to identify the negative prognostic factors associated with increased mortality. Furthermore, we briefly present only the parameters that demonstrated moderate or high statistical significance.

Methods and Materials

Based on the purpose and objectives of the research, the design and methodology have been defined, with its main characteristics being: retrospective - spanning over an 8-year interval - January 1, 2014 - December 31, 2020, single-center in Bucharest, descriptive and correlational, non-interventional.

The eligibility criteria were as follows:

- Diagnosis of breast cancer;
- Female sex;
- Stage IIA-IIIB (M0);
- Single tumor, excluding multifocal and bilateral cases;
- Age > 18 years.

In our research, we aimed to identify prognostic correlations that could assist in understanding the disease progression and treatment response. For this purpose, we used one-year survival from the time of diagnosis as our primary indicator. This is a widely accepted criterion in medical literature for evaluating the efficacy of a treatment or the severity of a disease. Analyzing one-year survival allowed us to establish connections between various variables such as age, disease stage, and type of treatment, and the long-term prognosis of patients.

Finally, for the study 213 patiens were eligible.

The research is carried out in compliance with all ethical norms regarding scientific research, in force both at the European Union and national level - Law 206/2004 on good conduct in scientific research, scientific development and innovation. At the same time, given the fact that research is conducted on human subjects, all the recommendations of the Declaration of Helsinki will be respected.

Results

Tumor Markers

Among the preoperative laboratory analyses, elevated values of the tumor markers ACE and CA 15-3 were correlated with increased mortality. The mean difference for the group of patients who passed away compared to those still alive was 1.25 ng/dl (p=0.003) for ACE and 9.54 (p=0.012) for CA 15-3 (*Table 1* and *Fig. 1*).

Table 1. Comparative statistical data regarding the value of tumor markers in relation to mortality

	Group	N	Mean	SD	SE	Coefficient of variation
AFP	0	171	128.299	57.111	4.367	0.445
	1	42	119.440	58.552	9.035	0.490
ACE	0	171	2.924	2.234	0.171	0.764
	1	42	4.179	3.033	0.468	0.726
CA 15 -3	0	171	42.663	22.129	1.692	0.519
	1	42	52.205	21.286	3.284	0.408
	t	df	p	Mean Difference	SE Difference	
AFP	0.896	211	0.371	8.858	9.884	
ACE	-3.023	211	0.003	-1.255	0.415	
CA 15 -3	-2.522	211	0.012	-9.542	3.783	

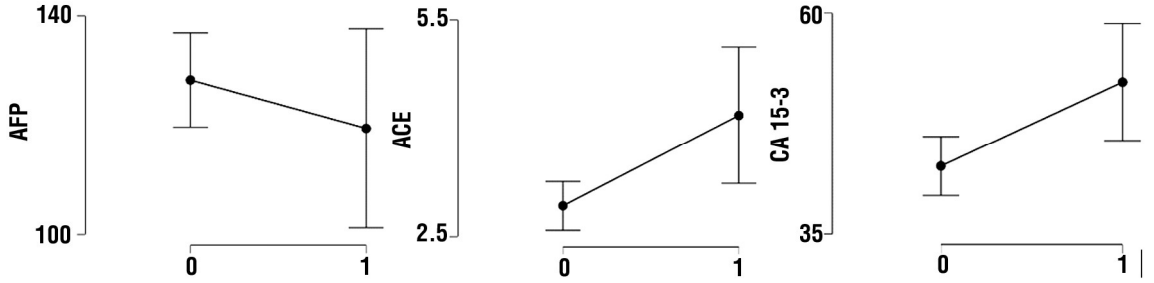

Figure 1. Comparative statistical data regarding the value of tumor markers in relation to mortality

Tumor Size

The size of the tumors was found to be higher in the case of patients who had passed away at the time of data collection – 22.63 ± 15.20 mm compared to 27.23 ± 16.35 mm, with a p-value of 0.085 (*Table 2* and *Fig. 2*).

Lymph Nodal Invasion

Lymph nodal invasion significantly influenced mortality, with the percentage being 7.86% for stage N0, while for stage N3, it was 59.25% - p < 0.001 (*Table 3*).

Immunohistochemistry

Among the elements considered in our study for immunohistochemical evaluation, the presence of ER and PR (Estrogen Receptor and Progesterone Receptor) were predictive factors (OR: 0.12, p < 0.001, and OR: 0.27, p < 0.001, respectively), while the presence of HER2 (Human Epidermal Growth Factor Receptor 2) represented a negative prognostic factor (OR: 2.37, p = 0.02) (*Tables 4-6*).

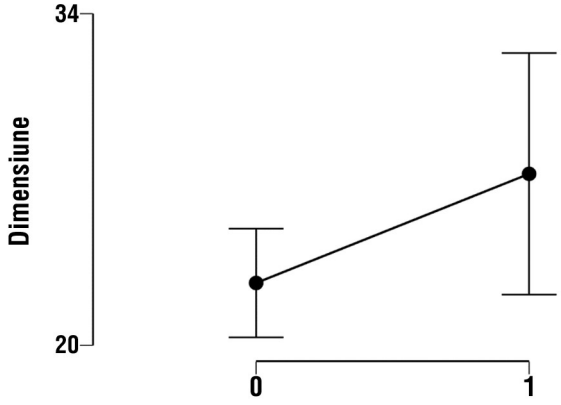

Figure 2. Comparative statistical data regarding the size of tumor formations in relation to mortality

Subtype

Among the 4 molecular subtypes in which cases were categorized according to histopathological results, Luminal A represented a protective factor (OR: 0.06, p < 0.01), while HER2-positive and Triple-negative subtypes were risk factors (OR: 3.20, p = 0.007, and OR: 12.07, p < 0.001, respectively), with Luminal B not showing statistical significance (p = 0.557) (*Tables 7-10*).

Table 2. Comparative statistical data regarding the size of tumors in relation to mortality

	Group	N	Mean	SD	SE	Coefficient of variation
Size	0	171	22.632	15.208	1.163	0.672
	1	42	27.238	16.357	2.524	0.601
	t		df	p	Mean Difference	SE Difference
Size	-1.733		211	0.085	-4.607	2.659

Table 3. The distribution of cases in relation to N stage and mortality

Stadiu N		DEATH 0	DEATH 1	Total
0	Count	82.000	7.000	89.000
	% within row	92.135%	7.865%	100.000%
	% within column	47.953%	16.667%	41.784%
1	Count	34.000	4.000	38.000
	% within row	89.474%	10.526%	100.000%
	% within column	19.883%	9.524%	17.840%
2	Count	44.000	15.000	59.000
	% within row	74.576%	25.424%	100.000%
	% within column	25.731%	35.714%	27.700%
3	Count	11.000	16.000	27.000
	% within row	40.741%	59.259%	100.000%
	% within column	6.433%	38.095%	12.676%
Total	Count	171.000	42.000	213.000
	% within row	80.282%	19.718%	100.000%
	% within column	100.000%	100.000%	100.000%

Chi-Squared Tests

	Value	df	p
χ^2	37.807	3	< .001
N	213		

Table 4. The distribution of cases in relation to the presence of estrogen receptors and mortality

ER+		DEATH 0	DEATH 1	Total
0	Count	66.000	35.000	101.000
	% within row	65.347%	34.653%	100.000%
	% within column	38.596%	83.333%	47.418%
1	Count	105.000	7.000	112.000
	% within row	93.750%	6.250%	100.000%
	% within column	61.404%	16.667%	52.582%
Total	Count	171.000	42.000	213.000
	% within row	80.282%	19.718%	100.000%
	% within column	100.000%	100.000%	100.000%

		95% Confidence Intervals		
	Odds Ratio	Lower	Upper	p
Odds ratio	0.126	0.053	0.299	
Fisher's exact test	0.127	0.045	0.312	< .001

Table 5. The distribution of cases in relation to the presence of estrogen receptors and mortality

PR+		DEATH 0	DEATH 1	Total
0	Count	86.000	33.000	119.000
	% within row	72.269%	27.731%	100.000%
	% within column	50.292%	78.571%	55.869%
1	Count	85.000	9.000	94.000
	% within row	90.426%	9.574%	100.000%
	% within column	49.708%	21.429%	44.131%
Total	Count	171.000	42.000	213.000
	% within row	80.282%	19.718%	100.000%
	% within column	100.000%	100.000%	100.000%

		95% Confidence Intervals		
	Odds Ratio	Lower	Upper	p
Odds ratio	0.276	0.125	0.611	
Fisher's exact test	0.278	0.110	0.638	< .001

Table 6. The distribution of cases in relation to the presence of estrogen receptors and mortality

		DEATH		
HER2+		**0**	**1**	**Total**
0	Count	130.000	24.000	154.000
	% within row	84.416%	15.584%	100.000%
	% within column	76.023%	57.143%	72.300%
1	Count	41.000	18.000	59.000
	% within row	69.492%	30.508%	100.000%
	% within column	23.977%	42.857%	27.700%
Total	Count	171.000	42.000	213.000
	% within row	80.282%	19.718%	100.000%
	% within column	100.000%	100.000%	100.000%

		95% Confidence Intervals		
	Odds Ratio	**Lower**	**Upper**	**p**
Odds ratio	2.378	1.175	4.812	
Fisher's exact test	2.367	1.095	5.074	0.020

Table 7. The distribution of cases in relation to the Luminal A subtype and mortality

		DEATH		
Luminal A		**0**	**1**	**Total**
0	Count	75.000	39.000	114.000
	% within row	65.789%	34.211%	100.000%
	% within column	43.860%	92.857%	53.521%
1	Count	96.000	3.000	99.000
	% within row	96.970%	3.030%	100.000%
	% within column	56.140%	7.143%	46.479%
Total	Count	171.000	42.000	213.000
	% within row	80.282%	19.718%	100.000%
	% within column	100.000%	100.000%	100.000%

		95% Confidence Intervals		
	Odds Ratio	**Lower**	**Upper**	**p**
Odds ratio	0.060	0.018	0.202	
Fisher's exact test	0.061	0.012	0.203	< .001

Table 8. The distribution of cases in relation to the Luminal B subtype and mortality

		DEATH		
Luminal B		**0**	**1**	**Total**
0	Count	125.000	33.000	158.000
	% within row	79.114%	20.886%	100.000%
	% within column	73.099%	78.571%	74.178%
1	Count	46.000	9.000	55.000
	% within row	83.636%	16.364%	100.000%
	% within column	26.901%	21.429%	25.822%
Total	Count	171.000	42.000	213.000
	% within row	80.282%	19.718%	100.000%
	% within column	100.000%	100.000%	100.000%

		95% Confidence Intervals		
	Odds Ratio	**Lower**	**Upper**	**p**
Odds ratio	0.741	0.329	1.667	
Fisher's exact test	0.742	0.290	1.741	0.558

Table 9. The distribution of cases in relation to the HER2 subtype and mortality

HER2		DEATH 0	DEATH 1	Total
0	Count	152.000	30.000	182.000
	% within row	83.516%	16.484%	100.000%
	% within column	88.889%	71.429%	85.446%
1	Count	19.000	12.000	31.000
	% within row	61.290%	38.710%	100.000%
	% within column	11.111%	28.571%	14.554%
Total	Count	171.000	42.000	213.000
	% within row	80.282%	19.718%	100.000%
	% within column	100.000%	100.000%	100.000%

		95% Confidence Intervals		
	Odds Ratio	Lower	Upper	p
Odds ratio	3.200	1.407	7.280	
Fisher's exact test	3.178	1.267	7.774	0.007

Table 10. The distribution of cases in relation to Triple negative subtype and mortality

Triple negative		DEATH 0	DEATH 1	Total
0	Count	161.000	24.000	185.000
	% within row	87.027%	12.973%	100.000%
	% within column	94.152%	57.143%	86.854%
1	Count	10.000	18.000	28.000
	% within row	35.714%	64.286%	100.000%
	% within column	5.848%	42.857%	13.146%
Total	Count	171.000	42.000	213.000
	% within row	80.282%	19.718%	100.000%
	% within column	100.000%	100.000%	100.000%

		95% Confidence Intervals		
	Odds Ratio	Lower	Upper	p
Odds ratio	12.075	4.988	29.229	
Fisher's exact test	11.853	4.578	32.503	< .001

Discussions

Due to its benefits of simple clinical availability, dynamic monitoring, non-invasiveness, and affordable testing, serum tumour marker has developed into a potent tool for patient follow-up. Preoperative CEA values have been shown to correlate with pathological stage, tumour size, and depend on stage. The level of CEA in the blood of breast cancer patients is strongly influenced by the size of the primary and metastatic tumours. In the identification of breast cancer, CA 15-3 and other, more specialised markers are taking the place of CEA. Studies claim that the CEA test is not a reliable diagnostic method for identifying breast cancer (3), (4). Correlating CEA, CA 15-3 and clinicopathological features we can accurately identify individuals with metastatic breast cancer (5). ESMO and ASCO recommendations do not advocate systematic monitoring of tumoral markers in the surgical follow-up stage of early breast cancer due to a lack of survival benefit, it is nevertheless commonly utilised in clinical practise (6), (7).

CA 15-3 is more useful in determining the prognosis of breast cancer and to monitor the efficacy of therapy as it was shown that the serum concentration and the proportion of patients with elevated values of this marker tend to increase with the severity (stage) of the disease and/or size of the tumor (8).

The present study only examined the preoperative elavated values of the tumor markers ACE and CA 15-3 which were correlated with increased mortality.

However, the expression of these tumor markers is also correlated with other individual factors like, age, metabolism disorders or chronic inflammatory states (9), which were not taken into consideration.

The properties of the cancer stem cells determine the growth and metastatic potential of the three parallel processes; an aggressive cancer is one that develops rapidly in the breast, has a propensity to invade one or more axillary nodes, and has a propensity to form distant metastases. There is a relationship between aggressiveness and growth characteristics of the underlying cancer.

Lymph node metastases are markers of the aggressive nature of breast cancer. The extent of the breast cancer and the lymph node metastases are both indicators of the presence of distant metastases now or in the future (10, (11,12).

The studies show a mean survival rate at 15 years of 47.1% (40.4–53.8) for the tumors between 21-50mm (10), (13), which corelates with our results that the size of the tumors was found to be higher in the case of patients who had passed away at the time of data collection – 27.23 ± 16.35 mm.

Lymph nodal invasion significantly influenced mortality, with the percentage being 7.86% for stage N0, while for stage N3, it was 59.25%, results, similar to other studies developed (14,15).

Since around 70–75% of invasive breast carcinomas have considerably increased ER expression, the oestrogen receptor (ER) is a crucial risk factor. In accordance with current guidelines, both initial invasive tumours and recurring lesions must have their ER expression measured. This process is necessary to identify the patients who will benefit the most from the use of endocrine treatment, namely selective oestrogen receptor modulators, pure oestrogen receptor downregulators, or third-generation aromatase inhibitors (16). Patients with high ER expression often have much better clinical outcomes, therefore even while the diagnosis of changed ER expression is extremely important for choosing the right medication, ER expression may also serve as a prognostic factor. Greater PR expression is favourably correlated with overall survival, time of recurrence, and poorer progression, whereas lower PR levels are often linked with a more aggressive disease, worse prognosis, and longer times to recurrence and progression . As a result, determining the PR expression has a significant impact on the treatment of patients with breast cancer. The predictive power of PR expression is still debatable (2, 17).

Human epidermal growth factor receptor 2 (HER2) overexpression is one of the earliest events during breast carcinogenesis, and it accounts for 15–25% of breast cancers. As a result, HER2 status is primarily relevant when choosing the best management for breast cancer patients. The detection rate of metastatic or recurring breast tumours is also increased by HER2 from 50% to even more than 80%. The overexpression is also correlated with a significantly shorter disease-free period (18,19).

Our study showed that the presence of ER and PR were predictive factors (OR: 0.12, $p<0.001$, and OR: 0.27, $p<0.001$, respectively), while the presence of HER2 represented a negative prognostic risk factor.

Triple negative tumours are an unique type. The pacients have palpable tumours more frequently and are also younger. They have a higher chance of having BRCA mutations. Even though TN tumours are bigger, lymph node metastases are less common in them, which should be taken into account if the present methods for staging and prognosis are enlarged (20)–(22). Patients with TN malignancies had worse overall survival rates and increased rates of local-regional recurrence, results obtained in our study as well.

In clinical practice, the findings related to breast cancer prognostic markers offer a roadmap for tailoring treatments to individual patients. Elevated levels of tumor markers ACE and CA 15-3 serve as indicators, allowing clinicians to categorize patients into a higher risk group. This stratification not only facilitates aggressive monitoring but also suggests the potential need for more intensive treatment regimens for those facing an increased risk of mortality.

The presence or absence of specific receptors further refines therapeutic choices. For patients with a positive status for Estrogen and Progesterone Receptors (ER and PR), hormone therapies such as tamoxifen or aromatase inhibitors might be effective. Conversely, a negative status for the Human Epidermal Growth Factor Receptor 2 (HER2) points towards the potential benefits of targeted therapies like trastuzumab.

Furthermore, understanding the molecular subtype of a patient's breast cancer is pivotal in guiding treatment decisions. For instance, the Luminal A subtype, known for its protective effects, might suggest that patients do not require as aggressive treatments. On the other hand, the identification of HER2-Positive and Triple-Negative subtypes as risk factors indicates the need for a more vigilant and targeted approach in patient management.

The retrospective manner of conducting the study, without the follow up of eventually developing metastatic cancer or the other treatment methods used in the therapy are some of the limits of this study.

Conclusion

There is a significant rise in breast cancer death rates worldwide during the past 25 years, which may be related to the disease's rising incidence and prevalence. Health policy officials in all nations should take note of this rising trend, especially in low- and middle-income areas where the time of diagnosis is delayed.

The assessment of tumor size, histological grade and lymph node stage is currently the most practical outcome measure available, documented by the literature and confirmed also in the present study, providing at the same time the prognosis for the management of people with breast cancer.

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