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Research Article

The Prognostic and Predictive role of DR70 immunoassay in Patients with Advanced (Metastatic) Breast Cancer

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Abstract

Objectives: DR-70 is a newly developed immunoassay that detects fibrin degradation products in blood. To the best of our knowledge, no previous study has investigated the prognostic and predictive value of DR-70 in patients with advanced breast cancer.

Methods: Seventy-four metastatic breast cancer patients and 35 healthy volunteers were enrolled prospectively. Blood samples were collected before and after the treatment, and PET-CT imaging was performed accordingly.

Results: The median age was 54 (range 27-89) years. N=47 (63.5%) were luminal breast cancer, n=20 (27%) were HER2 type, and n=7 (9.5%) were TNBC. The medianDR-70 levels of patients and healthy volunteers were significantly different 0.91(0.22-10) and 0.39(0.22-0.93) (p<0.001), respectively. There was no correlation between pre-treatment DR-70 and CEA, CA15-3 levels (p=0.68, p=0.43), respectively. The basal value of DR70 was not significant in predicting survival (p=0.29). A level of 55 % and above decrease in the DR70 values before and after treatment was found to be a good prognostic factor. There was A significant correlation between DR70 response and disease control (p<0.001).

Conclusion: DR70 response is a good predictive marker for response evaluation and a good marker for prognostication In patients with advanced breast cancer.

Keywords: DR70, metastatic breast cancer, prognosis, predictive value

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Breast cancer is the most common cancer in women worldwide and is the second leading cause of cancer-related death in developed countries, with an increasing incidence and mortality.[1] In the last two decades, there have been tremendous treatment changes in both non-metastatic and metastatic stages. Tumor markers are essential tools for oncologists to predict response and prognosis in disease management and improve patient outcomes. Therefore, the discovery of new markers for response evaluation has gained the utmost importance. Serum tumor markers are one of these tools used for response evaluation.

Quantitative measurements of CEA, CA15-3, and CA125 are well-known tumor markers being used in routine daily practice in disease monitoring.[2, 3] But there are still controversies and unmet needs for disease monitoring, prognostication, and diagnosis. Hence, developing new biomarkers that could be helpful in routine clinical practice is still of interest to researchers.

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Cancer is a clinical state consistent with the tendency to activate coagulation and fibrinolytic systems.[4] DR70 immunoassay is an FDA-approved test that measures both fibrin and fibrin degradation products. The prognostic, predictive, and diagnostic importance of DR70 immunoassay has been studied in multiple cancer types.[5-8] To the best of our knowledge, the significance of DR70 in diagnosis has been studied, but in the advanced stage, it has not been reviewed yet.[9]

Our study aimed to evaluate the predictive and prognostic value of DR-70 in metastatic breast cancer with unspecified molecular subtypes.

Methods

Patients and Data

Seventy-four metastatic female breast cancer patients and 35 healthy females were enrolled in the study. All of the patients enrolled were females with advanced breast cancer. A consent form was collected before the initiation of systemic therapy. Blood samples were picked before the initiation of systemic therapy. Patients' response evaluation was performed with FDG PET CT three months after the treatment. Second blood samples were also collected after systemic therapy. Serum CEA and CA15-3 levels were also studied before and after the treatment. Response evaluation was performed based on the PET Response Criteria in Solid Tumors (PERCIST). The study protocol was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (date of approval: 4 September 2015, protocol code: 09.2015.370).

A 5 ml of peripheral blood sample was obtained from each participant. After waiting at room temperature for 30 minutes, the blood was centrifuged at 1500 rpm for 10 minutes. All serum samples were stored at -80 C until the DR-70 level was analyzed. The serum concentration of DR-70 (µg/mL) was measured using AMDL DR-70 kits (AMDL, Inc., Tustin, CA, USA) according to the manufacturer's instructions. This enzyme-linked immunosorbent assay-based serological test was developed to quantify serum levels of FDPs.

We used PERCIST criteria to evaluate the response to the therapy. The patients were categorized into two groups as imaging responders and non-responders. Non-responders included patients whose disease progression was confirmed by imaging, while responders included patients with complete response, partial response, and stable disease.

Statistical Analysis

Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) version 25.0 (SPSS Inc., Chicago, IL, USA). Comparisons between categorical variables were made using Pearson's χ^2-square test or Fisher's exact test. The normality of the distribution of continuous variables was tested by the Kolmogorov-Smirnov test, the Kruskal-Wallis test, and the Mann-Whitney U test was used to make intergroup comparisons for parameters that did not indicate a normal distribution. The clinical significance and the optimal cut-off value of DR70 were determined using ROC curve analysis. The OS was defined using the Kaplan-Meier method and log-rank test. The influence of potential factors on OS was determined using univariate and multivariate Cox proportional hazards analyses. The relative risk of each factor was demonstrated using hazard ratios (HRs) and 95% corresponding confidence intervals (CIs). Significance in univariate analyses was regarded as $p<0.1$, whereas $p<0.05$ was considered to indicate a statistically significant difference for other results.

Results

Clinical Characteristics of the Study Population

Seventy-four patients with advanced breast cancer were enrolled between August 2017 and June 2018. The median age was 54 (range 27-89) years. 47 (63.5%) were luminal breast cancer, 20 (27%) were HER' type, and 7 (9.5%) were TNBC. All of the patients' response evaluation was performed with PET-CT. 34 (45.9%) of patients were enrolled just before first-line treatment, and the remaining 40 (54.1%) had previously received one or more lines of treatment. Second blood sampling for DR-70 was performed in 54 (73%) patients, and the remainder could not be evaluated due to loss of follow-up or death. The characteristics of the participants are presented in Table 1.

Table 1. Clinical Characteristics of Patients

Median Age	54 (27-89)
Tumor Molecular subtype	
Luminal	47 (63.5%)
Her2 type	20 (27%)
TNBC	7 (9.5%)
Treatment Line	
First Line	34 (45.9%)
≥Second Line	40 (54.1%)
Type of Treatment	
Chemotherapy	22 (48.6%)
Endocrine therapy	36 (29.7%)
Targeted therapy	16 (21.6%)
Blood sampling	
Before treatment	74 (100%)
After treatment	54 (73%)

The Relationship Between Clinicopathologic Characteristics and DR70

The medianDR-70 levels of patients and healthy volunteers were sinificantly different 0.91(0.22-10) and 0.39(0.22-0.93) (p<0.001), respectively. The median DR70 levels in patients before treatment receiving first-line systemic therapy were significantly lower than the patients receiving second or further lines of therapy (1.54 (0.25-6.30) vs. 0.63 (0.22-10) p=0.036). There were no significant differences between the mean DR-70 levels in terms of age above and below 50 (p=0.059)and the molecular breast cancer subtype (p=0.658) (Table 2).

The Correlation Between Pre-treatment CEA, CA15-3, and DR-70 Values

There was no correlation between pre-treatment DR-70 and CEA, CA15-3 levels (p=0.68, p=0.43 respectively); on the other hand, there was a weak positive correlation was present between CEA and CA 15-3 levels (p=0.001, r=0.405).

The Prognostic Role Of DR70

To evaluate the prognostic significance of DR70, a median cut-off value of 0.9 was found in 74 patients with metastatic breast cancer. When these patients were categorized as below 0.9 and above, the basal value of DR70 was not significant in predicting survival (p=0.29) (Fig. 1). Also, when cox regression analysis was performed, no significant difference was found ((P=0.327) HR 1,11 (95% CI, 0.89-1.37) (Fig. 1).

In the study, post-treatment blood samples could be obtained from 54 of the 74 patients whose initial blood was drawn. DR70 reduction levels were measured in 54 patients whose DR70 levels were evaluated before and after treatment.

When a Roc-curve analysis was performed, a 55% or more reduction in DR70 in 54 metastatic breast cancer patients was considered a good prognostic factor when calculated as the cut-off value (Table 3, Fig. 2).

Table 2. Clinicopathologic Characteristics and DR70

	Median (min-max)	p
<50 age (n=30)	0.61 (0.22-6.00)	0.059*
>50 age (n=44)	1.34 (0.25-10.00)	
Lum (n=47)	1.06 (0.22-6.35)	0.658**
Her2 (n=20)	0.91 (0.25-10.00)	
TNBC (n=7)	0.62 (0.22-2.83)	
1 line (n=34)	1.54 (0.25-6.30)	0.036*
>1 line (n=40)	0.63 (0.22-10)	
Patients (n=74)	0.91 (0.22-10)	<0.001*
Control (n=35)	0.39 (0.22-0.93)	

*Mann-Whitney U-Test; **Kruskal Wallis Test.

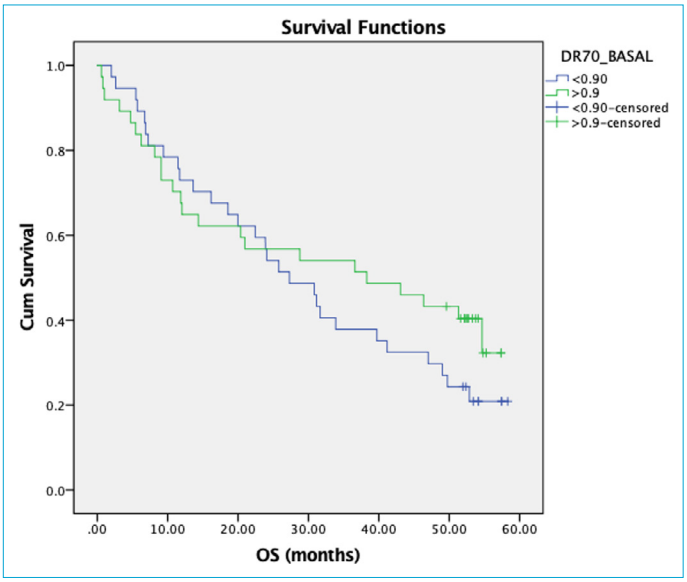

Figure 1. Kaplan-Meier curves showing overall survival stratified by DR70 median values.

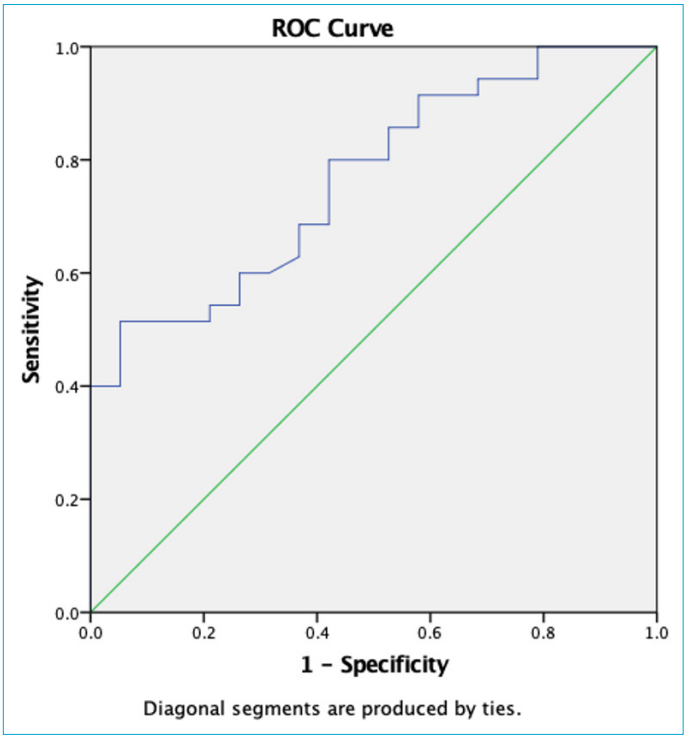

Figure 2. DR70 ROC Curve analysis by decline rate.

The depth of decrease in DR70 level is a good prognostic factor for the disease. A decrease in the DR70 level of 55 % and above is a good prognostic factor (Fig. 3).

The Predictive Role of Dr70 in Response Evaluati (Disease Monitoring)

Initial and end-of-treatment DR70 levels of 54 patients were evaluated. Disease control was achieved in 38 pa-

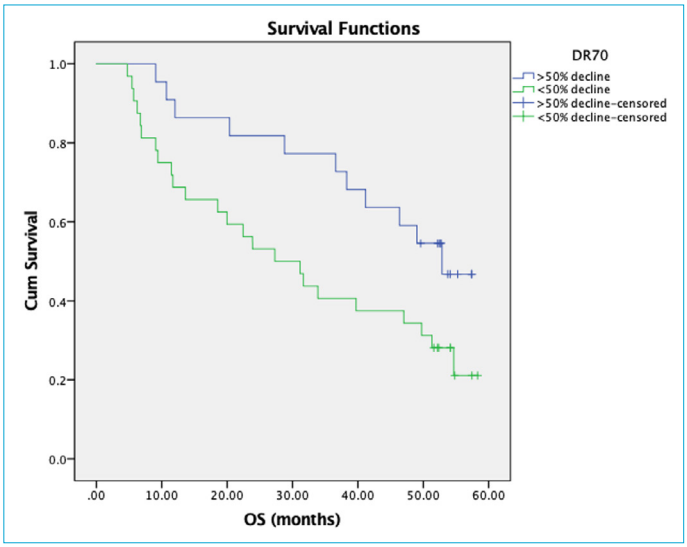

Figure 3. Kaplan-Meier curves showing overall survival stratified by DR70 decline rate.

tients, and disease progression was detected in 16 patients. DR70 response was detected in 35 of 38 patients with disease control. An increase in DR70 levels was detected in all 16 patients whose disease progressed (p<0.001) (Table 4).

The role of Baseline DR70 in Detecting Metastatic Disease

When basal DR70 levels of 74 metastatic and 35 non-metastatic patients were examined, it was found that the DR70 level of metastatic patients was significantly higher (Mann-u: p<0.001). However, not all of these patients were newly diagnosed patients. When we looked at the diagnostic meaning of DR70 by only taking the newly diagnosed ones, a value of 0.51 with a sensitivity of 79.4% and a specificity of 85.7% was obtained. (AUC:0.873 CI: 0.781-0.964) Figure 4.

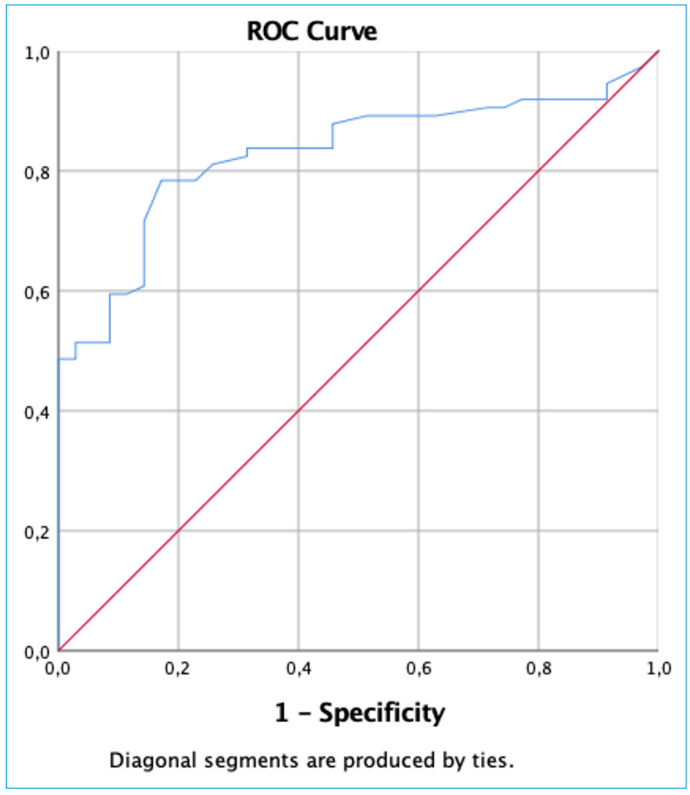

Figure 4. DR70 ROC Curve analysis by basal DR70 in determining metastatic disease.

Discussion

Breast cancer is the most common malignancy and the leading cause of cancer-related mortality in women worldwide. [10] And most of these patients are dying as a consequence of disease progression. There are many new treatment options in the management of advanced breast cancer. Clinical radiological and supportive tumor markers are used to evaluate the patient's response after treatment initiation. At this point, serum tumor markers are an essential guide because they are cheaper and easier to apply. However, tumor mark-

Table 3. Sensitivity and specifity of DR70 decline rate

DEATH	AUC	%95 CI	Cut-Off	Sensitivity	Specificity	p
DR70 decline rate	0.76	0.64-0.89	0.55	0.65	0.64	0.01

Table 4. The correlation between DR70 and imaging response after treatment

	Controlled Disease (CR-PR-SD)	Progressive Disease (PD)	Total	p
DR70 decrease	35	0	35	<0.001*
DR70 increase	3	16	19	
Total	38	16	54	

*Chi-Square test.

ers are not sensitive in every patient, and their sensitivity and specificity vary. Therefore, there is still a need for easily applicable, practical, and effective tumor markers.

Cancer is known to be directly related to the activation of coagulation and the fibrinolytic system.[11] several studies have indicated that FDP levels are elevated in patients with cancer.[12] The DR-70 immunoassay measures both Fibrin and Fibrinogen Degradation Products in human serum samples.[13]

Andre et al. evaluated the DR70 level for monitoring in metastatic colon cancer patients in their study in 2014. As a result, it has been shown that dr7 may be significant for disease monitoring in patients with low CEA levels.[14]

The level of DR70 immunoassay at the time of diagnosis was found to be higher, especially in gastrointestinal cancers, compared to the healthy population. But, DR70 studies in breast cancer are limited. In terms of breast cancer screening programs, its use for diagnostic purposes is low. For example, in the cross-sectional screening in 2004, in which 4169 people were included, the mean DR70 level was 0.83±0.65 µg/ml (range: 0.00 (0.0001)~7.42 µg/ml) in healthy subjects, while it was 2.70±2.33 µg/ml (range: 0.12~9.30 µg/ml) in the population diagnosed with cancer (n=42).[15] This discordance may be related to the high basal fibrin level among different cancer types. For this reason, it can be thought that the role of the DR70 test in disease monitoring rather than diagnosis may be more valuable. Likewise, in our study, when the treatment response rate and the change in DR70 levels in patients with metastatic breast cancer were examined, it was observed that it was significant in disease monitoring.

In the study by Akin et al., DR70 response was well correlated with treatment response in patients with gastroesophageal cancer. A low DR70 baseline level was found to be associated with more prolonged overall survival. And 25% or more reduction in DR70 level was associated with better overall and progression-free survival.[8] In our study, when the median DR70 value of 0.9 was taken as the cutoff in patients with metastatic breast cancer, no overall survival difference was found between the groups above and below 0.9. However, overall survival was significantly prolonged in those with a 50% or more Dr70 decline.

To conclude, this is the first study evaluating the prognostic and predictive value of DR70 immunoassay in metastatic breast cancer patients. This study demonstrated that DR70 is correlated well with treatment response evaluation and prognosis.

Disclosures

Ethics Committee Approval: Marmara University Faculty of Medicine Clinical Research Ethics Committee (Date of approval: 4 September 2015, protocol code: 09.2015.370).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – N.A.B., S.K.; Design – S.K.; Supervision – P.F.Y., F.D.; Materials – S.K., T.A.T., O.A.; Data collection &/or processing – S.K., T.A.T., O.A., B.A., I.N.O.; Analysis and/or interpretation – I.N.O., S.K.; Literature search – I.N.O., S.K.; Writing I.N.O., S.K.; Critical review – F.D.

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