The Prognostic Value of High Pretreatment Plasma D-Dimer Levels in Non-Metastatic Breast Cancer Patients with Absence of Venous Thromboembolism

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ABSTRACT

Systemic activation of coagulation and fibrinolysis is frequently observed in cancer patients without thrombosis. Recent studies have showed the association between D-Dimer (DD) and metastatic spread and prognosis of cancer. We aimed to investigate the prognostic value of DD in patients with non metestatic breast cancer (nMBC) and evaluated the DD levels and other variables for overall survival (OS) using univariate and multivariate analyses in 448 patients. The median follow-up time was 50 months (3-151 months). There was only significant relationship between DD and distant metastases (p= 0.052). Performance status (PS) (p< 0.001 and < 0.001), stage (p< 0.001 and < 0.001) , CEA (p< 0.001 and < 0.001), CA 15-3 (p< 0.001 and < 0.001) and DD (p< 0.001 and 0.034) were determined as prognostic factors for OS in univariate analysis. In multivariate analysis, PS (ECOG 0 vs ECOG 1, p= 0.022; ECOG 0 vs ECOG ≥2, (p< 0.001), stage (stage I vs stage II, p= 0.566; stage I vs stage III, p= 0.033), the CA 15-3 (p= 0.048) and DD levels (p= 0.015) were determined as independent prognostic factors for OS . In conclusion, pretreatment high DD level is an important prognostic factor in patients with non metastatic breast cancer and high DD levels were associated with poor outcome.

Keywords: D-Dimer, Non-metastatic breast cancer, Prognosis

ÖZET

Tedavi Öncesi Yüksek D-Dimer Düzeylerinin Venöz Tromboembolisi Olmayan Non-Metastatik Meme Kanserli Hastalardaki Prognostik Önemi

Koagülasyon ve fibrinolizin sistemik aktivasyonu sıklıkla tromboz olmayan kanser hastalarında gözlenir. Son yıllarda yapılan çalışmalar, D-Dimer (DD) ve metastatik yayılım ve kanser prognoz arasındaki ilişkiyi göstermiştir. Biz non-metastatik meme kanseri (nMBC) olan hastalarda DD prognostik değerini araştırmayı amaçladık. D-Dimer düzeyleri, genel sağkalımı (OS) etkileyebilecek diğer değişkenler, 448 hastada tek değişkenli ve çok değişkenli kullanarak değerlendirildi. Ortalama takip süresi 58.46 ± 1.8 ay idi. Sadece DD ile uzak metastaz (p= 0.052) arasındaki anlamlı bir ilişki saptandı. Performans durumu (PS) (p< 0.001 ve <0.001), evre (p< 0.001 ve < 0.001), CEA (p< 0.001 ve < 0.001), Ca 15,3 (p< 0.001 ve < 0.001) ve DD (p< 0.001 ve 0.034) tek değişkenli analizde OS için prognostik faktörler olarak belirlendi. Çok değişkenli analizde, PS (ECOG 0 vs ECOG 1, p= 0.022; ECOG 0 vs ECOG ≥ 2 ve yüksek (p< 0.001), evre (Evre I vs evre II, s vs = 0.566; evre I vs evre III, p= 0.033), Ca15,3 (p= 0.048) ve DD düzeyleri (p = 0.015) Os için bağımsız risk faktörleri olarak belirlendi. Sonuç olarak, tedavi öncesi yüksek DD düzeyleri nMBC olan hastarada önemli bir prognostik faktördür ve kötü prognoz ile ilişkilidir.

Anahtar Kelimeler: D-Dimer, Non-Metastatik meme kanseri, Prognoz

INTRODUCTION

Breast cancer is the most common female cancer and represents a heterogeneous group of tumors which present with varied behaviors and altered response to therapy. Biological markers, hormonal status, tumor size, histological grade and subgroups status, lymph node involvement have prognostic and/or predictive value and they are important factors in selecting appropriate treatments.[1]

Although clinical and experimental trials have demonstrated the relationship between cancer and hemostasis, the exact mechanism is not fully understood.[2] Thus, systemic activation of coagulation and hemostatic system in cancer patients without thromboembolism have been under investigation.[2-4]

D-dimer, a fibrin degradation product, plays an important role in activation of coagulation, angiogenesis, progression and invasion of tumor.[5,6]

Cancer patients and even healthy adults with elevated D-dimer levels have higher mortality compared to general population.[3,7] In addition, prognostic value of elevated D-dimer levels in lung cancer and colorectal cancer have been reported.[8,9] And also it was shown that D-dimer had similar prognostic activity similar to the clinically widely used classic tumor markers. Thus, it could be accepted as a potential prognostic marker.[10,11]

The aim of this study was investigation of prognostic value of D-dimer in non-metastatic breast cancer patients without thromboembolism.

MATERIALS AND METHODS

Four hundred forty eight consecutive patients with histologically confirmed breast cancer and radiologically confirmed non-metastatic breast cancer admitted to Oncology Unit of Cumhuriyet University Faculty of Medicine between January 2006 and June 2013 were included in this study. All patients were over 18 years-old.

Patients with coagulation disturbances, symptomatic for thromboembolic diseases, suffering from malnutrion or who had chronic disease such as chronic kidney disease were excluded. This study was approved by the local ethical committee of Cumhuriyet University.

History and physical examination of the patients were evaluated carefully. Eastern Cooperative Oncology Group performance status (ECOG PS) score, a complete blood cell count and chemistry analysis were recorded at the time of diagnosis. The stage was evaluated according to the 2010 TNM classification developed by the International Union against Cancer and the American Joint Committee on Cancer.

Demographic, clinical and pathological features of the patients were retrieved from the hospital records. The survival data of the patients were obtained from hospital records and the survival data of non-followed patients were obtained by calling them. Menopausal status, grade, hormone receptor status, perineural and lymphovascular invasion, stage, and nodal status of the patients were recorded to the study data base.

Disease-free survival (DFS) is defined as the period from date of diagnosis until date of first recurrence of locoregional or systemic. And overall survival (OS) was defined as the time between the date of diagnosis and last contact or death.

The first line treatments received by the patients after breast cancer diagnosis were as follows: surgical treatment was not preferred in 4 (1%) patients, 275 (61%) patients underwent modified radical mastectomy, and 169 (38%) patients underwent breast conserving surgery. Axillary treatment was not preferred in 12 (3%) patients, 374 (83%) underwent axillary dissection, and 62 (14%) patients had sentinel lymph node sampling. Neoadjuvant chemotherapy was administered to 20 (5%) patients and 391 (87%) patients received adjuvant chemotherapy. Radiotherapy and hormonal therapy was administered to 339 (76%) and 337 (75%) patients, respectively.

For statistical analysis, Statistical Package for Social Sciences (SPSS) for Windows 14.0 program was used. For descriptive statistics mean, standard deviation, frequency, and median were used. Categorical data were compared statistically using chi-square or Fisher's exact tests. The survival rates were calculated using the Kaplan-Meier analysis. Kaplan-Meier curves comparing DFS and OS between patient characteristics were constructed and log-rank testing was used to compare these censored outcomes. Associations between patient characteristics concerning median OS and median PFS were assessed using the log-rank test in univariable analysis. Variables were found to be

Table 1. Demographic and histopathologic features

Demographic features	No. of patients (%)
Gender	
Male	3 (1)
Female	445 (99)
Menopause status	
Premenopause	201 (45)
Postmenopause	244 (55)
Comorbidity	197 (44)
Localization	
Unilateral	438 (98)
Bilateral	10 (2)
ECOG performance status	
ECOG0	300 (67)
ECOG1	127 (28)
ECOG ≥2	21 (5)
Stage	
Stage I	87 (20)
Stage II	198 (44)
Stage III	163 (36)
Histopathologic features	No. of patients (%)
Histopathology	
IDC	343 (77)
ILC	19 (4)
Mikst	37 (8)
Other	49(11)
Grade	
Grade 1	105 (26)
Grade 2	188 (47)
Grade 3	110 (27)
Lymphovascular invasion	
Negative	157 (48)
Positive	172 (52)
Perineural invasion	
Negative	200 (66)
Positive	101 (34)
Estrogen receptor	
Negative	124 (28)
Positive	316 (72)
Progesteron receptor	
Negative	148 (34)
Positive	289 (66)
HER2	
Negative	237 (57)
Positive	181 (43)

significant if 2-sided P value was <.05 on univariate testing. We also employed the Cox proportional hazards model for multivariable analysis. Multivariate analysis (Cox regression analysis) was used for the evaluation of independent risk factors that had an effect on survival. The p values of ≤ 0.05 were accepted as statistically significant.

RESULTS

In this study, the data of 448 breast cancer patients were analyzed. The patients were 445 (99%) women and 3 (1%) men. The median age of patients at the time of the cancer diagnosis was 51 years (range, 18-89). Patients' demographic and histopathologic characteristics are summarized in Table 1.

The relationship between D-dimer and tumor markers, clinical stage, lymph node status, hormone status, HER2, distant metastasis and locoregional relapse were shown in Table 2. According to the table 2, there was no significant relationship between D-dimer and tumor markers, clinical stage, lymph node status, hormone status, HER2, locoregional relapse and developing distant metastasis. The median follow-up time was 50 months (3-151 months). Univariate analyses showed performance status (p< 0.001 and < 0.001), stage (p< 0.001 and < 0.001), CEA levels (p< 0.001 and < 0.001), CA 15-3 levels (p< 0.001 and < 0.001) and D-Dimer levels (p< 0.001 and 0.034) were determined as prognostic factors for overall survival and Disease-free survival in univariate analysis. The prognostic factors that affected the OS and DFS of patients in univariate survival analysis are shown Table 3.

In univariate cox regression analysis, it was found that performance status (ECOG 0 vs ECOG 1, p= 0.001; ECOG 0 vs ECOG ≥ 2, p< 0.001), progressing stage (III) (stage I vs stage II, p= 0.80; stage I vs stage III, p= 0.012), CEA (≤5 ng/mL vs >5 ng/mL, p= 0.001), the CA 15-3 levels (≤ 31,3 U/mL vs > 31.3 U/mL, p= 0.001) and D-Dimer levels (≤ 232 ng/mL vs > 232 ng/mL p= 0.002) were determined as prognostic factors affecting the survival time of the patients with breast cancer for OS. Performance status (ECOG 0 vs ECOG 1, p < 0.001; ECOG 0 vs ECOG ≥ 2, p < 0.001), progressing stage (III) (stage I vs stage II, p= 0.873; stage I vs stage III, p= 0.008), CEA (≤5 ng/mL vs >5 ng/mL, p< 0.001), CA 15-3 (≤ 31.3 U/mL vs > 31.3

Table 2. Tumor markers, clinical stage, lymph node status, hormone status, HER2, developing distance metastasis, and locoregional relaps relations between D-dimer

	D-dimer ≤ 232 ng/mL No. of patients (%)	D-dimer >232 ng/mL No. of patients (%)	p value
Developing distance metastasis			
No	252 (70)	108 (30)	*0.052
Yes	53 (60)	35 (40)	
Locoregional relaps			
No	291 (69)	133 (31)	0.202
Yes	14 (58)	10 (42)	
Stage			
Stage I	48 (64)	27 (36)	0.711
Stage II	135 (68)	63 (32)	
Stage III	113 (69)	50 (31)	
Lymph node			
Negative	125 (67)	61 (33)	0.438
Positive	175 (68)	89 (32)	
CEA[1]			
≤5 ng/mL	282 (69)	126 (31)	0.277
>5 ng/mL	20 (63)	12 (37)	
CA 15-3[2]			
≤31,3 U/mL	271 (68)	124 (31)	0.414
>31,3 U/mL	31 (60)	16 (34)	
Estrogen receptor			
Negative	80 (65)	44 (35)	0.178
Positive	220 (70)	96 (30)	
Progesteron receptor			
Negative	96 (65)	52 (35)	0.188
Positive	201 (70)	88 (30)	
HER2			
Negative	161 (68)	76 (32)	0.541
Positive	123 (68)	58 (32)	

[1] CEA: Carsinoembryonic antigen; [2] CA 15-3: Cancer antigen 15,3

U/mL, p< 0.001), and D-Dimer levels (≤232 ng/mL vs >232 ng/mL p= 0.002) were determined as as prognostic factors affecting the survival time of the patients with breast cancer for DFS. Results of multivariate analysis were given in Table 4.

In multivariate analysis, performance status (ECOG 0 vs ECOG 1, p= 0.022; ECOG 0 vs ECOG ≥ 2, p< 0.001), stage (stage I vs stage II, p = 0.566; stage I vs stage III, p= 0.033), the CA 15-3 levels (p= 0.048) and D-Dimer levels (p= 0.015) were determined as independent prognostic factors for overall survival. Performance status (ECOG 0 vs ECOG 1, p< 0.001; ECOG 0 vs ECOG ≥ 2, p< 0.001), stage (stage I vs stage II, p= 0.898; stage I vs stage III, p= 0.008), CEA, CA 15-3 (p=0.003), and D-Dimer levels (p= 0.080) were determined as independent prognostic factors for DFS. Results of multivariate analysis were given in Table 5.

Table 3. The prognostic factors that affected patients survival in univariate analysis

	No. of patients	5 years OS[1] (%)	p value	5 years DFS[2] (%)	p value
Menopause status					
Premenopause	201	87	0.762	76	0.123
Postmenopause	244	87		80	
ECOG PS[3]					
ECOG 0	300	92	<0.001	85	<0.001
ECOG 1	127	83		69	
ECOG ≥2	21	43		34	
Grade					
Grade 1	105	88	0.823	83	0.186
Grade 2	188	86		74	
Grade 3	110	83		77	
LVI[4]					
No	157	86	0.268	81	0.109
Yes	172	81		71	
PNI[5]					
No	200	81	0.328	76	0.691
Yes	101	84		74	
Stage					
Stage I	75	93	<0.001	87	<0.001
Stage II	198	92		88	
Stage III	163	77		61	
CEA[6]					
≤5 ng/mL	408	89	<0.001	82	<0.001
>5 ng/mL	32	74		41	
CA 15-3[7]					
≤31,3 U/mL	395	90	<0.001	82	<0.001
>31,3 U/mL	47	72		51	
D-Dimer					
≤232 ng/mL	305	90	<0.001	81	0.034
>232 ng/mL	143	81		71	

[1] OS: Overall survival; [2] DFS: Disease-free survival; [3] ECOG PS: Eastern Cooperative Oncology Group performance status
[4] LVI: Lymphovascular invasion; [5] PNI: Perineural invasion; [6] CEA: Carsinoembryonic antigen; [7] CA 15-3: Cancer antigen 15,3

DISCUSSION

D-dimer increases in various disorders including VTE, cardiovascular disease and cancer. In addition, elevated D-dimer levels were shown in healthy adult population. In one study, performed by Di Castelnuovo et al., it was shown that elevated D-Dimer level was an independent risk factor for any cause of death.[7,12]

Systemic activation of coagulation and hemostasis plays central role in angiogenesis, invasion, tumor progression and metastatic spread. Although pathophysiology of this activation is not completely understood, studies have been reported that observed it in cancer patients without thromboembolism. Also, it has been shown that elevated D-dimer level had an important prognostic role on prognosis.[13-15]

Table 4. Prognostic factors affecting the survival time of the patients with breast cancer in univariate cox regression analysis

	Overall survival		
	Hazard ratio	**%95 confidence interval**	**p value**
ECOG PS[1]			
ECOG 0 vs 1	2.70	1.48-4.93	0.001
ECOG 0 vs ≥2	8.46	4.32-16.54	<0.001
Stage			
Stage I vs II	0.88	0.31-2.43	0.80
Stage I vs III	3.34	1.31-8.51	0.012
CA 15-3[2]			
≤ 31,3 U/mL vs >31,3 U/mL	3.97	2.27-6.95	<0.001
CEA3			
≤5 ng/mL vs >5 ng/mL	3.22	1.61-6.46	0.001
D-dimer			
≤ 232 ng/mL vs >232 ng/mL	2.31	1.37-3.89	0.002
Disease-free survival			
ECOG PS1			
ECOG 0 vs 1			<0.001
ECOG 0 vs ≥2			<0.001
Stage			
Stage I vs II	0.92	0.33-2.54	0.873
Stage I vs III	3.54	1.39-9.00	0.008
CA 15-3[2]			
≤ 31,3 U/mL vs >31,3 U/mL			<0.001
CEA[3]			
≤5 ng/mL vs >5 ng/mL			<0.001
D-dimer			
≤ 232 ng/mL vs >232 ng/mL	2.27	1.36-8.20	0.002

[1] ECOG PS: Eastern Cooperative Oncology Group performance status; [2] CA 15-3: Cancer antigen 15,3; 3 CEA: Carsinoembryonic antigen

It was known that clinical stage, lymph node involvement were prognostic factors for breast cancer. In a study performed by Blackwell et al.[2], a significant relationship was shown between elevated D-dimer levels and them. These findings indicated that high D-dimer levels could be used as an unfavorable prognostic factor, but these should not be considered lonely. In a study performed by Tas et al.[16] it was shown that patients with advanced breast cancer had significant high D-dimer levels when compared to patients with early breast cancer. Prognostic importance of lymphonodal status of breast cancer has been described. Although the significant relationship existed between the presence of elevated D-dimer and involved axillary lymph nodes was reported by Blackwell et al.[2], it was refuted by Fregoni et al.[17] They showed that there was no correlation between plasma D-dimer levels and lymph node involvement in breast cancer.[17] Like Fregoni et al., we have found that there is no significant difference between lymph node involvement and D-dimer levels. However, a borderline significance between developing distant metastasis and D-dimer was found. This relationship is likely to be a result of the relationship between the high D-dimer levels with tumor invasion. Also,

Table 5. Independent prognostic factors affecting the survival time of the patients with breast cancer in multivariate analysis

		Overall survival	
	Hazard ratio	**%95 confidence interval**	**p value**
ECOG PS[1]			
ECOG 0 vs 1	2.09	1.11-3.91	0.022
ECOG 0 vs ≥2	4.59	2.07-10.18	<0.001
Stage			
Stage I vs II	0.73	0.26-2.11	0.56
Stage I vs III	2.82	1.08-7.35	0.033
CA 15-3[2]			
≤3 1,3 U/mL vs >31,3 U/mL	1.91	1.01-3.62	0.048
D-dimer			
≤ 232 ng/mL vs >232 ng/mL	2.01	1.14-3.54	*0.015
Disease-free survival			
ECOG PS[1]			
ECOG 0 vs 1	2.45	1.55-3.88	<0.001
ECOG 0 vs ≥2	4.39	2.31-8.37	<0.001
Stage			
Stage I vs	0.89	0.31-2.57	0.84
Stage I vs III	2.61	1.28-5.34	0.008
CEA[3]			
≤ 5 ng/mL vs >5 ng/mL	2.43	1.28-5.34	0.003
D-dimer			
≤ 232 ng/mL vs >232 ng/mL	1.47	0.95-2.27	*0.080

[1] ECOG PS: Eastern Cooperative Oncology Group performance status; [2] CA 15-3: Cancer antigen 15,3; [3] CEA: Carsinoembryonic antigen

we did not find any relationship between D-Dimer levels and locoregional relapse and stage.

It is known that tumor markers have prognostic value in many types of cancers. The role of D-dimer as a tumor marker was evaluated in many studies. In a study performed by Nagy et al.[11], the relationship between elevated D-dimer levels in patients with breast and colonic cancer and elevated tumor markers were shown. In another study, Pedrazzani et al. could not find any relationship in colonic cancer.[18] They suggested that the most reliable prognostic factor was CEA. Oya et al.[19], found a relationship between CEA and D-Dimer. Besides, the sensitivity and specificity of combination of D-Dimer and tumor marker were shown by Gadducci et al.[20] Although tumor marker and elevated D-Dimer level were found as a poor prognostic factor in this study, we found have no correlation between them. Thus, the role of D-dimer as a tumor marker is still questionable.

Recently, studies have demonstrated that triple-negative breast cancer (TNBC) had shorter survival than non-TNBC. D-dimer levels were significantly high in patients with TNBC than non-TNBC and D-dimer level indicates clinically progressive disease.[21] Although the patients with TNBC had aggressive clinical course and had high baseline D-Dimer levels, no difference in D-dimer levels when comparing TNBC and non-TNBC patients were found in a study performed by Batschauer et al.[22] Likewise, we found that there was no relationship between D-dimer levels and hormonal status and HER 2.

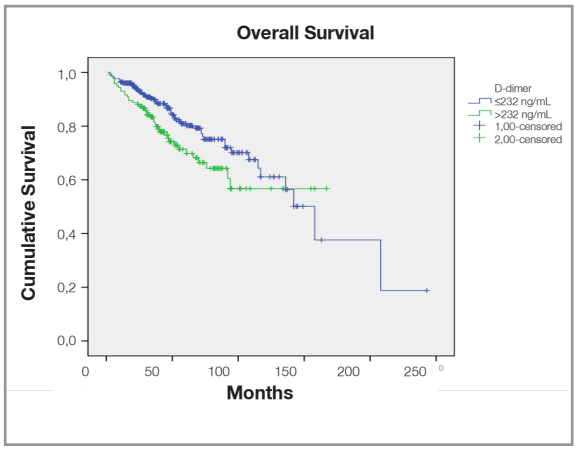

Figure 1. Correlation between D-dimer level and overall survival

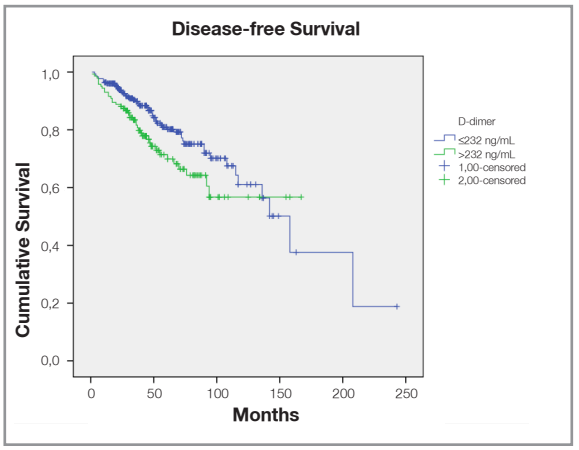

Figure 2. Correlation between D-dimer level and disease-free survival

Recent studies have shown a relationship between D-dimer and prognosis in cancer patients without VTE. Elevated D-dimer levels indicated poor prognosis and increased mortality risk.[4] Zhang et al.[23] evaluated the mortality risk of patients with lung cancer who had undergone surgery. They showed that elevated D-Dimer levels were significant prognostic factors for operable patients with lung cancer. Besides, short survival and poor response to the treatment in elevated D-dimer levels were found by Kurt et al.[24] It was also supported by other studies.[25-28] In our study, the patients who had baseline elevated D-Dimer levels were related with lower 5 year estimated OS rates (Figure 1) and 5 year estimated DFS rates (Figure 2). The 5 year OS rates of patients having low vs. elevated D-dimer levels were 90% vs. 81% respectively. The 5 year DFS rates of patients low vs. elevated D-dimer levels were 81% vs. 71% respectively. Besides, advanced stage, poor performance status, and high CA 15-3 are independent poor prognostic factors for OS. Advanced stage, poor performance status, and high CEA are independent poor prognostic factors for DFS.

As a conclusion, activation of hemostasis in cancer patients plays central role in angiogenesis, progression and metastatic spread and D-dimer is a biomarker that shows activation of hemostasis. Besides, it is an inexpensive and easily available blood test and elevated D-dimer level indicates poor prognosis and increased mortality risk. Thus, it could be useable as a prognostic factor in non-metastatic breast cancer.

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