

# Coagulation tests show significant differences in patients with breast cancer

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**Abstract** Activated coagulation and fibrinolytic system in cancer patients is associated with tumor stroma formation and metastasis in different cancer types. The aim of this study is to explore the correlation of blood coagulation assays for various clinicopathologic factors in breast cancer patients. A total of 123 female breast cancer patients were enrolled into the study. All the patients were treatment naïve. Pretreatment blood coagulation tests including PT, APTT, PTA, INR, D-dimer, fibrinogen levels, and platelet counts were evaluated. Median age of diagnosis was 51 years old (range 26–82). Twenty-two percent of the group consisted of metastatic breast cancer patients. The plasma level of all coagulation tests revealed statistically significant difference between patient and control group except for PT ( $p < 0.001$  for all variables except for PT;  $p = 0.08$ ). Elderly age ( $> 50$  years) was associated with higher D-dimer levels ( $p = 0.003$ ). Metastatic patients exhibited significantly higher D-dimer values when compared with early breast cancer patients ( $p = 0.049$ ). Advanced tumor stage (T3 and T4) was associated with higher INR ( $p = 0.05$ ) and lower PTA ( $p = 0.025$ ). In conclusion, coagulation tests show significant differences in patients with breast cancer.

**Keywords** Coagulation · Breast cancer · Test

## Introduction

Biology of cancer is a complicated process involving profound changes in different physiological systems such as hemostasis and vascular endothelial functions conferring

increased risk of thrombosis [1]. These alterations trigger thromboembolic events resulting in morbidity and mortality [2, 3].

The relationship between cancer and coagulation is not solely an issue of increased thromboembolic complications. Several reports have reinforced the concept of a connection between activated coagulation and angiogenesis in human cancer. Tumor stroma formation, an essential step of tumorigenesis, is particularly contributed by activation of coagulation in the perivascular region [4]. Patients with tumors of lung, pancreas, and gastrointestinal tract are supposed to be more prone to hypercoagulable state [5]. Previous studies with breast cancer patients have also demonstrated a hypercoagulable state with elevated markers of coagulation such as fibrinogen, tissue factor, and thrombin-antithrombin (TAT) complex [6–8]. Secretion of procoagulant factors by tumor cells triggers the deposition of fibrin, promoting angiogenesis and tumor cell growth. Fibrin deposition surrounding the tumor is assumed to be the result of a series of events initiated by the development of leaky tumor-associated blood vessels.

Homeostasis within this exaggerated coagulation process is always accompanied by fibrinolysis [9]. D-dimer is formed as a product of degraded fibrinogen during fibrinolysis and is elevated in various solid tumors including colorectal, ovarian, lung, and breast cancer [10–12]. In patients with colorectal cancer, D-dimer levels have been shown to correlate with depth of tumor invasion at the time of surgical excision [10]. D-dimer levels may also be elevated at the time of diagnosis and decrease after adjuvant anthracycline-based chemotherapy in early stage breast cancer patients [13–15]. Prognostic implications of coagulation tests for various tumors have been reported so far, but the relationship between coagulation parameters and clinicopathologic characteristics of breast cancer has not been outlined clearly. The aims of the current study are to confirm whether some coagulation abnormalities are more frequently encountered in patients with breast cancer and to

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**Table 1** Patient characteristics

Characteristics	%
No. of patients: <i>n</i> =123	
Age, years	
Median (range): 51 (26–82)	
<50	49
≥50	51
T status	
T1/T2/T3/T4	30/51/4/15
N status	
N0/N1/N2/N3	29/31/27/13
M status	
M1/M0	22/78
Histological grade	
I/II/III	11/45/44
ER status	
–/+	25/75
PR status	
–/+	42/58
HER-2 status	
–/+	23/77
Serum hemoglobin level (12 g/dl)	
Low/normal	39/61
Serum WBC count (11 000)	
Normal/elevated	98/2
Serum platelet level count (350 000)	
Normal/elevated	93/7
Serum LDH level (450 U/l)	
Normal/elevated	88/12
Erythrocyte sedimentation rate (40/h)	
Normal/elevated	72/28
Response to chemotherapy	
Responsive	77
Non-responsive	23

delineate the correlation of these coagulation tests with other clinical and laboratory variables.

**Table 2** The values of serum coagulation assays in patients with breast cancer and in healthy controls

Coagulation assays	Patients ( <i>n</i> =123)		Controls ( <i>n</i> =26)		<i>p</i> value
	Median	Range	Median	Range	
D-dimer (IU/ml)	205.2	0–4 152	32.0	0–1 185	<0.001
Fibrinogen (mg/dl)	312.5	131–719	235.5	166–439	<0.001
PT (s)	14.8	12.0–22.1	14.1	10.9–16.2	0.08
APTT (s)	26.8	12.7–44	31.9	24.6–36.1	<0.001
PTA (%)	77.0	37–127	90.4	71.6–139	<0.001
INR	1.12	0.91–1.63	1.01	0.79–1.15	<0.001
Platelet ( $\times 10^3/\text{mm}^3$ )	318	39–490	201	163–254	<0.001

## Patients and methods

A total of 123 female breast cancer patients admitted to Istanbul University, Institute of Oncology were enrolled into the study. Diagnosis of breast cancer was histologically proved either with tru-cut biopsy of the primary lesion or metastatic site and staged according to the sixth edition of AJCC. All the patients were treatment naïve for at least 3 months before accrual, and those who received oral/parenteral anticoagulants or those with history of thrombosis within the last 3 months were excluded from the study.

For histologic evaluation, tissue sections (2 mm) were deparaffinized and stained using H&E. Grading of tumors was established according to the modified Bloom-Richardson grading system [16]. Estrogen receptor (ER), progesterone receptor (PR), and HER-2 status were evaluated in the sample sections using appropriate antibodies. The immunohistochemical staining was assessed upon visual inspection with an optical microscope and considered as positive if the percentage of cells staining positive were more than 5 %. In case of 2(+) staining by IHC, HER-2 gene amplification was analyzed by fluorescent in situ hybridization (FISH).

## Treatment

All patients were treated with the multidisciplinary approach. Overall, 99 (83 %) patients received an anthracycline-based regimen, 19 (16 %) received hormone therapy either as aromatase inhibitor or tamoxifen ± LHRH analogues and two patients were followed up without any treatment due to early stage (<1 cm). Seventy-four patients received treatment in adjuvant and 16 patients in the neoadjuvant setting. The response to treatment was evaluated according to revised RECIST criteria version 1.1. Institutional review board approval was obtained from each subject prior to the commencement of the study.

**Table 3** Results (median and range) of comparisons between the coagulation tests and various clinical parameters

Parameters	Coagulation tests						
	D-dimer (IU/ml)	Fibrinogen (mg/dl)	PT (s)	APTT (s)	PTA (%)	INR	PLT ( $\times 10^3/\text{mm}^3$ )
Age, years							
<50	174 (22–1 073)	296 (167–674)	14.7 (12.6–17.7)	27.1 (20.0–34.1)	77 (56–113)	1.11 (0.95–1.63)	278 (123–722)
$\geq 50$	345 (0–4 152) ( $p=0.003$ )	332 (131–719) ( $p=0.061$ )	14.9 (12–22.1) ( $p=0.97$ )	25.9 (20.1–44.0) ( $p=0.34$ )	75 (37–127) ( $p=0.90$ )	1.12 (0.91–1.63) ( $p=0.92$ )	260 (39–491) ( $p=0.130$ )
T status							
T1+T2	253 (0–3 575)	320 (167–719)	14.5 (12.0–22.1)	27.0 (20.0–44.0)	82 (37–127)	1.09 (0.91–1.63)	272 (120–491)
T3+T4	205 (22–724) ( $p=0.337$ )	290 (131–405) ( $p=0.204$ )	15.3 (12.8–17.0) ( $p=0.091$ )	27.9 (20.1–35.2) ( $p=0.663$ )	70 (59–91) ( $p=0.05$ )	1.15 (1.04–1.54) ( $p=0.025$ )	260 (155–722) ( $p=0.630$ )
N status							
(–)	205 (0–1 059)	284 (167–652)	14.5 (12.6–22.1)	27.1 (20.0–35.2)	83 (37–113)	1.08 (0.96–1.63)	267 (120–490)
(+)	210 (22–3 575) ( $p=0.79$ )	331.5 (131–719) ( $p=0.128$ )	14.8 (12.0–17.7) ( $p=0.476$ )	27.05 (20.1–35.2) ( $p=0.514$ )	77 (56–127) ( $p=0.496$ )	1.12 (0.91–1.63) ( $p=0.380$ )	272 (153–722) ( $p=0.725$ )
M status							
(–)	205 (0–3 575)	312 (167–674)	14.7 (12.0–22.1)	27.2 (20.0–44.0)	77 (37–127)	1.11 (0.91–1.63)	240 (39–449)
(+)	407 (43–4 152) ( $p=0.049$ )	331 (131–719) ( $p=0.560$ )	15.4 (12.8–17.0) ( $p=0.163$ )	25.9 (20.1–35.2) ( $p=0.193$ )	69 (59–93) ( $p=0.111$ )	1.16 (1.04–1.54) ( $p=0.106$ )	269 (120–722) ( $p=0.035$ )
Histological grade							
I+II	183 (0–3 575)	316 (131–511)	14.3 (12.0–22.1)	27.0 (20.1–43.1)	75 (59–107)	1.10 (0.95–1.54)	260 (120–491)
III	313 (22–785) ( $p=0.506$ )	317 (167–674) ( $p=0.249$ )	15.0 (13.3–17.0) ( $p=0.014$ )	26.8 (20.0–44.0) ( $p=0.436$ )	83 (37–127) ( $p=0.137$ )	1.10 (0.91–1.63) ( $p=0.560$ )	278 (123–722) ( $p=0.154$ )
ER status							
(–)	183 (43–1 059)	345 (167–674)	14.3 (12.4–22.1)	25.7 (20.9–35.0)	84 (37–117)	1.09 (0.94–1.63)	274 (123–449)
(+)	262 (0–3 575) ( $p=0.435$ )	301 (131–719) ( $p=0.217$ )	14.9 (12.0–17.6) ( $p=0.318$ )	27.1 (20.0–44.0) ( $p=0.105$ )	75 (56–127) ( $p=0.612$ )	1.12 (0.91–1.62) ( $p=0.793$ )	260 (120–491) ( $p=0.335$ )
PR status							
(–)	205 (22–1 215)	351 (131–674)	14.5 (12.0–22.1)	26.8 (20.0–35.2)	81 (37–120)	1.10 (0.91–1.63)	272 (168–449)
(+)	206 (0–3 575) ( $p=0.971$ )	294 (177–719) ( $p=0.280$ )	15.0 (12.7–17.6) ( $p=0.207$ )	26.9 (20.1–44.0) ( $p=0.60$ )	75 (56–110) ( $p=0.397$ )	1.12 (0.96–1.62) ( $p=0.621$ )	261 (120–491) ( $p=0.224$ )
HER-2 status							
(–)	216 (0–3 575)	314 (167–719)	14.8 (12.0–22.1)	26.8 (20.0–44.0)	77 (37–117)	1.12 (0.91–1.63)	262 (120–490)
(+)	164 (43–3 575) ( $p=0.333$ )	302 (131–446) ( $p=0.810$ )	14.8 (12.4–16.7) ( $p=0.475$ )	26.3 (20.9–35.2) ( $p=0.368$ )	74 (61–117) ( $p=0.737$ )	1.12 (0.94–1.43) ( $p=0.524$ )	270 (123–491) ( $p=0.478$ )
Serum hemoglobin level							
Low	199 (22–4 152)	314 (177–719)	14.9 (12.6–17.7)	26.3 (12.7–34.9)	75 (56–113)	1.10 (0.95–1.63)	264 (147–722)
Normal	205	313	14.5	27.4	83	1.09	268.5

**Table 3** (continued)

Parameters	Coagulation tests						
	D-dimer (IU/ml)	Fibrinogen (mg/dl)	PT (s)	APTT (s)	PTA (%)	INR	PLT ( $\times 10^3/\text{mm}^3$ )
	(0–1 422) ( <i>p</i> =0.659)	(131–674) ( <i>p</i> =0.852)	(12.0–22.1) ( <i>p</i> =0.366)	(20.9–44.0) ( <i>p</i> =0.018)	(37–127) ( <i>p</i> =0.354)	(0.91–1.63) ( <i>p</i> =0.356)	(39–449) ( <i>p</i> =0.852)
Serum WBC count							
Normal	205 (0–4 152)	314 (131–719)	14.8 (12.0–22.1)	26.8 (12.7–44.0)	77 (37–127)	1.12 (0.91–1.63)	267 (39–722)
Elevated	447 (171–724) ( <i>p</i> =0.532)	249 (167–331) ( <i>p</i> =0.324)	14.4 (12.7–16.1) ( <i>p</i> =0.870)	29.8 (27.1–32.6) ( <i>p</i> =0.28)	78 (62–94) ( <i>p</i> =0.847)	1.13 (1.05–1.21) ( <i>p</i> =0.869)	305.5 (209–420) ( <i>p</i> =0.806)
Serum platelet count							
Normal	216 (0–4 152)	317 (131–719)	14.8 (12.0–22.1)	26.9 (20.0–44.0)	76 (37–120)	1.12 (0.91–1.63)	–
Elevated	171 (108–1 072) ( <i>p</i> =0.415)	307 (167–470) ( <i>p</i> =0.477)	14.5 (12.6–15.6) ( <i>p</i> =0.329)	26.0 (12.7–27.4) ( <i>p</i> =0.154)	85 (67–113) ( <i>p</i> =0.351)	1.07 (0.96–1.17) ( <i>p</i> =0.310)	–
ESR							
Normal	183 (0–4 152)	297 (167–674)	14.6 (12.7–17.6)	27.1 (20.1–44.0)	80 (56–107)	1.10 (0.95–1.62)	267 (120–464)
Elevated	253 (108–3 575) ( <i>p</i> =0.374)	358 (257–719) ( <i>p</i> =0.005)	15.2 (12.6–22.1) ( <i>p</i> =0.025)	26.6 (12.7–35.0) ( <i>p</i> =0.371)	71 (37–113) ( <i>p</i> =0.034)	1.16 (0.96–1.63) ( <i>p</i> =0.045)	294 (234–490) ( <i>p</i> =0.022)
Serum LDH level							
Normal	183 (0–3 575)	312 (167–674)	14.6 (12.0–17)	26.8 (20.1–44.0)	79 (59–120)	1.10 (0.91–1.63)	344 (147–490)
Elevated	390 (97–4 152) ( <i>p</i> =0.076)	407 (131–719) ( <i>p</i> =0.40)	15.5 (12.6–22.1) ( <i>p</i> =0.233)	24.0 (12.7–35.2) ( <i>p</i> =0.310)	68 (37–113) ( <i>p</i> =0.263)	1.10 (0.91–1.54) ( <i>p</i> =0.161)	398 (194–432) ( <i>p</i> =0.563)
Response to chemotherapy							
Responsive	205 (22–4 152)	364 (131–470)	15.5 (12.4–17.6)	27.3 (22.6–35.3)	68 (56–117)	1.10 (0.94–1.62)	259 (39–499)
Non-responsive	182 (157–724) ( <i>p</i> =0.97)	313 (177–361) ( <i>p</i> =0.13)	15.3 (14.3–16.7) ( <i>p</i> =0.664)	25.9 (20.1–32.6) ( <i>p</i> =0.231)	69 (61–88) ( <i>p</i> =0.664)	1.10 (1.04–1.35) ( <i>p</i> =0.354)	215.5 (147–294) ( <i>p</i> =0.04)
Last status							
Dead	524 (324–724)	290 (203–331)	15.4 (13.6–16.3)	26.8 (23.0–32.6)	70 (62–93)	1.16 (1.06–1.46)	266 (39–491)
Alive	205 (0–4 152) ( <i>p</i> =0.26)	314 (131–719) ( <i>p</i> =0.367)	14.7 (12.0–22.1) ( <i>p</i> =0.395)	26.9 (20.0–44.0) ( <i>p</i> =0.97)	77 (37–127) ( <i>p</i> =0.377)	1.12 (0.91–1.63) ( <i>p</i> =0.414)	209 (155–722) ( <i>p</i> =0.693)

### Blood collection and tests

Blood samples in patients with operated patients were obtained at least 3 weeks after surgery and during the first visit of metastatic patients in the clinics. The blood samples of the control group which consisted of 26 female subjects without any history of malignancy or anticoagulant usage were collected at the beginning of study. Five milliliters of peripheral blood was drawn into citrated tubes for the measurement of D-dimer, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR)

and stored for a maximum of 2 days at  $-20\text{ }^{\circ}\text{C}$ . D-dimer values were determined by Microparticle Enzyme Immunoassay (MEIA) using AxSYM analyzer following the manufacturer's instructions. Commercially available reagents provided by a kinetic nephelometric detection system using Diagon Dia Timer 4 were employed for PT, APTT, and fibrinogen measurement.

### Statistical analysis

Comparisons of continuous variables including D-dimer, fibrinogen, PT, and APTT in different subgroups were

performed with Mann-Whitney *U* test. Relationships between categorical variables were compared using a chi-square test. Survival was calculated from the date of accrual to death resulting from any cause or to last contact with the patient or any family member. The Kaplan-Meier method was used for estimation of survival distribution; univariate survival curve differences were assessed by the log-rank test. A *p* value <0.05 was considered significant. Statistical analysis was carried out using SPSS 16.0 software.

## Results

Between February 2010 and June 2011, 123 consecutive female patients with breast cancer were enrolled into the study. Median age of diagnosis was 51 years old (range 26 to 82) (Table 1). Twenty-two percent of the group consisted of metastatic breast cancer patients where the most frequent site of metastasis was bone (78 %). Majority of the patients received anthracycline-based chemotherapy; 19 patients were treated only with hormone therapy.

### Comparison of coagulation tests between patients and healthy controls

The control group comprised age and sex-matched individuals without history of malignancy. Comparison of coagulation tests between patients and controls including D-dimer, fibrinogen (F), activated partial thromboplastin time (APTT), prothrombin activity (PTA), international normalized ratio (INR), and platelet counts revealed a significant difference between

the two groups ( $p < 0.001$ ) (Table 2). Additionally, there was a tendency toward increased PT in the patient group, but it was not statistically significant ( $p = 0.08$ ).

### Correlation of coagulation tests with clinical and laboratory variables

Elderly age (>50 years) was associated with higher D-dimer levels (median 174 vs 345 U/ml,  $p = 0.003$ ) (Table 3). Similarly, metastatic patients exhibited significantly higher D-dimer values when compared with early breast cancer patients ( $p = 0.049$ ). Advanced tumor stage (T3 and T4 vs T1 and T2) was associated with higher INR (median 1.15 vs 1.09,  $p = 0.05$ ) and concordantly lower prothrombin activity (82 vs 70 %,  $p = 0.025$ ). Nodal involvement did not seem to have an influence on coagulation parameters. However, histological grade of tumor had a correlation with prothrombin time; grade 3 tumors were associated with prolonged PT (15 vs 14.4 s,  $p = 0.014$ ).

Higher erythrocyte sedimentation rates (ESR) (>40 mm/h) reflecting inflammatory response were associated with high fibrinogen levels (358 vs 297 mg/dl,  $p = 0.005$ ). Besides, elevated ESR was clearly correlated with prolonged PT ( $p = 0.025$ ) and INR ( $p = 0.045$ ), low prothrombin activity ( $p = 0.034$ ), and higher platelet counts ( $p = 0.022$ ).

Receptor status including ER, PR, and HER-2 did not affect coagulation parameters evidently (Table 4). When patients were analyzed according to the tumors' receptor status such as triple negative or hormone negative (ER -, PR -, and HER-2 positive or negative) or triple positive (ER +, PR +,

**Table 4** Correlations of distributions and prognostic assays between coagulation tests and subgroups of patients according to hormone receptor status

		Triple(-) (n=10) (%)	<i>p</i> value	Triple(+) (n=10) (%)	<i>p</i> value	ER(+)/PR(+) HER-2(-) (n=48) (%)	<i>p</i> value	Hormone negative ER(-)/PR(-) (n=24) (%)	<i>p</i> value
D-dimer	Normal	33.3	0.674	42.9	0.721	48.3	0.891	58.3	0.754
	Elevated	66.7		52.7		51.7		41.7	
Fibrinogen	Normal	60.0	0.642	66.7	0.362	48.4	0.902	36.4	0.515
	Elevated	40.0		33.3		51.6		63.6	
PT	Normal	83.3	0.207	57.1	0.689	45.7	0.459	72.7	0.204
	Elevated	16.7		42.9		54.3		27.3	
APTT	Normal	66.7	0.676	57.1	0.721	45.7	0.378	70.0	0.313
	Elevated	33.3		42.9		54.3		30.0	
PTA	Normal	16.7	0.090	42.9	0.512	60	0.458	36.4	0.333
	Elevated	83.3		57.1		40		63.6	
INR	Normal	66.7	0.502	66.7	0.455	48.6	0.620	54.5	0.605
	Elevated	33.3		33.3		51.4		45.5	
PLT	Normal	70.0	0.079	100	0.160	95.8	0.057	30.4	0.187
	Elevated	30.0		0		4.2		69.6	

HER-2 +) groups, no significant relationship was detected with respect to coagulation tests.

### Survival analysis

Median follow-up time was 9.1 months (range 2–56 months). During follow-up, five (4 %) patients were dead due to disease-related events. Univariate analysis of survival revealed that advanced tumor stage and leukocytosis were indicators of poorer overall survival (Table 5). Since numbers of events were scarce during follow-up due to high overall survival rates among breast cancer patients, none of the

coagulation assays was determined as a prognostic factor on survival.

### Discussion

The processes of hemostasis/fibrinolysis and angiogenesis are closely linked physiological systems that remain silent under resting conditions, but in case of malignancy, these highly activated mechanisms may be involved in tumor expansion and invasive behavior.

The fibrinolytic system includes a broad spectrum of proteolytic enzymes with pathophysiological functions in several processes such as tumor invasion, angiogenesis, and reproduction. The main enzyme of the plasminogen activator system, plasmin is responsible for degradation of fibrin into soluble degradation products. Plasminogen activators (PA) urokinase-type plasminogen activator (uPA), and tissue type plasminogen activator (PAIs) are serine proteases that catalyze the cleavage of inactive plasminogen to plasmin [17]; PAs are secreted by many cells including tumor cells [18]. Through the proteolytic activity of malignant cells, the extracellular matrix and basal membrane of tumor stroma are degraded, enabling invasion of adjacent tissues and migration of tumor cells [19]. Thus, products of the induced fibrinolytic process such as D-dimer have been investigated as a marker for distinguishing benign disorders from malignancies and evaluating invasiveness in various tumors [15, 20–22]. Our results are consistent with the previous data reflecting the significant difference between patient and control group concerning coagulation parameters which involve fibrinogen, aPTT, and INR in addition to D-dimer levels [23, 24].

Elevated D-dimer levels as a predictor of tumor overload have been confirmed in different studies for lung cancer and gynecologic cancer types previously [25, 26]. Similarly, preoperative D-dimer levels have provided support for the role of increased levels in predicting vascular invasion, advanced tumor stage, and poor postoperative survival in colorectal cancer patients [27]. Among breast cancer patients, plasma D-dimer levels were increased in progressive metastatic disease correlating with tumor load, number of metastatic sites, and progression kinetics [12]. Our study confirmed the utility of elevated D-dimer levels in predicting extent of disease, since there was a statistically significant difference between metastatic and early breast cancer patients ( $p=0.049$ ). Besides, advanced tumor stage correlated with elevated INR ( $p=0.025$ ) and reduced prothrombin activity ( $p=0.05$ ), indirectly reflecting an ongoing consumption of coagulation assays through the exaggerated fibrinolytic process. Although previously a few reports have mentioned a relationship between elevated D-dimer levels and involved axillary lymph nodes [20, 28], we did not find such a correlation in our study group. In concordance with our results, lymphonodal status

**Table 5** Univariate analyses of survival

Characteristics		Twelve-month survival rate (%)	<i>p</i>
Age (years)	<50	87.8	0.167
	≥50	66.7	
T stage	T1+2	100.0	<0.001
	T3+4	74.7	
Node	(-)	100.0	0.393
	(+)	94.1	
ER	(-)	88.8	0.263
	(+)	95.7	
PR	(-)	93.1	0.681
	(+)	94.1	
HER-2	(-)	93.3	0.681
	(+)	94.1	
Hemoglobin	Low	97.7	0.769
	Normal	91.3	
WBC	Normal	100.0	<0.001
	Elevated	96.5	
LDH	Normal	100.0	0.591
	Elevated	97.2	
Response to chemotherapy	Yes	100.0	0.479
	No	80.0	
D-dimer	Normal	100.0	0.157
	Elevated	89.2	
Fibrinogen	Normal	97.1	0.739
	Elevated	90.0	
PT	Normal	92.9	0.856
	Elevated	90.9	
APTT	Normal	93.5	0.832
	Elevated	80.0	
PTA	Normal	88.7	0.459
	Elevated	95.0	
INR	Normal	92.9	0.860
	Elevated	90.9	
PLT	Normal	91.6	0.653
	Elevated	96.7	



was not defined as a factor affecting D-dimer values in the other study involving hormone receptor negative breast cancer patients [24]. However, we were able to demonstrate a relationship between histological grade and PT; grade 3 tumors were associated with prolonged PT ( $p=0.014$ ). So far, to our knowledge no association between histological grade and coagulation tests has been described.

Hormone receptor status is one of the most relevant biological factors determining prognosis. Particularly, regardless of tumor size or nodal status, triple negativity is depicted as an independent negative prognostic factor, reflecting the aggressive nature of this tumor (TNBC-2). The current study also aimed to define the effect of hormone receptor status on coagulation parameters. When patients were analyzed according to their receptor status as triple negative, triple positive, hormone receptor positive (ER +, PR +, HER-2 -) or hormone receptor negative (ER -, PR -, HER-2 +/-) subtypes, no significant difference was detected according to variation of coagulation parameters. Comparison of D-dimer values of triple-negative and non-triple-negative breast cancer patients had not yielded a significant difference in the previous study, in agreement with our findings [24]. Furthermore, in a recent study investigating the relationship between fibrinolytic cascade and clinicopathologic variables, increased levels of D-dimer were not shown to be related with histological subtypes and hormone receptor status [12]. Probably, receptor status is an irrelevant factor for tumor progression kinetics via the fibrinolytic system.

In conclusion, almost all coagulation tests show significant difference in patients with breast cancer. The current study supports the significance of increased plasma D-dimer as a predictor for advanced stage disease. Since fibrin degradation products reflect an ongoing fibrinogen metabolism within the actively remodeled tumor stroma, considering the amount of these products as a marker for disease load seems justified. As D-dimer tests are neither time consuming nor expensive, this proposal appears to be suitable for daily practices deserving further investigation.

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