

Plasma D-Dimer Levels Correlated With Advanced Breast Carcinoma in Female Patients: A Prospective Study at Baghdad Teaching Hospital

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Abstract- Advanced breast cancer is a common disease among female gender in the world. There is a correlation between cancer and hypercoagulation. In a cancer state, there is an increase in the level of cross-linked fibrin degradation product (d-dimer) which indicates systemic activation of fibrinolysis and hemostasis. So, there is a relation between increase d-dimer value and advanced breast disease. To study the relation between preoperative plasma d-dimer level and tumor extension, choose the proper option of treatment, and to decrease morbidity and mortality in patients with breast carcinoma, a prospective study (cohort study) was done at Baghdad teaching hospital (department of surgery) from Jan 2014 to Jan 2016. Seventy patients were categorized into two equal groups, group one with breast carcinoma, and group two with benign breast tumor. Plasma d-dimer levels were compared for each group and in relation to (tumor size, stage, grade, lymphovascular invasion, and lymph nodes involvement). The d-dimer level was normal in group two (<0.25 mg/l) and high in group one in other words, the d-dimer level was increasing in advanced breast carcinoma group with enlarged tumor size, higher stage and grade, lymphovascular invasion and lymph nodes' involvement. Plasma d-dimer levels were a good prognostic factor in breast carcinoma especially in advanced breast carcinoma, and it could be considered a factor for clinical stage progression lymphovascular invasion, and metastasis.

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Introduction

In female patients, breast cancer is the commonest malignant neoplasm and denotes a diversified collection of tumors that exhibit different progressions and changing reaction to therapy. Biological indicators, the status of hormones, histological grading and subclasses' status, tumor size, and lymph node embroilment have predictive and/or prognostic importance, and they are the primary factors in nominate proper management (1).

Although clinical and experimental trials have demonstrated the relationship between cancer and hemostasis but the exact mechanism is not fully understood (2).

Thus, systemic activation of coagulation and hemostatic system in all cancer patients without thromboembolism has been still under investigation (2).

Advanced breast cancer is either locally advanced or metastatic spread. There is a correlation between cancer and hypercoagulation. Global hemostasis is more

frequently triggered in patients with cancer. This systemic activation has been included in (angiogenesis, progression, metastatic spread) of tumor cells. Elevated d-dimer levels, which is produced by degradation of cross-linked fibrin; points to worldwide activation of fibrinolysis and hemostasis (3).

In breast cancer, an elevation of plasma d-dimer is linked and correlated with locally advanced breast cancer or metastasis to axillary lymph nodes or distant metastasis. Advanced breast cancer includes the most serious of the five possible stages (stage 3 and 4) (4).

Stage 3 is locally advanced breast carcinoma, in other words, the disease has metastasis to lymph nodes or another tissue in the breast but not to farther sites in the body, while in stage 4 of the disease there is metastatic breast cancer to other organs mainly the liver, lungs, bones, and brain (5).

The foremost step in tumor metastasis is remodeling and fibrin deposition in the tumor extracellular matrix. A tumor to effectively metastasize from its original site, it

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must undertake many coerece steps, this includes the assault into either the vascular or lymphatic lumen, conveyance through the circulation, and creation of viability in base tissues. Cross-linked fibrin serves as a stable framework in the extracellular matrix for endothelial cell migration when tumor cell migration and angiogenesis while invasion (6).

Remodeling of extracellular fibrin is primary for angiogenesis in tumors, and activation of intravascular fibrin fashioning and dissolution is occurring in the plasma of the patients. In apposition to other indices of fibrinolysis pathway activation, like levels of plasminogen activator inhibitor and pralines plasminogen activator, which shown prognostic significance in breast cancer's patients (7).

Furthermore, activation of the coagulation system, minutely thrombin generation and fibrin figuration and degradation, have been included in angiogenesis, tumor progression, tumor cell stealth, and metastatic spread (8). Thrombin is a fundamental enzyme in the process of blood coagulation and leads to the transformation of fibrinogen to fibrin, which is the end result of blood coagulation and lastly gives rise to the formation of a fibrin clot. Tumor cells also retain intensive procoagulant activities that stimulate regional activation of the coagulation system and deposition of fibrin.

The aim of this study was to confirm the relation between increase d-dimer levels and advanced breast carcinoma in female patients.

Materials and Methods

The study was performed at Baghdad Teaching Hospital (Department of Surgery) from Jan-2014 to Jan-2016. Seventy female patients with breast cancer were included in this study. They were divided into two groups according to history, clinical examination, and triple assessment of the disease. Group one; included 35 patients diagnosed with malignant breast cancer their age ranged between 25 and 65 years. The other 35 patients (Group two) were diagnosed as having benign breast disease, and their age ranged between 20 and 50 years.

Exclusion criteria

we excluded (11 patients)

1-patients with other cancer, e.g. cervical and colorectal carcinoma (1 patient).

2-Smokers (5 patients).

3- Patients with venous thromboembolic diseases (2 patients).

4- Unstable angina (1 patient).

5-Severe infection (pneumonia) (1 patient).

6-Patient on Aspirin (1 patient).

Blood venous samples (3 ml) were collected from the patients before any surgical intervention, and clinical staging was done including; tumor size, site, nodal involvement, and distant metastases (TNM). Ultrasound of abdomen and chest x-ray were taken to each patient. Grading of the disease was done by histopathological study including lymph node involvement, lymphovascular invasion, and a number of lymph nodes involved by tumor. The patients who were enrolled in the present study were treated by either lumpectomy or modified mastectomy and axillary dissection. The samples were sent for histopathological study as mentioned above. The data were analyzed by standard deviation and *P*-value in the comparison between two groups. *P*<0.05 was considered significant (9).

Results

All patients enrolled in our study were females. Seventy patients were randomly selected, age in group one from 25-65 years (mean 45 years), group two from 20-50-year-old (mean 35). In 70% of the patients, the site of the lump was an upper outer quadrant of the breast.

In group one, 30% were premenopausal, and 70% were postmenopausal while in group two, 98% of them were premenopausal and 2% were postmenopausal.

In group one, 4 (11.4%) patients had d-dimer level <0.25 mg/l, 11 (31.4%) patients had level ranged (0.25-0.50 mg/l), 13 (37.1%) patients had level ranged (0.5-1 mg/l) and 7 (20%) patients had level ranged (1-2 mg/l), while in group two, 34 (97.1%) patients have level (0.25 mg/l) and only 1 patient (2.8%) had level ranged (0.25-0.50 mg/l), as shown in table 1.

Table 2 showed the mean and standard deviation of d-dimer level distributed according to the stage of the disease. It was found that d-dimer level was significantly increased in breast cancer patients compared with group two. Patients with stage Iliia and Ibis showed significant differences (0.4 ± 0.25820 , 0.4857 ± 0.27946) compared with the normal d-dimer level in group two. While stage Iliac and Jib showed highly significant differences (0.5200 ± 0.25884 , 0.6455 ± 0.28413) in the normal value of group two.

Table 1. Level of plasma d-dimer among group one and group two studied patients

D-dimer level (mg/l)	Patients in group one	Patients in group two
0.25	4(11.4%)	34(97.1%)
(0.25-0.50)	11(31.4%)	1(2.8%)
(0.5-1)	13(37.1%)	-
(1-2)	7(20%)	-
Total	35	35

Table 2. The mean, standard deviation (mean ± SD) of d-dimer level distributed according to the stage of the disease

Stages of disease (S)	Mean of d-dimer level*	No. of patients studied	Std. Deviation
S I	0.1000	2	0.00000
s II a	0.4000	5	0.25820
s II b	0.4857	8	0.27946
s III a	0.5200	7	0.25884
s III b	0.6455	11	0.28413
s III c	1.1000	1	.
s IV	1.0000	1	.

*Normal d-dimer level<0.25 mg/l

It was noticed that when there was an increase in tumor size, there was also an elevation in the mean of plasma d-dimer level. In T1, four patients with tumor size had d-dimer value 7.2 mg/l, 12 patients with tumor size

T2 had mean d-dimer (29.17 mg/l), five patients with tumor size T3 had (8.9 mg/l) mean of the plasma d-dimer level, and other 14 patients had tumor size T 4 with d-dimer level of 54.12 mg/l, (Table 3).

Table 3. The tumor size distributed according to the level of the plasma d-dimer in group one

Tumor size type	Number of patients	Mean of D-dimer (mg/L)
T1 (< 2cm)	4	7.2400
T2 (2-5 cm)	12	29.1700
T3 (> 5 cm)	5	8.9000
T4 (any size spread beyond breast tissue)	14	54.1700
Total	35	34.3347

A significant relationship was observed between histopathological grade and mean of level d-dimer at $P \leq 0.01$. The result revealed when there was an increased grade of the disease, there was an elevation in the level of d-dimer. In group one, 7 patients (20.0%), with histopathological grade I tumor, had the mean of d-dimer

(1.8 mg/l), while 12 patients (34.3%) with grade II disease, had a mean of 2.8 mg/l. Other 16 patients (45.7%) with grade III had a mean level of plasma d-dimer (12.4) mg/l. The difference was significant at $P \geq 0.01$, (Table 4).

Table 4. Histopathological grade distributed in comparison to the level of the plasma d-dimer.

Histopathological grade	No. of patients	d-dimer mean
I	7	1.7 (10.06)
II	12	2.8 (16.57)
III	16	12.4 (73.37)

Significant at $P \leq 0.01$

Table 5 shows the lymphovascular invasion of the disease distributed according to d-dimer level. In group A, out of 24 patients (68.6%) with lymphovascular invasion had a mean value of (4.2 mg/l) while group B 11 patients (31.4%) had no lymphovascular invasion with the mean of d-dimer with (1.7 mg/l), (Table 5).

Table 5. Lymphovascular invasion of the disease distributed according to d- dimer level.

Lymphovascular invasion of the disease	Number of patients (%)	Mean of the d-dimer level (mg/l)
Group A (with lymph vascular invasion)	24(68.6%)	4.2
Group B (without lymph vascular invasion)	11(31.4%)	1.7
Total	35(100%)	

Table 6 shows lymph nodes involved among patients studied distributed according to d-dimer level. In group A out of 29 patients (82.9%) with lymph nodes' involvement, the mean of the d-dimer level was 4 mg/l, and in group B only 6 patients (17.1%) with no lymph node involvement had mean d-dimer level of 0.25 mg/l.

Table 6. Lymph nodes involved among patient studied distributed according to d-dimer level

Lymph nodes involved	Number of patients (%)	Mean of d-dimer level(mg/l)
Group A (Involved)	29 (82.4)	4
Group B (Not involved)	6(17.6)	0.25
Total	35(100%)	

Discussion

The antigens of fibrin d-dimer are an unparalleled indicator of the primary enzymatic dissolution, product of cross-linked fibrin by plasmin dissolve the cross-linked fibrin to liberate fibrin degradation products and reveal the d-dimer antigen. Systemic standards of d-dimer are an index of fibrin transition in the circulation (9). Plasma d-dimer levels are elevated in many clinical conditions like smoking, infection, pregnancy, old age, trauma, tumors, and others (11), an addendum to the diagnostic use of d-dimer, it could be of conceivable prognostic use in many conditions.

There are different factors in which elevation of d-dimer may occur including venothroboembolic (VTE), cardiovascular disease and cancer. In addition, d-dimer levels levitation were shown in a healthy adult population. Although the pathophysiology of this activation is not completely yet clear. The previous and the present studies reported elevation of d-dimer in cancer without thromboembolism. Also, it has been shown in the present study that increased level of d-dimer has a clear prognostic role on the prognosis of the breast cancer; many studies documented the role of the plasma d-dimer who has important value affecting prognosis in many types of cancers. A study was done by Nagy *et al.*, and Dire *et al.*, (12,13) who has established a correlation between increased d-dimer levels in patients with breast cancer and elevated tumor markers lead to increased mortality risks. This result was in agreement with the present study. A study was done by Di Castelnuovo *et al.*,

(14) who noticed that d-dimer level elevation is an indicator for distant metastasis.

Tumor grade, nodal involvement, size, and stage play a primary role in the prognosis of long-dated survival, though those factors importance decrease with time (15). A strong correlation is noticed between the lymph node involvement which is essential for the affirmation of clinical extent, stage and treatment, clinical extent, stage, and a number of metastatic nodules with d-dimer plasma levels. Our results were in line with Blackwell *et al.*, (16). Also, we documented that plasma d-dimer level is a pointer for lymphovascular invasion, clinical stage, and lymph node involvement in operable breast cancer. Zhang *et al.*, (17) also suggested that noticeable fibrin dissolution, as calculated by the level of plasma d-dimer, is a clinically essential indicator for lymphovascular invasion and then tumor metastasis in operable breast cancer. Di Micro *et al.*, (18) also proclaim that d-dimer plasma levels were increased in patients with gastric cancer. The conclusion of the present study also specified that plasma d-dimer levels are elevated in patients with extensive tumors, advanced T, N and TNM stage in studied patients.

Joins *et al.*, (19) studied renaissance rates among patients revealed by screening in contrast to those discovered without screening. After modification for tumor violence (tumor grade, nodal involvement, size, age, management, PR- status, HER-2), hence excluding bias towards recognition of inactive cancers (length bias), the avail of screening for the prognosis for breast cancer (BC) patients stayed obvious, this indicates that other

agents explain the indolent demeanor of BC revealed by screening. Hence, until this agent is established, discovery mode should probably be counted as a prognostic factor and thus be considered into account in patient treatment (20).

Levels of plasma d-dimer were a good prognostic factor in breast carcinoma especially in advanced breast carcinoma and may also be considered as a good indicator for determining clinical stage progression of the disease, lymphovascular invasion, and metastasis. Activation coagulation and fibrinolysis system in patients with cancer are combined with tumor formation and metastasis in various cancer types.

After time linear analysis with sequent measurements of d-dimer levels would be required to analyze their association with disease progression advanced breast cancer, we also recommend using INR, PT in addition to d-dimer value. We noticed that INR, PT also were increased in same time with the increase of d-dimer level in relation to increasing (tumor size, stage of disease, lymph node involvement, and lymphovascular invasion), INR and PT are easiest available and cost-effective methods.

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