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ORIGINAL STUDY

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Association of Peripheral Blood Parameters with TNM Stage of Breast Cancer

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Abstract

Background: Breast cancer is the most frequently diagnosed cancer in women worldwide. Cancer cells can directly activate the blood-clotting cascade and cause thrombosis. Elevated D-dimer levels show that hemostasis and fibrinolysis are activated globally. It is commonly recognized that systemic inflammatory reactions contribute significantly to the advancement of cancer. Among other inflammatory markers, neutrophil-to-lymphocyte ratios (NLRs) strongly correlate with prognoses in early-stage breast malignancies.

Objectives: To investigate the relationship between pretreatment plasma D-dimer level and Neutrophile to Lymphocyte Ratio to TNM stage of Breast cancer.

Materials and methods: A cross- sectional study was conducted on breast cancer patients in the holy city of Karbala Sixty female patients aged 18 years and above with confirmed breast cancer were enrolled in the study. Laboratory analysis includes pretreatment complete blood count (for Neutrophile to Lymphocyte Ratio estimation) and quantitative D-Dimer level determination. The relation of plasma D-dimer levels and (NLR) with tumor size, regional lymph node state, and distant metastasis of Breast cancer was assessed.

Results: The results of the study showed a significant difference in the mean of plasma D-dimer levels and Neutrophil to Lymphocyte Ratio (NLR) among tumor size, regional lymph node state, and distant metastasis of Breast cancer. The D-Dimer levels and Neutrophil-Lymphocyte ratio were higher in patients with a higher stage.

Conclusion: Plasma D-Dimer levels and Neutrophil-Lymphocyte are important markers that had a significant association with TNM stage of Breast cancer.

Keywords: Breast cancer, Thrombosis, D-dimer, Inflammation, Neutrophil-Lymphocyte ratio

1. Introduction

In the world, women are diagnosed with breast cancer more often than any other cancer. In recent years, the mortality rate from breast cancer has declined in most Western countries due to better treatments and earlier identification. Still, in both Europe and the US, breast cancer is the third most common cause of cancer-related mortality [1].

In Iraq, breast cancer constituted 21.2% of all cancer cases in 2022 and accounted for 35.9% of all new cancer cases among females of all ages. It is also the first malignancy to rank among all demographics. Breast cancer accounts for 23.6% of all cancer-related deaths, placing it in the first place [2].

Breast cancer is an unpredictable illness with a wide range of manifestations, from molecular characteristics to clinical presentation, and a potentially different prognosis. Of the several histological subtypes of breast cancer, invasive ductal carcinoma (IDC) accounts for the majority of cases, representing over 75% of the total population [3].

Classical aspects, such as the patient's age, tumor size, histological type, grading, and staging of the tumor, hormonal receptor status, including the presence of ER, PR, and HER-2 (human epidermal growth factor receptor), and markers of cell proliferation, impact the treatment and prognosis of breast cancer [4].

Patients with carcinoma typically have inappropriate activation of both coagulation and fibrinolysis,

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especially if they have metastasis [5]. Hypercoagulation and cancer have an association; systemic hemostasis is more commonly triggered in cancer patients. Angiogenesis, progression, and the metastatic dissemination of tumors have all been linked to this systemic excitation. D-dimer is created when cross-linked fibrin breaks down; it is increased in cancer and indicates that fibrinolysis and hemostasis have been activated globally [6].

Plasma levels of d-dimer are elevated in many clinical conditions such as deep venous thrombosis (DVT), disseminated intravascular coagulation (DIC), and pulmonary embolism (PE), smoking, infection, pregnancy, old age, trauma, tumors, and others [7].

Patients with lung, breast, colorectal, and stomach cancers all had elevated plasma D-dimer levels, and research has shown a strong correlation between these levels and the prognosis of solid tumors [8]. A correlation between D-dimer level and tumor stage, spread to lymph nodes, and long-term survival in patients with solid tumors, including breast cancer, has been established by prior research [9].

It is commonly acknowledged that widespread inflammation contributes significantly to the progression of cancer. Inflammatory cells control the tumor microenvironment, which is obviously implicated in the neoplastic process and stimulates migration, proliferation, and disease consequences [1].

Neutrophil-to-lymphocyte ratio (NLR), one measure of inflammation, is strongly correlated with prognoses in early-stage breast malignancies. Researchers hypothesize a close relationship between inflammation and breast malignancies, involving both preventive measures against cancer cells and the promotion of tumor progression, although the specific processes underlying these peripheral markers for prognosis remain unknown [10].

It has been demonstrated that in breast cancer patients, a high NLR is predictive of poor overall survival and disease-free survival [11]. The relationship between a raised NLR and a bad prognostic impact may be related to diminished lymphocyte-mediated tumor response and increased neutrophil-dependent inflammation, although the precise processes behind this association are yet unclear [12].

It is well recognized that neutrophils control the tumor microenvironment and generate growth factors, chemokines, and cytokines that can stimulate angiogenesis, tumor cell immigration, and proliferation. Lymphocytes, on the other hand, are responsible for the immune response specific to tumor infiltration by T lymphocytes, as well as the anticancer activity mediated by cytotoxic T cells [13].

2. Materials and methods

A cross- sectional study was conducted on women with breast cancer in the holy city of Karbala, the study extended from September 2023 to May 2024. Sixty female patients aged 18 years and above with confirmed breast cancer were enrolled in this study. A number of exclusion criteria for the patients were adopted, such as those who received chemotherapy,radiotherapy or had recent surgery,active infection, or history of previous thrombotic events.

2.1. Collection of data

Each patient was reviewed, and the data were collected with informed consent obtained from all participants. This included sociodemographic data such as age, drug intake, chemotherapy,radiotherapy, past-medical history,history of thrombotic events,history of surgery, presence of active infection, and family history. Clinicopathological details about the patients were obtained from patient records, including tumor size, regional lymph node metastasis,distant metastasis.

2.2. Sampling methods

For laboratory analysis,pretreatment 4 ml of blood was drawn from each patient.2ml of blood in EDTA tube for complete blood count (CBC) from which the NLR was calculated. The CBC was performed by ADVIA 2120i (an automated Hematology analyzer, Siemens, Germany). 1.8 ml of blood in sodium citerate tube for quantitative determination of plasma D-dimer levels via Abbott (ARCHITECT ci4100 System) autoanalyzer. The Quantia D-Dimer reagents were used.

2.3. Statistical analysis

SPSS® software (version 23.0 for Linux® operating system) was used to perform statistical analysis of data for this study.

2.4. Ethical approval

The ethical approval for the study was obtained from the ethics committee in the pathology department as well as from the council of the College of Medicine/ University of Babylon. The agreement of health authorities in the included centers was obtained. Document number (6-10, 25/6/2023).

Table 1. TNM stage of study patients (n = 60).

TNM stage		Frequency	Percentage (%)
T status	T0	1	1.7%
	T1	9	15.0%
	T2	32	53.3%
	T3	8	13.3%
	T4	10	16.7%
N status	N0	16	26.7%
	N1	21	35.0%
	N2	23	38.3%
M status	M0	47	78.3%
	M1	13	21.7%

3. Results

Distribution of the study patients according to TNM stage (Table 1)

The mean differences of plasma D-dimer levels (ng/ml) according to tumor size (T categories) (N = 60):

There was a significant difference among T categories regarding D-Dimer means (P-value < 0.001), (Table 2).

The mean differences of plasma D-dimer level (ng/ml) according to regional lymph node state (N categories) (N = 60):

Comparison between D-Dimer and N categories showed that there was a significant relationship with P-value = 0.001 (Table 3).

The mean differences of plasma D-dimer level (ng/ml) according to distant metastasis (M categories) (n = 60):

D-Dimer was found to be significantly different between M0 category (96.8 ± 64.5) and M1 category (219.3 ± 99.2), P-value = 0.001 (Table 4).

The mean differences of Neutrophil-Lymphocyte Ratio(NLR) according to tumor size (T categories) (n = 60):

There were significant differences within the categories. P-value = 0.002, (Table 5).

The mean differences of Neutrophil-Lymphocyte Ratio(NLR) according to regional lymph node (N categories) (n = 60):

Comparison between NLR and N categories showed that there was no significant difference in NLR between N categories, P-value = 0.236 (Table 6).

The mean differences of Neutrophil-Lymphocyte Ratio(NLR) according to distant metastasis (M categories) (n = 60):

NLR was found to be significantly different between M0 category (1.990 ± 0.502) and M1 category (2.978 ± 0.908), P-value = 0.002 (Table 7).

Table 2. The mean differences of plasma D-dimer level (ng/ml) according to tumor size (T categories) (N = 60).

		D-Dimer (ng/ml)		
T stage	N	Mean ± SD	Range	P-value
T1	10	62.7 ± 37.0	33.0–157.0	<**0.001***
T2	32	108.2 ± 62.3	27.0–283.0	
T3	8	145.5 ± 89.7	34.0–290.0	
T4	10	214.7 ± 125.7	41.0–388.0	
Total	60	123.3 ± 88.5	27.0–388.0	

* Significant at P ≤ 0.05.

Table 3. The mean differences of plasma D-dimer level (ng/ml) according to regional lymph node state (N categories)(N = 60).

		D-Dimer (ng/ml)		
N stage	N	Mean ± SD	Range	P-value
N0	16	77.3 ± 34.7	34–157	**0.001***
N1	17	105.5 ± 73.4	27–290	
N2	15	171.7 ± 105.0	50–388	
Total	60	123.3 ± 88.5	27–388	

* Significant at P ≤ 0.05.

Table 4. The mean differences of plasma D-dimer level (ng/ml) according to metastasis (M categories) (n = 60).

		D-Dimer (ng/ml)		
M stage	N	Mean	SD	P-value
M0	47	96.8	64.5	**0.001***
M1	13	219.3	99.2	
Total	60	123.3	88.5	

* Significant at P ≤ 0.05.

Table 5. The mean differences of Neutrophil-Lymphocyte Ratio(NLR) according to tumor size (T categories) (n = 60).

		NLR		
T stage	N	Mean ± SD	Range	P-value
T1	10	1.936 ± 1.002	1.096–4.333	**0.002***
T2	32	2.044 ± 0.445	0.933–2.879	
T3	8	3.029 ± 0.733	2.219–4.453	
T4	10	2.323 ± 0.771	1.488–3.511	
Total	60	2.204 ± 0.730	0.933–4.453	

* Significant at P ≤ 0.05.

4. Discussion

In the present study, there were significant differences in plasma levels of D-dimer (ng/ml) regarding

Table 6. The mean differences of Neutrophil-Lymphocyte Ratio(NLR) according to regional lymph node (N categories) (n = 60).

		NLR		
N stage	N	Mean ± SD	Range	P-value
N0	16	1.908 ± 0.814	1.096–4.333	0.163
N1	21	2.258 ± 0.551	0.933–3.114	
N2	23	2.336 ± 0.782	1.998–2.674	
Total	60	2.204 ± 0.730	0.933–4.453	

* Significant at P ≤ 0.05. NLR = neutrophil to lymphocyte ratio, N = Node, SD = standard devation.

Table 7. The mean differences of Neutrophil-Lymphocyte Ratio(NLR) according to metastasis (M categories) (n = 60).

		NLR		
M stage	N	Mean	SD	P-value
M0	47	1.990	0.502	**0.002***
M1	13	2.978	0.908	
Total	60	2.204	0.730	

* Significant at P ≤ 0.05.

tumor size. Our results were in agreement with previous studies by Giaccherini *et al*. [14] and Bhavesh *et al*. [15] in which the tumor size was a significant determinant of D-dimer level. In contrast, a study by Halugodu et al. [16] showed that the D-dimer did not correlate with tumor size. Hence, the relationship was statistically not significant.

The current work demonstrated a statistically significant correlation between the state of the axillary lymph nodes and the levels of D dimer. Our results were consistent with Hermansyah *et al.* [17], Gochhait *et al*. [18] and Giaccherini *et al*. [14], all of them had showed there was a significant link between D-dimer and lymph node involvement. However, Multani *et al*. [19] and Fregoni *et al*. [20] did not find a significant relationships between lymph node status and levels of D-dimer.

In our research, plasma D-Dimer level was found to be significantly different between M0 category and M1 category in agreement with Dai *et al*. [21] and Dharamsi *et al.* [22] who found a positive association between plasma D-dimer levels and metastasis in breast cancer patients. In cancer patients, distant metastasis is the primary factor contributing to a poor prognosis and treatment resistance [23]. A study has shown that active coagulation, often observed in cancer, plays a crucial role in the spread of cancer [24]. In cancer patients, the coagulation/fibrinolytic system is involved, which may aid in the spread of the disease.

The current study showed that the NLR correlated significantly with tumor size. Fujimoto *et al*. [10] and Ferroni *et al*. [25], reported that the NLR had correlated significantly with tumor size.In the other hand,a study by Tekyol *et al*. [26] showed that there was no statistically significant relationship between the NLR levels and tumor size of Breast cancer patients.

Our data found that there was a no significant association between the NLR values and lymph node status, that was compatible with Anwar *et al*. [27] who also reported there was no significant NLR differences found according to axillary node status. However, a study by Ferroni *et al*. [25] found that lymph node involvement was significantly associated with high NLR.

In our study, NLR was found to be significantly different between M0 category and M1 category, similar to Cho *et al*. [28] and Dirican *et al*. [29] reported that the distant metastasis of the tumor was significantly correlated with high NLR. This association highlights the importance of the tumor immune milieu, which fosters the growth of aberrant cells and signals their activity through an increase in non-invasive blood cell markers like NLR.

5. Conclusion

There was a significant association between pretreatment plasma D-Dimer levels and Neutrophile to lymphocyte Ratio and tumor size, lymph node involvement, and tumor metastasis.

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