D-dimer as a Predictive Factor of Axillary Lymph Node Metastases in Operable Breast Cancer Patients

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ABSTRACT

Background: Axillary lymph node (ALN) involvement in breast cancer (BC) is considered to be a significant factor in determining the diseases' extent at the moment. The spreading capacity of cancerous cells may linearly correlate with its activity level, which in turn alter the coagulation function as commonly represented by fibrin degradation biomarker i.e., D-dimer. Although ALN metastatic status is eventually should be perceptible in physical examinations or other diagnostic modalities, an additional marker to estimate the lymph node extent should be considered in the pre-operative sessions. Objective: To provide the correlation between elevated D-dimer level and ALN metastatic status positivity among BC patients. Methods: This cross-sectional study was conducted at the Teaching Hospital of Universitas Sumatera Utara by retrieving outpatients' medical records from June 2018 to January 2019, encompassing 111 female patients. The ALN involvement status was recorded along with plasma D-dimer level in which the value of 500 ng/mL was considered to be elevated. Results: From the 102 eligible participants, 47.1% and 70.6% were confirmed with elevated D-dimer level and ALN involved respectively. Further analysis of those variables demonstrated a considerable diagnostic performance for sensitivity (64.4%), specificity (79.1%), PPV (80.9%), NPV (61.8%), accuracy (70.6%) and statistically significant results (P = .001). Conclusion: Elevated D-dimer level may be influenced by cancerous spread capacity in the lymphatic system, as it also eventually correlated with coagulation system dysregulation. Therefore, it is suggested that the role of D-dimer measurement is recommended to be explored further in BC diagnostic workup.

Keywords: axillary lymph node, breast cancer, D-dimer.

1. BACKGROUND

Breast cancer (BC) in women is considered to be one of the most remarkable malignancies globally and associated with actively changing practices and therapeutic efficacy measurement since the oncologic science of BC were investigated thoroughly at the moment. BC is also the major cause of mortality in women between the ages of 20 and 59 considering it is expected to be encompassing 30% of all new cancer disease in women out of 2019. BC has many degrees of heterogeneous growth (1). Clinical manifestation e.g., cancer lymph nodes metastasis stage (TNM), chemical receptor expression, human epidermal development factor 2 (HER2) expression, and metastasis may delineate the severity and extent of BC. Aside from routinely used malignancy growth markers i.e., carcinoembryonic antigen and cancer antigen 15-3; we direly required an additional establishing biomarker to assist differential analysis and diagnostic judgment (2–4).

Cancerous cells often metastasized to axillary lymph nodes (ALN), and ALN metastatic status is currently possessing a prognostic factor in early phase of BCs’ development, influencing possible managing and therapeutic approach in the next sequence (5). Accordingly, ALN metastasis is a significant pre-metastasis features and the presentation of those metastases may contribute to overall malignancy grading system. In fact, patients with ALN micro- and/or macrometastases positive BC have a low disease-free survival
rate either shortly or after numerous years since diagnosis confirmation (6, 7).

Connection between tumorigenesis and hypercoagulation states in patients with malignancy had been discussed plethora times in oncologic forum. Dysregulation of blood clotting system as induced by tumor-related activity primarily in its microenvironment may frames an endless loop between mis-activated coagulation function and the underlying malignancy itself. And as mentioned earlier, a BC’s severity may be represented by presence of lymph node metastasis hence partially depicting its cancerous activity, in which will furtherly influencing fibrinolysis rate as represented by elevated D-dimer level. Moreover, tumor turnout rate is eventually connected to hyperfibrinolysis (enhancement of cross-connected fibrin disintegration), manifesting as a response toward over-activated fibrin formation by foundational actuation of cancer cells e.g., growth angiogenesis, tumor movement, and metastatic spread; possibly perceived in lymph node-related spread as well. Those coagulation framework initiation, along with microthrombi creation and increasing turn-rate of overall fibrin product will elevate D-dimer level subsequently, considering the latter parameter possess an ability to represent fibrin remodelling activity (8–12).

2. OBJECTIVE
This study aims to investigate the role of elevated D-dimer level as an indicator of lymph nodes metastasis specifically in axillary region among BC patients, as early findings and rational timings of treatment initiation are critical in estimating the prognosis later.

3. MATERIAL AND METHODS
This cross-sectional study was conducted at the Teaching Hospital of Universitas Sumatera Utara. The patients’ data were retrieved from outpatients ward medical records from June 2018 to January 2019. A total of 111 female patients with invasive/infiltrative breast cancer were included in this study. This study had been supervised and ethically approved by Universitas Sumatera Utara ethics committee (No:382/TGL/KEPK FK USU-RSUP HAM/2019).

Eligibility criteria
We restricted the populations in patients with confirmed BC stage I-III, hence excluding stage IV patients. After we conclude the operation and neo-adjuvant therapy, we confirmed the histopathology status in the lymph node if there was any LNM.

Blood venous samples (3 ccs) were collected from all patients before any surgical and pharmacological intervention undertaken, and we did clinical staging including; tumor size, site, nodal involvement, distant metastases (TNM). Grading of the disease was done by a histopathological study including lymph involvement, lymphovascular invasion, and several 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. We sent the samples for histopathological study as mentioned above. P-value of <.05 after Chi-Square analysis as applied and executed by utilizing IBM SPSS 24 software was considered statistically significant. The D-dimer measurement was carried out in ng/mL to achieve test standardization among global studies in similar method. The value of <500 ng/mL were considered to be normal or ‘relatively low’ D-dimer. Conversely, elevation of D-dimer level can be confirmed in patients with >500 ng/mL results after the specimens had been detected by immunoassays method.

4. RESULTS
This study encompassing an analysis of 102 women which passed the eligibility criteria mentioned earlier, since 9 individuals in this early phase of this study were excluded due to insufficient data in either ALN involvement status and/or D-dimer level outcomes. Table 1 showed tumor characteristics distribution among samples distributed according to the stage of the disease. Based on tumor size type, the T1 (<2 cm) found in one patient (0.9%), T2 size (2-5 cm) are found in 8 patients (7.8%), T3 (>5 cm) is found in 12 patients (11.8%), and T4 which classified as any size spread beyond breast tissues are found in 81 patients (79.5%). In ALN involvement status data report as the primary intention of this study, 72 patients (70.6%) were reported to be positively involved or metastatically confirmed. Following, D-dimer level examination were demonstrating comparable rate of normal-and-elevated populations, as 48 participants (47.1%) were disclosing elevated D-dimer level.

| Variables          | Number of patients (n) | Percentages (%) |
|--------------------|------------------------|-----------------|
| Tumour size type   |                        |                 |
| T1                 | 1                      | 0.9%            |
| T2                 | 8                      | 7.8%            |
| T3                 | 12                     | 11.8%           |
| T4                 | 81                     | 79.5%           |
| Lymph node status  |                        |                 |
| Metastasis         | 72                     | 70.6%           |
| Non-metastasis     | 30                     | 29.4%           |
| Metastasis         |                        |                 |
| Yes                | 37                     | 36.3%           |
| No                 | 65                     | 63.7%           |
| Grade              |                        |                 |
| Low                | 54                     | 53%             |
| High               | 48                     | 47%             |
| D-dimer level      |                        |                 |
| Low (<500 ng)      | 54                     | 52.9%           |
| High (>500 ng)     | 48                     | 47.1%           |
| Total              | 102                    | 100%            |

Table 2. Axillary lymph node metastasis status as correlated to D-dimer levels. *Pearson Chi-Square analysis significant outcomes above. P-value of <.05 after Chi-Square analysis as applied and executed by utilizing IBM SPSS 24 software was considered statistically significant. The D-dimer measurement was carried out in ng/mL to achieve test standardization among global studies in similar method. The value of <500 ng/mL were considered to be normal or ‘relatively low’ D-dimer. Conversely, elevation of D-dimer level can be confirmed in patients with >500 ng/mL results after the specimens had been detected by immunoassays method.

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We observed a significant relationship between the ALN metastasis of the diseases as correlated D-dimers’ level p-value of 0.001 shown in Table 2. The result exhibited that the involvement of ALN in a BC can be represented by elevation of d-dimer. Further analysis of D-dimer as a diagnostic tool to estimate ALN involvement also had been carried out in this study; as the sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were 64.4%, 79.1%, 80.9%, 61.8%, and 70.6% respectively. Those relatively mediocre but acceptable diagnostic performance results were probably originated from high false-negative (FN) results, reducing the value of Sn and NVP. However, we also found a favorable Sp and PPV outcomes, since D-dimer analysis was relatively low in risk for disclosing false-positive (FP) results. Consequently, the presence of elevated D-dimer in a BCs’ cases generally (or even in patients with higher probability of developing metastatic disease), should raise a suspicion for ALN involvement; especially in the settings of inadequate physical examination or micro-metastatic focus.

5. DISCUSSION

D-dimer is numerously investigated in almost every haemato-oncologic science e.g., coagulopathy and malignancy; or primarily BC as the main focus of this study. The pathophysiology of D-dimer elevation in those disorders has not been completely understood, yet recent studies or literatures that its role in cancer patients probably should be considered than ever. This study is suggesting that elevation of D-dimer level may presenting a significant prognostic value, practically defining the extent of ALN involvement as well hence disclosing part of disease severity or even contribute to overall grading system. Fibrin metabolism and regulation as delineated by D-dimer level in plasma is a currently investigated yet potentially core-acting biomarker to prognosticate lymphatic invasion status and early growth metastasis in confirmed BC. Although the role of the other BC predictive factor e.g., estrogen and/or progesterone receptor (ER/PR) expressivity, human-epidermal receptor (HER)-2 status, tumor size, and histopathological investigations (HPE) are unquestionably essential in establishing the most anticipated course of disease, another functioning marker should be considered to support the primary workup of BC, or at least representing how active a malignancy was.

Angiogenesis, often considered to be pivotal in tumorigenesis itself, crucial enough to be actively correlated with disease activity at some extents or spreading capacity to other systems, or organs as observed in ALN involvement. The subsequent outcomes of those cancer pathophysiologic features are an increase in fibrin degradation rate; hence it is plausible to assume higher D-dimer level to represent fibrin by-product breakdown may be eventually influenced by a perceivably higher grade or spread of a cancerous focus. D-dimer basically acted as a reflection of dysregulation of physiologic coagulation function and fibrinolysis activity in a person (13–15). Our data also corresponded with the other global studies in similar subjects. Ghadbian in 2018 had mentioned that populations with involved ALN possesses significantly higher mean of D-dimer level (4 mg/L) compared to non-involved group (0.25 mg/L); according to its correlation analysis, there was a strong association of both variables and it does significantly influence the affirmation of clinical staging (16). Rajendran et al., and Srivastava et al., also demonstrated that BC patients with high ALN status (N1) are presented with higher baseline D-dimer levels significantly (712.0 ± 936.6 ng/mL and 772.3 ± 168.6 ng/mL) compared to lower grade of ALN involvement (17, 18).

Furthermore, Kataria dan Juneja in their study also had demonstrated that the role of D-dimer elevation should be considered to diagnose BC itself; since the study reported that non-ALN involved BC group D-dimer was 1,354 ± 1,315 ng/mL, even though the elevation was significantly remarkable in the ALN involved group within 2,896 ± 1,865 ng/mL (12). In fact, a systematic review and meta-analysis by Lu et al., in 2016 had conducted an investigation toward the mean and standard deviation (SD) of plasma D-dimer among ALN-metastasis confirmed vs. not-involved group. The analysis toward 8 different studies concluded the result of standardized mean difference (SMD) to 0.79 [0.50, 1.09] with 95% CI, albeit our opinion in those analysis method should be converted to single common unit since SMD does not attach to any measurement tools hence it is challenging to interpret whether certain value should fall under suspicion. Nevertheless, the value of 0.79 in SMD may suggest a statistically meaningful and influential results to establish the correlation between elevated D-dimer results and ALN involvement (1). Therefore, those data are compatible with our findings, since we found there was an observable correlation between elevated D-dimer and ALN metastatic positivity; additionally since its diagnostic performance was in a relatively acceptable range to be applied routinely.

We acknowledged that some studies had conducted an analysis toward D-dimer elevation and ALN metastasis in recent decades, however. An establishing remark to determine the true role of D-dimer in malignancy specifically BC should be conducted, as many evidences had provided some noteworthy proof regarding the function of D-dimer measurement in pre-treated operable BC. To that reason, we believe further investigation by reviewing the variables systematically or even quantitatively may suffice to answer the predicting role of D-dimer in upcoming years, thus an agreement or justification of its measurement in routine workup can be achieved and better apprehension of the correlation between tumor reactivity and fibrin breakdown or coagulation disorders may be understood generally.

6. CONCLUSION

Plasma D-dimer levels are a decent prognostic and predictive marker for BC, or malignancy in general. In this study, a correlation was observed between elevated D-dimer level above certain value (500 ng/mL) and ALN
metastatic positivity; as a part in completing a framework of evidence to support the theory of tumor spreading capacity may be represented by an alteration in coagulation biomarker. Consequently, we suggest that an elevation of D-dimer level should raise the physician awareness of a relatively aggressive form of cancer, or higher grade of solid tumor hence careful consideration in further management and rationale of therapeutic approach can be achieved.

- **Patient Consent Form:** Since this study utilizes patients’ medical record, no consent form or any kind of direct agreement collected from the participants; and considering the study was conducted at teaching hospitals of Universitas Sumatera Utara (a state university), all patients had agreed the data to be collected by the formal researchers (or authors) to fulfill our and global educational purpose.
- **Authors contribution:** We arranged the role of each author according to CRediT taxonomy to capture the contributions better. Which are: Conceptualization: DH, NNF, RBN, DRS; Data Curation: DH, RBN; Formal Analysis: DH, NNF, RBN; Funding Acquisition: None; Investigation: DH, NNF, RBN; Methodology: DH, NNF; Project Administration: DH, DRS; Resources: DH, RBN; Software: NNF, RBN; Supervision: DH, DRS; Validation: DH, NNF; Visualization: DH, RBN; Writing-original draft: DH, NNF, RBN; Writing-review & editing: DH, NNF, RBN, DRS. All authors had acknowledged the final version of manuscript before any submission was made.
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