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The Role of Plasma D-dimer Level Measurement to Assist Breast Cancer Histopathological Grading

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Abstract

BACKGROUND: The histopathological grades identification is unquestionably essential to determine the most effective approach in oncologic management, specifically in breast cancer (BC) as the most common malignancy diagnosed worldwide. Complex and micro-level alterations of coagulation function of the host may occur at some point since the reactivity of the tumor cells byproduct will dysregulate its physiologic function; as represented by the higher rate of fibrinolysis which in turn increase the D-dimer level.

AIM: The study aims to provide the correlation between the level of d-dimer and histopathological grades in BC patients.

METHODS: A total of 111 females with confirmed BC were included in this study, which was conducted from March to September 2021 at the teaching hospital of Universitas Sumatera Utara. After thorough clinical information analysis, the histopathological examination (HPE) was conducted to confirm the malignancy and graded based on the Bloom-Richardson grading system; therefore, the HPEs were classified into slow/moderate or poorly differentiated. The D-dimer value of >0.5 mg/L was indicated as an elevated level.

RESULTS: From the 102 eligible patients to be included in the final evaluation, it was observed that 46.1% and 52.9% of the participants were presumed with elevated D-dimer level and high-grade carcinoma, respectively. The elevated D-dimer level results percentage was substantially more common in high-grade BC (72.3%, the positive predictive value analysis. Other parameters, for example, sensitivity (63.0%), specificity (72.9%), and negative predictive value (63.6%) were found to be statistically accurate ($p < 0.001$).

CONCLUSION: The influence of tumor cells differentiation toward coagulation system or fibrin metabolism dysfunction is observable in this study. Hence, the role D-dimer level measurement should be investigated further to assist the BCs' grading determination workup.

Introduction

Breast cancer (BC) is the most common malignancy diagnosed worldwide and exhibited a particularly diverse spectrum as well-which influences its nature and progressiveness behavior in oncologic science. To date, several parameters had been elaborated to estimate the current BCs' states, especially the histopathological grading assessment which virtually posed as the sine qua non of the disease predictability, affecting the survival aspect approximation in later years. Accordingly, the identification of several potential biomarkers to predict the histological grading itself is highly discussed albeit its controversial findings and ambivalence interpretations.

The hypercoagulable state may occur as a result of complex and partially understood interactions between the byproduct of tumor cells and the host blood clotting cascade. The activation of the latter pathway will eventually lead to the systemic activation of hemostasis as a result of the induction of several procoagulant properties, for example, tissue factor; or even the inhibition of the physiologic anticoagulant mechanism itself. Theoretically, the hemostasis event is by any means correlated with the malignancy tissue activity, either a locally advanced lesion or its metastatic spread as observed in advanced BC; considering the interplay of fibrin remodeling is clearly involved in all sequences of neoplasm tissues development predominantly the angiogenesis which unquestionably essential for the tumor cells progression [1], [2], [3], [4]. Further dysregulation of the blood clotting function will result in a perceivably higher rate of fibrinolysis or ongoing fibrinogen metabolism as observed in advanced solid tumors and their procoagulant activities, with or without metastasis, however. The estimation of the histological gradings' status quo is still eminently practicable as the more undifferentiated tumor cells tend to be more aggressive as well; thus, will more likely to alter the hemostasis and lead to tumor-related hyperfibrinolysis as the response of overly-activated blood clot or fibrin formation [3], [5], [6], [7].

Therefore, the elevation of D-dimer as the product of fibrin degradation is conveyed as a functional biomarker to approximate the BCs' histological grading, reckoning its capability in representing hemostasis activation, fibrinolysis, and guesstimating the diffuse intravascular coagulation enhancement following the advancement of a tumor grading. In this study, we aim to provide the correlation between the level of D-dimer, and its histopathological grading considering the possibility of D-dimers' elevation is not as simple as an epiphenomenon of BC, but also delineating the tumor cells grading.

Materials and Methods

This study was conducted at the teaching hospital of Universitas Sumatera Utara in Medan, Indonesia from March to September 2021. A total of 111 females with confirmed BC cases as admitted to the department of surgical oncology in the same institutions were included in this study. The ethical consideration had been supervised and considered by the Universitas Sumatera Utara ethics committee (327/KEP/USU/2021).

Eligibility criteria

Female with BC as confirmed by histopathological examination (HPE) diagnostic procedure without any restriction regarding its assessment results based on the modified Bloom-Richardson grading system (BRS) or also commonly termed as Nottingham Histologic Score system.

Before any initial assessment was conducted, the diagnosis of breast lump was acquired from the candidates, along with additional information to support our diagnostic procedures for further malignancy screening. We collected the blood venous samples (3 ccs) from all included and eligible participants before any kind of intervention (i.e., either pharmacologically or surgical treatment) was administered and clinical staging was determined, for example, tumor size, metastatic lesion, or primarily HPE-based diagnosis. All HPE results were previously reported by the department of pathological anatomy in the same institutions, before sample analysis request by the surgical oncology department.

The D-dimer level was measured in mg/L to standardize our findings with the other investigation worldwide; the value of >0.5 mg/L was presumed as an elevated D-dimer level. The specimens were detected using the immunoassays to detect the D-dimer domain in fibrinogen which manifested specifically by its monoclonal antibodies. Regarding the HPE result establishment, the samples were addressed to the surgical pathology department for diagnostic confirmation. We also have clarified our judgment as "low grade or well-to-moderately differentiated" BC if the findings were grade 1 and 2 following the BRS evaluation method; accordingly, grade 3 findings are concluded as "high grade or poorly differentiated" BC considering its exceptional appearance histologically.

The data analysis was carried out using IBM SPSS 24 software to measure the comparison between both arms using Pearson Chi-square since the presumption regarding the influence of cancer activities to its biological marker is clear, and the analysis were conducted toward graded variables, hence parametric analysis was primarily undertaken. The p-value of <.05 was considered to be statistically significant. We also conducted the receiver operating characteristic (ROC) curve analysis to demonstrate the area under the curve (AUC) regarding the correlation between D-dimer and histopathological analysis to delineate the analysis more illustratively.

Results

All of the enrolled patients in this study were females; 9 participants were excluded from the final analysis as we did not collect sufficient data in either HPE findings or D-dimer level measurement outcomes. Henceforth, there are only 102 eligible participants to be included in the final evaluation. In our primary objective analysis, we found that 47 (46.1%) patients manifested an elevated level of D-dimer value (>0.5 mg/L). Secondarily, the report from the HPE revealed that 54 (52.9%) of the subjects are diagnosed with high-grade carcinoma of the breast (grade 3 BC in histologic findings according to BRS system) as shown in Table 1.

Table 1: Participants' characteristics

Parameters	n	%
Age (years)		
<40	12	11.8
41–50	43	42.1
51–60	36	35.3
61–70	11	10.8
>70	0	0.0
Tumor size type		
T1	1	1.0
T2	8	7.8
T3	23	22.5
T4	70	68.6
Lymph node involvement		
Yes	72	70.6
No	30	29.4
Metastatic status		
Yes	37	36.3
No	65	63.7
Histological grading		
High grade	54	52.9
Low grade	48	47.1
D–dimer level		
Elevated	47	46.1
Normal	55	53.9
Total	102	100.0

From the latter table, a substantially higher percentage of elevated D-dimer levels are found in

high-grade BC as represented by 34 patients (72.3%); or referred to as positive predictive value (PPV) of elevated D-dimer level, relatively by HPE as the gold standard in this analysis. Consequently, the negative predictive value (NPV) of the D-dimer assessment in this study was 63.6%, which applies the same presumption as earlier interpretation. We also conducted sensitivity and specificity analysis in this study; respectively, the results are 63.0% and 72.9% for the D-dimer elevation test to predict histopathological gradings of BC in our study.

Table 2: The cross tabulations and Chi-square analysis to determine the correlation between D-dimer level and histological grading results in this study

Parameter	Histological grading		Total	p-value*
	High grade	Low grade		
D-dimer				
Elevated	34	13	47	0.001
Normal	20	35	55	
Total	54	48	102	

*The applied p- value in this table is the result of Pearson Chi-square analysis which falls below the significance cut-off point of 0.05, therefore this correlation was concluded to be statistically significant.

Our investigation of the correlation between both variables using Chi-square tests exhibited a significant outcome; the association between elevated D-dimer value and higher grade of HPE results (or vice versa) are represented by the $p < 0.05$ (in which our findings revealed the $p = 0.001$)-as listed in Table 2, with the Pearson correlation of 0.359 (low positive correlation). Further analysis toward lymph node and distant metastatic status exhibited a significant association ($p < 0.05$), although it was negligible since the Pearson correlation value were 0.208 and 0.243 respectively (Table 3a and b). ROC curve analysis of the correlation between D-dimer and histopathological results are presented in Figure 1 with the AUC value of 0.561, in which we found the diagnostic accuracies and histopathological grades estimation of D-dimer to be relatively unsatisfactory according to our finding.

Table 3a: The cross tabulations and Chi-square analysis to determine the correlation between D-dimer level and lymph node (A) and distant (B) metastatic status in this study

Parameter	Lymph node metastatic		Total	p-value*
	Present	Absent		
D-dimer				
Elevated	34	21	55	0.036
Normal	38	9	55	
Total	72	30	102	
Table 3b				
Parameter	Distant metastatic		Total	p-value*
	Present	Absent		
D-dimer				
Elevated	14	41	55	0.014
Normal	23	24	47	
Total	37	65	102	

*The applied p-value in this table is the result of Pearson bivariate analysis which falls below the significance cut-off point of 0.05, therefore this correlation was concluded to be statistically significant.

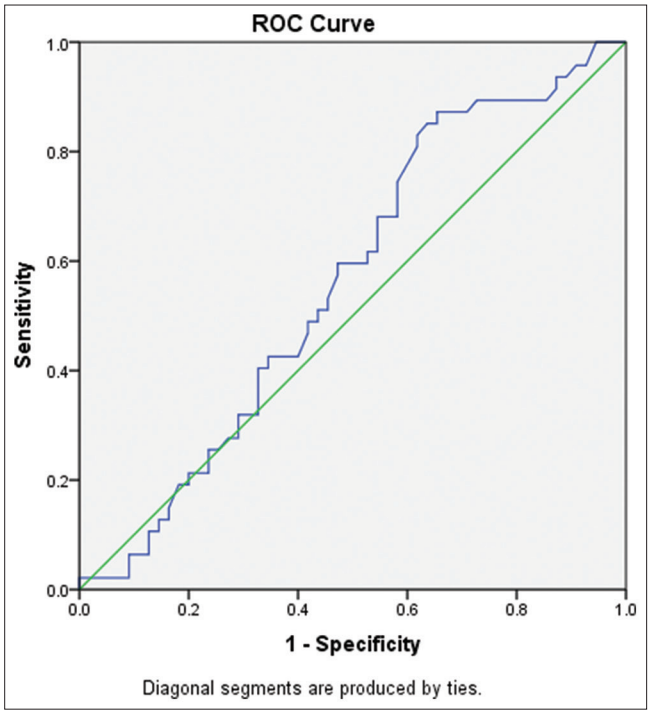

Figure 1: Receiver operating characteristic curve of D-dimer and histopathological results with the area under the curve value of 0.561 as analyzed this study

Discussion

In the last decades, the number of BC diagnosed worldwide is increasing at an alarming rate and certainly, the digit itself will be enumerated in the later years-considering such a significant increase in the global population or even the corresponding risk factors of breast malignancy. Prognostic and prediction, posed as the most commonly discussed issues in oncologic medicine, whilst influencing the treatment strategies; it's also offered a reliable approach for the malignancy monitoring, further projection, or even reflecting the current histologic grading in the initial phase of screening. Thereby, in our perspective to contemplate the potential role of D-dimer, we viewed its predictive value to determine its correlation with HPE as necessary to be established. Although to date, there are several options to be applied to as prognostic and predictive indicator, for example, estrogen or progesterone receptor expression, human-epidermal receptor 2 status, tumor size, lymph node involvement, or even the histopathological degree essentially; the presence of additional determination factor, that is, D-dimer may provide some auxiliary foundation for the diagnostic workup.

The role of D-dimer in conveying a representing information regarding the hemostasis or fibrin remodeling activity is a well-known capability, as the parameter itself is a byproduct of coagulation and fibrinolysis (or fibrin transition in circulation) hence reported to be elevated in several pathologic condition-just as BC to exemplify [8], [9]. The angiogenesis event is considerably crucial for the tumor tissues development particularly in its spreading capacity to the other organs, that is, metastasis occurrence unquestionably involves the activation of the coagulation system, along with the increased level of the overall fibrin metabolism as seen in all malignancy.

Upregulation of multiple cancerous activities is also linearly correlated with the alteration of the individuals' hematological activity, as seen in advanced cases of malignancy; whether in the metastatic spread or even histologically deteriorated hence displayed perceptively higher HPE grading [2], [6], [7], [10], [11], [12]. Several reviews also had disclosed the association between an elevated level of D-dimer and the unfavorable prognostic value, highlighting the ability of tumor cells to promote blood coagulation system, increased platelet activity, or vascular endothelial cells to some degree. The presumption was also established by the findings of there is a correlation between the latter mechanism and tumors' migratory and development behavior, reasonably justifying the activated coagulation system acts as a facilitator for tumor cells metastasis-or its cellular progression [4], [11], [13], [14], [15].

According to our findings, the elevated D-dimer level demonstrated a statistically remarkable predictive value toward a higher grade of HPE outcomes ($p < 0.0001$). The sensitivity and specificity of the elevated D-dimer were 63.0% and 72.9%, respectively. The results were preeminent considering the fact that we are currently implementing the point of 0.5000 mg/dL as elevated D-dimer cut-off, henceforth significantly better diagnostic performance can be achieved by adjusting the cut-off point-in which a higher value may possess higher specificity as well. Correspondingly, either the PPV or NPV also manifested similar results as our previous analysis. It is crucial to be noted that we had previously designed our analysis to be compatible with the Chi-square crosstabulations, therefore the decision regarding its diagnostic accuracy-relative to our applied laboratory or HPE final conclusion. The association of D-dimer and metastatic status were barely observed in this study even though it was statistically significant according to its p-value.

Harish *et al*., in 2018 also investigated similar variables in India; our findings were consistent with their conclusion as the association between the elevated D-dimer levels and BRS results are established; represented by the higher median value of D-dimer in higher histopathological gradings' level and significant $p < 0.05$ in every possible association conducted; however, in this study there was a remarkable correlation of D-dimer and lymphovascular invasion [9]. The findings were also in line with the investigation results of Ghadhban in 2018; it appeared that there was a linear connection between the D-dimer mean value and histopathological gradings, as the higher HPE conclusion may suggest an elevated D-dimer value as well [8]. Another study by Batschauer *et al*. showed there was no significant correlation between D-dimers level and both clinical and histopathological findings ($p > 0.213$), however. It is noteworthy to mention that the latter investigation also applied immuno-histochemical detection of several transcription factors, for example, p53, Ki-67, and also, the exclusively assessed the correlation of D-dimer elevation and those factors expression; therefore does not apply any direct analysis toward the BRS method as we implemented in this study [16].

To the best of our knowledge, this is the first study to evaluate the both sensitivity and specificity of D-dimer elevation to detect grade III carcinoma of the breast. Even though the existence of the other parameter, for example, lymphovascular invasion and metastatic status is remarkably influencing the prognostic judgment, the consideration of the other relatively non-invasive test certainly potential to become a favorable initial screening test. Henceforth, we believed further inquiry is highly necessary to determine the role of D-dimer in predicting high-grade BC in the future, thus better understanding regarding its pivotal capacity in early diagnostic procedures can be decided.

Conclusion

The activation of the coagulation system and fibrin metabolism are highly affected by the degree of tumor cells, whether it is undifferentiated histologic findings or its metastasis status. This cross-sectional study suggests that there is a possible role of D-dimer level workup in BC diagnostic procedures and its diagnostic capability should be considered to estimate the tumor histological grading, or prognosticate the patient's further condition at some extent. Moreover, larger scale investigations or systematic analysis study of the correlation between d-dimer and histological grading is necessary to confirm its clinical relevance in further practice.

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