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Analysis of D-Dimer Levels Based on Histopathological Grading of Breast Cancer

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ABSTRACT

Background: *Elevated D-dimer levels, has been associated with advanced stage, metastasis, and poor prognosis in breast cancer. However, it remains unclear whether D-dimer also correlates with histopathological grade as an indicator of intrinsic tumor aggressiveness.* ***Objective:*** *To evaluate the association between plasma D-dimer levels and histopathological grading of invasive breast cancer.* ***Methods:*** *This cross-sectional study included 180 untreated female patients with primary invasive breast cancer, comprising 60 cases each of Grade I, Grade II, and Grade III tumors. Plasma D-dimer levels were measured using a latex-enhanced immunoturbidimetric assay, and histological grading was determined according to the Nottingham system. Data were analyzed using the Kruskal–Wallis test, ANOVA on log-transformed values, post-hoc tests, and ANCOVA with adjustment for age, body mass index, clinical stage, C-reactive protein, lymphovascular invasion, and molecular subtype. Receiver operating characteristic analysis was performed to distinguish Grade III from lower grades.* ***Results:*** *Median D-dimer levels increased progressively from Grade I (501.7 ng/mL) to Grade II (831.0 ng/mL) and Grade III (1312.9 ng/mL), with a statistically significant overall difference ($p < 0.001$). Receiver operating characteristic analysis for identifying Grade III yielded an Area Under the Curve of 0.960 with an optimal cut-off of 965.5 ng/mL, Fibrinogen Equivalent Unit (sensitivity 91.7%, specificity 90.0%).* ***Conclusion:*** *Plasma D-dimer levels are significantly associated with histopathological grade in invasive breast cancer, regardless of potential confounders. D-dimer testing may help identify patients with high-grade tumors early, support risk stratification, guide intensive treatment, and alert clinicians to possible thromboembolic complications, especially in resource-limited settings.*

1. INTRODUCTION

Breast cancer remains the leading malignancy among women and a major health concern globally and in Indonesia, where late-stage presentation is frequent. Prognosis relies on clinical, pathological, and molecular factors, with histopathological grade—a measure of tumor aggressiveness—playing a central role in prediction. It remains unclear if D-dimer, a coagulation biomarker, reflects intrinsic tumor biology as defined by standardized grading, particularly in

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Indonesia. Limited data directly address this, leaving uncertainty about the biomarker's role in mirroring tumor-grade–associated aggressiveness.

Recent interest has focused on blood-based biomarkers, such as D-dimer, a fibrin degradation product that indicates coagulation activation. Elevated D-dimer is widely used to assess thromboembolic risk, and cancer is known to induce a hypercoagulable state. Its potential as a marker of tumor biology is under investigation.

The pathophysiological basis of D-dimer elevation in cancer is multifactorial. Tumor cells can directly activate coagulation pathways by expressing tissue factor and cancer procoagulant, and they can also induce systemic inflammation that augments thrombin generation.[9] Furthermore, tumor-associated angiogenesis, vascular invasion, and the release of extracellular vesicles contribute to a prothrombotic state. These mechanisms not only predispose cancer patients to thromboembolic events but also appear to correlate with tumor burden, metastatic potential, and overall prognosis. Several clinical studies have reported that elevated D-dimer levels in breast cancer patients are associated with advanced stage, nodal involvement, distant metastasis, and decreased survival.[5,10] However, the relationship between D-dimer levels and histopathological grade, an independent prognostic factor, remains less clearly defined. [11]

Understanding the association between D-dimer levels and histopathological grading has direct clinical relevance. If higher tumor grades are consistently associated with elevated D-dimer, this widely available, rapid, and low-cost assay could be used as a simple adjunct to flag patients with biologically aggressive disease, even before or alongside definitive histopathological reporting—particularly in settings where access to timely, high-quality pathology services is limited. [12,13]

Most prior studies address D-dimer in relation to staging and thromboembolic risk, with limited information on its association with tumor differentiation grade. Establishing this link could refine prognostic models and guide therapy intensity.

2. METHODS

This study was an observational, cross-sectional study aimed at evaluating the relationship between plasma D-dimer levels and histopathological grading of invasive breast cancer. The study aims to analyze plasma D-dimer levels in patients with invasive breast cancer and to compare them across histopathological grades as determined by the Nottingham system. A total of 180 subjects were recruited through consecutive sampling from female patients aged 35 years or older who had a confirmed diagnosis of primary invasive breast cancer based on histopathological examination and had not received any anticancer therapy, including surgery, chemotherapy, radiotherapy, targeted therapy, or hormonal therapy. The study was conducted over a 12-month period at Pasar Mingu General Hospital and Tarakan General Hospital for subject recruitment, at the anatomical pathology unit for histological grading, and at the clinical pathology coagulation laboratory for D-dimer testing.

Exclusion criteria included a history of venous thromboembolism within the past three months, major surgery or severe trauma within the past four weeks, acute infection or active inflammatory disease, pregnancy or postpartum period, decompensated liver disease or severe renal impairment, use of systemic anticoagulants within the past two weeks, suspicion of disseminated intravascular coagulation (DIC) or active bleeding, and the presence of another active malignancy or metastasis from a non-breast primary tumor. All participants who met the inclusion criteria and did not meet the exclusion criteria were provided with a full explanation of the study and signed written informed consent.

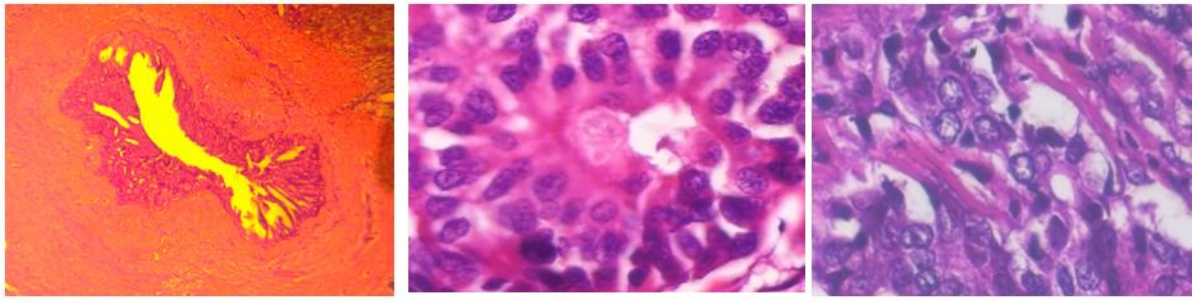
Blood specimens were collected in the morning between 08:00 and 10:00 hours prior to initiation of primary therapy. Peripheral venous blood was drawn into tubes containing 3.2% sodium citrate at a blood-to-anticoagulant ratio of 9:1. Samples were processed according to standard pre-analytical protocols: gently inverted 3–4 times, transported to the laboratory within

one hour, and centrifuged at 2.000–2.500 g for 15 minutes at room temperature to obtain platelet-poor plasma. If immediate analysis was not possible, plasma was stored at −80 °C and subjected to only a single freeze–thaw cycle.

Plasma D-dimer was measured in the clinical pathology laboratory using a latex-enhanced immunoturbidimetric method on an automated coagulation analyzer (Sysmex CS-2500). Two-level internal quality control was run with each batch. Results were expressed as ng/mL FEU. The laboratory reference value applied in this study was ≤500 ng/mL FEU (values above this threshold were considered elevated according to the manufacturer's instructions and the hospital laboratory standard). Laboratory personnel performing the assays were blinded to the histopathological grading results. Internal quality control was performed at two levels for each analytical run, targeting a coefficient of variation below 10%. The laboratory also participated in an external proficiency testing program when available.

Tumor histopathological grading was performed by two board-certified anatomical pathologists (YD and RAD) using the Nottingham/Bloom–Richardson system, assessing tubule formation, nuclear pleomorphism, and mitotic count. In cases of discrepancy, consensus was reached through discussion. In addition to grading, histological tumor type, lymphovascular invasion (LVI) status, and other supporting data, such as tumor size and axillary lymph node status, were recorded.

Figure 1.
Histopathological features of invasive primary breast cancer with hematoxylin and eosin (H&E) staining, from left to right: Grade I shows well-formed glandular structures with minimal nuclear atypia; Grade II displays moderately differentiated tumor cells with increased nuclear pleomorphism and reduced gland formation; and Grade III is characterized by poorly differentiated cells, marked nuclear atypia, and high mitotic activity



Statistical analysis began with assessment of the distribution of D-dimer data using the Shapiro–Wilk test. Data with a normal distribution were presented as mean ± standard deviation, whereas non-normally distributed data were presented as median and interquartile range. Comparisons of D-dimer levels across grades were performed using one-way ANOVA when assumptions of normality and homogeneity of variance were met, or the Kruskal–Wallis test when these assumptions were not fulfilled. Post hoc tests were applied with appropriate multiple-comparison corrections. To control for potential confounders such as age, body mass index, clinical stage, and C-reactive protein (CRP) levels, analysis of covariance (ANCOVA) or linear regression was applied. A two-tailed p-value < 0.05 was considered statistically significant, and analyses were performed using SPSS or Stata (latest version).

The study protocol was approved by the SMC Ethics Committee under approval number Etik/X/9/SMC/2023. Written informed consent was obtained from all participating patients prior to sample collection.

3. RESULTS

A total of 180 subjects with primary invasive breast cancer were analyzed, comprising 60 cases each of Grade I, Grade II, and Grade III tumors. The mean age was 55.3 years (range 34–80), with an average body mass index (BMI) of 25.5 kg/m^2. The distribution of D-dimer levels showed a progressive increase with higher histopathological grades.

Table 1.
Baseline Characteristics of the Study Population (N = 180)

Variable	Value
Total patients	180
Age, mean ± SD (years)	55.3 ± 9.7
BMI, mean ± SD (kg/m^2)	25.5 ± 3.8
AJCC stage I	46 (25.6%)
AJCC stage II	68 (37.8%)
AJCC stage III	54 (30.0%)
AJCC stage IV	12 (6.7%)
Nottingham grade I	60 (33.3%)
Nottingham grade II	60 (33.3%)
Nottingham grade III	60 (33.3%)
Lymphovascular invasion: No	128 (71.1%)
Lymphovascular invasion: Yes	52 (28.9%)
Molecular subtype: Luminal B	77 (42.8%)
Molecular subtype: Luminal A	44 (24.4%)
Molecular subtype: TNBC	39 (21.7%)
Molecular subtype: HER2-enriched	20 (11.1%)
Plasma D-dimer, median (IQR), ng/mL FEU	831.0 (604.2)
Plasma D-dimer, normal (≤500 ng/mL FEU), n (%)	36 (20.0%)
Plasma D-dimer, elevated (>500 ng/mL FEU), n (%)	144 (80.0%)

Table 2.
Descriptive statistics of D-dimer levels by grade

Grade	count	mean	std	median	min	max
I	60.0	506.62	182.01	501.7	200.0	964.9
II	60.0	817.57	228.46	831.0	268.1	1332.9
III	60.0	1301.75	252.6	1312.95	764.8	1765.6

The Shapiro–Wilk normality test for raw D-dimer values indicated a non-normal overall distribution ($p < 0.001$), although within-grade distributions approached normality. The Levene test for homogeneity of variance was not satisfied for either raw data ($p = 0.035$) or log10-transformed data ($p = 0.002$). Therefore, the Kruskal–Wallis test was employed as the primary statistical analysis.

The Kruskal–Wallis test demonstrated a significant difference in D-dimer levels among grades ($H = 124.958$, $p < 0.001$, epsilon-squared = 0.695). Post-hoc Mann–Whitney tests with Holm's correction confirmed significant differences between all grade pairs: Grade I vs. II, Grade I vs. III, and Grade II vs. III. One-way ANOVA on log10-transformed D-dimer values yielded similar results ($F = 146.86$, $p < 0.001$, eta-squared = 0.624), with consistent findings in the Tukey HSD post-hoc analysis.

Table 3.
Comparative analysis of D-dimer levels among grades

Test	Statistic	p-value	Effect Measurement
Kruskal–Wallis	H = 124.958	<0.001	Epsilon^2 = 0.695
ANOVA (log10)	F = 146.86	<0.001	Eta^2 = 0.624
Post-hoc Tukey	All significance	<.,001	-

An adjusted ANCOVA model including covariates for age, BMI, clinical stage, log-transformed C-reactive protein (CRP), lymphovascular invasion (LVI), and molecular subtype indicated that histopathological grade remained significantly associated with D-dimer levels after adjustment. CRP, stage, and LVI were also independently significant predictors.

Table 4.
ROC-derived diagnostic performance of plasma D-dimer for identifying high-grade (Grade III) invasive breast cancer

Metric	Value
AUC	0.960
Optimal cut-off (D-dimer)	965.5 ng/mL FEU
Sensitivity	91.7%
Specificity	90.0%
Youden index	0.817

Receiver operating characteristic (ROC) analysis distinguishing Grade III from Grades I–II yielded an area under the curve (AUC) of 0.960, with an optimal cutoff value of 965.5 ng/mL FEU, corresponding to a sensitivity of 91.7% and a specificity of 90.0%. The ROC analysis to discriminate Grade III from Grades I–II yielded an AUC of 0.960 (95% CI 0.93–0.98) with an optimal cut-off of 965.5 ng/mL FEU (sensitivity 91.7%, specificity 90.0%).

Figure 2.
Distribution of plasma D-dimer levels (ng/mL FEU) across Nottingham histological grades (I–III). Data are shown as median and interquartile range; circles indicate outliers. Overall comparison was performed using the Kruskal–Wallis test ($p < 0.001$), followed by pairwise Mann–Whitney tests with Holm correction, all of which remained significant.

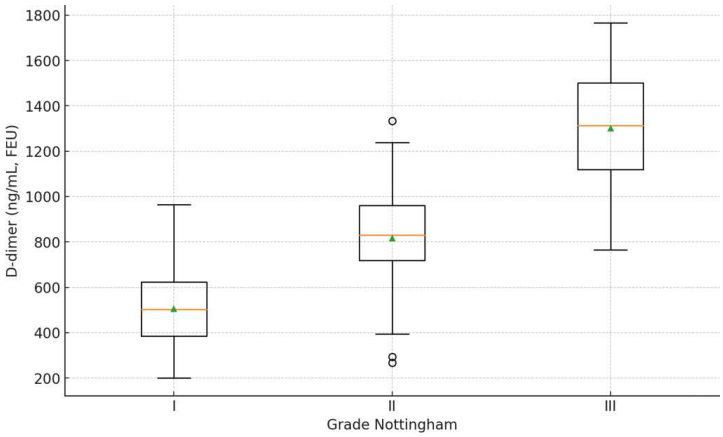
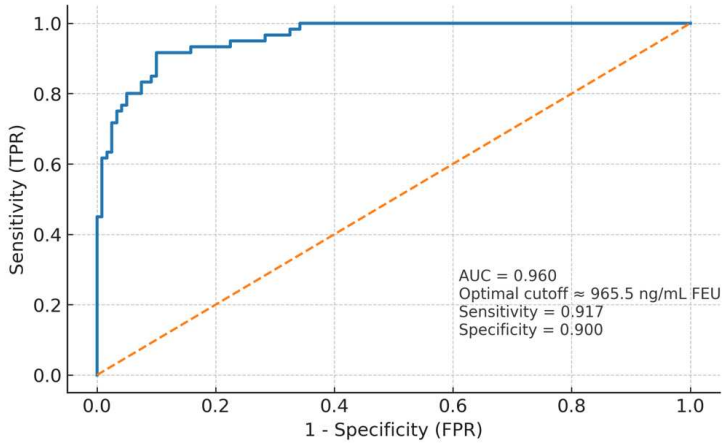


Figure 3.
Receiver Operating Characteristic (ROC) curve for distinguishing high-grade (Grade III) from lower-grade (Grade I–II) invasive breast cancer based on plasma D-dimer levels. ROC analysis yielded an AUC of 0.960 (95% CI 0.93–0.98). The optimal cut-off determined by the Youden index was 965.5 ng/mL FEU, providing 91.7% sensitivity and 90.0% specificity.



4. DISCUSSION

The study demonstrates a clear and statistically significant association between plasma D-dimer levels and histopathological grading in patients with invasive breast cancer. D-dimer concentrations increased progressively from Grade I to Grade III tumors, with all pairwise comparisons remaining significant even after controlling for relevant clinical and pathological covariates.[14] These findings suggest that D-dimer may reflect underlying tumor aggressiveness and serve as a potential adjunct prognostic biomarker. [11,15]

The observed relationship between higher histological grade and elevated D-dimer levels is consistent with the pathophysiological understanding of cancer-associated hypercoagulability. Poorly differentiated tumors (higher grades) are characterized by increased mitotic activity, greater nuclear pleomorphism, and reduced glandular formation, which are often accompanied by more aggressive biological behavior.[14,16,17] Such tumors are more likely to exhibit lymphovascular invasion, higher tumor burden, and enhanced angiogenesis, all of which contribute to the activation of coagulation pathways.[18] Tumor cells can express procoagulant factors such as tissue factor and cancer procoagulant, which initiate thrombin generation, while the inflammatory tumor microenvironment amplifies fibrin formation and subsequent fibrinolysis, thereby elevating circulating D-dimer levels. [14,16,19]

The findings were aligned with previous reports linking D-dimer elevation to adverse clinicopathological features in breast cancer, including advanced TNM stage, lymph node involvement, and distant metastasis. However, comparatively fewer studies have specifically examined the relationship between D-dimer and histological grading. By focusing on grade, our study adds nuance to the literature, suggesting that even in the absence of overt metastatic disease, D-dimer levels can provide information about intrinsic tumour aggressiveness. [3,5,9,14]

Importantly, the association between grade and D-dimer remained significant in the adjusted ANCOVA model, which accounted for age, BMI, clinical stage, CRP, LVI, and molecular subtype. The retention of statistical significance suggests that D-dimer captures biological processes not fully explained by these covariates. CRP, stage, and LVI were also independently associated with D-dimer, underscoring the interplay between systemic inflammation, tumor spread, and vascular invasion in driving hypercoagulability. [20,21]

The ROC analysis further supports the potential clinical utility of D-dimer, with an AUC of 0.960 for distinguishing Grade III from lower grades. The optimal threshold of 965.5 ng/mL FEU achieved both high sensitivity (91.7%) and specificity (90.0%), suggesting that D-dimer measurement could be integrated into pre-treatment evaluation to flag patients likely to harbor

high-grade tumors. Such early identification might guide more aggressive diagnostic workup or prompt consideration of intensified therapeutic strategies. [17,18]

To address potential clinical redundancy, this study explains why D-dimer remains relevant despite histopathological grade being a strong, routinely available prognostic marker. Histological grading is universally applied and is firmly linked to tumor aggression and outcome in invasive breast carcinoma.[3] In our data, higher grades, especially Grade III, ran parallel with higher D-dimer levels, which is in line with reports that D-dimer tends to rise in breast cancer with less favorable clinicopathological features. [2,10,20] This naturally leads to the question: if grade is already known, is D-dimer still necessary? We argue that D-dimer has an additive, not substitutive, role in at least three clinical windows. First, in patients with high-grade tumors but limited or delayed access to coagulation profiling, a strong grade–D-dimer correlation supports earlier vigilance for cancer-associated thrombosis and, in selected cases, may justify deferring repeat D-dimer testing.[5,15] Second, in patients whose risk is "borderline" on morphology, such as Grade II with lymphovascular invasion, raised inflammatory markers, or higher clinical stage, D-dimer acts as a circulating indicator of hypercoagulability/inflammation that morphology alone does not fully capture.[4,9,19] Third, histological grade is fixed once diagnosed, whereas D-dimer is repeatable and therefore useful for perioperative or on-treatment monitoring, as shown in follow-up and perioperative series. [15] Framing it this way makes clear that D-dimer is not to replace grading, but to sharpen risk identification, especially in settings where breast cancer still presents late and resources are uneven. [17] Nevertheless, the interpretation of elevated D-dimer in cancer must be approached cautiously. D-dimer is a non-specific marker, and its levels can be influenced by conditions such as venous thromboembolism, infection, trauma, and inflammatory diseases, many of which were excluded in our study to reduce confounding. Furthermore, the cross-sectional design precludes assessment of temporal changes in D-dimer or its predictive value for long-term outcomes such as recurrence or survival. [16]

This study has several limitations that should be acknowledged. First, its cross-sectional design precludes causal inference and does not allow evaluation of temporal changes in D-dimer in relation to disease course or treatment response. Second, D-dimer is a nonspecific marker that can be influenced by various conditions, and although we applied strict exclusion criteria to minimize major confounders, residual confounding cannot be fully ruled out. Third, the study was conducted in only two hospitals, which may limit the generalizability of the findings to other settings and populations with different case mixes or resource availability. Finally, we did not assess long-term clinical outcomes such as recurrence, thromboembolic events, or survival, nor did we evaluate dynamic changes in D-dimer levels during systemic therapy, surgery, or follow-up, so the prognostic and monitoring value of D-dimer in this context remains to be clarified in future longitudinal studies.

Future research should include longitudinal studies to evaluate whether D-dimer trends over time correlate with treatment response and disease progression, as well as multicenter validation to assess generalizability across different patient populations. Exploration of combined biomarker panels incorporating D-dimer, inflammatory markers, and molecular tumor characteristics could also improve prognostic accuracy.

5. CONCLUSION

This study indicates that D-dimer levels are significantly associated with histopathological grade in invasive breast cancer, independent of other clinical and pathological factors. These results highlight the potential role of D-dimer as a simple, accessible, and cost-effective adjunct to histopathological grading in the prognostic assessment of breast cancer patients.

6. ACKNOWLEDGEMENT

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