



High platelet count as a predicting factor of histopathological grading among invasive breast cancer individuals: a single centre experience from Indonesia

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ABSTRACT

Background: The interplay between platelet and breast cancer (BC) pathology may have the potential to represent the malignancy status itself, evidently through predicting the histopathological results of each individual. This study aims to elaborate on the diagnostic value of a higher platelet count or thrombocytosis and the histopathological status of invasive BC in our center, explaining its correlation from the diagnostic perspective.

Materials and methods: A retrospective cohort study was conducted using breast cancer patients' medical records from January to March 2022 at the Haji Adam Malik General Hospital, Medan, Indonesia. The patients' histopathological records and complete blood counts were collected from the hospital's medical records. We analyzed the risk analysis model in receiver operator characteristics analysis and diagnostic parameters, e.g., sensitivity and specificity, which we analyzed further using the correlation test to fulfill our objective.

Result: The mean age of the 69 subjects we included, in the final analysis, was 49.0 ± 11.1 years old, of whom 35 (50.7%) individuals were histologically confirmed to be high-grade BC. By applying the cut-off value of 299×10^3 cells/ μ L, the diagnostic value of a platelet count was 60.0% in sensitivity, 61.8% in specificity, and an area under the curve (AUC) value of 0.597 (0.462–0.732) in 95% confidence interval (CI) as presented by receiver operating characteristic (ROC). We also found that a higher platelet count may also predict the diagnosis of invasive BC by 2.423 times as shown in the odd ratio (OR) analysis.

Conclusion: Platelet counts investigation is an applicable yet potential hematological biomarker to predict invasive BC histopathological grading.

Key words: histological grading; invasive breast cancer; platelet levels; predictors

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Introduction

Breast cancer (BC) is the most commonly diagnosed malignancy among women as confirmed by the GLOBOCAN 2020 report, accountable for more than half-million mortalities worldwide [1, 2]. As a neoplastic process, cancer might sig-

nificantly alter its physiologic functioning, modifying the host system in molecular levels through a complex interaction between the cancerous cell and its surrounding microenvironment; eventually creating a concept of the biomarker as the “output” of those interplays. The biomarker's role in cancer detection has been rapidly escalating in

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recent years. Projected to assist the confirmatory diagnostic tool, the utilization of biomarkers isn't limited to a specific expression of a protein and its derivatives, routinely evaluated parameters, e.g., a platelet count may be capable as well of depicting the underlying neoplasm process or even its severity [3, 4].

As a solid tumor, BC's relationship with the host immune system is progressively recognized nowadays. as the interaction itself might mediate some remarkable and observable changes on pretreatment phase, signifying its possible role on predicting the nature of malignant transformation itself. Pretreatment thrombocytosis findings should raise suspicion for an underlying pathologic-utilization of platelet as induced by cancerous cells to facilitate its spread or survival in circulation, hence hypothetically associated with much severe cancer's entity, e.g., invasive breast cancer (IBC) or higher histological grading cancer [5]. The reciprocal interplay between the BC's invasiveness and immune response may cause the thrombocytosis to be eligible in representing cancer's severity, delineating its histopathological state, or prognosticating the patients by the information [6]. Therefore, this study aimed to elaborate on the role of thrombocytosis findings to predict the histological grading of IBC among patients in our center.

Materials and methods

This retrospective cohort study was conducted at our center of Haji Adam Malik General Hospital from January to March 2022 after the ethical approval had been granted by the ethics committee of the same center under the issue number of 29/Div.onko.RSUP.HAM/X/2022. We included the histopathologically confirmed BC patients with complete medical records from our system, either from the pathological reporting or thorough laboratory investigation to support the clinical judgment, in which they approved to participate in this study. Conversely, the exclusion criteria of this study are ongoing infection (both acute and chronic), proven and confirmed with autoimmune-related disease, routine steroid administration, and BC in a relapse status. The BC's grades were assessed by the Surgical Oncology installation in our centre, guided by the Bloom and Richardson guideline which combines three

sub-scores (nuclear pleomorphism, tubule formation, and mitotic count), resulting in a total score and derived grade. The combined ER/PR receptor status was positive when $\geq 10\%$ of tumor cells showed nuclear staining by immunohistochemistry (IHC) for either ER and PR. Pre-biopsy platelet counts were sent by the Department of Clinical Pathology of our centre, simultaneously assessed with routine hematologic testing for each inpatient's workup. The laboratory staff concluded the count by estimating a well-prepared blood smear after it was covered by monolayer oil immersion. The "estimated platelet count/ μL " formula was used by multiplying the average count in 10 view-fields to 15,000, thus the data were reported back to the oncologic ward's medical record.

The study was analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 25. The Kolmogorov-Smirnov (KS-test) determined the normality of continuous variable distribution. The data were reported as mean \pm standard deviation, ratio, 95% confidence interval (CI), cut-off value, sensitivity, and specificity. The Mann-Whitney test assessed the associations between stage and platelet counts. Chi-Square analyzed categorical data. The cut-off point for the ratio was determined using the receiver operating characteristic (ROC) curve by considering the sensitivity and specificity value. P-value of ≤ 0.05 was considered to be statistically significant.

Results

Table 1 summarizes the 69 participants we included in the final analysis regarding their demographic, pathological, and hematological characteristics. The participants' mean age was 49.0 ± 11.1 years old, classified into two main groups of cancer grading in which 50.7% of the total was high-grade IBC. The histopathological analysis revealed most of the subjects were classified into invasive carcinoma with no special type in 39 people (56.5%), and the mean value of platelet counts through the subjects was $301 \times 10^3 \pm 147 \times 10^3$ cells/ μL .

An ROC analysis performed the platelet count predictive value and identified their diagnostic values (sensitivity and specificity). According to the ROC curve, platelet emerged as potential markers since the identified area under

Table 1. Characteristics of subjects

Characteristics	Frequency (n, %)
Age (years old)	
Mean ± SD (min-max)	49.0 ± 11.1 (29–76)
Grade	
Low, intermediate	34 (49.3%)
High	35 (50.7%)
Histopathology	
Invasive carcinoma, no special type	39 (56.5%)
Invasive lobular carcinoma	14 (20.3%)
Invasive ductal carcinoma	8 (11.6%)
Mixed lobular-ductal carcinoma	4 (5.8%)
Special type carcinoma	4 (5.8%)
Platelet counts (platelet, x 10³ cells/μL)	
Mean ± SD (min-max)	301 ± 147 (34–746)/μL
Total	69 (100%)

SD — standard deviation

the curve (AUC) value was 0.597, indicating a considerable predictive parameter of a platelet count (Tab. 2). Furthermore, the cut-off point was also identified through ROC analysis, and it was shown that platelet had 60.0% sensitivity, and 61.8% specificity, within the optimal cut-off value of 299×10^3 cells/μL (p-value = 0.001, statistically significant). The latter statement also means there are significant differences between platelet levels in high-grade and low-grade invasive breast cancer. Table 2 presents the detail of the ROC analysis (Fig. 1). Table 3 further explains the calculated odd ratio (OR) of 2.423 by the applied cut-off value of 299×10^3 cells/μL, which statistically means that the odd of predicting a high-grade IBC is higher if the platelet count is higher than the aforementioned cut-off value.

Table 2. High grade of area under the curve (AUC), cut-off value, sensitivity, and specificity for platelet in invasive breast cancer patients

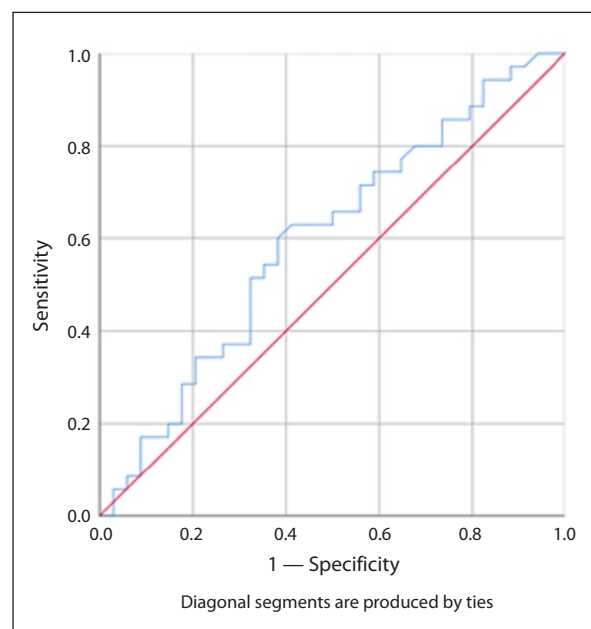
Grade	Parameter	AUC	95% CI	Cut-off value	Sensitivity (%)	Specificity (%)	p-value
High grade	Platelet counts	0.597	0.462-0.732	299×10^3 cells/μL	60.0%	61.8%	0.001*

*p < 0.05, statistically significant; CI — confidence interval

Table 3. Bivariate analysis of platelet counts and grading

Variable	Odds Ratio	95% CI	p-value
Platelet counts	2.423	0.921-6.375	0.001*

*p < 0.05, statistically significant; CI — confidence interval

**Figure 1.** Receiver operating characteristic (ROC) analysis of platelet counts as a predictor of grading in invasive breast cancer. The diagonal reference line acted as an indicator of no diagnostic value

Discussion

The role of a platelet count investigation among cancer patients remains to be a routinely evaluated serial-hematologic parameter, thus the physician might be able to gather some information on the patient's hemostatic status whether the suspected pathology has altered its function or count. However, the current molecular oncology science has proved that, possibly, there is an association between a high platelet count (thrombocytosis) and how malignant a malignancy can be. Lin et al. described this phenomenon as platelet-hi-

jacking in which cancer cells are used to facilitate and promote its growth either locally or through the systems. A hijack of normal cell functions is often considered a paraneoplastic feature of a solid tumor. By activating the platelet and its growth factors, the tumor cells may avoid the immune surveillance in circulation, acting as a “cloak” and thus prolonging its overall survival. The tumor cells can mimic the platelet’s molecular feature as well by adopting its megakaryocytic genes, e.g. γ IIB/ β 3, or platelet endothelial cell adhesion molecules. Extensive ADP expression by tumor cells may activate the platelet even further via the P2Y1 and P2Y12 receptors. Thus elevated platelet production rate, as enhanced by increased thrombopoietin (TPO) level, should be enough to cause a considerable thrombocytosis [7–9].

A pathomechanism called tumor cell-induced platelet aggregation (TCIPA) is known to be accountable for increasing the invasiveness or metastatic potential of the respective solid cancers by activating several mediators, e.g., ADP, thromboxane A2, etc. This survival function is molecularly meaningful in tumor spreading, particularly in the circulatory phase since circulating tumor cells are eventually a target of immunological reaction from natural killer (NK) cells or even intraluminal shear forces. Consequently, the aforementioned “shielding” effect by platelet through the TGF- β signaling pathway might protect the cancer cells from immunological elimination threat, even though evidence of cancerous cells’ intravasation also means that the cancer itself has been a locally advanced malignancy for a period of time. Thus, reasonably, higher-grade cancer may also alter its host immunological and hematological system to an even greater extent, potentially acting as a promising yet routinely assessed biomarker [5, 7, 10, 11].

Our study mainly focused on elaborating the association between the platelet count level and IBC’s grading due to its invasiveness which represents a highly active cancer, whilst hypothetically influencing the platelet’s quantity linearly with its severity. We found a positive correlation between the forementioned variables, though the “bridge” to perceive their interaction is debatable. A Canadian-based cohort study involving more than a half-hundred thousand individuals by Giannakeas et al. stated that though there was a higher risk

for diagnosing solid cancers among the thrombocytosis population, the phenomenon was absent in BC; delineating that the platelet-interplay in BC eventually remains questionable, hence more further elaboration is a necessity [12]. Nevertheless, several studies also outlined the prognostic significance of platelet counts, such as a clinical study by Stravodimou and Voutsadakis which reported longer progression-free survival (PFS) and overall survival (OS) in metastatic breast cancer patients without thrombocytosis with a hazard ratio (HR) value of 1.75 (1.01–3.02) in 95% CI ($p < 0.05$). Thus, although the association is debatable, a platelet count may have a considerable prognostic value to predict the outcomes since the initial presentation. Findings of thrombocytosis were known to be an indicator for individuals with higher risk of cancer-specific death, as it might delineate a disease activity or serve as a marker for possible residual post-definitive treatment which mostly means there is a need to intensify the approaches initially [13, 14].

Higher platelet counts also correlated with a higher circulating tumor cells (CTCs) count as proved by Bednarz-Knoll et al. Although their result is concordant with this study, we specifically correlate the higher platelet count with histopathological analysis (solid biopsy), rather than the previously proposed liquid biopsy. Bednarz-Knoll et al. basically concluded that a preoperative platelet count might partially delineate tumor’s severity by CTCs count, outlining that the need for anti-platelet therapy is progressively emerging. The use of antiplatelet treatment, e.g., aspirin, is also positively correlated with BC risk reduction as systematically reviewed by Leite et al. which investigated several multi-regional cohorts with the conclusion that aspirin (preferably low-dose) may serve as a protective factor of BC, partially explaining that the platelet-cancer interplay is pronounced in oncogenesis itself [15, 16]. Although a recently studied cohort by Cairat et al. marked the need for prolonged low-dose aspirin dose to reduce the BC risk, along with the finding that clopidogrel use is somehow associated with higher ER⁻ BC risk after 9 years of follow-up, on average [17].

Nevertheless, to our knowledge, this is the first study to explore the correlation between a higher platelet count or thrombocytosis and histologi-

cal grading result; albeit we may only indirectly present an indirect prognostic analysis of BC cases with a higher platelet count rather than stratify the findings with patients' survival. Even though the focus of the study itself is more diagnostic than prognostic, we believe there is a linear correlation between higher grade BC and worse clinical outcomes. Thus, predicting its histological grading might be beneficial in determining the need for very intensified approaches or more aggressive diagnostic confirmation. Whilst some limitation in this study persists, e.g. retrospective cohort design which is unquestionably prone to bias, we believe the objective of this study has been accomplished by elaborating the diagnostic value of thrombocytosis at BC early presentation. And although the limitations apply, our study has a unique component to assist a global oncologic progress in establishing a relatively attainable cancer-histological prediction method in the future through a basic hematologic workup in most centres.

Further statistical or laboratory elaboration might also benefit the progress to confirm our findings, especially by determining an optimal cut-off value of a platelet count. Considering the latter laboratory investigation or hematologic biomarkers are affordable and applicable in the settings of unavailability of the advanced facilities, our findings may benefit oncologists or even physicians in developing countries.

Conclusion

The higher platelet count results are associated with higher histopathological grading among invasive BC in our population since it might indirectly depict the currently occurring cancer-platelet interplay by simplifying the line between histological analysis and manifested host's reaction in hematological study. However, we also suggest the future investigation to be conducted on a cohort with a larger number of participants to confirm the underlying interplay and systematically review its association in the future.

Conflict of interest

None declared.

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Ethical declaration

The ethical approval to conduct this study has been granted by the ethical committee of Universitas Sumatera Utara.

Authors contribution

All authors' involvement was proportionated according to CRediT taxonomy to capture detailed contributions in the report of this case, which are: conceptualization: D.H., M.A.A., data curation: D.H., M.A.A., formal analysis: D.H., M.A.A., N.N.F., funding acquisition: not applicable; investigation: D.H., M.A.A., N.N.F., methodology: not applicable, project administration: D.H., N.N.F., resources: D.H., D.R.S., software: M.A.A., N.N.F., supervision: D.H., D.R.S., validation: D.H., D.R.S., writing — original draft: D.H., D.R.S., writing — review and edit: D.H., M.A.A., N.N.F, D.R.S.

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