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Immune Cell Counts, Systemic Immune Inflammation Index and Pan Inflammation Immune Value in Female Nigerian Breast Cancer Patients before Treatment

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Evidences suggest that breast cancer is associated with inflammation but blood based inflammation indices previously used to support this finding were calculated using only two blood cell parameters. The present study hypothesized that alterations of blood cell based inflammatory indices could differentiate breast cancer characteristics.
Objective: Considering the importance of immune cells in tumourigenesis, the present study investigated new inflammation index (pan inflammation immune value, PIIV), systemic immune

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inflammation index (SII), selected immune cell counts (neutrophils, lymphocytes, basophils and eosinophils) and platelets in breast cancer patients with different clinico-pathological characteristics.

Methods: A cross-sectional case-control study conducted on breast cancer patients from Radiation Oncology Department, University College Hospital, Ibadan, Nigeria. Blood cells were counted using automation while PIIV and SII were calculated in relation with breast clinico-pathological characteristics or patient's attributes.

Results: Most of the patients (67.4%) had monocyte counts below normal reference range. Mean total white blood cell (WBC), lymphocyte and SII were significantly increased in breast cancer patients compared with control. Mean total WBC and lymphocyte counts were significantly raised in early stage-, well-differentiated- and non-metastatic- breast cancer patients. Mean monocyte count was raised in invasive lobular-, well differentiated-, non-metastatic- and single positive- breast cancer patients. PIIV were raised in early stage-, poorly differentiated- and triple positive breast cancer patients. Mean WBC count and SII were significantly higher in obese breast cancer patients while PIIV was significantly increased in normotensive patients that were less than 40yrs old at diagnosis.

Conclusion: The study concluded that monocytes and lymphocytes are important immune cells at the early stage of breast cancer and that immune cell, SII or PIIV has differentiating potential for breast cancer characteristics.

Keywords: Breast cancer; pan-immune-inflammation value; prognosis.

1. INTRODUCTION

Breast cancer is the most common malignant tumor in females and the overall survival rate of patients has improved as a results of advancements in diagnosis and treatment, however, many low- and middle-income countries have increasing mortality rates.[1] In addition, breast cancer has prognostic heterogeneity making individualized precision treatment laborious.[1] In recent years, easy-to-obtain and blood-based immune inflammatory based indices such as neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been proven as potential independent prognostic factors in breast cancer.[2] But these indices considered only two immune cells. It is therefore necessary to identify alternative biomarkers for better prognosis and treatment predictions.

There is a growing evidence to suggest complex interactions between immune cells, platelets and malignant cells in tumour microenvironment. Tumor infiltration by inflammatory cells has been associated with favorable histopathological features and prognosis in numerous types of cancer.[3] Platelets secrete various growth factors and cytokines that promote angiogenesis, tumor growth, invasion and metastasis either directly or indirectly while macrophage is essential for immune-inflammatory response is implicated in tumorigenesis of breast cancer.[1] Lymphocyte is critical in the control tumour growth, neutrophils suppress cytolytic activity of lymphocytes and natural killer cells necessary for anti-tumour activities but neutrophils and monocyte-macrophages secrete tumour growth-promoting factors.[1, 3] Therefore, peripheral blood count is among the first investigation done on patient because alteration in hematological parameters influence disease progression, predicts disease severity and mortality risk. However, the usefulness of theses haematological parameters varies with clinic-pathological states.

It was observed that increased mean platelet volume was associated with larger tumors, higher stage, distant metastases and a poorer prognosis in patients with breast cancer.[2, 3] By contrast, Yao et al reported that there was no significant difference in survival between higher and lower mean platelet volumes. In addition, lower proportions of circulating monocytes were associated with a higher risk of breast cancer within 1 year of the blood collection, whereas higher proportions of circulating B cells were associated with a higher risk of breast cancer 4 or more years later.[4] Therefore, shifts in circulating leucocyte profiles appear to precede a breast cancer diagnosis and may serve as markers of time-dependent breast cancer risk. Considering the fact that blood parameters must have changed before or at cancer initiation and progression couples with inconsistencies of previous results, the present study compared blood cell counts in breast cancer patients with

control, determined frequencies of breast cancer patients with blood cell counts outside normal reference ranges and evaluate the potential prognostic role of white blood cell and platelet counts and their indices in determining group of breast cancer patients with worst prognosis.

2. METHODOLOGY

All breast cancer patients (a total of 184 consecutive patients) and 50 control were recruited following ethical approval from Joint University of Ibadan and University College Hospital, Ibadan, Nigeria Research Ethics Committee (UI/EC/14/0016). The patients were diagnosed in Department of Radiation Oncology, University College Hospital, Ibadan, Nigeria and had not received treatment yet. Exclusion criteria included: patients who had infectious diseases, autoimmune diseases, steroid administration and alcohol intake. Participants with haematological diseases or those with recent history of blood transfusion were also excluded from the study. Anticoagulated whole blood was processed for the determination of haematologic counts in 103/ml (total white blood cell, neutrophil, monocyte, lymphocyte, basophil, eosinophil, and platelet) using automated haematological analyser (Sysmex XN-450). Other data included breast cancer's clinicopathological characteristics (hand side position, duration, histopathology, immunohistochemistry, biopsy, metastasis and stage) and patient's attributes (blood pressure, age at diagnosis, age at menarche and waste:hip ratio). Blood cell-based-inflammation indices were calculated as SII=Platelets x Neutrophils/Lymphocytes and PIIV= Platelets x Neutrophils x Monocytes/Lymphocytes.[1, 3] Also, percentages of breast cancer patients having blood counts outside normal reference ranges were recorded WBC: 3.5-10.8 (x 10^3 cells/ml), neutrophil: 1.8-7.7 (x 10^3 cells/ml), lymphocyte: 3.5-9.0 (x 10^3 cells/ml), eosinophil: 0.0-0.5 (x 10^3 cells/ml), basophil: 0.0-0.1 (x 10^3 cells/ml), monocyte: 0.1-0.9 (x 10^3 cells/ml), platelet: 150-400 (x 10^3 cells/ml).[5]

Statistical Analysis: Data were presented as mean ± Standard deviation and compared using Student t-test, $p \leq 0.05$ was considered significant.

3. RESULTS

Breast cancer patients (32.6%-96.7%) had total- and differential-WBC within normal reference ranges while few (2.7%-20.1%) patients had blood cell counts above reference ranges. Most of the patients (67.4%) have monocyte counts below normal reference range. See Fig. 1. The mean WBC, lymphocyte count and SII were significantly increased while monocyte count was significantly reduced in breast cancer patients compared with control. See Table 1.

In Table 2; mean total WBC counts were significantly raised in early stage-, invasive lobular, well-differentiated- and non-metastatic-breast cancer patients. Mean neutrophil counts were raised in early stage-, invasive lobular-, well differentiated-, non-metastatic- and less than 1yr duration- breast cancer patients. Mean lymphocyte counts were raised in early stage-, well differentiated-, non-metastatic- and less than 1yr duration- breast cancer patients. Mean eosinophil counts were raised in early stage-, triple positive-, well differentiated-, and less than 1yr duration- breast cancer patients. Basophil counts were raised in late stage-, invasive ductal- and more than 1yr duration- breast cancer patients. Mean monocyte counts were raised in late stage-, invasive lobular-, well differentiated-, non-metastatic- and more than 1yr- breast cancer patients. Platelet counts were raised in right-breast cancer patients and more than 1yr duration- breast cancer patients. Basophil counts were raised in both-breasted cancer patients, late stage-, invasive ductal-, moderately differentiated-, more than 1yr duration- and triple positive- breast cancer patients. SII were raised in invasive ductal-, poorly differentiated-, more than 1yr duration- and triple positive- breast cancer patients. PIIV were raised in early stage-, poorly differentiated-, more than 1yr duration and triple positive breast cancer patients.

In Table 3; mean total WBC count was significantly higher in obese breast cancer patients while lymphocytes count was significantly higher in breast cancer patients less than 40yrs at diagnosis. Mean neutrophil count was increased in obese and older 15years menarche breast cancer patients. Mean basophil count was increased in normotensive while monocyte was increased in obese patents. SII were significantly increased in less than 40yrs old patients at diagnosis and obese patients while PIIV were significantly increased in less than 40yrs old patients at diagnosis, normotensive and more than 15yrs old menarche age.

Table 1. Blood cell counts, systemic inflammation indices and pan immune inflammation values in breast cancer patients compared with control

Variable	Breast Cancer (n=184)	Control (n=66)	Normal ranges
WBC($\times10^3$/mL)	7.54±1.4	6.23±4.4	3.5-10.8
N($\times10^3$/mL)	4.00±2.1	3.61±1.7	1.8-7.7
L($\times10^3$/mL)	5.75±2.16*	4.01±2.22	3.5-90
E($\times10^3$/mL)	0.21±0.13	0.1±0.01	0.0-0.5
B($\times10^3$/mL)	0.04±0.03	0.02±0.01	0.0-0.01
M($\times10^3$/mL)	0.30±0.10*	0.37±0.11	0.1-0.9
P($\times10^3$/mL)	296±111	200±99	150-400
PIIV	378.5±333.1	221±66	
SII	586±196*	288±92	

*WBC= Total White Blood cells, N=Neutrophils, L=Lymphocytes, E=Eosinophils, B=Basophils, M=Monocytes, P=Platelets, SII=Systemic Inflammation Indices, PIIV=Pan Immune Inflammation Value. *Significantly different*

4. DISCUSSION

Because of the complex interactions between the tumor and host immune-inflammatory responses, [2-4] the use of simple calculations combining just two blood cells inevitably limit the prediction power of such indices in the prognosis. The pan-immune-inflammation value (PIIV), a new comprehensive biomarker using combinations of neutrophil, platelet, monocyte, and lymphocyte counts, has been proven to be a predictor of survival outcomes in patients with metastatic colorectal cancer. However, SII have been extensively studied in cancer patients.[1] But till date, the prognostic value of PIIV is rarely reported in breast cancer. Therefore, this study aimed to clarify the differentiating potential of PIIV in breast cancer.

Mean total WBC counts were significantly raised in early stage-, invasive lobular-, well-differentiated- and non-metastatic-breast cancer patients. WBCs, including neutrophils and monocytes produce reactive oxygen species (ROS) and nitric oxide species (NOS), which are chemically reactive molecules. Unless ROS and NOS are properly neutralized by the antioxidant defense system, they can cause damage to cellular proteins, lipids, and DNA that may lead to the accumulation of genetic instability, affecting single nucleotide polymorphisms (SNPs) or upregulating the PI3K-Akt pathway for carcinogenesis.[6] A large-sample studies that attempted to evaluate the association between WBC counts and breast cancer risk have produced inconsistent results.[7] Akinbami *et al*.[8] reported that WBC counts were higher in patients with breast cancer than in controls. Our present study showed that more than half of our breast cancer patient had monocyte counts below normal reference ranges which might be as a result of shift of circulating monocytes into breast cancer locus for differentiation into M1 or M2 macrophages.

The phases in tumor immunoediting includes elimination, equilibrium, and escape but immune escape is very complicated involving tumor-associated antigens, tumor gene mutation, immune cells and inflammatory microenvironment therefore the tumor microenvironment (TME) includes not only the tumor cells but also immune and inflammatory cells.[3] One study reported that neutrophils promote tumor cell growth and progression by secreting cytokines and chemokines so as to offer a proper microenvironment for tumor cells.[1-3] Tumor-associated macrophages (TAMs) are derived from circulating monocytes and play a crucial role in the formation of TME by promoting tumor progression and metastasis.[9] The characteristics of the TME are hypoxia, chronic inflammation, and immunosuppression, which make a more complex network mechanism to regulate the relationship between systemic inflammation, local immune response, cancer progression, and patient survival.[3, 6, 9] In addition, systemic inflammatory response has been identified to affect survival in a number of malignancies and white blood cells are key mediators in systemic inflammation.[3] Thus explaining significantly increased mean WBC and lymphocyte counts in breast cancer patients compared with control. It might therefore be conjectured that raised WBC counts in breast cancer before treatment might be due to raised lymphocyte number. Moreso, eosinophils and basophils with receptors for IgE might not be relevant in breast cancer tumour genesis, thus not significantly different between patients and controls.

Table 2. Blood cell counts, systemic inflammation indices and pan immune inflammation values in different breast cancer characteristics

Breast cancer characteristic	WBC (×10^3/mL)	N (×10^3/mL)	L (×10^3/mL)	E (×10^3/mL)	B (×10^3/mL)	M (×10^3/mL)	P (×10^3/mL)	SII	PIIV
Stages of Breast cancer									
Early (113)	9.11± 2.09*	3.66±2.08*	5.94±5.47*	0.21±0.10*	0.01±0.01	0.21±0.10*	251.5±129	549±80	226.3±17.0*
Late (69)	4.90±4.5	2.51±1.17	1.66±2.57	0.23±0.20	0.05±0.02*	0.13±0.16	265±120	628±40	55.6±24.0
Histopathology									
Invasive ductal (169)	6.13±4.07	2.53±1.87	3.28±2.36	0.16±0.02	0.01±0.01*	0.19±0.20	246.76±120	609±274	239.3±35.8
Invasive lobular (70)	8.83±6.04*	4.13±2.37*	3.66±2.81	0.18±0.03	0.000±0.00	0.49±0.23*	219.7±139	323±251	226.5±64.6
Biopsy									
Poorly differentiated (49)	5.98±3.53	2.29±1.56	2.81±2.41	0.18±0.02	0.01±0.005	0.64±0.15	221.5±94.2	659±454	258±123.5
Well differentiated (42)	6.81±5.11	2.91±2.30	3.63±2.68*	0.21±0.21	0.01±0.004	0.99±0.19*	238.9±110.9	259±189	103±93.3*
Metastasis									
Metastatic (61)	5.94±3.55	2.35±1.80	3.01±2.21	0.17±0.02	0.01±0.04	0.72±0.11	228±93.9	679±256	102±100
Non metastatic (123)	6.38±4.50*	2.73±1.97*	3.41±2.43*	0.17±0.02	0.01±0.07	0.9±0.17*	254±113.6	540.3±269	283.6±99.0
Cancer duration									
<1yrs (26)	6.85±5.38	2.93±2.8	3.71±3.00*	0.12±0.10*	0.00±0.00	0.12±0.10	193.9±68.0	181.5±152	122.6±49.00
≥1yrs (13)	5.04±2.89	2.68±2.1	1.88±2.89	0.10±0.11	0.20±0.10*	0.60±0.20*	243.3±84.5	529±203*	267.9±85.0*
Immunohistochemistry									
Triple +ve(11)	5.18±1.17	1.69±0.70	2.57±1.71	0.30±0.11*	0.01±0.01	0.11±0.10*	223±98	679±172*	260±120*
Triple -ve (12)	5.08±3.2	1.82±0.53	2.53±1.27	0.10±0.09	0.02±0.01	0.42±0.20	198±108	212.±150	201±110

*SII=Systemic Inflammation Indices, PIIV=Pan Immune Inflammation Value. *Significantly different*

Table 3. Blood cell counts, systemic inflammation indices and pan immune inflammation values inrelation to breast cancer patient's attributes

	WBC (×10^3/mL)	N (×10^3/mL)	L (×10^3/mL)	E (×10^3/mL)	B (×10^3/mL)	M (×10^3/mL)	P (×10^3/mL)	SII	PIIV
Age at diagnosis									
<40yrs (35)	5.92±3.66	2.70±2.10	2.78±1.78	0.21±0.20	0.03±0.02	0.11±0.010	269±104.6*	497.3±67.6*	269.1±100*
≥40yrs (147)	6.31±4.33	2.59±1.88	3.41±2.40*	0.20±0.21	0.01±0.01	0.10±0.10	239±123	167.8±32.4	134.8±129
Body weight									
Non-obese (60)	5.84±3.99	2.54±1.63	3.00±2.47	0.71±0.27	0.01±0.009	0.09±0.11	245±117	251±22.1	141±98
Obese (100)	7.26±4.81*	2.94±2.32*	3.79±2.67	0.90±0.20	0.013±0.08	0.11±0.10*	236±100	538±59.0*	133±58
Body pressure									
Normotensive (102)	6.47±4.35	2.69±1.89	3.57±2.53	0.18±0.10	0.02±0.01*	0.10±0.10	252.7±127	537.4±292	288±58*
Hypertensive(79)	6.01±4.05	2.55±1.97	2.99±2.10	0.15±0.11	0.01±0.01	0.10±0.11	236.3±116	661±228	111±76
Age at menarche									
<15yrs (57)	6.14±3.82	2.44±2.01	3.29±2.28	0.11±0.11	0.03±0.02	0.07±0.11	237.6±141	522.6 ±276	199±80
≥15yrs (123)	6.30±4.38	2.72±1.87*	3.35±2.40	0.19±0.10	0.01±0.01	0.11±0.10*	250.6±110	621±260	293± 54*

*WBC= Total White Blood cells, N=Neutrophils, L=Lymphocytes, E=Eosinophils, B=Basophils, M=Monocytes, P=Platelets, SII=Systemic Inflammation Indices, PIIV=Pan Immune Inflammation Value. *Significantly different*

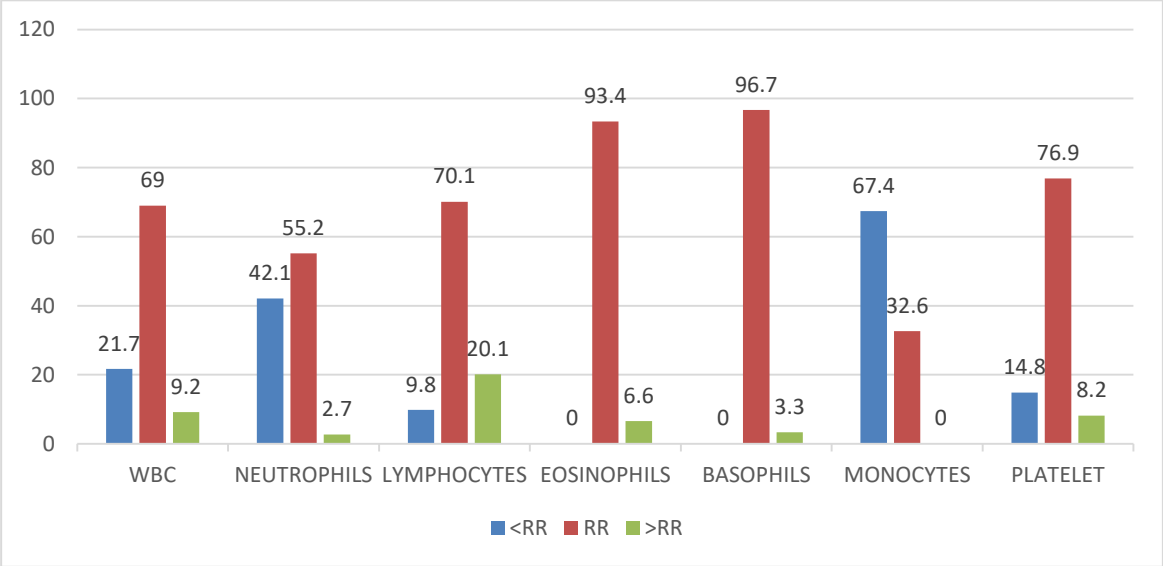

Fig. 1. Frequency of breast cancer patients having blood cell values below, within or above normal reference ranges

Elevated total leucocytic count predicts poorer prognosis and increased mean platelet volume was associated with larger tumors, higher stage, distant metastases and a poorer prognosis in patients with breast cancer, whereas patients with a lower neutrophil count had a shorter time to metastasis development.[10] PIIV is a combination of platelets, neutrophils, monocyte and lymphocytes while SII is a combination of platelets, neutrophils and lymphocytes.[1-4] Therefore raised lymphocyte counts and reduced monocyte number means that patients with low PIIV have a better prognosis while patients with high SII bad prognosis. A study showed that low pan-immune-inflammation-value predicts better chemotherapy response and survival in breast cancer patients treated with neoadjuvant chemotherapy.[11] Another results of a meta-analysis suggested that an elevated SII predicts poor survival outcomes and is associated with clinicopathological features that indicate tumor progression of breast cancer.[12] These two suggestions are supported by our findings of significantly increased SII in obese, invasive ductal-, poorly differentiated-, more than 1yr duration- and triple positive- breast cancer patients, while PIIV were significantly increased in early stage- and triple positive breast cancer patients.

5. CONCLUSION

In conclusion, breast cancer patients before commencement of treatment are presented with derangement of certain blood counts and that no specific blood cell or indices is specific for a clinicopathological attribute of breast cancer. Thus, the present study provided evidences suggesting major contributions of lymphocytes, monocytes and low-grade inflammation to cancer development.

CONSENT

As per international standard or university standard, patient (s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical approval obtained from Joint University of Ibadan and University College Hospital, Ibadan, Nigeria Research Ethics Committee (UI/EC/14/0016).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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