

Short Communication

Immune-nutritional indices in female Nigerian breast cancer patients with different tumour characteristics

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ABBREVIATIONS

CRP = C-reactive protein

OPNI = Onodera's prognostic nutritional index

CALLY = CRP-Albumin-Lymphocyte index

HALP = Haemoglobin, Albumin, Lymphocyte and Platelet score

Abstract: Breast cancer presents varied and complex clinicopathological features which make its management individualistic, prolonged and expensive, thus the need to differentiate each type of breast cancer using cheap and easy to perform investigations. This study evaluated the differentiation potential of extensive immune-nutritional indices which combined serum C-reactive protein (CRP), haemoglobin, albumin levels, blood lymphocyte and platelet counts in breast cancer patients of different status. The aim of this study was to investigate whether pre-treatment Onodera's prognostic nutritional index (OPNI), CRP-Albumin-Lymphocyte (CALLY) index and the Haemoglobin, Albumin, Lymphocyte and Platelet (HALP) scores differ with breast cancer characteristics. We enrolled a total of 135 consecutive newly diagnosed breast cancer patients who were not on any treatment from Radiation Oncology Department, University College Hospital, Ibadan, Nigeria. Lymphocyte count, platelet count and haemoglobin levels were determined using auto-analyser while serum CRP and albumin levels were measured using ELISA. Immune-nutritional indices (OPNI, CALLY and HALP) were calculated. Haemoglobin concentration, serum albumin level, OPNI, CALLY and HALP were significantly decreased while serum CRP was significantly raised in breast cancer patients compared with control. Mean values of OPNI, CALLY and HALP were significantly decreased in late stage breast cancer patients compared with early stage breast cancer patients, while only CALLY was significantly decreased in poorly differentiated and metastatic breast cancer patients compared with well differentiated and non-metastatic breast cancer patients respectively. This study confirmed the presence of malnutrition and inflammation in breast cancer patients, especially late-stage, poorly differentiated and metastatic groups. This calls for monitoring of liver functions in all cases of breast cancer.

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INTRODUCTION

There has been a steady increase in the incidence of breast cancer in Nigeria, and a major cause of cancer-related deaths worldwide (Adebamowo and Ajayi, 2000). Breast cancer disease in Nigeria is usually presented at late stage resulting to poor treatment outcomes (Adebamowo and Ajayi, 2000). Different reasons have been adduced to late presentation including illiteracy or low education, fear of diagnosis, ignorance, denial, belief in unorthodox therapies and faith healing (Adisa et al., 2011). Studies from different parts of Nigeria and most developing countries showed that most breast cancer patients presented in stages III and IV with metastatic disease and invasive ductal carcinoma (Ntekim et al., 2009). Considering the high predominance of late stage and metastatic breast cancer among Nigerians, the authors of the present study recruited these groups of breast cancer patients to further understand the basis of the occurrence and possibly recommend strategies to mitigate against the advancement of breast cancers to these stages.

Increasing evidence supports that immune cells, inflammation and nutrition are involved in the initiation and progression of breast cancer (Arinola et al., 2021, Jimoh et al., 2023). Albumin, hemoglobin levels, lymphocytes, C-RP and platelet counts are easily acquired laboratory data reflecting inflammation and nutrition status. Numerous studies have reported the importance of serum albumin concentration, haemoglobin level, lymphocyte and platelet counts for breast cancer monitoring (Xiang et al., 2022). However, the disadvantage of these indicators is that each reflects only one aspect of inflammation or nutrition episode. It was earlier concluded that the combination of this individual factor to calculate an index could have more accurate and differentiating power than a single marker (Xu et al., 2022).

Serum albumin, as one of the mostly commonly used markers for assessing patients' nutritional status is produced by the liver and is acting as a key antioxidant, detoxifier and transporter of important nutrients (Levitt and Levitt 2016). Normal serum albumin level reduced the risk of death in breast cancer patients by 72% and contributed to poor survival of breast cancer patients (Lis et al., 2003), while CRP as a systemic inflammatory marker plays a role in human innate immunity produced by the liver under the transcriptional control of interleukin-6 is associated with significant increase of breast cancer risk and poor outcome (Kolberg et al., 2021).

Platelets promote the survival of circulating tumor cells in the blood stream and facilitate their extravasation and the colonization of new microenvironments. Also, *platelets support tumor growth and angiogenesis* (Lal et al., 2013). However, tumor infiltration lymphocyte in breast cancer microenvironment is associated with better patient prognosis because of ability to eliminate tumor cells and controls tumor growth (De Nardo et al., 2007). PNI consists of albumin, lymphocytes or C-reactive protein (CRP), which may reflect the balance between the pro-tumor inflammatory status and nutritional status has been widely used as a predictor of survival in breast cancer patients (Onodera et al., 1984).

While the study on indices combining two blood cell counts in breast cancer patients is common, reports on novel index combining haemoglobin, albumin levels, lymphocyte and platelet counts (HALP) in breast cancer is rare (Duran et al., 2022). However, literatures on HALP and other immune-nutritional indices using combination four different blood parameters of Nigerian breast cancer patients is not encountered by the authors. In this study, we investigated if differences exists index in immune-nutritional indices (OPNI, CALLY and

HALP) of breast cancer patients of varied histological characteristics and stages. The strength of this study is that it provided information about immunity, inflammation, nutrition and liver function test of breast cancer patients using simple low-cost, fast and easy procedures.

MATERIALS AND METHODS

Participants: We included a total of 135 consecutive newly confirmed breast cancer patients from the Department of Radiation Oncology, University College Hospital, Ibadan, Nigeria. All patients were not on any treatment. Ethical approval for the study was obtained from Joint University of Ibadan and University College Hospital, Ibadan, Nigeria Research Ethics Committee (UI/EC/23/0065).

Inclusion criteria: All women who were clinically diagnosed and histopathologically confirmed as breast cancer patients.

Exclusion criteria: Patients on chemotherapy and radiotherapy and patients on anti-platelet therapy. Control participants were recruited from female staff of University College Hospital who were apparently healthy without laboratory and clinically confirmed diseases. Five (5) ml blood sample was collected.

Laboratory analysis and calculation of indices: Two ml was dispensed into bottle containing anti-coagulants for complete blood count using haematology auto-analyser (haematology autoanalyser (Sysmex XN-450) while 3ml was dispensed into plain bottles without anticoagulant for serum separation to determine the concentrations of albumin and CRP using ELISA as previously described (Arinola et al., 2022). HALP was calculated as hemoglobin level \times albumin level \times lymphocyte/platelet count (Duran et al., 2022). CALLY index was as serum albumin level \times absolute lymphocyte count / CRP level $\times 10^4$ (Lida et al., 2022). PNI was calculated as $10 \times$ albumin + $0.005 \times$ total lymphocyte count (Onodera et al., 1984).

Statistical analysis: Results were presented as mean \pm S.D. The difference between the mean was determined using Student t-test and p-value ≤ 0.05 was considered significant.

RESULTS

In Table 1, haemoglobin concentration, serum albumin level, OPNI, CALLY and HALP were significantly lower while serum CRP was significantly raised in breast cancer patients compared with control. In Table 2, OPNI, CALLY and HALP were significantly decreased in late stage breast cancer patients compared with early stage breast cancer patients, while only CALLY was significantly decreased in poorly differentiated and metastatic breast cancer patients compared with well differentiated and non-metastatic breast cancer patients respectively.

Table 1: Mean selected blood cell counts, Haemoglobin concentration, C-RP and albumin levels, OPNI, CALLY and HALP in breast cancer patients compared with control.

| Variables | Breast Cancer (n=135) | Control (n=42) |
|-----------------------------------|-----------------------|------------------|
| Lymphocytes (x10 ⁹ /L) | 3.88 \pm 2.30 | 2.94 \pm 2.40 |
| Platelets (x10 ⁹ /L) | 303 \pm 92.40 | 283 \pm 186.40 |
| Haemoglobin (g/L) | 123 \pm 32.40* | 135 \pm 43.02 |
| CRP (mg/L) | 8.30 \pm 2.60* | 3.34 \pm 1.00 |
| Albumin (g/L) | 35.72 \pm 5.66* | 50.20 \pm 4.92 |
| OPNI | 34.81 \pm 9.07* | 46.09 \pm 5.5 |
| CALLY | 1.40 \pm 0.5* | 2.65 \pm 1.0 |
| HALP | 33.04 \pm 14.8* | 45.98 \pm 15.7 |

Onodera's prognostic nutritional index=OPNI, CRP-Albumin-Lymphocyte index = CALLY, Haemoglobin, Albumin, Lymphocyte and Platelet score = HALP. *Significantly different.

DISCUSSION

Breast cancer is among the most common female cancers worldwide, and its development or progression is influenced by inflammation, nutrition, and the immune status. However, most previous breast cancer studies concentrated on cancer characteristics neglecting host factors that can affect oncologic outcomes, such as patients' nutrition and systemic inflammatory status (Grivennikov et al., 2010). Since breast cancer varies in presentation and progression, a more careful personalized therapeutic and fast affordable differentiating strategy may be

needed. Previously determined nutritional and inflammatory parameters in cancer prognosis [C-reactive protein, neutrophil-to-lymphocyte ratio, Naples prognostic score, platelet-to-lymphocyte ratio, controlling nutritional status (CONUT) score, monocyte-to-lymphocyte ratio and Glasgow prognostic score] (Njoku et al., 2021, Jimoh et al., 2023) have limited clinical translational evidences. Therefore, present study evaluated the differentiating potentials of indices of immune-nutritional (PNI, HALP and CALLY) in breast cancer patients of different characteristics.

Table 2: Mean values of OPNI, CALLY and HALP in different breast cancer characteristics.

| Breast cancer characteristic | OPNI | CALLY | HALP |
|--------------------------------|-------------------|------------------|------------------|
| Stages of Breast cancer | | | |
| Early (86) | 33.98 \pm 8.77 | 1.55 \pm 0.43 | 36.03 \pm 4.9 |
| Late (49) | 26.01 \pm 9.00* | 0.89 \pm 0.40* | 29.22 \pm 5.0* |
| Histopathology | | | |
| Invasive ductal (90) | 34.00 \pm 6.37 | 2.00 \pm 1.22 | 34.30 \pm 3.00 |
| Invasive lobular (45) | 33.99 \pm 11.00 | 1.90 \pm 0.58 | 32.44 \pm 9.45 |
| Biopsy | | | |
| Poorly differentiated (46) | 29.01 \pm 7.77 | 1.90 \pm 0.09* | 30.26 \pm 11.2 |
| Well differentiated (39) | 30.39 \pm 4.00 | 2.56 \pm 0.10 | 32.60 \pm 11.8 |
| Metastasis | | | |
| Metastatic (55) | 32.19 \pm 8.00 | 0.99 \pm 0.89* | 34.46 \pm 4.90 |
| Non metastatic (99) | 33.31 \pm 7.90 | 1.87 \pm 1.2 | 35.00 \pm 1.70 |

Onodera's prognostic nutritional index=OPNI, CRP-Albumin-Lymphocyte index = CALLY, Haemoglobin, Albumin, Lymphocyte and Platelet score = HALP. *Significantly different.

Albumin is a primary protein synthesized in the liver used for evaluation of liver function. As a negative acute-phase protein, systemic inflammation causes its microvascular permeability and reduced circulating level (Levitt and Levitt 2016). Also anorexia induced by psychological stress, skeletal muscle wasting, low physical activity, poor quality of life, cancer related-anaemia, -malnutrition and food intake dysfunction (Yoshimura et al., 2020) causes a decrease in serum albumin level which ultimately contribute to the poor survival outcomes. Therefore, decreased serum albumin level is expected as found in this study. Previous studies have found that inflammation leads to a decrease in the levels of serum albumin in breast cancer patients (Xiang et al., 2022). Albumin is a key antioxidant, detoxifier and transporter of important nutrients (Levitt and Levitt 2016), thus hypoalbuminemia might be one of the causes of oxidative stress and failure of certain immune components which might promote tumor growth especially in metastatic and late stage breast cancer patients. Low haemoglobin level worsens hypoxia, which supports cancer progression and low haemoglobin count signifies anaemia, which is common in cancer patients results from nutritional deficiency (folate, iron and vitamins), advanced malignancy, increased hepcidin and reactive oxygen species stress (Maccio et al., 2015). This supports our finding of decreased HALP in late-stage breast cancer patients.

Lymphocytes are vital in immune defense against tumor cells whose infiltration into tumour microenvironment releases cytotoxic factors, resulting in apoptosis of cancer cells. Moreso, lymphocytes can performs cancer immune-surveillance to inhibit tumour cell proliferation, invasion and metastasis and ultimately leading to apoptotic death of tumour cells (De Nardo et al., 2007). However, platelets promote the survival of circulating tumor cells and *support tumor growth* (Lal et al., 2013). Platelet count is often increased in patients with solid cancer as an indication of chronic inflammation and cancer progression (Lida et al., 2022). In the present study, we found slightly increased platelet counts in breast cancer patients. It is opinion of the present authors that for continuous anti-cancer functioning of lymphocyte, its number needs to be optimal. Therefore, slightly raised number of circulating lymphocytes in breast cancer patients could be to counterbalance the pro-cancer functions of the circulating platelets.

CRP is an acute phase protein produced by the hepatocytes regulated by IL-6 and tumor necrosis factor in response to inflammation (Kolberg et al., 2021). Several studies have confirmed that high circulating CRP levels were associated with poor survival in cancer patients as a result of CRP involvement in acceleration of angiogenesis via increasing the circulating

levels of vascular growth factors and interleukins (Chen et al., 2011). Increased CRP in breast cancer patients indicates ongoing inflammation, progression of the tumor burden and local tissue damage in breast cancer patients considered for this study especially metastatic and advanced ones.

The prognostic nutritional index (PNI) is a composite measure of immune-nutritional status and liver function test which incorporates serum albumin and total lymphocyte counts (Onodera et al., 1984). A low PNI has been shown to be a negative prognostic factor in cancers of the breast. Low PNI means hypoalbuminemia and/or lymphocytopenia reflecting malnutrition, impaired protein synthesis in the liver, tumor development and progression suggesting the importance of immune and nutrition based interventions for breast cancer patients particularly late-stage breast cancer patients having low OPNI.

HALP score is a biomarker that has received much attention in recent years which is a combination of inflammatory responses (lymphocyte and platelet counts) and malnutrition variables (hemoglobin and albumin) (Duran et al., 2022). Our finding of low mean value of HALP corroborates the report of Peng et al (2018). HALP reflects cancer-related anaemia, a likely consequence of advanced malignancy, nutritional deficiency and chronic blood loss (Peng et al., 2018). A low HALP score in our breast cancer indicates a state of malnutrition and systemic inflammation which was pronounced in late-stage breast cancer groups. The CALLY index, another newly proposed prognostic biomarker for liver function, immune system status, and inflammatory component of the tumour microenvironment, was calculated using serum CRP concentration, serum albumin concentration, and peripheral lymphocyte count (Lida et al., 2022). Decreases in albumin and increases in CRP is a response to exacerbations of inflammation in cancer tissue. Taken together, significantly decreased CALLY index reflects systemic inflammatory response, malnutrition and deranged synthetic liver function to breast cancer especially in poorly differentiated, metastatic and late-stage breast cancer groups.

Strengths and Limitations

Some of the strengths of this study are as follows: To our knowledge, this is the first study to explore the impact of three nutritional-immune indices (PNI, CALLY and HALP) in differentiating breast cancer characteristics. These indices are inexpensive, convenient, and simple to calculate from the results of routine laboratory tests therefore it is likely to have high utility in daily clinical practice. All in all, our results should be validated through further large-scale, multi-institutional, prospective studies before the indices can be recommended for general clinical use. However, this study also has some limitations. First, this was a single-center clinical study. Second, we only obtained haemoglobin counts, albumin levels, lymphocyte counts and platelet counts at diagnosis but not at later time points.

CONCLUSION

The three immuno-nutritional indices determined in this study reflects the synthetic functions of liver apart from confirming the states of malnutrition and inflammation in breast cancer patients, which pre-disposes to delayed wound healing, poor response to therapy, prolonged hospital stay and poor outcomes resulting to increased morbidity and mortality. The high accessibility and cost-effectiveness of analyzing PNI, CALLY and HALP may give physicians useful information for optimizing personalised treatment based on nutrition and immune manipulation.

Conflict of interest: None.

REFERENCES

Adebamowo CA, Ajayi OO. 2000. Breast cancer in Nigeria. *West Afr J Med.* 19(3):179-191.
 Adisa AO, Arowolo OA, Akinkuolie AA, Titiloye NA, Alatise OI, Lawa OO *et al.* 2011. Metastatic breast cancer in a

Nigerian tertiary hospital. *Afr Health Sci.* Jun;11(2):279-84.
 Arinola GO, Edem FV, Odetunde AB, Olopade CO, Olopade OI. 2021. Serum Inflammation Biomarkers and Micronutrient Levels in Nigerian Breast Cancer Patients with Different Hormonal Immunohistochemistry Status. *Arch Breast Cancer.* 8(4):329-337. doi:10.32768/ABC.202184329-337
 Arinola O.G *et al.* 2022. Levels of Plasma C-reactive protein, Albumin and Pre-Albumin in Nigerian COVID-19 Patients. *Annals of Medical Research.* 29(1): 46-51
 Chen HH, Chen IH, Liao CT, Wei FC, Lee LY, Huang SF. 2011. Preoperative circulating C-reactive protein levels predict pathological aggressiveness in oral squamous cell carcinoma: a retrospective clinical study. *Clin Otolaryngol.* 36:147-53.
 DeNardo DG, Coussens LM. 2007. Inflammation and breast cancer. Balancing immune response: crosstalk between adaptive and innate immune cells during breast cancer progression. *Breast Cancer Res.* 9:212.
 Duran A, Pulat H, Cay F, Topal U. 2022. Importance of HALP Score in Breast Cancer and its Diagnostic Value in Predicting Axillary Lymph Node Status. *J Coll Physicians Surg Pak.* 32(6):734-739. doi: 10.29271/jcpsp.2022.06.734. PMID: 35686404.
 Grivennikov SI, Greten F.R. 2010. Karin M. Immunity, Inflammation, and Cancer. *Cell,* 140 (6), 883-899. pmid:20303878.
 Iida H, Tani M, Komeda K, Nomi T, Matsushima H, Tanaka S, Ueno M, Nakai T, Maehira H, Mori H, Matsui K, Hirokawa F, Kaibori M, Kubo S. 2022. Superiority of CRP-albumin-lymphocyte index (CALLY index) as a non-invasive prognostic biomarker after hepatectomy for hepatocellular carcinoma. *HPB.* Jan;24(1):101-115. doi: 10.1016/j.hpb.2021.06.414. Epub 2021 Jun 22. PMID: 34244053.
 Jimoh MA, Edem VF, Arinola GO. 2023. Immune cell counts, systemic immune inflammation index and pan inflammation immune value in female Nigerian breast cancer patients before treatment. *Asian Journal of Immunology.* 6 (1): 112-119
 Kolberg H, Edimiris A, Hoffmann O, Wetzig S, Shaheen M, Stephanou M, and Kolberg-Liedtke C. 2021. The role of C-reactive protein (CRP) as a prognostic biomarker in patients with early breast cancer (EBC) treated with neoadjuvant chemotherapy (NACT). *Journal of Clinical Oncology.* 39:15_suppl, e12545-e12545
 Lal I., Dittus K, Holmes CE. 2013. Platelets, coagulation and fibrinolysis in breast cancer progression. *Breast Cancer Res* 15, 207.
 Levitt D. G.; Levitt M. D. 2016. Human Serum Albumin Homeostasis: A New Look at the Roles of Synthesis, Catabolism, Renal and Gastrointestinal Excretion, and the Clinical Value of Serum Albumin Measurements. *Int. J. Gen. Med.* 9: 229. pmid:27486341.
 Lis CG, Grutsch JF, Vashi PG, Lammersfeld CA. 2003. Is serum albumin an independent predictor of survival in patients with breast cancer? *J Parenter Enteral Nutr.* 27:10-15.
 Maccio A, Madeddu C, Gramignano G, Mulas C, Tanca L, Cherchi MC, et al. 2015. The role of inflammation, iron, and nutritional status in cancer-related anemia: results of a large, prospective, observational study. *Haematologica.* 100(1):124-132.
 Njoku K.; Ramchander N. C.; Wan Y. L.; Barr C. E.; Crosbie E. J. 2021. Pre-Treatment Inflammatory Parameters Predict Survival from Endometrial Cancer: A Prospective Database Analysis. *Gynecol. Oncol.* pmid:34802721.
 Ntekim A, Nufu FT, Campbell OB. 2009. Breast cancer in young women in Ibadan, Nigeria. *Afr Health Sci.* Dec;9(4):242-246.
 Onodera T., Goseki N., Kosaki G. 1984. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi.* 85(9):1001-1005.
 Peng, D., Zhang, Cj., Tang, Q. et al. 2018. Prognostic significance of the combination of preoperative

- hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) in patients with renal cell carcinoma after nephrectomy. *BMC Urol* 18, 20 <https://doi.org/10.1186/s12894-018-0333-8>
- Xiang, M., Zhang, H., Tian, J., Yuan, Y., Xu, Z., & Chen, J. 2022. Low serum albumin levels and high neutrophil counts are predictive of a poorer prognosis in patients with metastatic breast cancer. *Oncology Letters*, 24, 432. <https://doi.org/10.3892/ol.2022.13552>
- Xu, T., Zhang, SM., Wu, HM. et al. 2022. Prognostic significance of prognostic nutritional index and systemic immune-inflammation index in patients after curative breast cancer resection: a retrospective cohort study. *BMC Cancer*. 22: 1128. <https://doi.org/10.1186/s12885-022-10218-x>
- Yoshimura T, Suzuki H, Takayama H, Higashi S, Hirano Y, Tezuka M. et al. 2020. Impact of Preoperative Low Prognostic Nutritional Index and High Intramuscular Adipose Tissue Content on Outcomes of Patients with Oral Squamous Cell Carcinoma. *Cancers (Basel)*. 12:3167.