

SJMLS - 8(1) - 008

Selected Biomarkers of Coagulation Disturbance in Newly Diagnosed Breast Cancer PatientsJoseph E. Udosen¹, Euphoria C. Akwiwu^{2*}, Valerie E. Njar², David U. Akpotuzor², Dennis Abunimye², Josephine O. Akpotuzor²Department of Surgery, University of Calabar, Calabar, Nigeria¹, Department of Haematology and Blood Transfusion Science, University of Calabar, Calabar, Nigeria².Author for Correspondence *: ecakwiwu@gmail.com / +234-803-677-7296 / ORCID Number: 0000-0001-6097-557X. <https://dx.doi.org/10.4314/sokjmls.v8i1.8>.**Abstract**

Coagulation disturbance can be quite detrimental to health, whether as a primary disorder or secondary to other medical conditions. The risk of thrombosis has been previously reported in breast cancer. This case-control study purposively enrolled 50 newly diagnosed female breast cancer patients. Quick's One-stage method was used for prothrombin time (PT) and activated partial thromboplastin time (APTT) tests, while fibrin plate lysis method was used for euglobulin lysis time (ELT) assessment. Data analysis was carried out on statistical package for social sciences (SPSS) version 20.0. A p-value ≤ 0.05 was considered significant. Mean values of PT, APTT and ELT of newly diagnosed breast cancer patients were compared to values from control subjects. The ELT was significantly prolonged in the breast cancer patients compared to that of controls ($p = 0.001$). These measured parameters were further compared within the breast cancer group on the basis of hours of immobility per day into three categories (<3 hours, 3-6 hours and >6 hours). Subjects with more than 6 hours of immobility per day had significantly prolonged ELT compared to those with lesser hours of immobility. This study concludes that fibrinolytic challenge exists in breast cancer prior to commencement of treatment particularly among patients with increasing immobility.

Key words: Breast cancer, coagulation, fibrinolysis, immobility

Introduction

Awareness and detection of breast cancer have

been improving in recent times both globally and locally (Akpotuzor *et al.*, 2011; Azubuike *et al.*, 2018; WHO, 2022). The condition, however, is associated with high mortality (WHO, 2019; Fatiregun *et al.*, 2020). It is important to appreciate indicators of derangement at different levels of the disease management. Haemostasis is vital to health, while coagulation disturbance can be quite detrimental. Whether as a primary disorder or secondary to other medical conditions, derangement in haemostasis confers some level of morbidity and mortality risks. Thrombogenesis may be linked to endothelial activation or hypercoagulability. Its occurrence in cancer is generally viewed from its relationship with inflammation (Razak *et al.*, 2018; Chen *et al.*, 2022). Inflammatory processes can arise in thrombosis due to the endothelial injuries and thrombogenesis, while systemic inflammation also modifies the coagulation process and promotes thrombogenesis. Apparently, the occurrence of one instigates the involvement of the other in a continuous vicious cycle barring timely and proper intervention (Buxhofer-Ausch *et al.*, 2016; Monie and DeLoughery, 2017). The risk of thrombosis has been previously reported in breast cancer patients receiving post-operative chemotherapy (Udosen *et al.*, 2022). The study observed that although no significant changes occurred in the platelet count between breast cancer patients and control group, a significant increase was observed in the platelet-to-lymphocyte ratio among breast cancer patients. Thrombosis is associated with poor prognosis in breast cancer and warrants indicators for timely detection (Zhang *et al.*, 2017; Zhu *et al.*, 2017;

Guo *et al.*, 2019). In addition to the pathophysiology of breast cancer, the current treatment approaches including surgery, chemotherapy and radiotherapy increase the risk of activated coagulation by exerting adverse changes to vascular membrane (Razak *et al.*, 2018; Olasehinde *et al.*, 2021; Chen *et al.*, 2022). While the impact of treatment may not always be easy to ascertain, screening for coagulation disturbance in newly diagnosed subjects would be helpful in differentiating effect of treatment from that occurring due to the cancer itself. In addition, finding from this study could provide necessary guide towards suitable adjustments in treatment options and protocols. This study considered fibrinogenesis and fibrinolysis in screening for coagulation disturbance among newly diagnosed breast cancer patients. Prothrombin time (PT) for the extrinsic pathway and activated partial thromboplastin time (APTT) for the intrinsic pathway were used to screen for possible derangement in fibrinogenesis, while euglobulin lysis time was used to check fibrinolytic involvement.

Materials and method

This case-control study purposively enrolled 50 female breast cancer patients at the verge of treatment commencement. They were accessing medical care at University of Calabar Teaching Hospital in Calabar, Southern Nigeria. Ethical considerations were duly observed and approval obtained from the institution's committee on ethics. Informed consent was also obtained from the study participants.

A structured questionnaire was administered by two trained interviewers to obtain information on hospital reporting, commencement of treatment and impact of the condition with regards to average daily hours of immobility. Only those confirmed from their hospital folders as “yet to commence treatment” were eventually enrolled. Blood sample was collected from each participant to obtain citrated plasma for the selected coagulation studies. The Quick's One-stage method was used for PT and APTT tests, while fibrin plate lysis method was used for ELT assessment.

Data analysis was carried out on statistical package for social sciences (SPSS) version 20.0. Student t-test and one-way analysis of variance were used as statistical tools to analyse the difference between means. A p-value 0.05 was considered significant.

Results

Mean values of PT, APTT and ELT of preoperative breast cancer patients compared to values from control subjects are shown in Table 1. The ELT was significantly prolonged in the breast cancer patients compared to that of controls (p = 0.001).

These measured parameters were further compared within the breast cancer group on the basis of hours of immobility per day into three categories (<3 hours, 3-6 hours and >6 hours). Subjects with more than 6 hours of immobility per day had significantly prolonged ELT compared to those with lesser hours of immobility (Table 2).

Table 1: Coagulation parameters of test and control subjects

Parameters	Breast cancer patients (n = 50)	Control (n = 50)	P value
PT	12.30 ± 1.18	12.02 ± 1.11	0.066
APTT	35.30 ± 2.04	35.24 ± 1.08	0.830
ELT	166.18 ± 29.32	127.14 ± 11.56	0.001*

Values are expressed as Mean ± Standard deviation; PT = Prothrombin Time; APTT = Activated Partial Thromboplastin Time; ELT = Euglobulin Lysis Time

Table 2: Coagulation parameters of subjects based on hours of immobility

	< 3 hours (n = 17)	3 – 6 hours (n = 19)	> 6 hours (n = 14)	P value
PT	12.35 ± 1.26	12.32 ± 1.15	12.21 ± 1.20	0.887
APTT	35.00 ± 1.54	35.32 ± 2.10	36.04 ± 2.14	0.565
ELT	146.24 ± 23.32	158.35 ± 16.58	201.57 ± 12.01#	0.001*

Values are expressed as Mean ± Standard deviation; PT = Prothrombin Time; APTT = Activated Partial Thromboplastin Time; ELT = Euglobulin Lysis Time

Discussion

This study looked into selected biomarkers of coagulation disturbance in breast cancer patients yet to undergo treatment. Among the measured parameters, which includes PT, APTT and ELT. Only the ELT was found to be significantly prolonged in breast cancer patients compared to control subjects (p = 0.001). This observation signifies impaired fibrinolytic activity in breast cancer. Previous reports on breast cancer reveal a range of haematological derangements (Zhang *et al.*, 2017; Zhu *et al.*, 2017). Specifically in the study area, there are indications of heightened inflammatory and thrombotic risks during post-operative chemotherapy (Udosen *et al.*, 2022). Generally, the relationship between cancer and inflammation have been known. Considering that thrombotic processes could be instigated by inflammatory mechanisms and vice versa, it is important to monitor coagulation pathways in conditions such as breast cancer. The uncertainty as to whether coagulation disturbance exists prior to commencement of treatment or is occasioned by the adverse effect of treatment has been an issue. The finding of prolonged ELT prior to treatment, thus, reveals the need to monitor the fibrinolytic pathway before and during treatment for breast cancer.

The pathophysiology of malignant conditions in relation to invasiveness and infiltration is reflected in reduced blood cell counts and alterations particularly as detection may late (Ibrahim *et al.*, 2016; Kifle *et al.*, 2019). Advanced stage breast cancer remains a challenge in the study locality as early reporting

and timely detection of health conditions are hampered by poor healthcare coverage (Akpotuzor *et al.*, 2011; Akwiwu *et al.*, 2021; Ndem *et al.*, 2021; Udosen *et al.*, 2023). The toll of tumour vascularization and metastasis as the disease progresses can be quite exhausting. Thus, the experience of fatigue may result in increasing hours of immobility for affected persons. Immobility is among the myriads of risk factors recognized for increased risk of thrombosis (Cushman, 2007). The pathogenesis of venous thrombus formation as represented by the Virchow's triad includes venous stasis, hypercoagulability and endothelial damage/activation (Monie *et al.*, 2017; Mouabbi *et al.*, 2017). The present study observed significantly prolonged ELT in breast cancer patients with more than 6 hours of immobility per day (p = 0.001). Apart from the cycle of inflammation and thrombosis that emanates directly from the presence of malignancy, coagulation disturbance could be secondary to the breast cancer occurrence via increased immobility. Addressing this aspect in breast cancer management would be worth considering. This study concludes that fibrinolytic challenge exists in breast cancer prior to commencement of treatment particularly among patients with increasing immobility.

Conflict of interest

Authors declare no conflict of interest

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Citation: Joseph E. Udosen, Euphoria C. Akwiwu, Valerie E. Njar, David U. Akpotuzor, Dennis Abunimye, Josephine O. Akpotuzor. Selected Biomarkers of Coagulation Disturbance in Newly Diagnosed Breast Cancer Patients. *Sokoto Journal of Medical Laboratory Science*; **8(1)**: 60-64. <https://dx.doi.org/10.4314/sokjmls.v8i1.8>

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