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Assessment of plasma levels of D-dimer and lipid profile in women with breast cancer on chemotherapy at Nnamdi Azikiwe university teaching hospital, Nnewi

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Abstract

Background and Aim of study: To assess the risk of cardiotoxicity through the evaluation of D-dimer level and lipid profile in women with breast cancer with chemotherapy and without chemotherapy in NAUTH, Nnewi, Nigeria.

Methodology: This was a cross-sectional study which consisted of 120 participants (40) women with breast cancer on chemotherapy, 40 women with breast cancer not on chemotherapy and 40 apparently healthy controls. The concentration of D-dimer and fasting lipid profile was assayed using immunoturbidiometric and spectrophotometric method respectively. Anthropometric parameters were measured using standard laboratory methods

Results: The mean level of D-dimer was significantly higher in women with breast cancer on and not on chemotherapy when compared with control participants (P<0.05 respectively). The mean Tc, TG and LDLc levels were significantly higher while HDLc was significantly lower in women with breast cancer on and not on chemotherapy when compared with control (P<0.05). Tc, TG and LDLc levels were significantly higher while, HDLc was significantly lower in women with breast cancer on chemotherapy when compared with those not on chemotherapy (P < 0.05).

Conclusion: This indicates increased activation of fibrinolysis and heamostasis with dyslipidemia which may result to venous thrombosis predisposing the affected individuals to the risk of cardiotoxicity and increase mortality.

Keywords: D-dimer; Chemotherapy; Breast cancer; Women lipid profile.

1. Introduction

Breast cancer is the uncontrolled proliferation of cells which starts in breast cells and attains malignancy. It comprises of a heterogeneous group of tumours that display marked variation in clinical presentation, morphology, molecular features, biological behaviour, and response to therapy [1]. It is an invasive tumor that develops in the mammary gland from the inner lining of the milk ducts or the lobules that supply the ducts with milk [2]. Breast cancer is the most deadly type of cancer [3] and number one cause of cancer mortality in women worldwide [4]. Breast cancer in female is the

most common malignant neoplasm and represents a diversified group of tumors, which exhibit different behaviors and altered response to therapy [5]. Biological markers, hormonal status, histological grading and subgroups status, tumor size, lymph node embroilment have predictive and prognostic value and they are the important factors in determining appropriate treatments [5].

Poor screening or testing for the relevant biomarkers in breast carcinogenesis and quality of cancer control strategies in the country is another major factor [6]. Nigeria has one of the world's highest age-standardized mortality rates of BC and the highest in Africa [7]. The International Agency Research on Cancer (IARC) recorded 28,380 new breast cancer cases in Nigeria in 2020, representing 22.7% of new cancers and accounting for the highest proportion of all cancer types [8].

Cardiovascular disease (CVD) remains the leading cause of mortality in women [9], while breast cancer is the number one threat to women's health. Improvement in early detection and treatment of breast cancer have led to an increased number of breast cancer survivors who are at risk of long-term cardiovascular complication due to the cancer treatments [10]. The most recent European Society of Cardiology (ESC) position paper on cancer treatments and cardiovascular toxicity suggests that identifying high-risk participants prior to the administration of cancer therapy may allow treatment modifications to decrease the risk of subsequently developing cardiotoxicity [11].

Cardiovascular diseases and breast cancer have several overlapping risk factors, such as age, tobacco use, diet, obesity, smoking and sedentary lifestyle. Additionally, current breast cancer treatments can have a negative impact on cardiovascular health (eg, left ventricular dysfunction, accelerated cardiovascular diseases), and for women with pre-existing cardiovascular diseases, this might influence cancer treatment decisions by both the participant and the provider [12]. The risk of cardiovascular diseases (heart failure (HF), myocardial ischemia, and hypertension) is high, and development of cardiovascular diseases risk factors (obesity and dyslipidaemia) is higher in older breast cancer survivors than the risk of tumor recurrence [13].

D-dimer (MW 180 kDa) is the final product of fibrin degradation [14]. It consists of the remnants of all three chains (α, β and γ chains) of fibrinogen cross linked by disulfide bonds [14]. D-dimer is the smallest fragment of the degradation product of fibrous protein and a valuable biomarker of thrombin formation and fibrinolysis [15]. Elevated levels of D-dimer have been found in the blood of participants with pulmonary embolism (PE), deep vein thrombosis (DVT), and atherosclerosis. In pathological conditions, the concentrations of D-dimer can increase, such as injury, cancer, or infections [17]. The elevated level of D-dimer in blood is believed to be a reliable marker of pathological coagulation that underlies the pathogenesis of most cardiovascular diseases [17]. It is widely used to exclude the diagnosis of deep vein thrombosis.

Previous studies by Harish *et al.* [20] has shown elevated D-dimer levels in women with breast cancer on chemotherapy. This is supported by similar studies in treatment of breast cancer with chemotherapy, severe complication such as : venous thrombosis of the lower extremities and the consequent pulmonary embolism [16] these can be diagnosed using D-dimer, as it's known to be a marker for endogenous fibronolysis [18]. The purpose of using D-dimer as a marker of endogenous fibrinolysis is because of its negative predictive value (NPV) and sensitivity. Moreover, It is cost effective for detection of patients with breast cancer who might be predisposed to thromboembolic phenomenom [18]. As a clinician, before ordering for assessment of D-dimer test, it is important to know the patients probability for deep venous thrombosis (DVT) [17]. So in this, a categorization method has been set up by Wells *et al.* [19] and they are as following: Low clinical probability (LCP), intermediate clinical probability (ICP), and high clinical probability (HCP) with the prevalence rate of LCP, ICP and HCP being < 5 %, 15 %, 70% respectively. Furthermore, in pulmonary embolism (PE) wells and Geneva score is used along with the clinicians Judgment for detecting the prevalence of PE and the rates are as follows in this case: 8%, 28%, and 74% in patients with LCP, ICP, and HCP, respectively [17,23]. Treatment of breast cancer patients using chemotherapy can contribute to thromboembolic diseases [22]. Immunochemotherapy has shown to be effective by disabling the pathways to immune activation [21, 24]. Elevated D-dimer levels has shown to be related to advanced breast cancer disease including breast cancer stage 3 and 4 [20].

Lipids like cholesterol are absorbed through the intestine and carried throughout the body via the lipoproteins and they are used for energy, steroid formation and bile acid formation [25]. Pappan *et al.* [27] state that dyslipidemia can result from changes or imbalances in any of the following contributors to the pathway through which lipoproteins are transported: cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and high-density lipoproteins. Dsylipidemia is abnormal levels of lipids in the blood and this can lead to cardiovascular diseases [25].

Malignancies like breast cancer has shown some disturbances in lipoprotein and lipid profile levels [27, 28]. Recent studies by Wei *et al.* [31] have noted correlation between breast cancer and elevated lipid profile levels. Chemotherapy,

the treatment given to breast cancer patients is important in control of the disease and general survival of these individuals [30]. Due to this, cardiovascular complications such as: heart failure, myocardial ischemia, and hypertension arise [31].

Previous studies have noted a significant association between venous thromboembolism, pulmonary embolism and breast cancer and its burden [32]. Furthermore, studies on the cardiovascular risk in women with breast cancer on chemotherapy and not on chemotherapy has indicated several morbidities [31,32] as a result of venous and arterial thrombotic event [24,32] using D-dimer and lipid profile in assessment of risk status [33,34]. Therefore, it is imperative to assess the lipid profile and D-dimer levels in women with breast cancer on chemotherapy and not on chemotherapy.

2. Materials and method

2.1. Study design

This was a cross sectional study designed to assess D-dimer and lipid profile levels in women with breast cancer on chemotherapy and not on chemotherapy in NAUTH, Nnewi, Nigeria. A total of One hundred and twenty (120) women were recruited for this study. This consisted of forty (40) women with breast cancer on chemotherapy, forty (40) women with breast cancer not on chemotherapy and forty (40) apparently healthy control. Socio-demographic and clinical characteristic data were collected using an interviewer - administered questionnaire. The weight and height of each subject were measured using a standard beam balance. Blood pressure was measured using a sphygmomanometer and a stethoscope.

2.2. Ethical approval

The ethical approval for this research was obtained from the board of ethics committee of Nnamdi Azikiwe University Teaching Hospital, Nnewi, with reference no: NAUTH/CS/66/VOL.13/VER.3/275/2021/058.

2.3. Informed Consent

Before commencement, informed consent of all the participants was obtained before enrolment into the study. The participants were assured of confidentiality of information obtained from them during and after the study.

2.4. Inclusion criteria

Women within the age of 30-60 years old with breast cancer on chemotherapy and not on chemotherapy. Participants who had mastectomy and were on chemotherapy were also involved.

2.5. Exclusion criteria

The individuals excluded from this study were: men of all ages, men with breast cancer, women with known cardiovascular diseases, pregnant women, hypertensive and diabetic women, participants who are unable to provide informed consent.

2.6. Blood Sample collection and storage

Five milliliters (5mls) of blood sample was collected from each subject involved in the research work by venipuncture technique under aseptic conditions from the antecubital vein. Three milliliters (3mls) was dispensed into a well labeled plain container while two milliliters (2mls) was dispensed into an anticoagulant tube containing two hundred microliter (220μl) of trisodium citrate. The plasma and serum were obtained by centrifuging at 4000rpm for 10 minutes. The sera and plasma were dispensed into another properly labelled container and stored frozen at -20^{0}C for a period of one month prior to analysis.

2.7. Laboratory Method

2.7.1. Determination of D-dimer

D-dimer was determined using Immunoturbidimetric method as described by Torok-Nagy *et al.* [37]

2.8. Serum Fasting Lipid profile

2.8.1. Determination of Total Cholesterol

Total cholesterol was determined using the enzymatic method as described by Allain *et al.*[38]

2.8.2. Determination of serum High Density Lipoprotein

High density lipoprotein was determined using enzymatic method as described by Herrman *et al.*[39]

2.8.3. Serum Triglycerides

Serum triglycerides was determined by using enzymatic method as described by Fossati and prencipe [40].

2.8.4. Low Density Lipoprotein – cholesterol/very low density lipoprotein-Cholesterol

Low density lipoprotein cholesterol was calculated using Friedewald equation as described by Friedewald *et al.*[41]

2.8.5. Anthropometric measurement

The weight and height of each participant were measured using a standard beam balance scale and a stadiometer respectively. Body mass index (BMI) was calculated as weight (kg) divided by height squared in meters.

$$BMI\ (Kg/m2) = Weight\ (Kg)/Height2\ (m2).$$

Also, systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured using sphygmomanometer and stethoscope.

2.9. Statistical Analysis

Statistical package for social sciences version 23.0 was used for data analysis. Data obtained was analyzed using ANOVA, Independent t-test and Pearson Correlation. Results were deemed significant at p <0.05.

3. Results

The mean value of systolic blood pressure (SBP) was significantly higher in women with breast cancer on chemotherapy (119.77±14.49) and their counterpart not on chemotherapy (115.87±11.66) when compared with control (112.33±11.64) (P< 0.05 respectively). Similarly, the mean value of SBP was significantly higher in women with breast cancer on chemotherapy (119.77±14.49) when compared with their counterpart not on chemotherapy (115.87±11.66) (P=0.010).

The mean value of diastolic blood pressure (DBP) was significantly higher in women with breast cancer on chemotherapy (78.57±13.75) and not on chemotherapy (77.07±11.98) when compared with control (72.17±9.98) (P< 0.05 respectively). (Table 1).

The mean plasma levels of D-dimer was significantly higher in women with breast cancer on chemotherapy (8.23±0.45) and not on chemotherapy (8.28±1.07) when compared with control (7.92±0.39) (P< 0.05 respectively). (Table 2).

There were significantly higher levels of TC, TG, LDLc, VLDLc with lower HDLc in women with breast cancer on chemotherapy (5.07±0.97, 1.74±1.84, 2.94±0.65, 0.79±0.84 and 1.25±0.39) and women not on chemotherapy (4.59±0.84, 1.27±0.45, 2.69±0.64, 0.58±0.20 and 1.29±0.42) when compared with control group (4.73±0.56, 1.25±0.46, 2.74±0.57, 0.57±0.20 and 1.33±0.50) (p < 0.05 respectively).

The mean levels of TC, TG, LDLc and VLDLc were significantly higher in women with breast cancer on chemotherapy (5.07±0.97, 1.74±1.84, 2.94±0.65, 0.79±0.84) when compared with their counterparts not on chemotherapy (4.59±0.84, 1.27±0.45, 2.69±0.64, 0.58±0.20) (p < 0.05 respectively). Conversely, the mean HDLc level (1.25±0.39) was significantly lower in women with breast cancer on chemotherapy when compared with those not on chemotherapy (1.29±0.42) (P= 0.010) (Table 2).

Significant positive correlation was observed when D-dimer was correlated with triglycerides and VLDLc in women with breast cancer on chemotherapy (r=0.424; P= 0.020 respectively). TC was significantly positively correlated with LDLc (r=0.830; P= 0.000), HDLc (r= 0.478; 0.008), VLDLc and TG (r= 0.557; P=0.001) in women with breast cancer on

chemotherapy (Table 3). Similarly, TC was significantly correlated with LDLc (r=0.830; P= 0.000) HDLc (r= 0.478; 0.008) in women with breast cancer not on chemotherapy (Table 4).

Table 1 Values of Anthropometric and blood pressure variables in women with breast cancer on chemotherapy, women with breast cancer not on chemotherapy and control participant

Group	BMI	SBP	DBP
BC on Chemotherapy (A) n = 40	25.59±5.60	119.77±14.49	78.57±13.75
BC not on Chemotherapy (B) n = 40	25.50±4.11	115.87±11.66	77.07±11.98
Control (C) n = 40	25.40±4.84	112.33±11.64	72.17±9..98
F-test	0.090	4.580	3.330
p-value	0.080	0.030	0.046
A vs B	0.960	0.010	1.000
Avs C	0.870	0.000	0.030
B vs C	0.670	0.040	0.035

Key: BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure p-value (< 0.05) = statistically significant; p-value (>0.05) = Not statistically significant; n= number of participants affected by a variable. BC= Breast cancer

Table 2 Levels of D-dimer and lipid profile in women with breast cancer on chemotherapy, not on chemotherapy and control group

Group	D-dimer	TC	TG	HDL-c	LDL-c	VLDL-c
BC on chemotherapy (A)N=40	8.23±0.45	5.07±0.97	1.74±1.84	1.25±0.39	2.94±0.65	0.79±0.84
BC not on Chemotherapy	8.28±1.07	4.59±0.84	1.27±0.45	1.29±0.42	2.69±0.64	0.58±0.20
Control group (C) n=40	7.92±0.39	4.73±0.56	1.25±0.46	1.33±0.50	2.74±0.57	0.57±0.20
F-test	4.306	4.905	5.794	5.304	4.324	3.794
P- value	0.006	0.006	0.002	0.009	0.002	0.020
A vs B	0.060	0.000	0.000	0.010	0.000	0.003
A vs C	0.030	0.303	0.000	0.000	0.006	0.000
B vs C	0.010	1.000	0.950	0.020	0.600	0.950

Key: A = women with breast cancer on chemotherapy B = Women with breast cancer not on chemotherapy C = control participants TC= Total cholesterol TG=Triglycerides HDL-C= High density lipoprotein cholesterol LDL- C= Low density lipoprotein cholesterol VLDL-C= Very low density lipoprotein

Table 3 Correlation between D-dimer and lipid profile in women with breast cancer on chemotherapy

Parameter	r	P-value
D-dimer Vs TC	0.341	0.065
D-dimer Vs TG	0.424	0.020*
D-dimer Vs HDL-C	0.091	0.634
D-dimer Vs LDL-C	0.225	0.231
D-dimer Vs VLDL-C	0.424	0.020*

TC Vs LDL-C	0.830	0.000*
TC Vs HDL-C	0.478	0.008*
TC Vs VLDL-C	0.557	0.001*
TC Vs TG	0.557	0.001*

Key: TC = Total cholesterol TG= Triglycerides HDL-C =High density lipoprotein-Cholesterol LDL-C= Low density lipoprotein-Cholesterol VLDL-C= Very low density lipoprotein Cholesterol r = correlationcoefficient P-value (< 0.05) = statistically significant; P-value (>0.05) = Not statistically significant.

Table 4 Correlation between D-dimer and lipid profile levels in women with breast cancer not on chemotherapy

Parameter	R	P-value
D-dimer Vs TC	0.007	0.969
D-dimer Vs TG	0.071	0.711
D-dimer Vs HDL-C	0.148	0.434
D-dimer Vs LDL-C	-0.099	0.604
D-dimer Vs VLDL-C	0.071	0.711
TC Vs LDL-C	0.851	0.000*
TC Vs HDL-C	0.572	0.001*
TC Vs VLDL-C	0.228	0.225
TC Vs TG	0.228	0.225

Key: TC = Total cholesterol TG=Triglycerides HDL-C = High density lipoprotein-Cholesterol LDL-C= Low density lipoprotein-Cholesterol VLDL-C= Very low density lipoprotein Cholesterol r = correlation P-value (< 0.05) = statistically significant; P-value (>0.05) = Not statistically significant.

4. Discussion

There was significantly higher mean value of SBP and DBP in women with breast on chemotherapy when compared with their counterparts not on chemotherapy. A significantly higher SBP and DBP was observed in women with breast cancer on chemotherapy when compared with control. Also, there was significantly higher mean value of SBP and DBP in women with breast cancer not on chemotherapy in comparison with control participants.

Elevated blood pressure is a characteristic of hypertension, clinically [42]. Over the years, there has been several observational studies done linking hypertension to breast cancer [43-45]. Research has shown that hypertension is more common in women receiving chemotherapy and this could be due to direct vascular and renal effect of the cancer therapy [42]. Hypertension and blood pressure begin to emerge as soon as breast cancer patients start treatment on breast cancer, this can lead to an increased risk of cardiovascular disease and death [42, 43]. Prevalence of hypertension has found indications on women with breast cancer on chemotherapy whom had obviously survived longer due to this therapy [43,47] but, increasing their risk of cardiovascular diseases. Prior research has revealed that most morbidities as a result of cardiovascular diseases were in women with breast cancer receiving chemotherapy [45]. Worthy to note are the chemotherapeutic drugs said to increase blood pressure and they are [46]: Poly (ADP) ribose Polymerase inhibitor like; Niraparib [49] which induces hypertension at 19 %, Aromatase like; Anastrozole [48]13%, letrozole [48] 8%, Exemestane [48] 10% and mToR inhibitors like; Evrolimus and sirolimus 13 %. [49].

In a recent NORA (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer) study, Niraparib was used in treatment of breast cancer it was noted that hypertension occurred in quite a number of people and when Niraparib was given in combination VSPIs [49], there was a turnout of 56% cases of hypertension observed [55]. Similarly, some studies have identified the use of aromatase inhibitors and its increase risk of cardiovascular diseases and mortality [50, 51]. The underlying pathophysiology in implication of high blood pressure due to chemotherapy are as a result of reduced nitric oxide generation, oxidative stress, endothelin-1, prostaglandins, endothelial dysfunction, increased sympathetic outflow, and microvascular rarefaction [52,53]. In addition, genetic polymorphisms in vascular endothelial growth factor receptors in which drugs like VASPIs induced blood pressure has been observed [45,54]. The

significantly higher blood pressure in women with breast cancer on chemotherapy in this study, is in consonance with reports by Yan *et al*. [73] in association of hypertension and breast cancer which showed high levels of blood pressure in women with breast cancer on chemotherapy. Also reports by Jordana *et al*. [43] validated the findings of this study.

This study revealed high blood pressure levels in women with breast cancer not on chemotherapy. This is supported by evidence from studies carried out by the authors Chu *et al*. [55] and Maitaland *et al*. [56] in prevalence of hypertension in breast cancer women before start of chemotherapy.

There was significantly higher mean levels of D-dimer in women with breast cancer on chemotherapy and in women with breast cancer not on chemotherapy when compared with control. Earlier in our introduction, we highlighted on the purpose of D-dimer in breast cancer especially in diagnosis of pulmonary embolism [16, 20]. Also, discussed were the negative predictive value and its sensitivity both in women with breast cancer on chemotherapy and not on chemotherapy [18] with categorization methods by well et al. before order of the test. The findings of this study is in support with previous researches which discovered elevated levels of D-dimer in women with breast cancer on chemotherapy and not on chemotherapy when compared with control participants [16,20,21].

The findings of this study revealed significant differences in lipid profile Parameters. There was significantly higher mean levels of TC, TG, LDLc and VLDLc with lower HDLc noted in women with breast cancer on chemotherapy when compared with women on breast cancer not on chemotherapy and control. Elevated blood levels of lipids is known as Dyslipdemia and this can increase the risk of cardiovascular diseases [27,36]. In this current findings, the elevated mean levels of lipid profile is in line with prior studies by Li *et al*.[60] in women with breast cancer on chemotherapy and not on chemotherapy and it showed significances in the lipid profile status of these individuals, with other authors highlighting specifically on TC, TG, LDLc and HDLc [58,59]. The proliferation of cancer cells led to an increase in TC, which in turn facilitated lipid biosynthesis and metabolism, resulting in elevated serum cholesterol levels in breast cancer patients [57]. Chemotherapy-induced endothelial dysfunction has been reported to cause insulin resistance, a decrease in cytokines, and alterations in lipid levels [61]. Triglycerides, one of the lipid profile component, is a crucial metric to investigate how chemotherapy affects women with breast cancer [57]. High amounts of TG may raise the risk of cardiovascular problems, according to Ma *et al*. [57]

Chemotherapy has been demonstrated to have side effects, particularly in relation to cardiovascular conditions such as heart failure, myocardial ischemia, and hypertension [60]. Women undergoing chemotherapy for breast cancer may experience cardiotoxicity as a result of both internal and extrinsic factors, such as the drug itself, dosage, mode of administration, cumulative dose, and number of treatment sessions [62]. Moreover, the development of cardiac dysfunction can also be attributed to the combination of several treatments [35,63]. Many chemotherapy medications, including anthracyclines like doxorubicin, have shown to cause dyslipidemia. The mechanism behind this is that lower ABCA1 gene and apoA1 expression in HepG2 cells and hepatocytes leads to much higher HDLc levels [63]. Furthermore, anthracyclines have also been found to be connected to a dose-related risk for heart failure and cardiomyopathy [64]. Retrospective studies have provided evidence that patients treated with anthracyclines and taxines, which are both associated with low risk factors, can tolerate doses of up to 300 mg/m2 and 400 mg/m2, respectively. This results in low and high rates of cardiovascular disease and heart failure development [63].

Significant positive correlation was observed when D-dimer was correlated with triglycerides and VLDLc in women with breast cancer on chemotherapy. This reveals the link between the effect of chemotherapy in activation of fibrinolysis and hemostasis [65] with changes in lipid levels, particularly elevated TG and VLDLc [29,30] . These highlight the significance of D-dimer's positive value and its potential effects on women undergoing chemotherapy for breast cancer [65,66]. Noting in addition the affected individuals' altered lipid profiles and their implications [60,63, 67]. The findings of this research is in consonance with prior studies which observed a significant positive correlation of D-dimer with TG and VLDLc in women with breast cancer on chemotherapy [31, 36, 67, 68].

TC was significantly positively correlated with LDLc, HDLc, VLDLc and TG in women with breast cancer on chemotherapy. This is as a result of the changes observed between the lipid profile parameters in women with breast cancer on chemotherapy [27, 58, 60]. This suggests the role of increased TC, HDLc, VLDLc and TG as significant predictors of coronary diseases [57, 69] and cardiotoxicity in women with breast cancer on chemotherapy [67,70]. Moreover, Triglycerides has shown to be a marker used to explore the impact of chemotherapy in women with breast cancer on chemotherapy and their corresponding not on chemotherapy [36].

TC was significantly correlated with LDLc, HDLc in women with breast cancer not on chemotherapy. This could be explained by additional risk variables that have the potential to significantly raise the lipid profile in breast cancer patients who are not receiving chemotherapy and their role in predicting coronary heart disease [44, 57, 69, 71, 72].

The findings of this study is in line with a study conducted by Borgquist *et al.*[72]which showed a significant positive correlation between TC and LDLc in women with breast not on chemotherapy.

5. Conclusion

This study showed elevated levels of D-dimer and lipid profile in women with breast cancer on chemotherapy when compared with breast cancer women not on chemotherapy and control. This indicates activation of fibrinolysis and hemaostasis with association of dyslipidemia which could predispose the affected individuals to risk of cardiotoxicity and increased mortality.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

All authors hereby declare that the experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki

Statement of informed consent

All authors declare that 'Written informed consent" was obtained from the patient for the publication of this research. A copy of written consent is available for review by editoral office/chief editor/editorial board members of this journal.

Authors contribution

The corresponding author, supervised by Nkiruka Rose Ukibe (Project supervisor) thoroughly saw that no stone was left unturned in all sections of this research in other to make it a valuable one. Other authors involved: Oluchukwu Maryrose Obiorah,, Chinenye Stellamaris Okeke, Olua Ekuma Sunday, Chinenye Anthonia Ogueze, Chidera Vivienne Obilo contributed in various sections of this research to give it a solid output.

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