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De Ritis Ratio and related Parameters among Breast Cancer Patients in a Southern Nigeria Population

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Abstract
De Ritis described the ratio between the serum levels of liver enzymes; aspartate transaminase (AST) and alanine transaminase (ALT). The central role of the liver in metabolism makes it a necessity that it functions optimally during chemotherapeutic administration, hence the consideration of associated parameters in the management of breast cancer. This study was conducted in University of Calabar Teaching Hospital, Calabar. It included 40 cases of pathologically diagnosed breast cancer female patients who were accessing post-operative chemotherapy. Another 40 apparently healthy females drawn from the general population served as controls. Ethical approval and written informed consent were duly sought and obtained. The present study measured the levels of total and conjugated bilirubin as well as the enzyme activities for aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase. Additionally, Unconjugated bilirubin derived from total and conjugated bilirubin as well as De Ritis ratio computed from aspartate aminotransferase and alanine aminotransferase were calculated. Standard colorimetric methods were used to determine the measured parameters, while derived parameters were calculated. The data obtained were analyzed in Statistical Package for Social Sciences (SPSS) using students t-test at 95% confidence level with p-value of $\leq$ 0.05. Apart from alanine aminotransferase that showed no significant difference, the mean values of other parameters were observed to be significantly higher among the breast cancer subjects compared to controls. The progression of the chemotherapy courses showed some observable effect on both derived parameters; Unconjugated Bilirubin and De Ritis ratio. The later showed a stable pattern of increment after commencement of post-operative chemotherapy. This study indicates that routine assessment of hepatic function and De Ritis ratio should be determined as part of breast cancer management.

Key words: Breast cancer, chemotherapy, De Ritis ratio, liver function tests

Introduction

Physiological contributions of the liver to overall health and wellbeing are well appreciated. Hepatic functions however could be challenged in the face of disease conditions either directly from the disease or the adverse effect of treatment. General pathophysiology of cancer, like many diseases, culminates into multi-organ involvement and subsequent damage (Obenauf and Massague, 2015; Nazario *et al.*, 2011). Organ malfunction/ dysfunction, thus often portrays disease progression and also predicts worsening outcome. Cancer remains an important disease entity that has dominated the medical world, and breast cancer is reportedly among the common cancers affecting women (Olasehinde *et al.,* 2021; Fatiregun *et al.,* 2018; Akpotuzor *et al.*, 2011). Unfortunately, poor health infrastructure militates against early detection and management of breast cancer in our society. Late reporting to hospital has been previously shown to impact on maternal healthcare in this region (Ndem *et al.,* 2021; Azubuike *et al.,* 2018; Egbe *et al.,* 2018). A major

consequence of this situation is that disease conditions are often detected at varying levels of progression. Against this background, indices of evaluation are desirable during the course of medical care to ensure proper management. The central role of the liver in metabolism makes it a necessity that its function be optimal. This is even more apparent with regards to care and management of diseases and medical conditions requiring chemotherapeutic administration, hence the consideration of associated parameters in the management of breast cancer.

The activities of liver-associated aminotransferases also known as transaminases have been traditionally used in assessment of liver function. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are both routinely assayed. This is in addition to bilirubin estimations including total bilirubin, conjugated bilirubin and the derivable unconjugated fraction. In the management of breast cancer, as with many other cancers, monitoring of indices of overall health status is imperative and guides treatment options and their administration. Some of these parameters have also been found to be prognostic biomarkers, thus aiding better management of patients. Added to the mentioned parameters, is alkaline phosphatase (ALP). Expressed mainly from the bones, it has been found useful in the assessment of cancer metastasis, hence its inclusion in routine tests for cancer management. In recent times however, derivatives of routine laboratory tests have emerged as better diagnostic/ prognostic markers of certain diseases, and advocacy for integration into local practice is documented (Akwiwu *et al*., 2022; Udosen *et al.*, 2022). This study investigated changes in the levels of total and conjugated bilirubin as well as the enzyme activities for aspartate transaminase, alanine transaminase and alkaline phosphatase. Unconjugated bilirubin was derived as the difference between total and conjugated bilirubin, while De Ritis ratio was a derivative of aspartate transaminase to alanine transaminase.

Materials and Methods

The study was conducted in University of Calabar Teaching Hospital, Calabar. It included 40 cases of pathologically diagnosed breast cancer (BC) patients who were accessing chemotherapy after undergoing surgical removal of the breast tumour. Another 40 apparently healthy females drawn from the general population served as controls. Ethical approval was obtained from the Health and Research Ethics Committee (HREC) of University of Calabar Teaching Hospital. Written informed consent was obtained from each participant enrolled in the research and confidentiality was maintained.

Standard colorimetric methods were used to determine AST, ALT, ALP Bilirubin levels using kits from Randox Laboratories Limited, UK. The AST-ALT ratio was calculated as well as Unconjugated Bilirubin which was derived mathematically as the difference between Total and Conjugated Bilirubin values. The data obtained were analyzed in Statistical Package for Social Sciences (SPSS version 22.0) using students t-test at 95% confidence level with p-value of ≤ 0.05.

Results

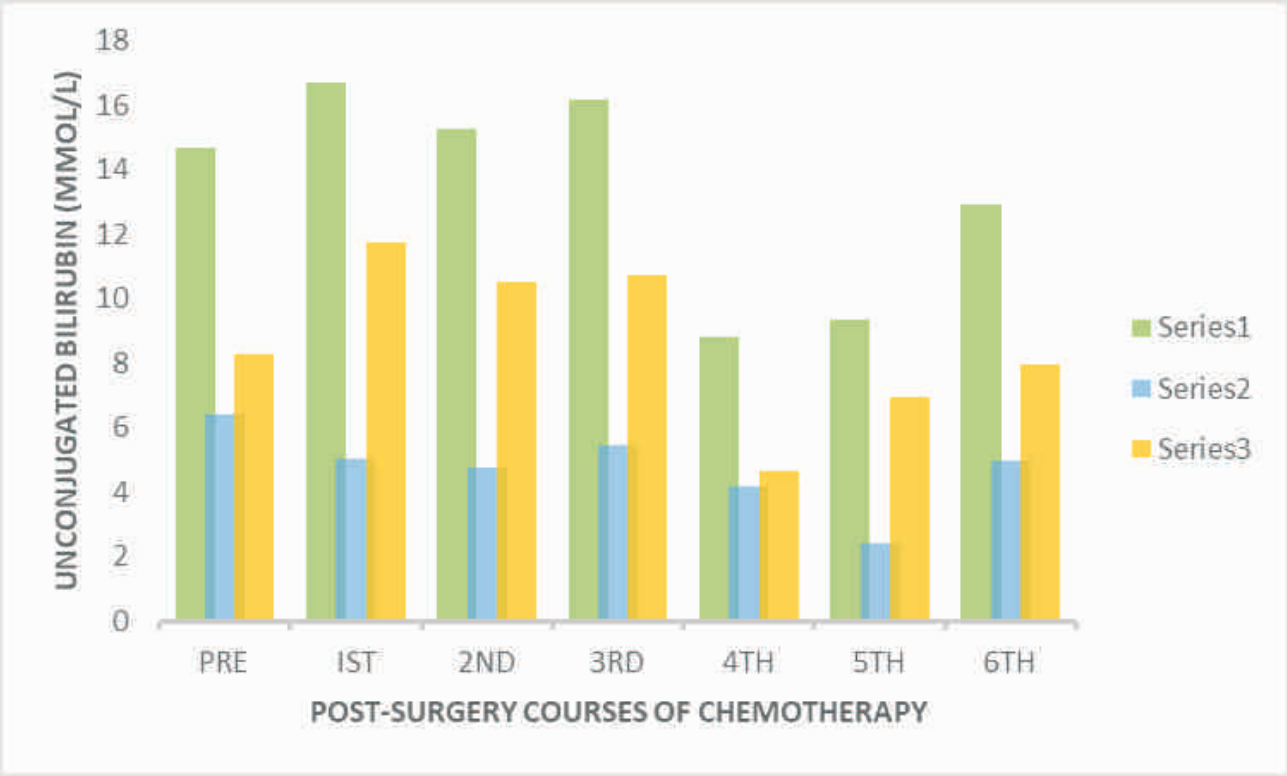
The present study compared mean values of Total Bilirubin, Conjugated Bilirubin, Unconjugated Bilirubin, aspartate transferase, alanine transferase, De Ritis ratio and alkaline phosphatase between breast cancer subjects and controls. Apart from alanine transferase that showed no significant difference, mean values of other parameters were observed to be significantly higher compared to values from control subjects (Table 1).

The progression of the chemotherapy courses showed some observable effect on both derived parameters; Unconjugated Bilirubin and De Ritis ratio. The later showed a stable pattern after commencement of post-operative chemotherapy (Figures 1 and 2).

Table 1: Levels of Bilirubin and some liver enzyme activities among Breast Cancer Patients and control group

Parameter	BC patients n=40	Control group n=40	p-value
TB (µmol/l)	13.54±7.26	10.01±2.48	0.005
CB (µmol/l)	4.83±3.07	3.44±0.98	0.008
UB (µmol/l)	8.71±5.48	6.56±2.01	0.023
AST (U/l)	25.78±17.54	18.00±4.27	0.008
ALT (U/l)	18.20±8.18	17.30±4.23	0.538
AST: ALT	1.68±1.11	1.01±0.12	0.001
ALP (U/l)	95.03±68.11	67.41±13.71	0.014

Key: *BC = Breast cancer, TB = total bilirubin, CB = conjugated bilirubin, UB = unconjugated bilirubin, AST = aspartate transaminase, ALT = alanine transaminase, AST: ALT = aspartate transaminase to alanine transaminase ratio, ALP = alkaline phosphatase.*



Key: *Series 1 = Total Bilirubin, Series 2 = Conjugated Bilirubin, Series 3 = Unconjugated Bilirubin*

Figure 1. Impact of treatment progression on Bilirubin levels among Breast Cancer Patients

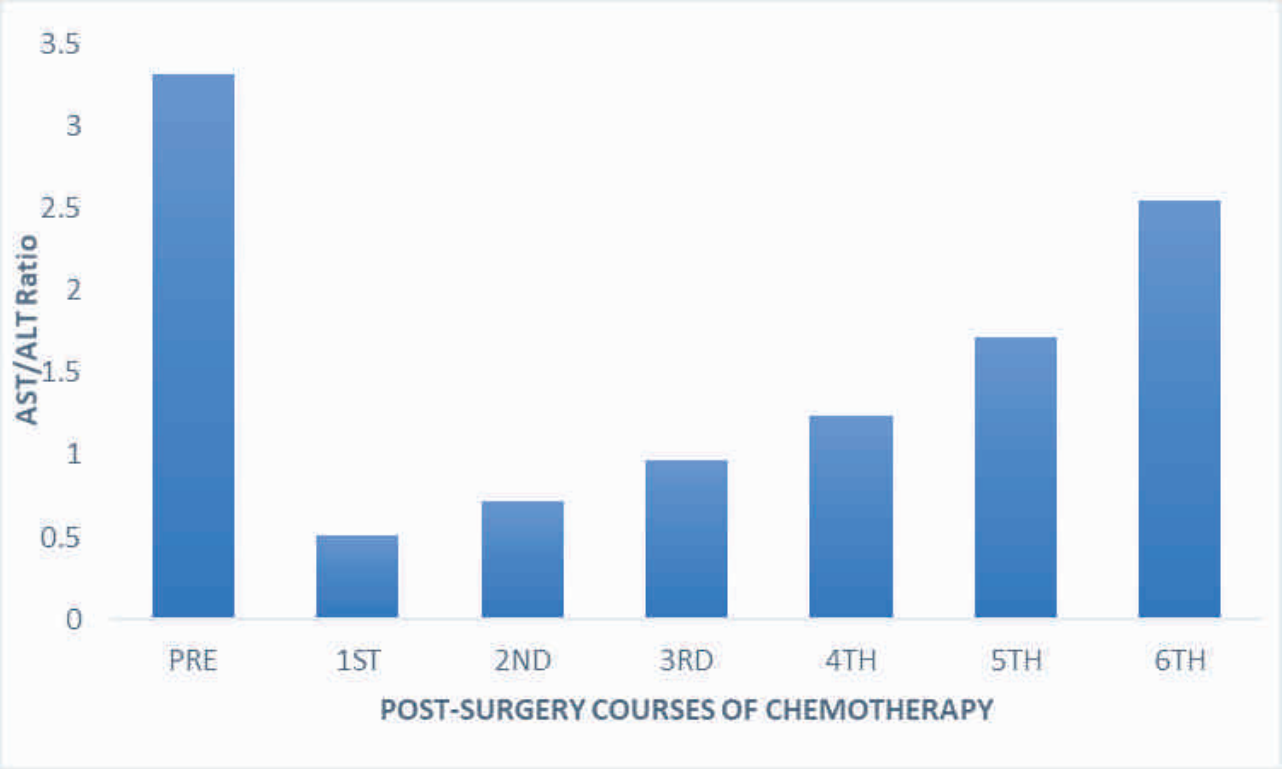


Figure 2. Impact of treatment progression on AST/ALT ratio among Breast Cancer Patients

Discussion

The present study on De Ritis ratio and related Parameters among Breast Cancer Patients in a Southern Nigeria population recorded hyperbilirubinemia, higher AST and ALP activities as well as higher De Ritis ratio among breast cancer patients compared to control subjects. This finding reflects liver involvement and systemic invasiveness in association with breast cancer. Bilirubin is the end-product of haem catabolism, and its estimation has found important diverse clinical applications. In diagnosis, prognosis and monitoring of treatment, bilirubin aids in the management of a wide range of disease conditions. The scientific unravelling of its anti-oxidative, anti-inflammatory and immunosuppressive properties has promoted the thought of its involvement in the pathogenesis of oxidative stressed associated diseases (Peng *et al.*, 2017). This line of argument thus assumes an inverse relationship between bilirubin levels and the risk of disease development. While this may hold through in some instances, studies in breast cancer share divergent views on the subject. In a study that engaged comparatively high statistical evaluations by using a combination of machine learning and classical statistical approaches, Inoguchi and Co-workers (2021) reported increased risk of breast cancer in patients with high bilirubin levels; a finding which the researchers thought was inconsistent with the concept of the protective effect of bilirubin. Hyperbilirubinemia in breast cancer appears to be associated with different outcomes depending on the invasiveness or otherwise of the breast tumour, but more importantly has been observed to increase with progression in chemotherapy course (Chauhan *et al.*, 2016; Damodar *et al.*, 2014; Wyld *et al.*, 2003; Alexandre *et al.*, 2000). The present study, apart from recording higher bilirubin levels in breast cancer, observed increases in bilirubin output (unconjugated bilirubin being consistently higher than the conjugated fraction) as treatment progressed.

Enzyme activities have been used in evaluating liver function in relation to health status. The aminotransferases (AST and ALT) are routinely assessed in determining hepatic involvement in disease conditions. In terms of organ specificity, ALT is understood to be a more liver-specific

measurement than AST. Interestingly, lower ALT has been observed in association with invasive cancer. The less liver-specific AST (being released at various other sites) is thought to be indicative of anaerobic glycolysis and tends to be higher in cancer. Thus, increased AST activity could be linked to higher cancer proliferation rates and more severe tissue damage (Ozaki *et al.*, 2020; Liu *et al*, 2014; Kawamoto *et al*., 2012; Ruhl and Everhart, 2012). Consequently, the co-existence of higher AST and lower ALT (which results in high AST/ALT ratio) may be related to the increased risk of cancer development through the pathophysiological mechanism. Associations between De Ritis ratio and different cancers exist including such as seen the urinary tract, respiratory organs, and the breast (Kobayashi *et al.,* 2022; Thornburg *et al.*, 2008). Considering that derived ratios from routinely assessed parameters are at no additional cost and readily accessible, there is growing advocacy for their integration into clinical practice particularly in resource-poor settings such as ours (Akwiwu *et al.*, 2022; Udosen *et al*., 2022). De Ritis ratio and its implications are being studied for different cancers. One such studies on urothelial carcinoma reported that higher De Ritis ratio was associated with inferior survival leading the authors to suggest the potential use of the parameter as a selection criterion for risk factor stratified management of urothelial carcinoma and adjuvant therapies (Hu *et al*., 2020). This study concludes that routine assessment of AST, ALT and De Ritis ratio could be included as part of the breast cancer management. Additionally, its implications in the journey of chemotherapeutic courses would be worth exploring.

Conflict of interest

All Authors declare no conflict of interest

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