# Early prediction of anthracycline -Induced Cardiomyopathy in Patients with Breast Cancer


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# Abstract

## Background

Cardiac Biomarkers, most prominently troponins and natriuretic peptides, have been evaluated for their ability to describe the risk of potential cardiac dysfunction in clinically asymptomatic patients. Early rises in cardiac troponin concentrations have consistently predicted the risk and severity of significant cardiac events in patients treated with anthracycline-based chemotherapy.

## Patients and methods:

This prospective study concluded **100** female patients known to have breast cancer scheduled to be treated with anthracycline chemotherapy, All candidates evaluated using routine laboratory assessment, conventional 2D echocardiography which done routinely for breast cancer patient in addition to cardiac serum biomarkers (BNP, troponin I) , as an indictors for early predictors of anthracycline induced Cardiomyopathy(AIC) .

And according to the alterations in LV systolic functions and cardiac biomarkers values during and after the completion of anthracycline treatment course, three groups were defined: **Group A** (Cardiomyopathy free- 65 patients) , **Group B** (subclinical Cardiomyopathy - 24 patients) and **Group C** (overt Cardiomyopathy - 11 patients) A Comparison between the three groups according to the incidence of AIC in correlation with the levels of cardiac biomarkers and changes of LV functions by standard 2D echo was done.

## Results

The study showed a statistical significant difference among different groups in cardiac biomarkers at 3 month ($p<0.001$) as Cardiomyopathy free patients had significantly lower Troponin I and BNP levels than patients with subclinical and overt Cardiomyopathy. However, there was no statistical significant difference between patients with subclinical and overt Cardiomyopathy at this stage of follow up.

While at 6 month follow up period ; patients with overt Cardiomyopathy had significantly higher Troponin I ($p=0.02$) and BNP ($p=0.01$), values than patients with subclinical Cardiomyopathy.

The Area under the curve for analysis of 3-month cardiac biomarkers (troponin I and BNP) for prediction of Cardiomyopathy among patients treated with anthracycline chemotherapy were 0.963 and 0.949 respectively with a statistically significant p value = 0.001.

The study revealed that at 3-month follow-up period a value of troponin I $\geq$ **0.96 ng/ml** and a value of serum BNP $\geq$ **316.5 pg/ml** were found to be the best cut-off points to predict subclinical Cardiomyopathy in patients treated with anthracycline with sensitivity reaching **100%** . Even if their LV EF is within normal level by the standard echocardiography assessment at that period.

## Conclusion:

Cardiac Biomarkers (troponin I and BNP) represent a novel, efficient, and robust clinical decision tool for the early detection of anthracycline -induced cardiotoxicity



**Keywords: anthracycline induced cardiomyopathy, cardiac biomarkers, breast cancer**

## INTRODUCTION

Due to earlier detection and highly effective multi-modality treatments, cancer has become a largely curable disease and a chronic illness. There were an estimated 11.7 million cancer survivors in 2007, a number that has grown from 3.0 million in 1970, to 9.8 million in 2001 (1).

The Centers for Disease Control estimated in 2007 that 64.8% of cancer survivors had lived at least 5 years past their initial diagnosis, and approximately 60% of survivors were at least 65 years old. Because of the now-chronic nature of malignant diseases, and the age composition of the survivors, the cardiac side effects of cancer treatments must be heeded. (2)

Cytotoxic chemotherapies such as doxorubicin, targeted therapies including trastuzumab,and radiotherapy have all been implicated as risk factors for subsequent cardiac disease. The timing of cardiac toxicity can vary from acutely during treatment, to chronically months after treatment completion.

The most clinically significant endpoint is impaired left ventricular ejection fraction (LVEF) and ensuing symptomatic heart failure. The current standard of detection is by serial echocardiography, a resource-intensive test whose accuracy is operator-dependent.

Biomarkers on the other hand, can be tested at closer intervals given its low-cost approach; and its accuracy is independent of operator skill. (3)

Most importantly, biomarkers have demonstrated the ability to predict cardiotoxicity before it becomes clinically apparent.

The use of cardiac biomarker in specific settings have been reviewed several times, and most recently in 2011 (2–6).

However, the role of biomarkers is continually redefined by ongoing investigations.

The purpose of this study is to investigates whether early alterations of myocardial blood biomarkers [BNP, troponin] predict incident Cardiomyopathy in patients with breast cancer during treatment with anthracyclines.

### Aim of the study

To assess new modalities as serum cardiac biomarkers [BNP, troponin] in detection of subclinical LV dysfunction in anthracycline-treated breast cancer patients compared with standard clinical assessment

## Subjects and Methods:

### Type of study

This study is a prospective study done at Cardiology and clinical oncology Departments at Suez Canal University Hospital.

### Study population

The study recruited **100** female patients newly diagnosed with breast cancer scheduled to be treated with anthracycline chemotherapy after radical /modified radical or conservative surgical mastectomy.

### Inclusion criteria:

(1) Age > 18 years breast cancer patients.
(2) provision of written informed consent signed
(3) Starting a new course of anthracycline according to international standardized protocols.
(4) Has a life expectancy greater than 12 months
(5) Normal estimated LV ejection fraction

**Exclusion criteria**

1) **Any history of cardiovascular disease and/or active cardiovascular treatment** (history of myocardial infarction, congestive heart failure, serious cardiac arrhythmia requiring medication, abnormal baseline ECG or evidence of left ventricular dysfunction or resting wall motion abnormalities on ECHO)
2) **Systemic diseases** (systemic hypertension, Diabetes mellitus, and chronic renal or liver disease, significant anemia…)
3) Prior External beam radiotherapy to chest wall (Mediastinal irradiation)
4) Estimated LVEF less than 50%
5) prior exposure to anthracycline-based chemotherapy

- All subjects were informed about the procedures and provided informed consent. The local ethics committee approved the study protocol.
- All subjects were evaluated using routine pre-chemotherapy laboratory tests, conventional 2D and 3D echocardiography in addition to serum cardiac biomarkers (BNP, troponin)
- All data and measurements taken at baseline, after the 3-month and 6-month of initiation chemotherapy, these time points (T0-T1 and T2) chosen because they corresponded to the scheduled oncological protocols.
- Anthracyclines induced cardiomyopathy (AIC) defined as: **The LVEF decreases more than 10% from the baseline plus the LVEF declines under 55% [7]**
- Anthracyclines induced Subclinical clinical LV cardiomyopathy defined as;

- **Abnormal (elevated) serum cardiac troponin I** (cut -off value 0.1 ng/ml) **[8]**
- **Abnormal (elevated) serum brain natriuretic peptide (BNP)** (BNP cut-off value of 100 pg/ml) **[20]**

- LVEF decrease may be further categorized as symptomatic or asymptomatic.
- The full echocardiographic studies were repeated in all patients within 24 hours of the end of the third month (T1)and sixth month (T2) of chemotherapy in cooperation with clinical oncology department
- According to the changes in LV systolic functions and serum cardiac biomarkers levels at the study time points, three groups were defined:

- **Group A (cardiomyopathy free):** patient who didn't develop subclinical LV cardiomyopathy or overt cardiomyopathy.
- **Group B (subclinical cardiomyopathy)** : patient who develop subclinical LV cardiomyopathy (elevation of troponin I and BNP level more than normal limit values) without changes in either 2D or 3D LVEF.
- **Group C (overt cardiomyopathy):** patient who develop Anthracyclines induced overt cardiomyopathy (AIC ) as mentioned above .

- Comparison between the three groups according to the incidence of AIC in correlation with the level cardiac biomarkers was done.

**Study Questionnaire**

All patients interviewed in a quiet environment allowing them to appropriately answer the study questionnaires (Appendix I) which include:

- Personal history, Symptoms of heart failure; Dyspnea (NYHA class), proximal nocturnal dyspnea (PND), palpitations, orthopnea or gallop. Risk factors for heart failure. Family history of cardiac disease.

▪ **Measurements**

Height, Weight, Body mass index (BMI), Body surface area (BSA) and Office blood pressure were measured to all study candidate by standard guidelines protocols.

**Serum Cardiac biomarkers assessment;**

- Serum brain natriuretic peptide (BNP) and troponin I were measured using the Dimension Vista 500 Intelligent Laboratory System (Siemens Healthcare Diagnostics, Deerfield, Illinois), using a 1- step, homogenous, sandwich chemiluminescent immunoassay based on LOCI technology .
- The limit of detection of BNP assay is 0.8 pg/ml. Typical within-laboratory imprecision for the assay is < 3 coefficient of variation at BNP concentration from 100 to 5,000 pg/ml.
- The highest value of BNP reported in healthy subjects aged <75 years is **100 pg/ml. [9]**
- The lower limit of detection of the troponin assay is **0.15 ng/mL**, and the 10% coefficient of variation is 0.04 g/L. **[8]**
- All values of BNP **100 pg/ml** and of troponin **0.15 ng/mL** were considered elevated and has been suggested for chemotherapy-related cardiomyopathy.
- Troponin I and BNP values were assessed at baseline (T0), after the third month (T1) and sixth month (T2) of anthracycline chemotherapy time course**.**

**Echocardiographic assessment**

- Examinations will be performed using a commercially available ultrasound machine equipped with STE, using a 2-MHz to 4-MHz transducer (*Philips Ultrasound* field service company, *EPIQ 7* Q lab version 10.8.5) machine. Digital echocardiographic data will be acquired during passively held end-expiration for offline analysis using a dedicated software package (EchoPAC version 9.0.1 for PC; *Philips Ultrasound* field service company).
- LV mass was determined from septal and posterior wall thickness and LV end diastolic dimensions, and indexed to body surface area.
- The LVEF was calculated using the modified Simpson's biplane method , the endocardial contour was manually traced at end-diastole and -systole; LV end-diastolic and -systolic volumes were determined using Simpson's method of disks and were used to derive LVEF .
- Transmitral global early (E) and global late (A) diastolic filling velocities, E deceleration time and isovolumic relaxation time were measured using conventional Doppler ultrasound. Left ventricular outflow tract pulsed Doppler was used to determine aortic valve opening and closure times, and LV ejection time. Pulsed-wave TDI velocities were assessed at the basal segments of each of the three longitudinal planes in the apical four-, three- and two-chamber views.
- Global systolic (Sm), global early (E') and global late (A') diastolic tissue velocities were measured to give regional values, and averaged to give global, basal longitudinal myocardial velocities.

**3D echocardiography assessment**

- Real-time 3D echocardiographic imaging was then performed in the same apical position using a matrix-array transducer. Full-volume acquisition, in which six adjacent sub volumes were captured over six consecutive cardiac cycles, was performed during a breath-hold to minimize artifact between sub volumes.

- Special care was taken to include the entire LV cavity within the pyramidal dataset. The 3D images were acquired at a minimum of 22 frames/s, and all images were digitally archived at the acquisition frame rate for offline analysis.
- Non foreshortened apical views were identified at end-diastole, and LV endocardial and epicardial boundaries were initialized.
- The 3D endocardial surface was then automatically detected with manual adjustments made as necessary, and was automatically tracked over time in 3D space with derivation of 3D LVEF
- Studies were excluded if either dropout of ≥4 wall segments or stitch artifact was present. To improve the reliability of tracking outcomes, each 3D echocardiogram was quantitated twice by a single observer, and the average of the 2 observations was used for analysis.

## Results

- The study showed a significant increasing in the proportion of overt and subclinical Cardiomyopathy among breast cancer patients treated with anthracycline from 3 month to 6-month follow up period. (figure 1) The incidence of overt Cardiomyopathy increase from **6%** after 3 months to reach **11%** after 6 months of the study , while the incidence of subclinical Cardiomyopathy increase form **10%** at 3 months to reach **24 %** at the end of the study.
- Table (1) shows the baseline characteristics of the studied sample; The mean age of the patients was 50.47 ± 10.9 years and the mean body mass index (BMI) was 33.80 ± 4.2, where almost 50% of them are postmenopausal. More than 95% of the cases were non-smoker with a negative family history of cardiac disease, there was no significant statistical difference among studied groups regarding baseline characteristics or an anthropometric measurements
- Table (2) shows that patients who developed overt Cardiomyopathy and subclinical Cardiomyopathy were significantly associated with more incidence of paroxysmal nocturnal dyspnea ($p=0.002$) and orthopnea ($p<0.001$) than those who were Cardiomyopathy free. Moreover, patients who developed overt Cardiomyopathy was significantly associated with more incidence of gallop rhythm ($p<0.001$) than those who were Cardiomyopathy free.
- Left side affection formed 65% of the breast cancer among the studied patients while right side affection formed 35% Moreover, stage II breast cancer formed 60% of the total studied patients, half of (group A) patients have stage I breast cancer in contrast to (group C) patient that 45% of them have stage III breast cancer (figure 2). Only four cases had metastasis majority of them were at group C patients, three cases (75%) had lung metastasis while one case had liver metastasis.
- Regarding treatment regimen, 75 % of the cases had Epirubicin as their Anthracycline based chemotherapy (figure 3). About 65% of the cases had 6 cycles chemotherapy where the overall anthracycline dose administered was 537.7 ± 81.5 mg/m2
- The overall anthracycline dose administered was 537.7 ± 81.5 mg/m2. We found that there was a statistical significant difference among different groups in the anthracycline dose where, on applying pairwise comparison, we found that patients with overt Cardiomyopathy had significantly higher anthracycline dose (581.82 ± 53.8 mg/m2) than Cardiomyopathy free patients (525.31 ± 83.36mg/m2) ($p=0.041$). (Table 3) (Figure 4)

- Table (4) showed the association between Cardiomyopathy and cardiac biomarkers at 3 month reveled that there was a statistical significant difference among different groups in cardiac biomarkers at 3 month ($p<0.001$). On applying post hoc test, we found that Cardiomyopathy free patients had significantly lower Troponin I and BNP levels than patients with subclinical and overt Cardiomyopathy.(figure 5)
- However, there was no statistical significant difference between patients with subclinical and overt Cardiomyopathy at this stage of follow up.
- Table (5) showed the association between Cardiomyopathy and cardiac biomarkers at 6 month reveled that that there was a statistical significant difference among different groups in cardiac biomarkers at 6 month ($p<0.001$). On applying post hoc test, we found that Cardiomyopathy free patients had significantly lower Troponin I and BNP levels than patients with subclinical and overt Cardiomyopathy (figure 6) .
- Moreover and in contrast to the 3-month follow up stage, patients with overt Cardiomyopathy had significantly higher Troponin I ($p=0.02$) and BNP ($p=0.01$), values than patients with subclinical Cardiomyopathy at 6 month follow up.
- Table (6 ) showed the Area under the curve for analysis of 3-month cardiac biomarkers (troponin I and BNP) 3D echo for prediction of Cardiomyopathy among patients treated with anthracycline chemotherapy were 0.963, 0.949 and 0.0.959, respectively with a statistically significant p value = 0.001.
- These findings as shown in figure (6 and 7) reveled the superiority of cardiac biomarker (troponin I and BNP) than estimated LVEF even by 3D echo in predication of LV Cardiomyopathy as early as 3 months among breast cancer patients on anthracycline therapy.
- Table (7) Diagnostic accuracy at different cut-off levels of different surrogates for prediction of Cardiomyopathy among patients treated with anthracycline
- At 3 -month follow up stage , Troponin I with a value of 0.96 ng/ml was found to be the best cut-off point to predict LV Cardiomyopathy with sensitivity = 100% and specificity = 94.4%.
- Similarly for BNP, a value of 316.5 pg/ml was found to be the best cut-off point with sensitivity = 90 % and specificity = 94.4%.
- On the other hand, for 3 -month study time point, estimated LVEF by 3D echo with a value of 59% has an only sensitivity = 72.7% and specificity = 100% for predication of LV Cardiomyopathy . (Table 8)
- Again, these data reinforce the better sensitivity of serum troponin I and serum BNP (100%, 90.9% respectively) than estimation of LVEF value even with advanced 3D echocardiography (72.7%) for prediction of LV Cardiomyopathy among the study groups as early as first 3 month after treatment with anthracycline chemotherapy.
- Finally, these previous results showed the value of cardiac biomarkers (troponin I and BNP) in promoting the sensitivity of early detection of LV cardiomyopathy to reach almost 100% instated of only 72.7% by assessment of LVEF % even by advanced 3D echo.

## Discussion

Because anthracycline-induced Cardiomyopathy is a type I Cardiomyopathy , detection of cardiomyocyte injury would be expected to identify those patients who may go on to develop left ventricular dysfunction. While several biomarkers have been investigated, troponin I (marker of cardiac injury) and BNP (marker of cardiac wall stress) have the greatest evidence of detecting changes in left ventricular function.

Cardinale et al have reported that the measurement of troponin I predicted the development of later cardiac events in patients treated with high doses of anthracyclines or chemotherapies and trastuzumab.[8]

The present study confirms the value of measuring troponin I and serum BNP in patients with breast cancer treated with anthracyclines and clarifies its optimal timing.

Although troponin I and serum BNP were not an independent predictors of early Cardiomyopathy , its measurement increase the sensitivity of these biomarkers from 74% to 100%, allowing a negative predictive value of 94%. Thus, measuring serum cardiac biomarkers (troponin I and BNP) may be of value in predicting the absence of toxicity of the breast cancer treatment.

In our study there was a statistical significant difference among the three groups in cardiac biomarkers at 3 and 6 month ($p<0.001$). Cardiomyopathy free (group A) patients had significantly lower Troponin I and BNP levels than patients with subclinical and overt Cardiomyopathy . However, there was no statistical significant difference between patients with subclinical and overt Cardiomyopathy

Moreover, patients with subclinical Cardiomyopathy had significantly lower Troponin I and BNP levels than patients with overt Cardiomyopathy ($p=0.02$) and ($p=0.01$), respectively.

In addition, individuals who have a persistent increase in troponin I following treatment with anthracyclines have a greater decrease in LVEF compared to those who only have an early troponin I release [8]

In the setting of anthracycline induced Cardiomyopathy , the rise in troponin may quantify both cardiomyocyte apoptosis and myofibril degradation more than necrosis and predicts Cardiomyopathy defined as fall in LVEF as well as major adverse cardiovascular events (MACE).

On another hand and in accordance with the present results, Feola *et al* [20], supported that the toxic effects following chemotherapy in breast cancer patients may be observed with plasma markers, including BNP, to detect left ventricular dysfunction that could provoke cardiac dysfunction [9]

Recent evidence also suggests that cancer itself may potentially increase BNP levels through cancer-associated inflammation, with patients suffering from metastatic disease having significantly higher BNP levels than those without metastatic involvement [9]. These confounding factors should definitely be taken into consideration during the interpretation of results

Our study revealed that a value of troponin I ≥ 0.96 ng/ml and a value of serum BNP ≥ 316.5 pg/ml were found to be the best cut-off points to predict subclinical Cardiomyopathy with a sensitivity = 100% and specificity = 94.4%, even if their LV EF is within normal level by the standard echocardiography assessment at that period

**Study limitations**

- A limitation include the relatively small sample size (100 patients), and the fact that sensitivity and specificity are likely overestimated because they were estimated from the same data used to define optimal cut points.
- In our study the incidence of subclinical and overt cardiomyopathy increase form 3 months to 6-month time points and if the follow up period were longer more cases would be discovered .
- Investigating the value of early myocardial alterations in the prediction of stronger end points, such as symptomatic heart failure or cardiac mortality would be of great interest, Because the incidence of these events is low, however, such a study would require a much greater number of patients and a longer follow-up.
- Although the prognostic value of RV dysfunction has not been demonstrated in our study or generally in patients treated with anthracycline chemotherapy , a quantitative assessment of RV dimensions and functions should be done for possible RV involvement

**Conclusion;**

Anthracycline induced cardiomyopathy is a growing source of significant morbidity and mortality. Current screening practices are suboptimal as they provided limited opportunity to Intervene and change the course of disease progression.

Serum cardiac biomarkers, and especially cardiac troponins and BNP in patients treated with Anthracycline chemotherapy, represent an effective method for monitoring cardiac status, And identifying patients who may benefit from early medical intervention

# References


| | |
|---|---|
| **1.** | Centers for Disease Control. Prevention. Cancer survivors – United States, 2007. *MMWR Morb Mortal Wkly Rep* (2011) **60**(9):269–72. |
| **2.** | Dolci A, Dominici R, Cardinale D, Sandri MT, Panteghini M. Biochemical markers for prediction of chemotherapy-induced cardiotoxicity: systematic review of the literature and recommendations for use. *Am J Clin Pathol* (2008) **130**(5):688–95. doi:10.1309/AJCPB66LRIIVMQDR |
| **3.** | Germanakis I, Anagnostatou N, Kalmanti M. Troponins and natriuretic peptides in the monitoring of anthracycline cardiotoxicity. *Pediatr Blood Cancer* (2008) **51**(3):327–33. doi:10.1002/pbc.21633 |
| **4.** | Mavinkurve-Groothuis AM, Kapusta L, Nir A, Groot-Loonen J. The role of biomarkers in the early detection of anthracycline-induced cardiotoxicity in children:areviewof theliterature. *Pediatr Hematol Oncol* (2008) **25**(7):655–64. doi:10.1080/08880010802244001 |
| **5.** | Cardinale D, Sandri MT. Role of biomarkers in chemotherapy-induced cardiotoxicity. *Prog Cardiovasc Dis* (2010) **53**(2):121–9. doi:10.1016/j.pcad.2010. 04.002 |
| **6.** | CardinaleD,SalvaticiM,SandriMT.Roleof biomarkersincardioncology. *Clin Chem Lab Med* (2011) **49**(12):1937–48. doi:10.1515/CCLM.2011.692 |
| **7.** | Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233–270. |
| **8.** | Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation* (2004) **109**(22):2749–54. doi:10.1161/01.CIR.0000130926.51766.CC |
| **9.** | Feola M, Garrone O, Occelli M, Francini A, Biggi A, et al. (2011) Cardiotoxicity after anthracycline chemotherapy in breast carcinoma: effects on left ventricular ejection fraction, troponin I and brain natriuretic peptide. Int J Cardiol 148: 194–198 S0167-5273(09)01575-7 [pii];10.1016/j.ijcard.2009.09.564 |

Figures and tables;

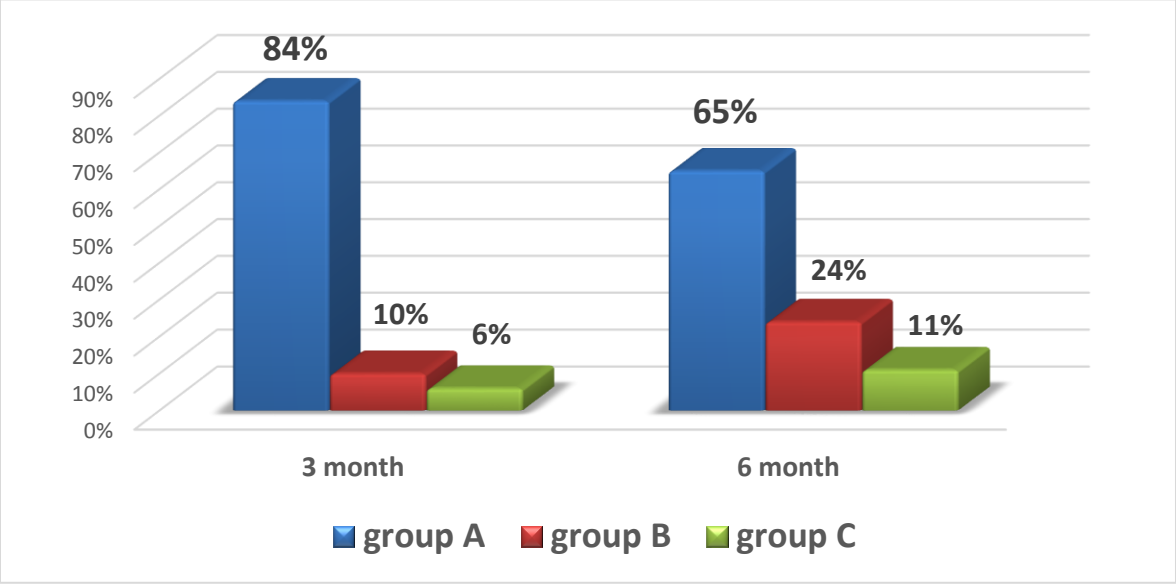



**Figure (1)** shows that prevalence of subclinical and overt Cardiomyopathy among patients on anthracycline chemotherapy at 3-month and 6-month follow up period.

**Table 1. Association between baseline characteristics and study groups (n= 100)**

| Variables | Total (n= 100) | Cardiomyopathy free (n=65) | Subclinical Cardiomyopathy (n=24) | Overt Cardiomyopathy (n=11) | p-value |
|---|---|---|---|---|---|
| **Age (years), mean ± SD** | 50.47 ± 10.9 | 48.62 ± 10.13 | 54.50 ± 11.47 | 52.64 ± 12.31 | 0.082 [a] |
| **History of menopause, n (%)** | | | | | |
| No | 51 (51) | 36 (55.4) | 9 (37.5) | 6 (54.5) | 0.32 [b] |
| Yes | 49 (49) | 29 (44.6) | 15 (62.5) | 5 (45.5) | |
| **Smoking** | | | | | |
| No | 95 (95) | 64 (98.4) | 22 (91.6) | 9 (81.8) | 0.38 [b] |
| Yes | 5 (49) | 1 (1.6) | 2 (8.4) | 2 (18.2) | |
| **+ve Family history of IHD** | | | | | |
| Present | 1(1%) | 0 | 1 (4.2) | 0 (0) | 0.035 [a] |
| Absent | 99(99%) | 65 (100) | 23 (95.8) | 11 (100) | |
| **Anthropometric measurements** | | | | | |
| Height (cm) | 161.11 ± 6.29 | 162.06 ± 6.46 | 159.08 ± 4.9 | 159.91 ± 7.2 | 0.056 [a] |
| Weight (kg) | 87.51 ± 10.11 | 86.46 ± 10.4 | 89.04 ± 10.26 | 90.36 ± 7.42 | 0.104 [a] |
| BMI (kg/m$^2$) | 33.80 ± 4.2 | 33 ± 4.17 | 35.22 ± 4.01 [β] | 35.48 ± 3.73 | 0.071 [a] |

[a] p-values are based on Kruskal Wallis test. Statistical significance at $P < 0.05$
[b] p-values are based on Chi-Square test. Statistical significance at $P < 0.05$
Values with superscript [β] are different from absent group.
Values with superscript [α] are different from subclinical Cardiomyopathy group.

**Table 2. Association between heart failure manifestations and study groups (n= 100)**

| Variables | Cardiomyopathy | | | p-value |
|---|---|---|---|---|
| | Group A (n=65) | Group B (n=24) | Group C (n=11) | |
| **Dyspnea** | | | | |
| Grade 1 | 41 (63.1) | 11 (45.8) | 5 (45.5%) | 0.74[a] |
| Grade 2 | 24 (36.9) | 13 (54.2) | 3 (27%) | |
| Grade 3 | 0 | 0 | 2(18) | |
| Grade 4 | 0 | 0 | 1 (10.5%) | |
| **Paroxysmal nocturnal dyspnea** | | | | |
| Absent | 65 (100) | 9 (37.5) | 4 (36.4) | **< 0.002** [a] |
| Present | 0 | 15 (62.5) | 7 (63.6) | |
| **Palpitation** | | | | |
| Absent | 0 | 1 (4.2) | 0 (0) | 0.35 [a] |
| Present | 65 (100) | 23 (95.8) | 11 (100) | |
| **Fatigue** | | | | |
| Absent | 61 (93.8) | 2 (8.3) | 0 (0) | 0.83 [a] |
| Present | 4 (6.2) | 22 (91.7) | 11 (100) | |
| **Orthopnea** | | | | |
| Absent | 65 (100) | 17 (70.8) | 5 (45.5) | **<0.001** [a] |
| Present | 0 | 7 (29.2) | 6 (54.5) | |
| **Lower limb edema** | | | | |
| Absent | 34 (52.3) | 17 (70.8) | 5 (45.5) | 0.13 [b] |
| Present | 31 (47.7) | 7 (29.2) | 6 (54.5) | |
| **Gallop rhythm** | | | | |
| Absent | 65 (100) | 24 (100) | 6 (54.5) | **<0.001** [a] |
| Present | 0 | 0 | 5 (45.5) | |

[a] p-values are based on Fisher Exact test. Statistical significance at P < 0.05
[b] p-values are based on Chi-Square test. Statistical significance at P < 0.05

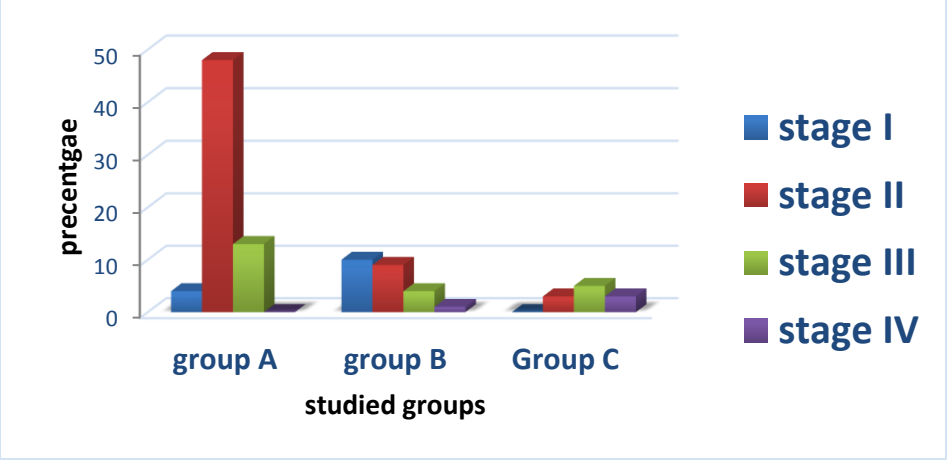



**Figure (2): Incidence of different Breast cancer stages among the studied groups**

**Table 3. Anthracycline regimens and Total anthracycline dose among the studied sample**

| **Anthracycline agent, n (%)** | **Total** | **Group A** | **Group B** | **Group C** | |
|---|---|---|---|---|---|
| Epirubicin | 75 (75) | 50 (76.9) | 21 (87.5) | 4 (36.4) | **0.007** [a] |
| Doxorubicin | 25 (25) | 15 (23.1) | 3 (12.5) | 7 (63.6) | |
| **Chemotherapy cycles, n (%)** | | | | | |
| 4 cycles | 24 (24) | 13 (20) | 9 (37.5) | 2 (18.2) | |
| 5 cycles | 11 (11) | 11 (16.9) | 0 | 0 | 0.70 [a] |
| 6 cycles | 65 (65) | 41 (63.1) | 15 (62.5) | 9 (81.8) | |
| **Total anthracycline dose, mean ± SD** | 537.7 ± 81.5 | 525.31 ± 83.36 | 550.96 ± 80.4 | 581.82 ± 53.8 β | **0.041** [b] |

[a] p-values are based on Fisher Exact test. Statistical significance at P < 0.05
[b] p-values are based on Mann Whitney U test. Statistical significance at P < 0.05

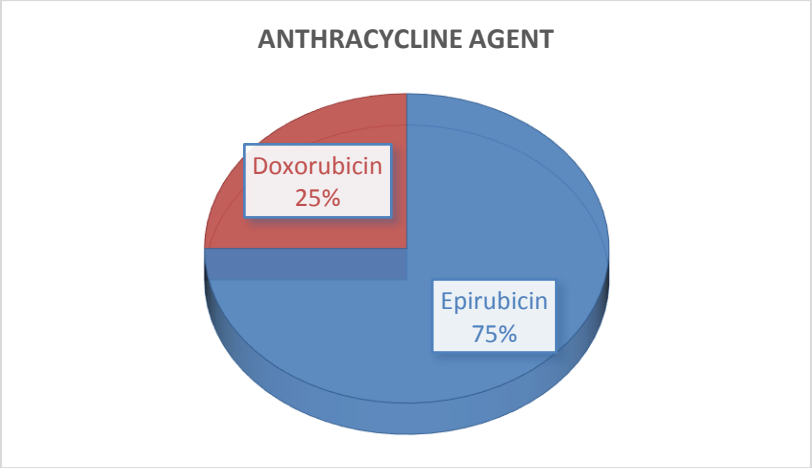



**Figure (3): Anthracycline agent used in chemotherapy protocol for management of breast cancer in the studied groups**

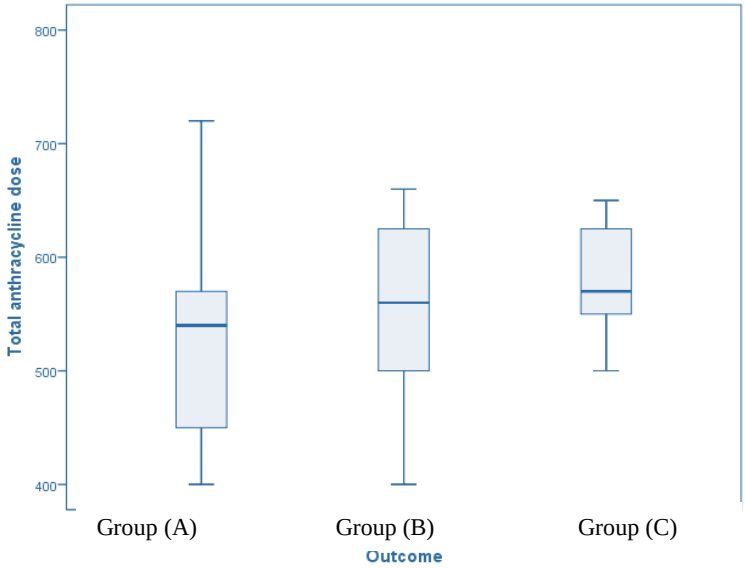



**Figure (4). Total anthracycline dose among the study groups**

**Table 4. Association between Cardiomyopathy and cardiac biomarkers at 3 month**

| Variables | Group A (n=84) | Group B (n=10) | Group C (n=6) | p-value |
|---|---|---|---|---|
| Troponin I (ng/ml) | 0.08 ± 0.03 | 4.75 ± 2.14 β | 3.83 ± 1.66 β | **<0.001** a |
| BNP (pg/ml) | 135.74 ± 73.72 | 462.90 ± 79.43 β | 442.17 ± 116.81 β | **<0.001** a |

a p-values are based on Kruskal Wallis test. Statistical significance at P < 0.05
Values with superscript β are different from absent group.

**Table 5. Association between Cardiomyopathy and cardiac biomarkers at 6 month**

| Variables | Cardiomyopathy free patients (n=65) | Subclinical Cardiomyopathy (n=24) | Overt Cardiomyopathy (n=11) | p-value |
|---|---|---|---|---|
| Troponin I (ng/ml) | 0.08 ± 0.03 | 0.66 ± 1.16 | 3.24 ± 1.17 α, β | **<0.001** a |
| BNP (pg/ml) | 131.83 ± 59.28 | 247.33 ± 91.73 β | 501.64 ± 89.46 α, β | **<0.001** a |

a p-values are based on Kruskal Wallis test. Statistical significance at P < 0.05
Values with superscript β are different from absent group.
Values with superscript α are different from subclinical Cardiomyopathy group

**Table 6 . Area under the curve for analysis of 3-month cardiac biomarkers, GLS and 3D echo for prediction of Cardiomyopathy among patients treated with anthracycline chemotherapy**

| Variable | Area | Stand. error | p-value | 95% CI |
|---|---|---|---|---|
| **3-month Troponin I** | 0.963 | 0.018 | **<0.001** | (0.928 – 0.999) |
| **3-month BNP** | 0.949 | 0.022 | **<0.001** | (0.907 – 0.992) |
| **3-month GLS** | 0.992 | 0.006 | **<0.001** | (0.98 – 1) |
| **3-month 3D echo** | 0.959 | 0.026 | **<0.001** | (0.907 – 1) |

**Table 7. Diagnostic accuracy at different cut-off levels of 3-month GLS, 3D echo, Troponin I and BNP for prediction of Cardiomyopathy among patients treated with anthracycline**

| Cut-off points | Sensitivity | Specificity | PPV* | NPV* | accuracy |
|---|---|---|---|---|---|
| **3-month GLS** | | | | | |
| 16.5 | 100% | 94.4% | 68.75% | 100% | 95% |
| **3-month Troponin I** | | | | | |
| 0.96 | 100% | 94.4% | 68.75% | 100% | 95% |
| **3-month BNP** | | | | | |
| 316.5 | 90.9% | 94.4% | 66.67% | 98.82% | 94% |
| **3-month 3D echo** | | | | | |
| 59 % | 72.7% | 100% | 100% | 96.74% | 97% |

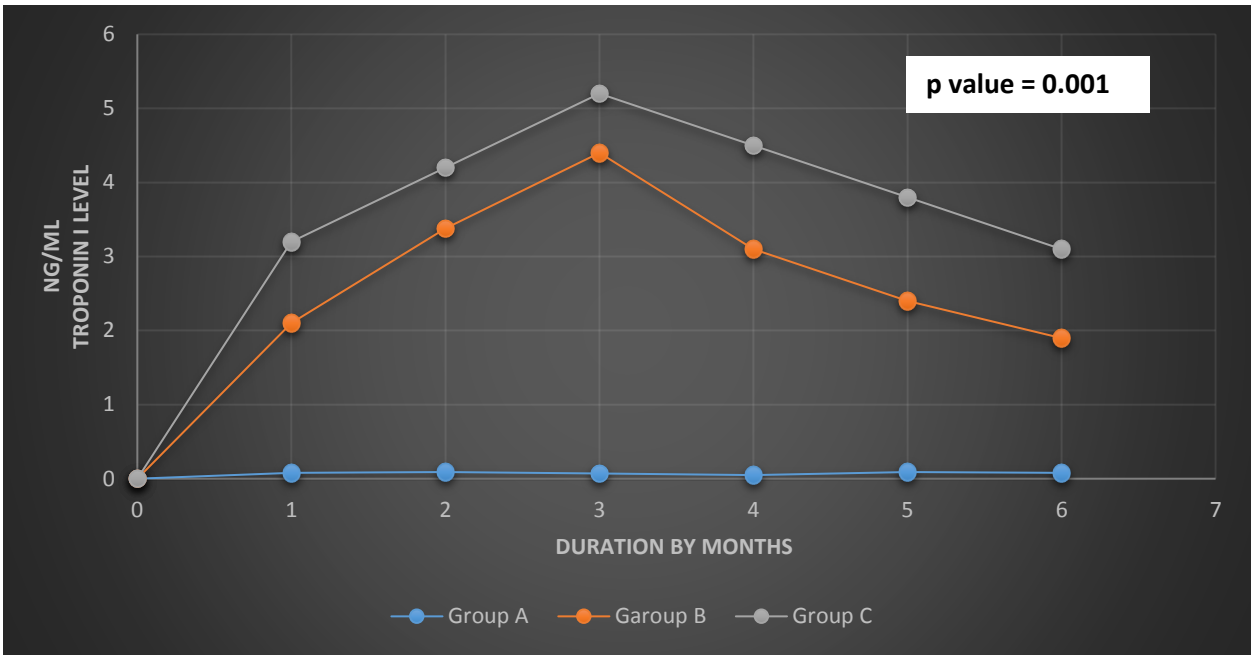



Figure (5) values of troponin I measurements among studied groups during different time points of the study course.

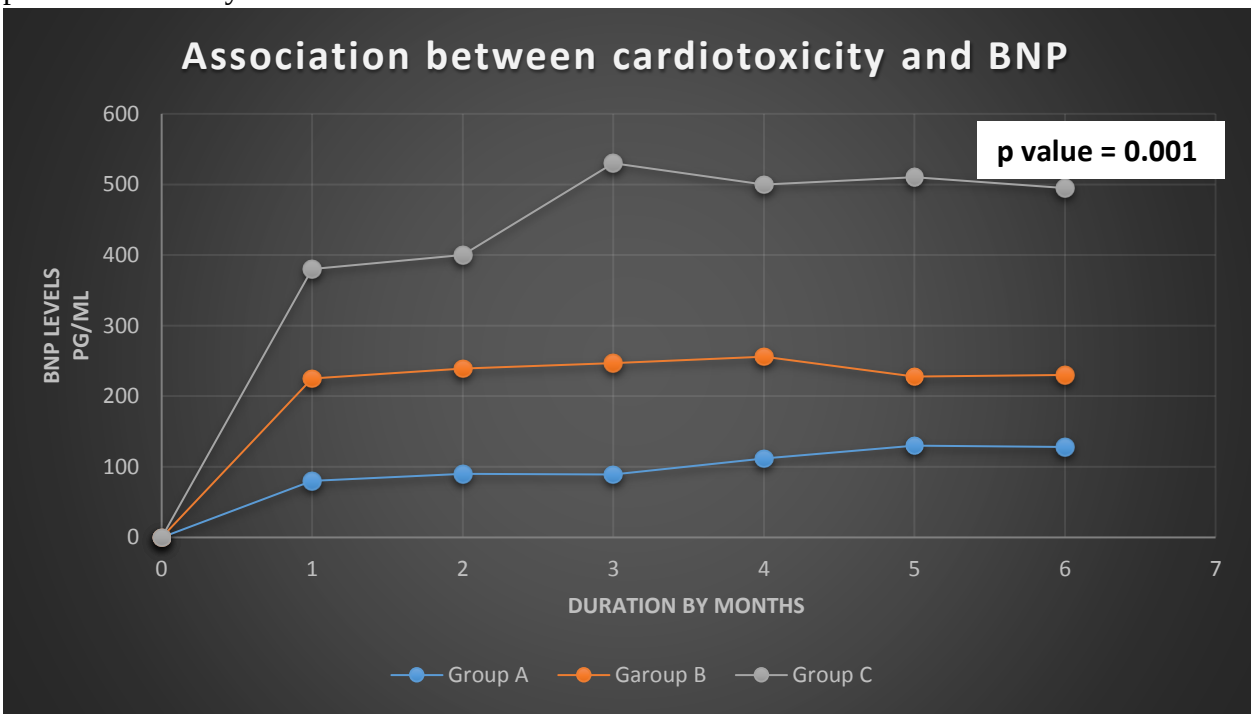



**Figure (6) pattern of serum BNP measurements among studied groups during different time points of the study course.**

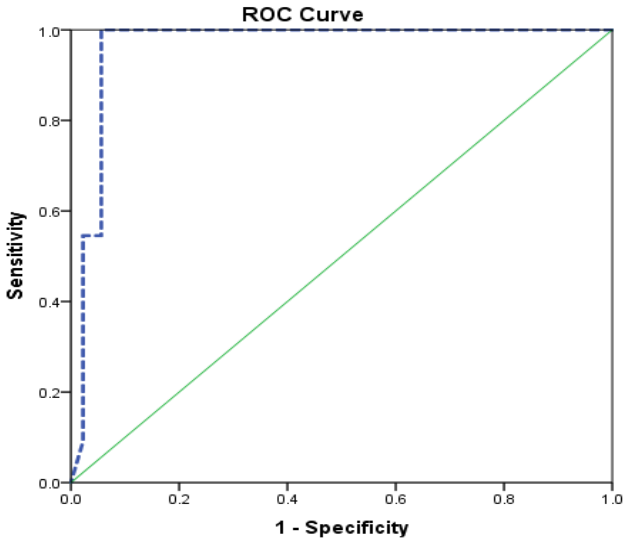



**Figure (7). ROC curve for the relationship between of 3 month Troponin I and cardiomyopathy among patients treated with anthracycline**

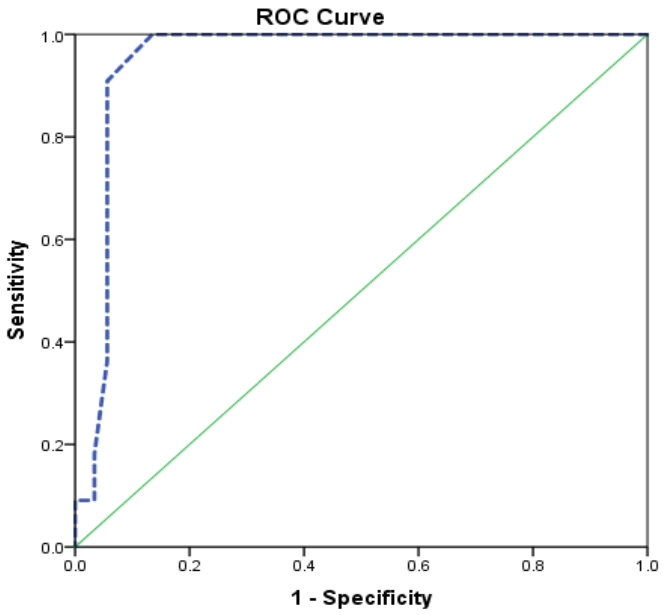



**Figure (8). ROC curve for the relationship between of 3 month BNP and Cardiomyopathy among patients treated with anthracycline**