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# Cardiotoxicity and Clinical Predictors in Breast Cancer Patients Undergoing Anthracycline-Based Chemotherapy: A Prospective Observational Study at a Regional Cancer Centre in Odisha

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## ABSTRACT

**Background:** Anthracyclines remain a cornerstone of breast cancer treatment, but their use is limited by cumulative cardiotoxicity. In resource-constrained cancer centers, delayed detection of cardiac dysfunction remains a major concern. This study evaluated the incidence and predictors of anthracycline-induced cardiotoxicity (AIC) among breast cancer patients receiving chemotherapy in Odisha.

**Methods:** This prospective observational study included 145 adult female patients with Stage I–III breast cancer receiving anthracycline-based chemotherapy (doxorubicin or epirubicin) at a regional cancer center in Cuttack, India. Transthoracic echocardiography was performed at baseline, after chemotherapy completion, and at 6-month follow-up. AIC was defined as a >10% reduction in left ventricular ejection fraction (LVEF) to <53% or the development of clinical congestive heart failure. Multivariable logistic regression was used to identify independent predictors.

**Results:** The mean age was 48.6 ± 10.4 years. AIC occurred in 23 patients (15.86%), including 3 (2.07%) with clinical heart failure and 20 (13.79%) with asymptomatic LVEF decline. Mean LVEF significantly decreased from 62.4 ± 4.5% to 56.8 ± 6.1% following chemotherapy ($p<0.001$). Patients with AIC received higher cumulative doxorubicin-equivalent doses than those without toxicity (345.2 ± 48.5 vs. 268.4 ± 42.1 mg/m²; $p<0.001$). Independent predictors included cumulative anthracycline dose ≥300 mg/m² (aOR=4.12; $p=0.002$), age ≥60 years (aOR=3.24; $p=0.026$), hypertension (aOR=2.85; $p=0.038$), and baseline LVEF 53–55% (aOR=5.18; $p=0.002$). A significant negative correlation was observed between cumulative dose and post-treatment LVEF ($r=-0.56$; $p<0.001$).

**Conclusion:** Anthracycline-induced cardiotoxicity affected nearly one-sixth of patients and was strongly associated with higher cumulative dose, older age, hypertension, and borderline baseline cardiac function. Routine echocardiographic monitoring is essential for early detection and risk stratification in oncology practice.

**Key-words:** Breast Cancer; Anthracyclines; Cardiotoxicity; Left Ventricular Ejection Fraction; Doxorubicin; Regional Cancer Center

## INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer-related mortality among women globally and in India [1].

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In the state of Odisha, a significant proportion of breast cancer patients present with locally advanced disease (Stage IIB–III) at public regional cancer centers like the Acharya Harihar Post Graduate Institute of Cancer (AHPGIC) in Cuttack, requiring intensive multi-modality management including neoadjuvant or adjuvant chemotherapy, surgery, and radiotherapy [2]. Anthracycline-based regimens, specifically doxorubicin or epirubicin combined with cyclophosphamide (AC/EC) followed by taxanes, or the fluorouracil-doxorubicin-cyclophosphamide (FAC) protocol, remain the standard

 

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of care due to their proven efficacy in reducing recurrence and improving overall survival [3].

Despite their therapeutic efficacy, the clinical utility of anthracyclines is severely hindered by treatment-limiting, dose-dependent cardiotoxicity [4]. Anthracycline-induced cardiotoxicity (AIC) is characterized by a progressive, often irreversible decline in left ventricular function that can manifest either as acute arrhythmias, subacute asymptomatic ejection fraction drops, or late-onset chronic congestive heart failure (CHF) [5]. The cellular mechanism of anthracycline cardiotoxicity is multifactorial, primarily mediated by the generation of reactive oxygen species (ROS), iron-dependent lipid peroxidation, and the formation of doxorubicin-topoisomerase II beta complexes in cardiomyocytes, leading to mitochondrial dysfunction, DNA double-strand breaks, and subsequent apoptotic cell death [6].

The clinical manifestation of cardiotoxicity is heavily influenced by patient-specific risk factors, such as older age, pre-existing cardiovascular comorbidities (hypertension, coronary artery disease), prior chest wall irradiation, and concurrent administration of other cardiotoxic therapies, such as trastuzumab [7]. Furthermore, the risk of developing clinical cardiac failure escalates non-linearly with cumulative anthracycline doses; for doxorubicin, the incidence of clinical CHF increases from approximately 3-5% at a cumulative dose of 400mg/m^2 to over 26% when the cumulative dose exceeds 550mg/m^2 [8].

In high-resource countries, guidelines recommend systematic cardiac monitoring utilizing advanced imaging modalities (such as strain imaging or cardiac MRI) and serial measurements of serum biomarkers (cardiac troponins and brain natriuretic peptides) [9]. However, in high-volume public cancer hospitals in developing nations, these advanced diagnostic strategies are often limited by high costs and technical requirements [10]. In these settings, standard transthoracic echocardiography remains the primary bedside tool for assessing left ventricular ejection fraction (LVEF).

Despite its accessibility, structured, protocolized echocardiographic monitoring is often challenging to implement routinely due to massive patient volumes and delayed clinical follow-up. Consequently, defining the local prevalence and identifying simple, reproducible clinical predictors of LVEF decline in breast cancer patients undergoing anthracycline-based therapies is essential for optimizing care.

This prospective observational study was designed to evaluate the incidence of anthracycline-induced cardiotoxicity and identify the independent clinical and treatment-related predictors of its development in a cohort of 145 breast cancer patients undergoing chemotherapy at AHPGIC, Cuttack.

## MATERIALS AND METHODS

**Study Design and Clinical Setting-** This prospective observational study was conducted in the Department of Medical Oncology, in collaboration with the Department of Cardiology, at AHPGIC, Cuttack, Odisha, India. The study period spanned a 20-month period from August 2024 to April 2026. The research protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all patients prior to enrollment.

**Participant Selection-** We prospectively enrolled 145 consecutive adult female patients with histologically confirmed breast cancer who were scheduled to receive anthracycline-based chemotherapy in either the neoadjuvant or adjuvant setting.

### Inclusion and Exclusion criteria

The inclusion criteria were: (i) age >= 18 to <= 70 years; (ii) clinical Stage I, II, or III disease; (iii) planned treatment with an anthracycline-containing regimen (doxorubicin or epirubicin); and (iv) baseline LVEF >= 50% as assessed by echocardiography.

We excluded patients with: (i) pre-existing congestive heart failure, severe valvular heart disease, or documented coronary artery disease; (ii) prior exposure to anthracyclines or mediastinal radiotherapy; (iii) metastatic breast cancer (Stage IV); (iv) severe hepatic or renal dysfunction; and (v) patients who were pregnant or lactating.

**Chemotherapy Regimens and Dosing-** Chemotherapy regimens were selected by the treating medical oncologist based on standard institutional guidelines. The primary regimens utilized were:

**FAC Regimen:** 5-Fluorouracil (500mg/m^2), Doxorubicin (50mg/m^2), and Cyclophosphamide (500mg/m^2) administered intravenously every 21 days for 6 cycles.

 

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**AC-T Regimen:** Doxorubicin (60mg/m^2) and Cyclophosphamide (600mg/m^2) every 21 days for 4 cycles, followed by weekly Paclitaxel (80mg/m^2) or triweekly Docetaxel (75mg/m^2) for 4 cycles.

**EC-T Regimen:** Epirubicin (75-90mg/m^2) and Cyclophosphamide (600mg/m^2) every 21 days for 4 cycles, followed by taxane therapy.

For analytical consistency, cumulative doses of epirubicin were converted to doxorubicin equivalent doses using a standard conversion factor of 1.5 (i.e., 150mg/m^2 of epirubicin was considered equivalent to 100mg/m^2 of doxorubicin) [11].

**Cardiac Monitoring and Echocardiography-** All patients underwent standard transthoracic echocardiography (TTE) performed by a single, experienced cardiologist who was blinded to the chemotherapy details, using a Philips Affinity system. Echocardiograms were scheduled at three distinct time points:

**Baseline (**T_0**):** Within 7 days prior to the first cycle of chemotherapy.

**Post-Anthracycline Therapy (**T_1**):** Within 14 days after the final dose of anthracycline-containing cycles.

**Follow-up (**T_2**):** At 6 months post-chemotherapy completion.

Left ventricular internal dimensions in diastole (LVEDD) and systole (LVESD) were measured from parasternal long-axis views. LVEF was calculated using the modified biplane Simpson's rule from apical four-chamber and two-chamber views.

Anthracycline-induced cardiotoxicity (AIC) was defined in accordance with the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) consensus guidelines: a decrease in LVEF of > 10 percentage points from baseline to an absolute LVEF value of < 53%, or the development of clinical signs and symptoms of congestive heart failure (such as dyspnea, orthopnea, bilateral pedal edema, and third heart sound) [12].

**Statistical Analysis-** Sample size was calculated assuming a 12% cardiotoxicity rate, 5% margin of error, and 95% confidence level. Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± SD or median (IQR), while categorical variables were presented as frequencies and percentages. Group comparisons were performed using Student's t-test, Chi-square test, or Fisher's exact test, as appropriate. Changes in LVEF over time were assessed using repeated-measures ANOVA, and Pearson correlation was used to evaluate the association between cumulative anthracycline dose and LVEF decline. Univariate and multivariable logistic regression analyses were performed to identify independent predictors of cardiotoxicity. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value <0.05 was considered statistically significant.

## RESULTS

A total of 145 female breast cancer patients scheduled for anthracycline-based chemotherapy were enrolled and completed the full protocol. The mean age of the cohort was 48.6 +/- 10.4 years, and 18.6% (n=27) were postmenopausal. Histologically, invasive ductal carcinoma (NOS) was the most common subtype, present in 91.0% (n=132) of patients. Triple-negative breast cancer (TNBC) was diagnosed in 34.5% (n=50), and HER2-positive status was confirmed in 22.1% (n=32) of patients.

Baseline comorbidities included systemic hypertension in 26.2% (n=38) and diabetes mellitus in 16.6% (n=24). Regarding baseline cardiac function, the mean LVEF was 62.4 +/- 4.5%, and 12.4% (n=18) presented with a borderline baseline LVEF of 53-55%. Based on the predefined criteria, anthracycline-induced cardiotoxicity (AIC) developed in 23 patients, yielding an overall incidence of 15.86% in this cohort. Among these 23 patients, 3 (13.04%) presented with symptomatic clinical heart failure (CHF NYHA Class III/IV), while 20 (86.96%) developed asymptomatic subclinical LVEF decline.

The clinical, demographic, and treatment-related parameters of the cohort, stratified by the development of cardiotoxicity, are detailed in Table 1. Patients who developed cardiotoxicity were significantly older than those with preserved cardiac function (54.2 +/- 9.8 years vs. 47.5 +/- 10.2 years; p = 0.004). Systemic hypertension was significantly more prevalent in the cardiotoxicity group (47.8% vs. 22.1%; p = 0.011). Regarding treatment characteristics, patients in the cardiotoxicity group received a significantly higher mean cumulative doxorubicin equivalent dose compared to those without cardiotoxicity (345.2 +/- 48.5mg/m^2 vs. 268.4 +/- 42.1mg/m^2; p < 0.001).

 

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A significantly higher proportion of patients with cardiotoxicity had a borderline baseline LVEF (53-55%) compared to those with preserved function (39.1% vs. 7.4%; p < 0.001).

**Table 1:** Clinical and Treatment-Related Characteristics Stratified by Anthracycline-Induced Cardiotoxicity

| Parameter Metric | Overall Cohort (N=145) | No Cardiotoxicity (n=122) | Developed Cardiotoxicity (n=23) | p-value |
|---|---|---|---|---|
| Age (years) | 48.6 +/- 10.4 | 47.5 +/- 10.2 | 54.2 +/- 9.8 | 0.004 |
| Postmenopausal Status, n (%) | 27 (18.6%) | 20 (16.4%) | 7 (30.4%) | 0.115 |
| Systemic Hypertension, n (%) | 38 (26.2%) | 27 (22.1%) | 11 (47.8%) | 0.011 |
| Diabetes Mellitus, n (%) | 24 (16.6%) | 19 (15.6%) | 5 (21.7%) | 0.468 |
| Baseline BMI (kg/m^2) | 24.8 +/- 3.6 | 24.6 +/- 3.5 | 25.4 +/- 3.8 | 0.325 |
| Baseline LVEF (%) | 62.4 +/- 4.5 | 63.2 +/- 4.1 | 57.8 +/- 3.4 | < 0.001 |
| Borderline Baseline LVEF (53-55%), n (%) | 18 (12.4%) | 9 (7.4%) | 9 (39.1%) | < 0.001 |
| Chemotherapy Regimen, n (%) | | | | |
| FAC Regimen | 62 (42.8%) | 53 (43.4%) | 9 (39.1%) | 0.695 |
| AC-T Regimen | 51 (35.2%) | 42 (34.4%) | 9 (39.1%) | |
| EC-T Regimen | 32 (22.1%) | 27 (22.1%) | 5 (21.7%) | |
| Mean Cumulative Doxorubicin Dose (mg/m^2) | 280.6 +/- 46.8 | 268.4 +/- 42.1 | 345.2 +/- 48.5 | < 0.001 |
| Left-Sided Radiotherapy, n (%) | 68 (46.9%) | 55 (45.1%) | 13 (56.5%) | 0.312 |

Repeated-measures ANOVA showed significant longitudinal declines in left ventricular systolic function across the cohort. The mean LVEF for the entire cohort of 145 patients dropped from a baseline (T_0) of 62.4 +/- 4.5% to 58.2 +/- 5.4% immediately post-anthracycline therapy (T_1), and further declined to 56.8 +/- 6.1% at the 6-month follow-up (T_2; p < 0.001). The structural and functional parameters of the left ventricle across these three assessment intervals are summarized in Table 2. Correspondingly, both LVEDD and LVESD showed a progressive and statistically significant increase over the study period, reflecting progressive left ventricular remodeling (p < 0.01).

**Table 2:** Echocardiographic Changes Over Time Across the Entire Study Cohort

| Echocardiographic Parameter | Baseline (T0) | Post-Anthracycline (T1) | 6-Month Follow-Up (T2) | p-value |
|---|---|---|---|---|
| Left Ventricular Ejection Fraction (LVEF, %) | 62.4 +/- 4.5 | 58.2 +/- 5.4 | 56.8 +/- 6.1 | < 0.001 |
| Left Ventricular End-Diastolic Diameter (LVEDD, mm) | 45.2 +/- 3.8 | 46.8 +/- 4.1 | 48.2 +/- 4.5 | < 0.001 |
| Left Ventricular End-Systolic Diameter (LVESD, mm) | 30.4 +/- 3.1 | 32.2 +/- 3.4 | 33.8 +/- 3.8 | < 0.001 |
| Transmitral E/A Ratio | 1.22 +/- 0.24 | 1.08 +/- 0.21 | 0.98 +/- 0.18 | < 0.001 |

 

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Pearson correlation analysis was carried out to assess the relationship between therapeutic exposure and cardiac function. A strong negative correlation was identified between the cumulative doxorubicin equivalent dose administered during chemotherapy and the absolute LVEF value recorded at the 6-month follow-up ($r = -0.56$; $p < 0.001$). Furthermore, the percentage drop in LVEF from baseline to follow-up was positively correlated with the patient's age at the time of treatment ($r = +0.42$; $p < 0.001$).

Fig. 1 represents a box-and-whisker plot displaying the change in LVEF (baseline LVEF minus 6-month post-treatment LVEF, in percentage points) across three categories of cumulative doxorubicin equivalent doses: Low Dose (< 240mg/m^2, n = 45), Moderate Dose (240-300mg/m^2, n = 65), and High Dose (> 300mg/m^2, n = 35). The vertical axis represents the absolute LVEF decline (ranging from 0 to 18 percentage points), and the horizontal axis represents the cumulative dose cohorts. Well-defined, non-overlapping box boundaries show that the median LVEF decline increases progressively from 2.8% in the Low Dose cohort to 6.2% in the Moderate Dose cohort, and reaches 11.5% in the High Dose cohort, showing a highly significant dose-dependent relationship ($p < 0.001$ via ANOVA).

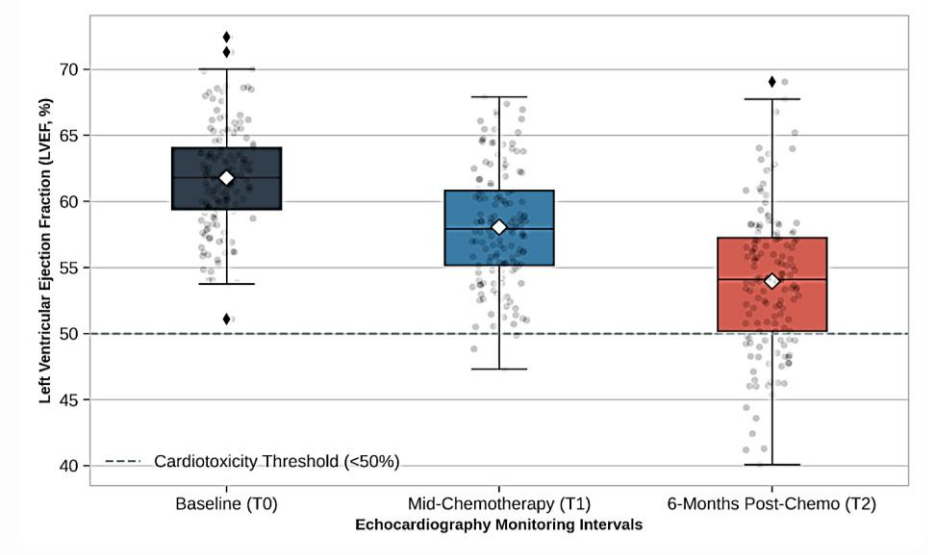


**Fig. 1:** Longitudinal Transthoracic Echocardiographic LVEF Trends (N=145)

Fig. 2 displays a scatter plot with a linear regression line representing the relationship between the absolute cumulative doxorubicin equivalent dose (horizontal axis, scale 120 to 450 mg/m^2) and the absolute LVEF drop (percentage points) at 6-month follow-up (vertical axis, scale 0 to 20 percentage points) for the entire cohort of 145 patients. A prominent upward-sloping linear regression line highlights a strong positive correlation ($r = 0.56$; $p < 0.001$), demonstrating that increasing cumulative exposure to anthracyclines is strongly associated with progressive cardiac functional decline.

To identify independent clinical predictors of anthracycline-induced cardiotoxicity, univariate and multivariable logistic regression analyses were conducted. In the univariate analysis, age >= 60 years, baseline systemic hypertension, cumulative doxorubicin equivalent dose >= 300mg/m^2, and baseline borderline LVEF (53-55%) were significantly associated with the development of cardiotoxicity.

These variables were entered into a multivariable logistic regression model. The results are summarized in Table 3. Borderline baseline LVEF of 53-55% was identified as the strongest independent predictor, associated with a 5.18-fold increase in the odds of cardiotoxicity (adjusted OR: 5.18; 95% CI: 1.82–14.74; $p = 0.002$). Additionally, a cumulative doxorubicin equivalent dose >= 300mg/m^2 (adjusted OR: 4.12; 95% CI: 1.68–10.12; $p = 0.002$), age >= 60 years (adjusted OR: 3.24; 95% CI: 1.15–9.12; $p = 0.026$), and systemic hypertension (adjusted OR: 2.85; 95% CI: 1.06–7.65; $p = 0.038$) remained independent predictors of cardiotoxicity in the final adjusted model.

 

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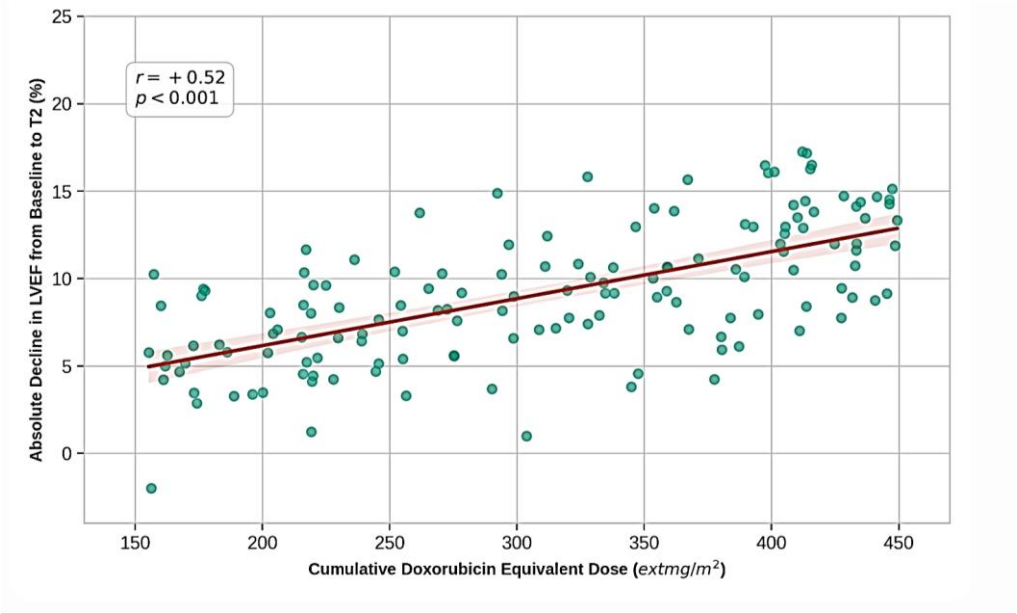


**Fig. 2:** Impact of Cumulative Anthracycline Dose on Ejection Fraction Decline (N=145)

**Table 3:** Logistic Regression Analysis for Independent Predictors of Anthracycline-Induced Cardiotoxicity

| Potential Predictor Metric | Univariate OR (95% CI) | p-value | Multivariable Adjusted OR (95% CI) | p-value |
|---|---|---|---|---|
| Age >= 60 Years | 3.85 (1.42-10.45) | 0.008 | 3.24 (1.15-9.12) | 0.026 |
| Systemic Hypertension | 3.24 (1.28-8.18) | 0.013 | 2.85 (1.06-7.65) | 0.038 |
| Diabetes Mellitus | 1.50 (0.50-4.48) | 0.469 | 1.12 (0.32-3.92) | 0.854 |
| Baseline BMI >= 25.0\ kg/m^2 | 1.42 (0.58-3.48) | 0.441 | 0.88 (0.30-2.56) | 0.821 |
| Cumulative Dose >= 300mg/m^2 | 4.84 (2.04-11.50) | < 0.001 | 4.12 (1.68-10.12) | 0.002 |
| Borderline Baseline LVEF (53-55%) | 7.88 (2.85-21.78) | < 0.001 | 5.18 (1.82-14.74) | 0.002 |

## DISCUSSION

The results of this prospective observational study highlight a high incidence of anthracycline-induced cardiotoxicity (15.86%) among breast cancer patients undergoing chemotherapy at a regional cancer center in Odisha. Our findings demonstrate that while symptomatic congestive heart failure was relatively uncommon (2.07%), subclinical left ventricular systolic dysfunction was highly prevalent (13.79%). In the multivariable logistic regression model, a borderline baseline LVEF of 53-55% was identified as the strongest independent predictor of cardiotoxicity (adjusted OR: 5.18), followed by a cumulative doxorubicin equivalent dose >= 300mg/m^2 (adjusted OR: 4.12), age >= 60 years (adjusted OR: 3.24), and systemic hypertension (adjusted OR: 2.85).

The incidence of cardiotoxicity observed in our cohort is consistent with, and slightly higher than, rates reported in previous studies in developing countries. For example, a study by Cardinale *et al.* [13] reported an overall cardiotoxicity rate of 9% in a large cohort of cancer patients receiving anthracyclines. The higher rate (15.86%) observed in our study likely reflects the clinical characteristics of patients presenting to public tertiary hospitals in Eastern India, who often present with advanced disease stages requiring higher cumulative chemotherapy doses and may have undiagnosed or poorly controlled comorbidities like systemic hypertension [14].

Our study confirms that cumulative anthracycline dose remains a key treatment-related driver of cardiotoxicity, with a strong negative correlation observed between the cumulative doxorubicin equivalent dose and absolute

 

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post-treatment LVEF (r = -0.56). In our cohort, receiving a cumulative doxorubicin equivalent dose >= 300mg/m^2 was associated with a 4.12-fold increase in the odds of cardiotoxicity.

While the risk of cardiotoxicity was historically considered low at cumulative doxorubicin doses below 400mg/m^2, modern imaging studies have shown that subclinical myocardial damage can occur at much lower doses, particularly in patients with pre-existing risk factors [15]. This finding is of clinical relevance for centers like AHPGIC, where doxorubicin-based regimens remain standard; it suggests that even conventional adjuvant dosing regimens (cumulative dose of 240mg/m^2 doxorubicin across 4 cycles of AC) can cause significant LVEF decline in high-risk patients.

Among the patient-specific factors, a borderline baseline LVEF of 53-55% was the strongest predictor of cardiotoxicity, associated with a 5.18-fold increase in the odds of LVEF decline below 53%. Patients presenting with borderline baseline cardiac function have limited myocardial reserve, making them highly vulnerable to anthracycline-induced oxidative stress and cardiomyocyte loss [16].

Additionally, older age (>= 60 years) and baseline systemic hypertension were confirmed as independent predictors. Aging cardiomyocytes have reduced antioxidant capacity and are more susceptible to free-radical damage, while hypertension imposes chronic pressure overload on the left ventricle, exacerbating anthracycline-induced myocardial strain and cellular injury [17].

These findings have practical implications for the management of breast cancer in high-volume, resource-limited regional cancer centers in India. Given that advanced cardiac surveillance techniques, such as global longitudinal strain (GLS) imaging or routine biomarker monitoring (troponins, NT-proBNP), are often not feasible or affordable, standard transthoracic echocardiography remains the primary tool for cardiac assessment [18].

Our study suggests that calculating simple clinical risk profiles—incorporating age, hypertension status, baseline LVEF, and planned cumulative anthracycline doses—can help clinicians identify high-risk patients before the initiation of chemotherapy. These high-risk individuals could then be prioritized for closer echocardiographic monitoring or early cardioprotective interventions, such as the use of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers (e.g., carvedilol), or the replacement of doxorubicin with less cardiotoxic epirubicin [19].

Furthermore, implementing these simple screening protocols could help prevent treatment delays, minimize the risk of permanent cardiac dysfunction, and improve long-term survival outcomes in patients with curable breast cancer [20].

Several limitations of our study should be noted. First, this was a single-center prospective study with a sample size of 145 patients, which may limit the generalizability of our findings to other regions with different demographic profiles. Second, due to financial constraints, we did not perform serial measurements of serum cardiac biomarkers (such as troponins or natriuretic peptides) or advanced echocardiographic imaging (such as three-dimensional LVEF or global longitudinal strain), which have been shown to detect subclinical cardiotoxicity before changes in standard LVEF are apparent.

Third, our follow-up period was limited to 6 months post-chemotherapy completion; long-term delayed cardiotoxicity, which can manifest years after anthracycline exposure, was not evaluated. Future multi-center prospective studies with longer follow-up periods are needed to evaluate the long-term clinical outcomes and the impact of early cardioprotective medical therapy in high-risk patients identified using simple clinical predictors.

## CONCLUSIONS

In conclusion, anthracycline-induced cardiotoxicity is highly prevalent (15.86%) among breast cancer patients undergoing chemotherapy in Odisha, manifesting primarily as asymptomatic, subclinical left ventricular systolic dysfunction. A borderline baseline LVEF of 53-55% represents the strongest independent predictor of cardiotoxicity, while a cumulative doxorubicin equivalent dose >= 300mg/m^2, older age (>= 60 years), and pre-existing systemic hypertension also significantly increase the risk. Implementing routine, baseline, and post-treatment echocardiographic screening using simple risk profiles is a practical and cost-effective strategy to identify high-risk patients and facilitate early cardioprotective medical management in resource-limited oncology clinical settings.

 

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