Anthracycline associated cardiotoxicity in a sub-Saharan African population - tertiary care experience

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Abstract

Background Anthracyclines are associated with irreversible cardiotoxicity, with changes in echocardiographic parameters preceding clinically manifest cardiac dysfunction. We sought to evaluate the incidence of early cardiac dysfunction post anthracyclines, and associated clinical, echocardiographic and treatment parameters in a sub-Saharan African population.

Methods Cancer patients aged ≥18years at anthracycline initiation with archived baseline echocardiograms, underwent repeat echocardiographic assessment. Cases (with cardiac dysfunction) had (1) >15% relative decline from baseline in global longitudinal strain (GLS), or (2) a decline in left ventricular ejection fraction (LVEF) from baseline to <53% with either (i) symptoms (assessed by the Duke Activity Status Index at follow-up echocardiogram) and LVEF decline by >5 to ≤10%, or (ii) LVEF decline >10% regardless of symptoms. Comparisons in clinical, echocardiographic and treatment parameters were made with controls (no cardiac dysfunction).

Results Among 141 patients (mean age, 47.7years ± 11.2, Africans 95%, females 85.1%, breast cancer 82%), 39 (27.7%) had cardiac dysfunciton at a mean inter-echocardiogram interval of 14.9months ± 14.3, mean cumulative anthracycline dose of 244.7mg/m 2 ± 72.2, and mean DASI score was 50.0 ± 13.3. Mean cardiotoxic doxorubicin equivalence dose was 236.7mg/m 2 ± 57.4 for cases and 217.3 ± 61.9 for controls [p = 0.033, OR = 1.00 (95% CI: 0.99 - 1.01)]. The assessed clinical, echocardiographic and treatment parameters were not associated with cardiac dysfunction.

Conclusion Incidence of early cardiac dysfunction after standard dose anthracyclines in an adult Sub-Saharan population is 27.7% at a mean follow-up of 14.9 months post anthracycline. Routine pre- and post-exposure cardiac assessment should be considered.

Background

Despite improvements in oncology resulting in better survival (1, 2), the benefits of chemotherapy are offset by adverse events, including cardiotoxicity (3). Cardiotoxicity may be acute, early or late, with the former being reversible, affecting < 1% and manifesting as supraventricular arrhythmias, temporary electrocardiogram changes or transient left ventricular (LV) dysfunction. The latter forms, irreversible and typified by anthracyclines (4, 5), occur at ≤ 1 year (early) and > 1 year (late) (6).

The cumulative lifetime anthracycline dose is a consistent risk factor for subsequent cardiotoxicity (7). This dose-dependent risk has led to capping the lifetime cumulative dose to < 360 mg/m^2 (6), and with a symptomatic heart failure incidence of 5% at a dose of 400 mg/m^2, the lowest possible dose is advised, with those receiving > 250 mg/m^2 being high risk (8). However, life-threatening cardiotoxicity may occur after a single dose (9), with no safe cut-off in childhood survivorship follow up studies (10) and suggested increased odds at > 201 mg/m^2 (11).

Black race is associated with increased risk of cardiotoxicity independent of their increased risk of systemic arterial hypertension and atherosclerotic cardiovascular disease (12) in both adults and children (13). Earlier studies, however, give disparate results with no association with race (14) and there is generally poor representation of blacks in adult risk evaluation studies (15). Other cardiotoxicity predictors include female gender, concurrent and prior treatment with cardiotoxic agents, age (> 65 years or < 18 years) (13), co-morbidities (renal failure, heart disease, systemic hypertension) (6) pre-treatment blood pressure and body surface area (BSA) (16). Epirubicin is less cardiotoxic compared to doxorubicin (17–19), and the final cardiotoxic profile when other non-anthracycline chemotherapy are co-administered may reflect a synergistic action (20). Risk prediction models have incorporated these factors to guide therapy and follow-up (7, 19–21). Altered metabolic profile related to anti-retroviral therapy) (22), promotion of endothelial activation and atheroma formation following systemic immune activity in Human Immunodeficiency Virus infected patients increases their risk of cardiovascular disease (23–25) and the synergistic effect of these factors may be aggravated by anthracycline co-administration (22).

Guidelines (6, 8) recommend peri-chemotherapy cardiac assessment by biomarker evaluation, volumetric assessments (echocardiography, magnetic resonancy imaging, multigated acquisition scan or global longitudinal strain (GLS) echocardiography, with the pre-chemotherapy modality used subsequently and a preference for GLS for early detection of cardiac dysfunction (6) due to its better sensitivity in this setting (26). Myocardial deformation measured by GLS, though limited by different vendor algorithms, is a reproducible means of assessing cardiac function, with less inter-operator variability than LVEF scored by Simpson's biplane, Teicholz or qualitatively (27). GLS abnormalities occur prior to an LVEF decline, with a baseline strain of < 19% and a relative reduction of ≥ 15% predicting later LVEF changes and symptomatic heart failure (28). Diastolic changes positively correlate with later systolic dysfunction (29), with E/a ratio (E-early and a-late, peak trans-mitral valve diastolic velocities) and e' (early diastolic lateral mitral annulus velocity) being useful assessments (30, 31).

Recommendations of timing of cardiac evaluation are heterogenous, with the American Society of Clinical Oncology and the European Society of Cardiology recommending an assessment on completion of treatment, with emphasis on those with elevated risk or subsequent/concurrent cardiotoxic treatment (6, 8), while the European Society of Medical Oncology recommends one at half the planned total dose, or at 300 mg/m^2 (without risk factors), or at 240 mg/m^2(age extremes with risk factors), or prior to the next dose, or at 3,6 and 12 months after the last dose (32).

The implications of early detection of cardiac dysfunction include adjusting treatments halting further cardiac decline, and earlier institution of therapy (angiotensin inhibitors, statins, beta-blockers, dexrazoxane) which can potentially prevent or halt progression into heart failure (33, 34). Heart failure resulting from systolic dysfunction with a 3.78 hazard ratio of death once developed (35), can manifest immediately post anthracycline (14).

This is the first study to evaluate clinical, echocardiographic and treatment parameters associated with early cardiac dysfunction, and the latter's incidence, as determined by echocardiography in an adult East-African population exposed to anthracyclines.

Methods

Patient selection

This was a longitudinal prospective cohort study with an embeded case-control design done at the Aga Khan University Hospital, Nairobi. From 14th October 2013 to 11th April 2019, anthracycline-exposed patients with cancer diagnoses were retrospectively identified from the chemotherapy pharmacy and review of admissions to the chemotherapy administration unit. This time-frame was chosen due to the availability of archived echocardiograms. Patient identifiers (hospital number, name) and contact information were obtained and a unique study number assigned. Of 504 identified patients, 241 fullfilled eligibility criteria: ≥18 years at first anthracycline dose, pre-anthracycline archived baseline echocardiogram done within one month and no prior anthracycline use nor known heart disease. 263 patients who did not fullfill eligible criteria were excluded. Eligible patients without a post-anthracycline archived echocardiogram done at least seven days after completion of anthracycline treatment (201 patients) were approached (through contact information or on scheduled hospital visits) and consented for a post-anthracycline echocardiogram. Eligible patients with available archived pre- and post-anthracycline echocardiograms (40 with paired studies available at study initiation and 101 with paired studies post study initiation acquired between October 2018 and April 2019) were further analysed. Eligible patients with ongoing anthracycline treatment at study conclusion, mortalities, unreacheable/unavailable and who did not give consent were further excluded (Fig. 1).

Echocardiogram procedures

All echocardiograms were acquired under cardiologist supervision. Echocardiograms were performed on VividQ© and Vivid7 Dimension© (General Electric) machines, using The Intersocietal Commission for the Accreditation of Echo Labs protocol for adult transthoracic echocardiography (36), and images were transferred to the offline vault. The minimum standard views aquired were the parasternal long axis and apical four-, two- and three-chamber views.

Post-processing of archived images was done using EchoPac® vendor software by the research team, supervised by an investigator. LVEF was calculated using modified Simpson's biplane method of discs on apical two and four chamber views, as per the American Society of Echocardiography/European Society of Echocardiography recommendations (37). Averaged heart rates, LV end diastolic and systolic volumes, stroke volumes (SV-absolute, indexed for BSA), GLS (from apical two, three and four chamber views), diastolic function (E/a, e') and dates of echocardiogram acquisition were captured.

Patients with cardiac dysfunction at follow-up echocardiogram satisfied the criteria as per 2016 European Society of Cardiology position paper on cancer treatment and cardiovascular toxicity (6): (1) A relative decline in GLS > 15%, (2) An LVEF absolute decline to < 53% and either (i) decline of > 10% regardless of symptoms, or (c) symtoms and an LVEF decline ≥ 5% to < 10%. Eligible patients not meeting all criteria were classified as having no dysfunction.

DASI capture

The Duke Activity Status Index (DASI) symptom questionnaire (Supplementary table 1) (which assesses functional capacity and has good validity, reliability and correlation [Spearman coefficient 0.80] in measuring functional capacity in heart failure (38) and estimating peak VO^2 (39)) was self/investigator administered within one month of post-anthracycline echocarcardiograms. Of 40 patients with post-anthracycline echocardiograms at study initiation, 8 had them done wihin one month of study initiation and their DASI information was captured. Symptomatic patients were considered those who scored below the maximum points of 58.2.

Risk factors evaluation

Patient-related factors obtained were age at first anthracycline dose, gender, race, pre-anthracycline height and weight, two independent blood pressure readings prior to chemotherapy, self-reported alcohol use, and smoking status, comorbidities (hypertension, diabetes, dyslipidemia) and review of cardioactive medication (β-blockers, angiotensin blockers, statins, diuretics, calcium channel blockers and dexrazoxane) (Supplementary table 2). The cumulative dose (absolute and BSA adjusted), number and dates of cycles, and weight at each cycle was obtained from chart reviews for chemotherapy administered (given sequentially or concurrently as per treatment protocol) in the inter-echocardiogram period. The radiation site, cumulative dose, fraction number and start with end dates were captured if done in the inter-echocardiogram period. Routine imaging radiology (radiograph, mammogram, computed tomography scan) was excluded.

Statistical methods

Based on the assumption of a cut-off of 201 mg/m^2 cumulative dose leading to cardiac dysfunction in proportions of 0.48 and 0.24 (for > 201 mg/m^2 and ≤ 201 mg/m^2 respectively) (11) and using the formular for determination of differences in proportions (40), a sample estimate of 146 patients (42 with dysfunction) was needed for $P < 0.05$ and power of 80%. The proportion of those with dysfunction who received ≤ 201 mg/m^2 and > 201 mg/m^2 of cumulative anthracyclines was 0.20 and 0.29 respectively, giving a standardized difference of 0.487, and a sample power of 82%. Data were entered into Epi InfoTM for windows V 7.2©, extracted to Microsoft Excel© and exported to IBM Statistical Package for the Social Sciences© version 25 (IBM®, Chicago, IL) for analysis. The date of baseline echocardiogram was considered time zero, and cumulative freqency of cardiac dysfunction was plotted against months between last anthracycline and follow up echocardiogram. Comparisons were made between those with and without cardiac dysfunction. Categorical variables were expressed as counts and percentages, while continuous variables were presented as means with standard deviations. Both dysfunction groups

(present or absent) were stratified by time from last anthracycline dose to follow up echocardiogram (≤ 1year, > 1 year), cumulative anthracycline dose (≤ 201 mg/m2, > 201 mg/m^2) and mean cycle duration (≤ 14days, > 14-21days, > 21 days) was done. Doxorubicin equivalence was calculated by factoring in the cardiotoxic potential of the anthracycline compared with conventional doxorubicin (Epirubicin-0.7, Daunorubicin-0.75, Idarubicin-0.53) (6). Independent variables were assessed for normality using the Shapiro-Wilk test. Univariate analysis was performed to identify variables significantly different between cases and controls. Fisher's exact and Chi square test was used to compare categorical variables whereas Mann-Whitney test was used to compare continuous variables. Pearson's correlation was used to examine associations between duration of follow up echocardiogram and changes in GLS and LVEF. Multivariate analysis was performed by linear regression, with stepwise selection multiple regression for determination of independent predictors of cardiotoxicity. Binary logistic regression was used to calculate odds ratios (OR). Statistical tests were 2-sided with significance set at $p < 0.05$.

Ethics and funding

Approval was obtained from Aga Khan University Hospital Research and Ethics Committee with funding obtained from institutional research seed grant.

Results

Of 141 patients analysed, 39 (27.7%) fulfilled cardiac dysfunction criteria, of whom 30 (76.92%) satisfied the GLS criterion (Table 1). Cumulative frequency of cardiac dysfunction against monthly quaters showed a linear relation (Central Illustration).

Baseline characteristics were similar in the two groups. The majority were Africans (95%), female (85.1%) and had breast cancer (82%) at a mean age at first anthracycline dose of 47.7 ± 11.2years. There were no differences in pre-anthracycline weight, BSA and body mass index. The proportions of those with diabetes, hypertension, human immunodeficiency virus, dyslipidaemia, self-reported alcohol use and smoking and pre-anthracycline blood pressure was similar in the two groups. The most frequently used cardiovascular drugs were angiotensin inhibitors (18.4%) (Table 2).

Seventy-four percent received conventional doxorubicin and 23% epirubicin (Table 3, Supplementary table 3) with 78% receiving ≤4 sessions. The mean duration between first and last anthracycline doses was 66.7 ± 31.7days, with 55.1% having a cycle duration of >14 to 21days. Mean anthracycline BSA adjusted dose was 244.7 ± 72.2mg/m^2. The mean cardiotoxic doxorubicin equivalence was different between the two groups (cardiac dysfunction-236.73 ± 57.4mg/m^2; No cardiac dysfunction -271.83 ± 61.9mg/m^2 p=0.033; OR 1.006 95% CI 0.999-1.012 p=0.096).

The cumulative absolute and BSA adjusted antimetabolite doses differed in the groups (p = 0.030 and p = 0.027 respectively), with only the no cardiac dysfunction group receiving Capecitabine. Trastuzumab was always used sequentially and there were no differences in the absolute or BSA adjusted doses of other chemotherapeutic agents (Table 2, Supplementary table 3).

Fifty-three patients (37.6%) received radiation (mean dose: 5906.9 ± 1004.7 cGy, mean fractions: 27.3 ± 5.7, mean duration: 37.4 ± 8.6days). Fifty patients (35.5%) received chest wall radiation with higher percentage of the cardiac dysfunction group receiving left sided chest wall radiation (28.2% vs 18.6%) (Table 2). There were no inter-group differences in radiation parameters.

The mean baseline and follow up LV end diastolic volume was 84.3ml ± 17.5 and 83.9ml ± 21.6, with a mean baseline and follow up LV end systolic volume of 35.6ml ± 9.8 and 38.1ml ± 12.5 and a mean baseline SV and SV index of 48.7ml ± 11.0 and 26.8ml/kg/m^2 ± 5.6. The LV end systolic volume was higher among the cases (42.0 ± 16.4 ml vs 36.6 ± 10.4 ml; p = 0.146). Both the follow up SV and SV index were lower among the cases (42.8ml ± 12.3 vs 47.0ml ± 11.4 for SV [p = 0.020]; 23.7ml/kg/m^2 ± 6.5 vs 25.8ml/kg/m^2 ± 5.94 for SV index [p = 0.022]). The cardiac dysfunction group had a higher baseline LVEF (59.7% ± 6.7 vs 57.4% ± 5.4, p = 0.024) and a higher baseline deformation measured by GLS (-19.6% ± 3.4 vs -18.3% ± 2.6, p = 0.027). The baseline E/A ratio and e' values were similar between the two groups, with a mean E/A of 1.22 ± 0.41 and mean e' of 0.12 ± 0.05. On follow up, both were lower among those with cardiac dysfunction (E/A: 1.02 ± 0.33 vs 1.16 ± 0.36, p = 0.019; e': 0.10 ± 0.05 vs 0.11 ± 0.05, p = 0.011). The mean duration between follow up echocardiogram and last anthracycline dose was 15.0 ± 14.3 months, with 21 (53.8%) of those with cardiac dysfunction and 52 of those withous cardiac dsyfunction (51.0%) having them done at ≤1 year (Table 4). Mean DASI scores and corresponding METS were similar in the groups (mean DASI: cardiac dysfunction 48.5 ± 13.4 No cardiac dysfunction 50.5 ± 13.2; METS: Cardiac dysfunction 8.7 ± 1.7 No cardiac dysfunction 9.0 ± 1.6).

Discussion

This was a study looking at factors associated with early anthracycline cardiotoxicity in a young, female, African population with breast cancer. The mean and median ages were comparable to similar studies in African Americans (12), local populations (41) and non-black cohorts (16). The large proportion of breast cancer patients reflects the predominant use of anthracyclines coupled with high prevalence.

Heterogeneity exists in study definitions of anthracycline cardiotoxicity: absolute fall ≥ 5 percentage points in LVEF (16), absolute value of LVEF < 50% (41), absolute value of LVEF < 45% or heart failure (12) and > 11% relative GLS decline from baseline (42), with no assessment of GLS in an African population. With varying definitions, comparison between studies are difficult. However, our cardiotoxicity prevalence was higher than 22% in an Australian study (cardiotoxicity - relative reduction in GLS > 11%) (42), and 20.7% in a study of non-blacks (Cardiotoxicity - >5 percentage points drop in LVEF on cardiac magnetic resonance imaging (16). Our study was also higher than 21% in a study by Sawaya et al, who defined cardiotoxicity on transthoracic echocardiography as a drop in LVEF > 5 percentage points (to < 55% with symptoms) or a drop in LVEF > 5 percentage points (to < 55% regardless of symptoms). In a study that looked at 2625 patients, 9% developed cardiac dysfunction, defined as a > 5 percentage points absolute LVEF drop to < 50% (34). However, our value was lower than local paediatric reports. Most of our patients fulfilled GLS criteria, emphasising the utility of this evaluation in early detection. Baseline GLS was better

in the cardiac dysfunction group, in contrast to suggestions that a worse value is predictive of cardiotoxicity (28).

Most patients received doxorubicin, similar to studies evaluating cardiotoxicity, with the majority getting ≤ 4 sessions, reflecting protocol guidelines for breast cancer treatment (43, 44). Cycle duration did not influence degree of cardiotoxicity. The duration between the first and last anthracycline did not confer risk, with the cardiac dysfunction group having a non-significant longer duration by one week. When the cardiotoxic effect was factored to the cumulative dose, anthracyclines use was significantly higher in cases, contributed by the greater use of doxorubicin, suggesting the lower cardiotoxicity of epirubicin. These findings mirror the known dose-dependent cardiotoxicity of anthracyclines, particularly doxorubicin. In addition, recommended doses are not free from cardiotoxic effects.

Our average duration of 14.3 months, with approximately half having an evaluation at ≤ 1 year, suggests that cardiotoxicity may occur at any time, as mirrored by studies which looked at pathological changes after one dose (18), echocardiographic changes at seven days after completion (16) or echocardiographic parameters at > 1 year (12). After a sharp rise in the first two quarters in our cohort, progress was linear, with half of the cohort showing changes by approximately one year.

The baseline BSA, body mass index and blood pressure did not influence development of cardiotoxicity as opposed to Kotwinski et. al (16), who studied a non-black population and used different cardiac dysfunction criteria. Adjusting dose for BSA ultimately factors weight and height in dose calculations and may correct for their possible influence.

The presence of comorbidities was minimal, reflecting the youth of the cohort. However, human immunodeficiency virus prevalence was higher than the national figure, particularly in cases, suggesting the its cardiovascular disease contribution and/or anti-retroviral therapy. However, no conclusions can be made due to the few numbers. Distribution of diabetes mirrored the national estimates and did not influence case assignment. Similarly, numbers were small. Blood pressure control was optimal overall, with the commonly used mediations mirroring suggestions of their utility in such a cohort (45). A sub-analysis of hypertensives found higher values in cases, suggesting that uncontrolled blood pressure prior to chemotherapy may predispose to cardiomyopathy.

The importance of multimodality treatment in cancer cannot be overstated. Antimetabolite use showed a protective effect, however, only controls received capecitabine, which has a large absolute dose per cycle compared to fluorouracil, and thus could skew the results towards significance. Also, none of the cases received capecitabine, hence associations of significance cannot be relied on. Though Trastuzumab is known to be associated with cardiac dysfunction, the numbers administered monoclonal antibodies were minimal (17% – 21 patients), hence conclusive assumptions cannot be arrived at. The other chemotherapeutic agents did not influence development of cardiotoxicity. Radiation to the left chest wall, which implies myocardial exposure, was non-significantly more in the cases (73.3%) than in the controls (54.3%), suggesting deleterious effects of concomitant radiation to the heart.

Diastolic function was significantly reduced in cases, and though diastolic function assessment is not recommended to guide therapy, it may add to the evaluation of cardiotoxicity and potentially be included in risk prediction models. Impaired ventricular filling may ultimately lead to increased LV filling pressures. Other studies have reported increased diastolic abnormalities in post-anthracycline cardiomyopathy (42). Heart rates at follow up were also increased among the cases, probably as a compensation for reduced SV, to maintain cardiac output.

Symptoms are a poor marker of early cardiac dysfunction, as a similar DASI score was achieved by both groups, with a non-significant lower value among cases. The corresponding METS were high, thus recommendations to have a cardiac evaluation upon symptom onset (6) may lead to missed opportunities to intervene, justifying a low threshold for the cardiac evaluation of anthracycline exposed individuals.

The study had some limitations. Despite DASI information not being captured in all patients, this did not influence case distribution, as those with DASI information were similar between the groups. A potential survivorship bias, where those with clinical heart failure may have succumbed prior to study initiation may be possible. Out of those who fulfilled all eligibility criteria but did not have follow up echocardiograms, 11.4% were mortalities. Pre-defined time points for echocardiograms would be able to characterize better when dysfunction would occur. The numbers for some factors were small and thus may not appropriately draw associations despite overall numbers being higher than studies that used GLS (140 in Boyd et al (42)).

Conclusion

In a young, predominantly female African population receiveing anthracyclines, the prevalence of development of early cardiac dysfunction post anthracycline was high. Baseline clinical and systolic and diastolic echocardiographic factors were not associated with development of cardiac dysfunction. Prospective studies assessing composite predictors including cardiac biomarkers, evaluating risk prediction models that factor in diastolic and systolic changes to guide therapy and follow up, assessing progressive serial decline in heart function or development of heart failure, validating our findings in a larger cohort are recommend.

Abbreviations

BSA	Body surface area
DASI	Duke assessment symptom index
e'	Mitral annulus lateral wall velocity (early)
E/A	Early (E) to late (A) diastolic transmitral velocity
GLS	Global longitudinal strain
LV	Left ventricular
LVEF	Left ventricular ejection fraction
SV	Stroke volume

Declarations

Ethics approval and consent to participate

Informed consent was obtained prior to acquisition of follow up echocardiograms for those who did not have follow up archived images at study initiation. Ethical approval was obtained from the Aga Khan University Hospital Nairobi Research and Ethics committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JOA, AJS, JM and AB were involved in conceptual design of all aspects of the study protocol (conceptual design, methodology, and critical appraisal of utility and clinical perspectives). JS was involved in the conceptualization of data collection and analysis planning in collaboration with the JOA, AJS, JM and AB and was involved in the drafting and critical appraisal of the final proposal. Data analysis and

interpretation was led by JS, JOA and AB with input from AJS and JM. All authors were involved in final manuscript drafting and critical appraisal, and final approval for submission for publication.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

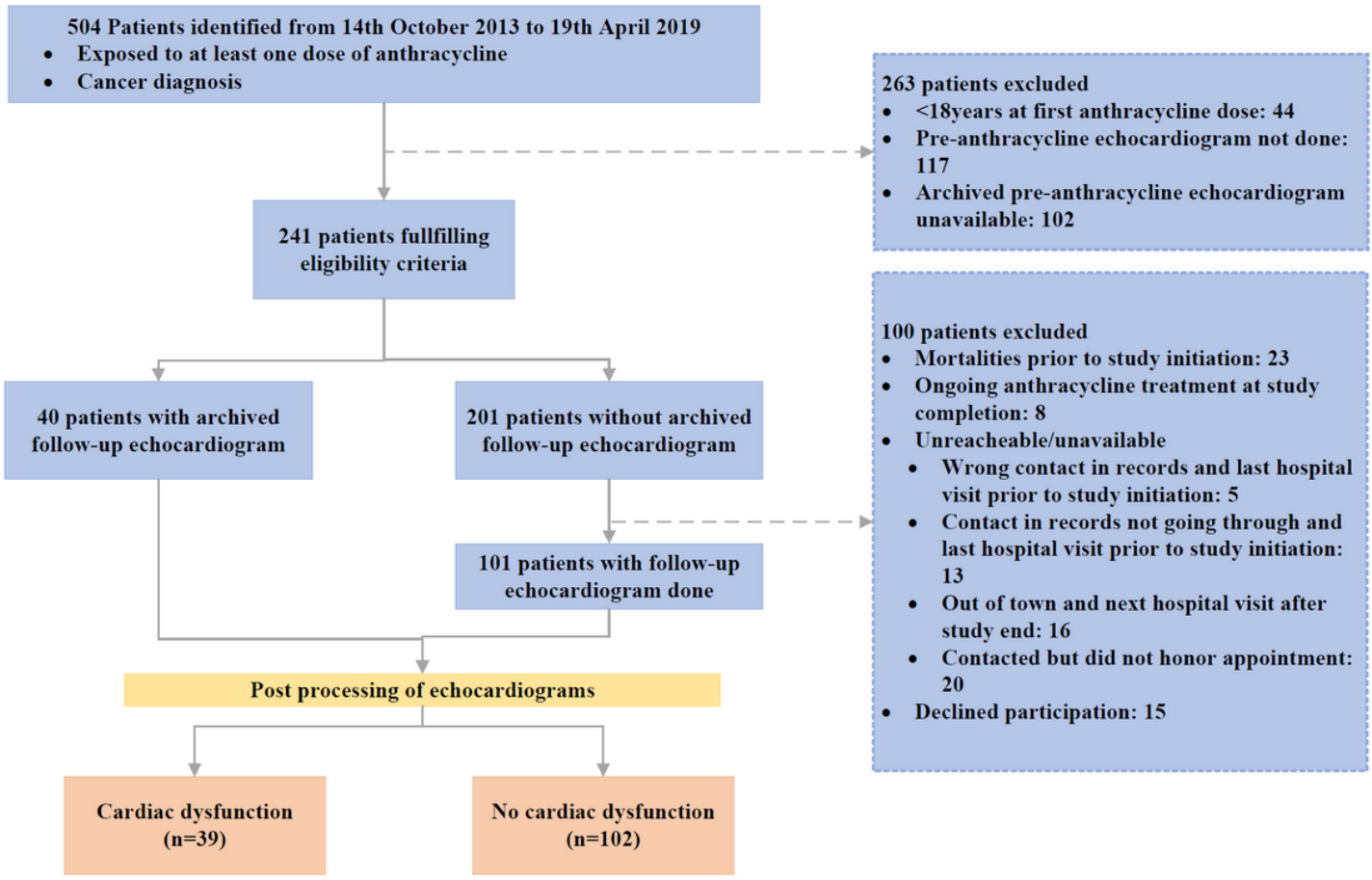

Figure 1

Patient recruitment Patients were retrospectively evaluated for eligibility. Of 241 patients who fulfilled eligibility criteria, 201 did not have a follow up echocardiogram and were invited for a follow-up assessment, out of whom 101 patients had them done. Overall, out of 504 anthracycline exposed patients, 363 (72%) were excluded.

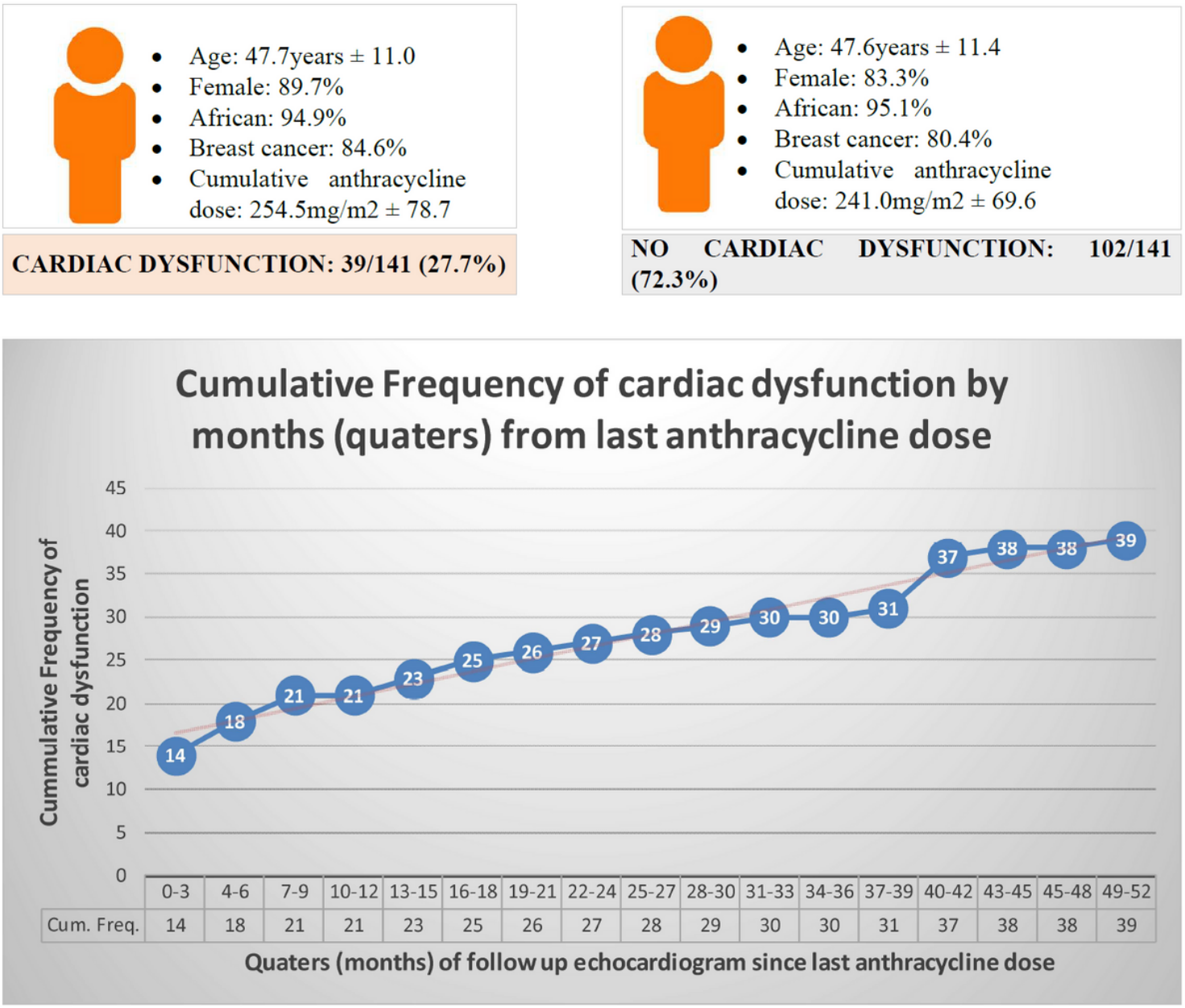

Figure 2

Cumulative frequency of cardiac dysfunction from last anthracycline The cumulative frequency of cardiac dysfunction was linear (trend line – light red). Half of the patients had developed cardiac dysfunction by one year. This group similar to those without dysfunction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytables.docx
- Tables.pdf