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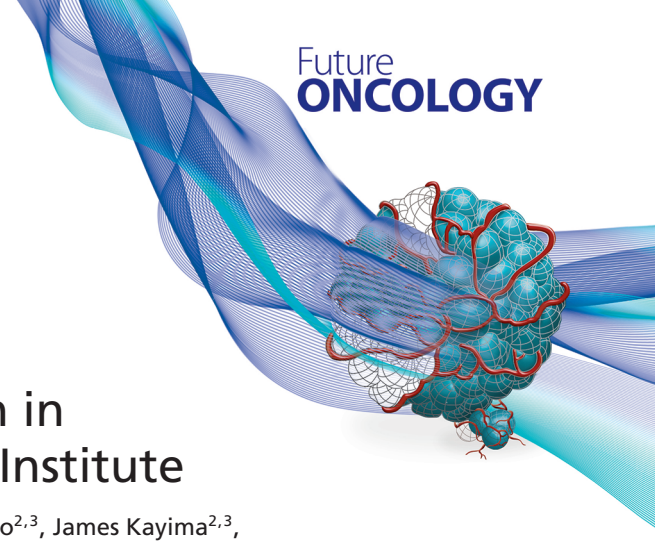

Detecting subclinical anthracycline therapy-related cardiac dysfunction in patients attending Uganda Cancer Institute

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Aims: To investigate the incidence of anthracycline therapy-related cardiac dysfunction (ATRCD) and its predictors among Ugandan cancer patients. **Patients & methods:** The study recruited 207 cancer patients who were followed for 6 months after ending anthracycline therapy. Global longitudinal strain and troponin-I were the diagnostic tools. **Results & conclusions:** The cumulative incidences of subclinical and clinical ATRCD were 35.0 and 8.8% respectively. The predictors of clinical ATRCD were HIV infection (hazard ratio [HR]: 3.04; 95% CI: 1.26–7.32; p = 0.013), lower baseline global longitudinal strain (HR: 0.61; 95% CI: 0.53–0.71; p < 0.001) and development of subclinical ATRCD at the end of anthracycline therapy (HR: 6.61; 95% CI: 2.60–16.82; p < 0.001). Cardiac surveillance at baseline and at ending of anthracycline therapy is essential to identify high-risk patients.

Plain language summary: Anthracyclines are drugs for treating many types of cancers. They may however be harmful to the heart. This anthracycline side effect will first cause subtle heart–cell injury that can be detected and treated if it is handled early. Therefore, this study aims to study patients in the Uganda Cancer Institute to find out how many patients can get and who are likely to get this side effect. We found that 35% of the patients had subtle heart–cell injury and 8.8% had a more severe form of heart–cell injury. The patients who lived with HIV, whose heart was weaker and who got subtle heart–cell injury immediately after treatment were more likely to get the severe form of the side effect. Patients who receive anthracycline therapy need to be monitored closely to prevent serious heart injury.

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Keywords: clinical anthracycline-related cardiac dysfunction • incidence • predictor • subclinical anthracycline therapy-related cardiac dysfunction

The economic and lifestyle transitions in sub-Saharan Africa have brought not only population growth and aging but also paradigm shifts of disease epidemiology from infectious diseases to non-communicable diseases including cancer [1]. The rising cancer burden in sub-Saharan Africa underlies the important role of anthracycline, which is still the chemotherapeutic drug class of choice for treating many cancers in the developing world [2]. In the Uganda Cancer Institute, more than half of the patients need anthracycline therapy [3].

Anthracyclines are a group of highly effective antineoplastic agents. Anthracycline therapy-related cardiac dysfunction (ATRCD) is the well-recognized and noxious cardiovascular side effect from this chemotherapy [4]. Proposed risk factors of ATRCD include patient-related risk factors such as increasing age, gender, Black race, postmenopausal status and pre-existing cardiac risk factors (e.g., hypertension, diabetes mellitus, smoking and coronary artery disease) [5–8]. Other risk factors of ATRCD are therapy-related, including use of combination cancer therapy (e.g., trastuzumab), addition of mediastinal irradiation and higher doses of anthracycline [5,9].

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Findings from the contemporary research suggest that anthracycline cardiotoxicity starts with asymptomatic subclinical myocardial cell damage that occurs before the declining in the left ventricular ejection fraction (LVEF) and the development of clinical heart failure [10,11]. Moreover, early detection and prompt therapy for cardiotoxicity appears crucial for the substantial recovery of cardiac function [10]. These findings imply the importance of cardiac monitoring and early treatment of anthracycline cardiotoxicity. Global longitudinal strain (GLS) by speckle tracking echocardiography (ECHO) and biomarkers (troponin-I) have been well studied and are recommended by current international guidelines as the diagnostic tools of subclinical ATRCD [12].

In the Uganda Cancer Institute, ECHO is performed on every patient who is planned for anthracycline therapy at the baseline. However, follow-up cardiac assessment is not done for the majority of the patients. This may make many patients with subclinical ATRCD go without detection of the disease and could lead to potential risk of overt heart failure later in life [11].

Detecting ATRCD at the subclinical stage will have a great impact on the long-term outcome of cancer survivors. Because of the lack of regular cardiac surveillance in Uganda, there is no data to reveal the burden and risk factors of subclinical and clinical ATRCD in the country. Therefore, there is no local protocol to guide the oncologists and cardiologists on monitoring and managing anthracycline cardiotoxicity effectively. We carried out this study to detect subclinical and clinical ATRCD using international guidelines, aiming to describe the incidence of ATRCD and identify the predictors of the disease 6 months after ending anthracycline therapy.

Materials & methods

This was a prospective cohort study that recruited cancer patients who were scheduled for anthracycline-based chemotherapy at the Uganda Cancer Institute.

The minimum number of participants required to determine the incidence of subclinical ATRCD was calculated using Kish Leslie's formula:

$$N = \frac{Z^2_{\alpha/2}\, p\,(1-p)}{d^2}$$

In the formula, Z_α is 1.96 for $\alpha = 0.05$, standard normal value at 5% two-tail level of significance; d is the tolerable sampling error (precision), 5%; p = 0.22 is the incidence of subclinical ATRCD among cancer patients in Boyd *et al.*'s study [13]; and N is the required sample size = 264. Considering loss to follow-up of 10% and early death, we increased the sample size to 355 patients. The minimum number of participants needed to investigated the predictors of subclinical ATRCD was calculated using Green's rule: N = 104 + K, where K is the number of independent variables. N is required sample size = 123. Therefore, the minimum number of patients required was determined by the larger sample size: 355.

The detailed description of the study design, patient selection and data collection have been published [14]. Briefly, between November 2018 and April 2021, 355 patients were recruited at the baseline (prechemotherapy). Among them, 207 patients completed anthracycline therapy and were followed up until 6 months after ending anthracycline therapy (Figure 1). At baseline, patients' demography, cancer profile and past medical history were recorded. Patients' symptoms, physical examinations, ECG, ECHO and laboratory data were collected at baseline, and two follow-up visits were conducted (end of anthracycline therapy and 6 months after ending anthracycline therapy).

Anthracycline & its administration

Nonliposomal doxorubicin (traditional formulation) was administered to the patients by slow intravenous infusion. Cumulative anthracycline dose was indexed by body surface area and recorded at the end of the chemotherapy.

Definition of subclinical ATRCD & clinical ATRCD

Subclinical ATRCD and clinical ATRCD were diagnosed using American Society of Echocardiography and the European Association of Cardiovascular Imaging criteria [12], outlined below.

Diagnostic criteria for subclinical ATRCD:

- LVEF ≥50% and a relative percentage decrease of GLS ≥15%, compared with baseline, and/or troponin-I becoming positive during follow-up.

Diagnostic criteria for clinical ATRCD:

- Decrease in LVEF of >10 percentage points, to a value of <50%.

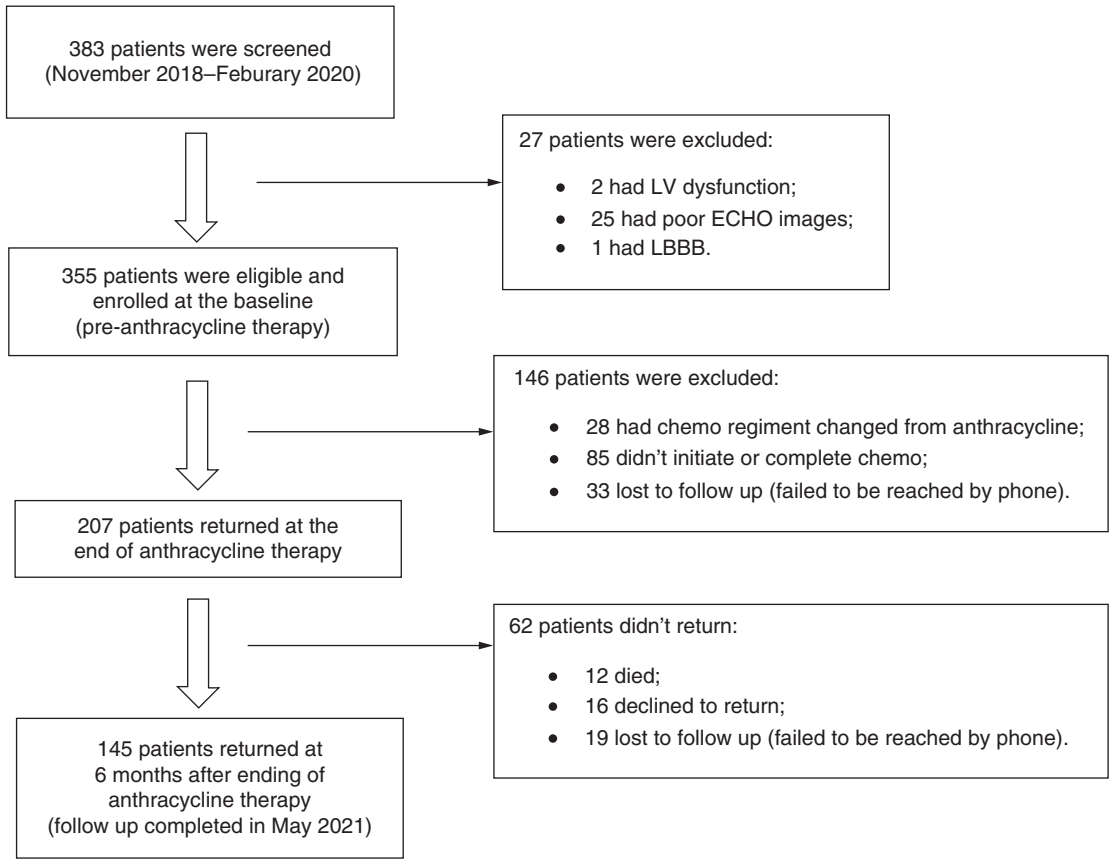

Figure 1. Patient flow chart. Between November 2018 and April 2021, 355 patients were recruited at the baseline (prechemotherapy). There were 207 patients who completed anthracycline therapy and returned for the second visit at the end of the anthracycline therapy. Among them, 145 patients came back for the third visit after 6 months, 27 patients died, 17 patients were last known alive and 19 patients were considered as lost to follow-up.
Chemo: Chemotherapy; ECHO: Echocardiography; LV: Left ventricle; LBBB: Left bundle branch block.

ECHO protocol & equipment

Transthoracic ECHO images were acquired using the Vivid E9® (GE Healthcare, KY, USA) ultrasonography machine by two cardiologists using a 1.5–4.6 MHz transducer (M5Sc). The assessment of all the conventional and speckle tracking ECHO parameters – including LVEF, stroke volume, cardiac index, mitral annular plane systolic exertion, mitral annular peak systolic velocities (S'), left ventricular global and regional longitudinal strain – are reported in the published baseline study [15].

To examine inter- and intra-observer reliability, we reassessed left ventricular longitudinal strain assessments in a random sample of ten patients. The intraclass correlation coefficients for inter- and intra-observer reliability were 0.93 and 0.91, respectively for left ventricular GLS assessments.

Statistical analysis

We analyzed the data using STATA v14 (Institute Inc., TX, USA). All continuous variables were expressed as a mean ± standard deviation and categorical variables as frequencies and percentages. Cumulative incidence of subclinical and clinical ATRCD were calculated using Aalen–Johansen estimator to take into account competing events. One-way analysis of variance (ANOVA) and Kruskal–Wallis test with *post hoc* analysis (2×2 comparison with Bonferroni correction) were used to compare the independent continuous variables. One-way repeated ANOVA with *post hoc* analysis (pairwise comparisons using Tukey's test) and Friedman's ANOVA with *post hoc* analysis (pairwise Wilcoxon signed-rank test) were used to compare dependent continuous variables, where appropriate. Chi-square test and Fisher's exact test were used to compare the categorical variables. To identify the predictors of subclinical and clinical ATRCD, hazard ratios (HRs) were calculated using competing risk regression with Fine–Gray modification. To control for the effect of the variables on the measures of association, all variables with a

Table 1. Patients' characteristics at the baseline and cancer profile.

Variable	Baseline (n = 207)
Age, medium (IQR)	42 (20–69)
Female, n (%)	178 (86.0)
Physical examination	
– BMI (kg/m^2), mean ± SD	25.25 ± 4.67
– SBP (mmHg), mean ± SD	130.18 ± 18.10
– DBP (mmHg), mean ± SD	77.27 ± 11.65
– SaO2 (%), mean ± SD	97.55 ± 1.88
ECOG performance status	
– 0, n (%) – 1, n (%) – 2, n (%)	179 (93.7) 8 (4.2) 4 (2.1)
Cardiovascular risk factors	
– Hypertension, n (%)	53 (25.6)
– Diabetes mellitus, n (%)	4 (1.9)
– Chronic kidney disease, n (%)	2 (1.0)
– HIV positive, n (%)	41 (19.8)
– Obesity, n (%)	17 (13.0)
– Alcohol use, n (%)	38 (18.4)
– Smoking	1 (0.5)
Cancer profile	
– Breast cancer, n (%)	162 (78.3)
– Non-Hodgkin's lymphoma, n (%)	15 (7.3)
– Hodgkin's lymphoma, n (%)	15 (7.3)
– Sarcomas, n (%)	15 (7.3)
– Stage 1, n (%)	27 (13.9)
– Stage 2, n (%)	37 (19.2)
– Stage 3, n (%)	92 (47.7)
– Stage 4, n (%)	37 (19.2)
– Cumulative dose of anthracycline, mg/m2 (mean ± SD)	309.06 ± 52.44

DBP: Diastolic blood pressure; ECOG: Eastern Cooperative Oncology Group; HR: Heart rate; IQR: Interquartile range; SaO2: Oxygen saturation; SBP: Systolic blood pressure; SD: Standard deviation.

p-value ≤ 0.2 were included in the multivariable model to predict subclinical ATRCD. A two-sided p-value < 0.05 was considered statistically significant for all analyses.

Results

In total, 207 patients enrolled at the baseline were able to complete anthracycline therapy and returned for the second visit at the end of the anthracycline therapy. Among them, 145 patients came back for the third visit after 6 months, 27 patients died, 17 patients were last known alive and 19 patients were considered as loss to follow-up (Figure 1). All the deaths were owing to cancer-related causes.

Patients' clinical characteristics

Among the 207 patient enrolled at the baseline, 178 (86.0%) were female, with a median (interquartile range) age of 42 (20–69) years. Patients' physical examination, Eastern Cooperative Oncology Group performance status, cardiovascular risk factors at the baseline and cancer profile are shown in Table 1. Breast cancer was the most commonly diagnosed cancer (162, 78.3%) in the group, followed by non-Hodgkin's lymphoma (15, 7.3%), Hodgkin's lymphoma (15, 7.3%) and sarcomas (15, 7.3%). Most patients were found to have stage 3 (47.7%) and stage 4 (19.2%) diseases.

Table 2 summarizes patients' laboratory, ECG, conventional and strain ECHO data at baseline and on each follow-up visit. During follow-up visits, there were significant reductions of hemoglobin, LVEF, mitral annular plane systolic exertion, tricuspid annular plane systolic exertion, stroke volume, GLS and all the regional longitudinal

Table 2. Patients' laboratory, ECG and echocardiographic data at each follow-up visit.

Variables (mean ± SD)	Baseline (n = 207)	2nd Visit (n = 207)	3rd Visit (n = 145)	p-value	*Post hoc* analysis					
					2nd visit versus baseline		3rd visit versus baseline		3rd visit versus 2nd visit	
					Mean difference	p-value†	Mean difference	p-value†	Mean difference	p-value†
Laboratory										
Hb (g/dl)	12.80 ± 1.93	11.95 ± 1.69	12.51 ± 1.66	**<0.001**	-0.86	**<0.001**	-0.28	0.159	0.57	**<0.001**
eGFR (ml/min/1.73m^2)	102.24 ± 30.62	102.99 ± 34.38	110.14 ± 36.01	0.2393						
Troponin-I (ng/ml)	0.09 ± 0.14	0.15 ± 0.19	0.18 ± 0.32	**0.005**	0.05	0.063	0.79	**0.006**	0.028	0.823
Electrocardiogram										
PR (ms)	153.01 ± 22.36	152.75 ± 20.54	153.78 ± 22.19	0.9399						
QTc (ms)	409.88 ± 29.70	409.83 ± 38.82	405.66 ± 35.65	0.1337						
Echocardiography										
LVEDV (ml)	67.50 ± 16.22	67.65 ± 17.58	70.08 ± 15.73	0.1366						
LVEF (%)	60.92 ± 5.78	57.54 ± 6.18	56.51 ± 8.55	**<0.001**	-3.42	**<0.001**	-4.17	**<0.001**	-0.75	0.634
TAPSE (mm)	24.51 ± 3.99	23.64 ± 4.22	22.99 ± 4.11	**0.0027**	-0.87	0.036	-1.63	**<0.001**	-0.76	0.169
MAPSE (mm)	14.67 ± 2.02	13.25 ± 2.07	13.19 ± 2.27	**<0.001**	-1.42	**<0.001**	-1.56	**<0.001**	-0.15	1
S' (mm)	9.54 ± 2.04	9.08 ± 2.06	8.97 ± 2.18	0.0017	-0.48	**0.006**	-0.51	**0.010**	-0.04	1
LVOT VTI (cm)	21.82 ± 4.14	19.54 ± 3.65	19.30 ± 4.08	**<0.001**	-2.38	**<0.001**	-2.58	**<0.001**	-0.2	1
SV (ml)	59.43 ± 15.76	49.71 ± 13.90	45.96 ± 13.67	**<0.001**	-9.77	**<0.001**	-13.2	**<0.001**	-3.43	0.017
CO (ml/min)	4.74 ± 1.32	4.08 ± 1.17	3.60 ± 1.08	**<0.001**	-0.69	**<0.001**	-1.07	**<0.001**	-0.38	**0.001**
Longitudinal strain										
GLS (%)	-20.90 ± 2.34	-19.60 ± 2.83	-18.75 ± 4.45	**<0.001**	-1.32	**<0.001**	-1.82	**<0.001**	-0.51	0.102
LAX (%)	-20.58 ± 3.11	-19.44 ± 3.40	-18.75 ± 3.74	**<0.001**	-1.17	**<0.001**	-1.79	**<0.001**	-0.62	0.175
A4C (%)	-20.48 ± 2.90	-19.29 ± 3.10	-18.50 ± 4.70	**<0.001**	-1.2	**<0.001**	-1.86	**<0.001**	-0.65	0.177
A2C (%)	-21.62 ± 2.99	-20.01 ± 3.10	-19.46 ± 3.72	**<0.001**	-1.6	**<0.001**	-2.09	**<0.001**	-0.49	0.266
Base (%)	-17.05 ± 2.68	-15.71 ± 2.95	-15.57 ± 3.36	**<0.001**	-1.36	**<0.001**	-1.64	**<0.001**	-0.28	0.838
Mid (%)	-20.11 ± 2.39	-18.94 ± 2.87	-18.55 ± 3.25	**<0.001**	-1.19	**<0.001**	-1.55	**<0.001**	-0.36	0.39
Apex (%)	-25.57 ± 3.80	-24.35 ± 4.27	-23.17 ± 4.41	**<0.001**	-1.24	**<0.001**	-2.05	**<0.001**	-0.8	0.092

The p-values that are statistically significant are highlighted in bold.
†p-value < 0.016 is considered significant.
A2C: Apical 2 chamber; A4C: Apical 4 chamber; CO: Cardiac output; eGFR: Estimated glomerular filtration rate; GLS: Global longitudinal strain; Hb: Hemoglobin; LAX: Apical long axis; LVEDV: Left ventricle end diastolic volume; LVEF: Left ventricle ejection fraction; LVOT VTI: Left ventricle outflow tract velocity time integral; MAPSE: Mitral annular plane systolic exertion; PR: PR interval; QTc: Corrected QT interval; S': Tissue Doppler peak systolic mitral annular velocity; SD: Standard deviation; SV: Stroke volume; TAPSE: Tricuspid annular plane systolic exertion.

strains. There was significant increase in trophonin-I. *Post hoc* analysis shows these significant changes mainly occurred comparing the second visit versus baseline and third visit versus baseline.

Incidence of ATRCD

The cumulative incidences of subclinical and clinical ATRCD at the end of anthracycline therapy were 25.1% (n = 52) and 2.9% (n = 6) respectively. The cumulative incidences of subclinical and clinical ATRCD at 6 months after ending anthracycline therapy were 35.0% (n = 69) and 8.8% (n = 16) respectively. The majority of the patients (75.3%) with subclinical ATRCD were diagnosed at the end of anthracycline therapy. Most of the patients (62.5%) with clinical ATRCD were diagnosed at 6 months after ending anthracycline therapy. All of the patients with subclinical ATRCD were free of heart failure symptoms. Only three of the 16 clinical ATRCD patients had heart failure symptoms. One of the symptomatic patients required hospitalization due to acute decompensated heart failure.

Most patients (56, 81.2%) with subclinical ATRCD were detected by GLS alone, eight (14.3%) patients were diagnosed by positive trophonin-I alone and five (7.2%) patients were diagnosed with subclinical ATRCD by both GLS and troponin-I.

Among the 52 the patients who were diagnosed with subclinical ATRCD at the second follow-up visit (end of the anthracycline therapy), 43 patients were able to come back for the third follow-up visit (6 months after ending

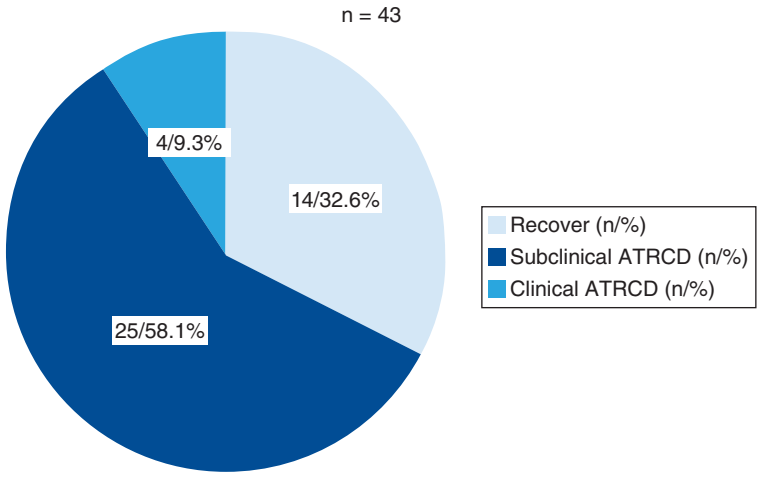

Figure 2. Outcome at 6 months after the end of anthracycline therapy for patients who were diagnosed with subclinical anthracycline therapy-related cardiac dysfunction. Among the 52 the patients who were diagnosed with subclinical ATRCD at the second follow-up visit (end of the anthracycline therapy), 43 patients were able to come back for the third follow-up visit (6 months after ending anthracycline therapy). At the third follow-up visit, 14/43 (32.6%) patients had full recovery of the global longitudinal strain and/or troponin-I, 25/43 (58.1%) patients still had subclinical ATRCD and 4/43 (9.3%) patients progressed to clinical ATRCD. ATRCD: Anthracycline therapy-related cardiac dysfunction.

anthracycline therapy). At the third follow-up visit, 14 of the 43 (32.6%) patients had full recovery of the GLS and/or troponin-I, 25 of the 43 (58.1%) patients still had subclinical ATRCD and 4 of the 43 (9.3%) patients progressed to clinical ATRCD (Figure 2.)

Supplementary Figure 1 shows the strain analysis for a case who received anthracycline. At the end of anthracycline therapy, the patient was diagnosed with subclinical ATRCD. At the follow-up 6 months after ending anthracycline therapy, the patient developed clinical ATRCD.

Predictors of ATRCD

Supplementary Table 1 shows the comparison of the variables among the three groups: patients who completed three study visits and were found to have normal cardiac function (no ATRCD, group 0), and patients who were diagnosed with subclinical (group 1) and clinical (group 2) ATRCD during follow-up visits. Following *post hoc* analysis, patients who were diagnosed with clinical ATRCD included a significantly higher proportion of patients who were HIV positive or had lower baseline LVEF and lower baseline GLS ($p < 0.016$). There were no differences regarding age, sex, physical examination, other cardiovascular risk factors, cancer type, stage, cumulative dose of anthracycline or chest radiation among the three groups.

At the end of follow-up, a lower LVEF and lower GLS than baseline was also observed in patients who did not develop subclinical or clinical ATRCD (LVEF from 60.9 ± 6% to 58.8 ± 7%; $p = 0.009$ and GLS from -20.9 ± 2% to -20.2 ± 2%; $p = 0.04$)

On univariable analysis for the predictors of subclinical ATRCD, female sex, alcohol consumption, breast cancer and cumulative anthracycline dose were found nearly not statistically significant ($p \approx 0.10$). However, no factor was found to predict subclinical ATRCD in the multivariable mode (Table 3). On univariable analysis, we found the development of clinical ATRCD associated with HIV positive status (HR = 3.04; 95% CI: 1.26–7.32; $p = 0.013$), lower baseline GLS (HR = 0.61; 95% CI: 0.53–0.71; $p < 0.001$), lower baseline mitral annular plane systolic exertion (HR = 0.72; 95% CI: 0.56–0.92; $p = 0.009$), lower baseline tissue Doppler mitral annular systolic velocity (HR = 0.72; 95% CI: 0.56–0.92; $p = 0.009$), lower baseline LVEF (HR = 0.78; 95% CI: 0.74–0.82; $p < 0.001$) and development of subclinical ATRCD at the end of anthracycline therapy (HR = 6.61; 95% CI: 2.60–16.82; $p < 0.001$; Table 3).

Discussion

In this cancer cohort which underwent anthracycline-based chemotherapy, for the first time in our setting, we implemented international cardiac surveillance recommendation. Patients were followed up to 6 months after ending anthracycline therapy, using GLS and trophonin-I as the tool of cardiac monitoring. We found a high cumulative incidence of subclinical ATRCD of 35.0% at 6 months after ending anthracycline therapy. The result is different from similar studies. In a cohort of 140 breast cancer patients, Boyd *et al.* reported that 22% patients were diagnosed with subclinical left ventricular dysfunction, defined by >11% reduction in GLS within 3 months of anthracycline therapy [13]. In another study, Negishi *et al.* followed up 159 anthracycline–trastuzumab-

Table 3. Predictors of developing anthracycline therapy-related cardiac dysfunction.

Predictor	Subclinical ATRCD				Clinical ATRCD	
	Univariable models		Multivariable model		Univariable models	
	Hazard ratio (95% CI)	p-value†	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value‡
Female	2.10 (0.89, 4.95)	**0.09**	1.73 (0.64, 4.71)	0.28	2.36 (0.31, 18.00)	0.408
Age, years	0.99 (0.98, 1.01)	0.607	0.98 (0.96, 1.01)	0.071	0.98 (0.94, 1.01)	0.162
Systolic BP, mmHg	0.99 (0.98, 1.01)	0.382			1.01 (0.99, 1.01)	0.189
Diastolic BP, mmHg	0.99 (0.97, 1.01)	0.342			1.04 (0.98, 1.01)	0.223
Hypertension	0.99 (0.62, 1.62)	0.994			1.57 (0.56, 4.37)	0.388
HIV positive	0.92 (0.52, 1.60)	0.757			3.04 (1.26, 7.32)	**0.013**
BMI	0.98 (0.94, 1.03)	0.527			1.06 (0.96, 1.18)	0.246
Taking alcohol	0.56 (0.29, 1.12)	**0.102**	0.60 (0.31, 1.16)	0.126	1.06 (0.30, 3.73)	0.326
Hemoglobin, g/dl	0.98 (0.87, 1.11)	0.789			1.28 (0.99, 1.64)	0.055
eGRF	0.99 (0.99, 1.00)	0.248			1.02 (0.99, 1.03)	0.24
Breast cancer	1.82 (0.95, 3.49)	**0.073**	1.13 (0.48, 2.61)	0.784	1.86 (0.43, 8.07)	0.405
Stage 3/4 disease	0.76 (0.49,1.19)	0.23			3.75 (0.88, 15.96)	0.074
Cumulative AT dose, mg/m^2	1.00 (0.99,1.01)	**0.138**	1.00 (0.99, 1.01)	0.177	1.01 (1.00, 1.02)	0.234
Left chest radiation	1.15 (0.65, 2.05)	0.632			0.64 (0.15, 2.66)	0.538
Right chest radiation	1.03 (0.28, 2.00)	0.253			0.34 (0.05, 2.46)	0.286
Baseline GLS	1.01 (0.98, 1.36)	0.769			0.61 (0.53, 0.71)	**<0.001**
Baseline MAPSE	1.01 (0.91, 1.11)	0.918			0.72 (0.56, 0.92)	**0.009**
Baseline S′	0.99 (0.89, 1.10)	0.886			0.74 (0.57, 0.97)	**0.030**
Impaired diastolic dysfunction	0.92 (0.57, 1.47)	0.722			1.11 (0.40, 3.12)	0.842
Baseline LVEF	1.03 (0.99, 1.07)	**0.051**	1.05 (0.89, 1.09)	0.086	0.78 (0.74, 0.82)	**<0.001**
Subclinical ATRCD at end of therapy					6.61 (2.60, 16.82)	**<0.001**

†p-values are highlighted in bold if less than 0.2.
‡p-values are highlighted in bold if less than 0.05.
AT: Anthracycline therapy; ATRCD: Anthracycline therapy-related cardiac dysfunction; BP: Blood pressure; eGFR: Estimated glomerular filtration rate; GLS: Global longitudinal strain; LVEF: Left ventricle ejection fraction; MAPSE: Mitral annular plane systolic exertion; S′: Tissue Doppler peak systolic mitral annular velocity.

treated patients [16]. At 7 months after completion of chemotherapy, 33% of patients were found to have a significant reduction (>11%) of GLS. Both studies [13,16] diagnosed subclinical anthracycline therapy-related cardiac dysfunction (ATRCD) by GLS alone, without troponin. Moreover, doxorubicin was the only cardiotoxic chemotherapy regimen received by our study patients. The different chemotherapy and diagnostic protocols and cutoffs of GLS value have contributed to different results among these studies and the present research.

The cumulative incidence of clinical ATRCD at 6 months after ending anthracycline therapy was 8.8%. This finding is similar with the result reported in the biggest cancer cohort by Cardinale and colleagues [10], who showed that the overall incidence of cardiotoxicity was 9% with the median follow-up of 5.2 years. They found that 98% of cases were diagnosed within the first year of ending anthracycline therapy. Given that patients in the present study were followed up to 6 months after anthracycline therapy, the 1-year cumulative incidence of clinical ATRCD could be higher in our study population than in Cardinale's study population.

Detection of subclinical ATRCD was made mainly by GLS alone in the present study. Only a few subclinical cases fulfilled troponin criteria, which is inconsistent with other registries [17]. This is most likely due to the troponin test used in our study, which was not an ultra-sensitive troponin test; therefore, it has a relatively lower sensitivity to detect cardiotoxicity.

Most of the patients (75.3%) with subclinical ATRCD were detected early (at the end of anthracycline therapy). In contrast, most of the patients (62.5%) with clinical ATRCD were diagnosed relatively late (at 6 months after ending anthracycline therapy) and four patients of the clinical ATRCD patients, who were diagnosed at the third visit, progressed from subclinical disease detected during the second visit. These observations underline that GLS reduction precedes left ventricular dysfunction in patients who later develop heart failure [18]. Strain abnormalities can be seen early despite preserved LVEF.

Consistent with other registries [10,17], all the patients who had subclinical ATRCD were asymptomatic for heart failure, and the rate of asymptomatic clinical ATRCD was high. In the large cancer cohort of the Cardinale group,

clinical cardiotoxicity occurred in 226 (9%) patients. Only 43 (19%) patients had moderate to severe heart failure symptoms (New York Heart Association class III–IV). The majority (183, 81%) were free of heart failure symptoms or had mild symptoms (New York Heart Association class II). All the patients who developed clinical cardiotoxicity were started on heart failure therapy, including angiotensin converting enzyme inhibitors and β-blockers. Full or partial LVEF recovery from cardiotoxicity were observed in 185 (82%) patients. Patients who did not recover were more symptomatic, less likely to achieve the target dose of heart failure therapy and associated with a worse cardiac outcome [10]. This reflects that the periodic cardiac monitoring leads to early detection and management of cardiotoxicity with easily available and affordable drugs, and therefore a better outcome.

At the end of follow-up, a lower LVEF and lower GLS than baseline was also observed in patients who did not develop subclinical or clinical ATRCD; the same trends have been observed in other studies [16,18–20]. This finding may imply there is still significant decline in myocardial contractility in patients who do not fulfill the criteria of ATRCD after anthracycline exposure. A longer follow-up period is needed to study the long-term trend of myocardial function after anthracycline exposure.

We identified some predictors of clinical ATRCD in univariable analysis, including being HIV positive, having lower baseline GLS and LVEF and having a diagnosis of subclinical ATRCD at the end of anthracycline therapy. Although the relationship between subclinical ATRCD and later development of clinical ATRCD risk is well-recognized [21–24], the association between HIV, baseline GLS, LVEF and cardiotoxicity development in adult patients has not been reported thus far.

We did not find any of the associations between baseline cardiovascular risk factors and the development of clinical disease that other researchers have reported [6–8]. However, we had previously found obesity was one of the most prevalent (13%) cardiovascular risk factors and associated with suboptimal (lower) baseline GLS (absolute GLS $\leq$18%) in the same cancer population [15]. Given that the present study showed the association between lower baseline GLS and the development of clinical ATRCD, we can still infer that obesity could be a predictor of ATRCD. In our study, even if the cumulative anthracycline dose appeared the highest in clinical ATRCD group and lowest in no cardiotoxicity group, the dose did not turn out to be a predictor of subclinical or clinical ATRCD. Elsewhere, ATRCD has been reported as dose-dependent [5]. We note that the relatively short follow-up period and the small event number for clinical ATRCD could have reduced the power of regression analysis; hence, it might have led to finding no associations between many of the factors and the outcome in the present study. A larger multicenter study with a longer follow-up period may be needed to further study the predictors of subclinical ATRCD and clinical ATRCD, particularly on cardiovascular risk factors and anthracycline doses in this population.

Limitations

At present, our study is the biggest anthracycline therapy cohort in Uganda. However, it has several limitations. First, being a single-center study, we included a population admitted to a single center. However, this center receives patients from all over Uganda, and there is therefore some national representation among population studied. Second, the high prevalence of women, driven by a high proportion of breast cancer patients in our study population, would limit the generalizability of our findings to the entire cancer population. Third, the COVID-19 pandemic posed a considerable challenge on patients' follow-up visits. Seventeen (8.2%) patients were not able or not willing to come back to the study site for a follow-up visit due to travel restrictions and the increased cost of traveling. Fourth, the ECHO observers were not blinded to patients' status – this could have led to potential bias. However, automatic software was used for the strain analysis and 2D LVEF measurement, which we think could have minimized the bias. Fifth, due to the relatively small number of clinical ATRCD events, the statistical power was reduced, and therefore a multivariable analysis to identify the independent predictors for clinical ATRCD was not performed. However, the one-way analysis of variance test and univariable analysis can still shed light on the independent predictors.

Conclusion

There is high cumulative incidence of ATRCD among Ugandan cancer patients. In this study, most of the patients who have ATRCD are detected at subclinical stage or asymptomatic clinical stage. Development of clinical ATRCD is associated with being HIV positive, having low baseline GLS or LVEF and having diagnosis of subclinical ATRCD at the end of anthracycline therapy. Therefore, cardiac surveillance at baseline and ending of anthracycline therapy is essential to identify patients at a high risk of developing clinical ATRCD in the future, particularly in HIV-

positive cancer patients. This can guide the establishment of local cardio-oncology guidelines in patients receiving anthracycline therapy, and an early start to pharmacological therapy could be considered.

Summary points

- Anthracycline-induced cardiotoxicity begins with subclinical myocardial cell injury, which can be detected by speckle tracking echocardiography imaging and the troponin level in the blood.
- In this cancer cohort which underwent anthracycline based chemotherapy, patients were followed up to 6 months after ending anthracycline therapy, using global longitudinal strain and trophonin-I as the major tools of cardiac monitoring.
- We found a high cumulative incidence of subclinical anthracycline therapy-related cardiac dysfunction (ATRCD) of 35.0% at 6 months after ending anthracycline therapy.
- The cumulative incidence of clinical ATRCD at 6 months of ending anthracycline therapy was 8.8%.
- Most of the patients who had ATRCD were detected at the subclinical stage or asymptomatic clinical stage.
- Development of clinical ATRCD is associated with being HIV positive, having a lower baseline global longitudinal strain or left ventricular ejection fraction and having diagnosis of subclinical ATRCD at the end of anthracycline therapy.
- Cardiac surveillance at baseline and ending of anthracycline therapy is essential to identify patients at a high risk of developing clinical ATRCD in the future, particularly in HIV-positive cancer patients.
- The results of the study can guide the establishment of local cardio-oncology guidelines in patients receiving anthracycline therapy, and an early start to pharmacological therapy could be considered.
- We did not find any of the associations between baseline cardiovascular risk factors, anthracycline doses and the development of ATRCD that other researchers have reported. A larger multicenter study with a longer follow-up period may be needed to further study the predictors of subclinical ATRCD and clinical ATRCD, particularly on cardiovascular risk factors and anthracycline doses in this population.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0116

Author contributions

W Zhang: substantial contributions to the conception and design of the work; the acquisition, analysis and interpretation of data for the work; drafting the work and revising it; final approval of the version to be published; agreement to be accountable for all aspects of the work. F Azibani: substantial contributions to the conception and design of the work; revising the work critically; final approval of the version to be published; agreement to be accountable for all aspects of the work. E Libhaber: substantial contributions to the analysis and interpretation of data for the work; revising the work critically; final approval of the version to be published; agreement to be accountable for all aspects of the work. I Ssinabulya: substantial contributions to the acquisition of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. J Leeta: substantial contributions to the acquisition of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. J Orem: substantial contributions to the conception of the work; revising the work critically; final approval of the version to be published; agreement to be accountable for all aspects of the work. K Sliwa: substantial contributions to the conception and design of the work and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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