

# Comparison of Patients' Phenotypes, Guideline-Directed Recommendations Compliance and Rates of Cardiotoxicity between Caribbean and United States Cardio-oncology Programs



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## ABSTRACT

**Background:** Little is known about the characteristics of oncological patients, cancer therapy-induced cardiotoxicity, and guidelines-directed interventions in the Caribbean; analysis of cardio-oncology services may shed light on this and clarify links between ethnicity, cultural, and local socioeconomic factors.

**Objectives:** This study compared patients' phenotypes, adherence to guidelines recommendations, and patterns of cardiotoxicity between two cardio-oncology programs: one in the Dominican Republic (DR) and the other in Chicago IL, United States (US).

**Methods:** Patients being considered for or treated with potentially cardiotoxic drugs were followed before, during, and after chemotherapy through both cardio-oncology clinics, where we recorded and compared clinical, demographic, and echocardiographic data.

**Results:** We studied 597 consecutive patients, 330 (55%) from the DR and 267 (45%) from the US. DR vs. US mean age  $55 \pm 13$  /  $52 \pm 13$  years; female 77 / 87% ( $p < 0.001$ ); breast cancer 57 / 73% ( $p < 0.001$ ); treated with anthracyclines + taxanes 47 / 40% ( $p = 0.151$ ); monoclonal antibodies + taxanes or platins 37 / 45% ( $p < 0.001$ ). Cardiotoxicity DR vs. US occurred in 15 / 7% ( $p = 0.001$ ); multivariate logistic regression (OR 2.29; 95% CI, 1.31–3.99;  $p < 0.005$ ) did not identify age  $>60$ , HTN, DM, BMI, tobacco or chemotherapy as predictors. Compliance with ASCO guidelines was similar among both cohorts.

**Conclusion:** Compared to the US cohort, the Caribbean cohort of cancer patients has similar rates of CV risk factors but a higher likelihood of developing drug-induced LV dysfunction. Programs' compliance with ASCO guidelines was equivalent. While further research is needed to ascertain regional variations of cardiotoxicity, these findings underline the relevance of cardio-oncology services in nations with limited resources and high CV risk.

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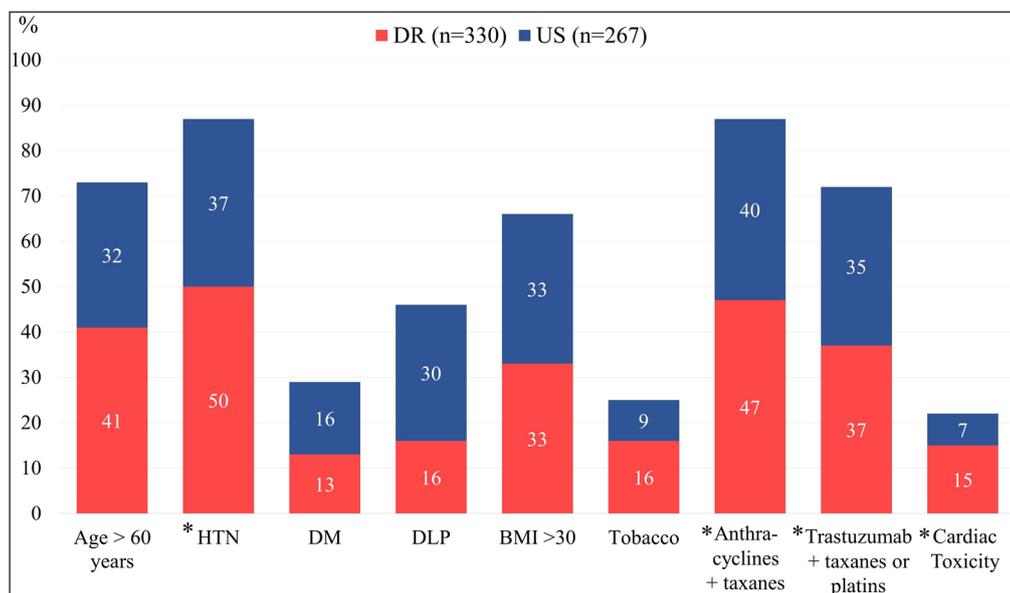


## RESULTS

From February 2016 to September 2019 a total of 597 consecutive patients were included, 330 (55%) from the DR cohort and 267 (45%) from the US cohort, who constituted the study group. Most referring providers (DR vs US 90 / 85%) were staff members of participating hospitals. Female gender was the most prevalent [254 (77%) / 232 (87%)] with a mean age of 54 years. Breast cancer was the most common amongst both cohorts. Risk factors for CTx and treatment combination of potentially cardiotoxic drugs were also analyzed, as shown in [Table 1](#).

The overall CTx rate was 15 / 7% ( $p < 0.001$ ): 31 (61%) / 12 (60%) had a reduction on EF  $>10\%$  to a value  $< 53\%$  plus a drop  $>15\%$  in GLS. In addition, 20 (39%) / 8 (40%) had a decline in GLS only, categorized as subclinical cardiotoxicity ([Figure 1: Central Illustration](#)). Signs and symptoms of heart failure were present in 3 / 2% of patients, and 1 / 1% required HF hospitalization. Multivariate logistic regression (OR 2.24; 95% CI, 1.28–3.91;  $p < 0.005$ ) did not identify age  $>60$ , HTN, DM, BMI, tobacco, or chemotherapy regimen as predictors of CTx, only DR ethnicity did ([Table 2](#)). At the first office visit, patients who developed CTx 4 / 0% had elevated blood pressure; otherwise, all other cardiovascular risk factors were controlled.

	DR (n = 330)	US (n = 267)	TOTAL (n = 597)	p
<b>Mean age – (yrs.)</b>	55 ± 13	52 ± 13	54 ± 13	
<b>Female gender – n (%)</b>	254 (77)	232 (87)	486 (81)	$p < 0.001$
<b>Type of cancer – n (%)</b>				
Breast cancer	189 (57)	195 (73)	384 (64)	$p < 0.001$
Colon cancer	36 (11)	0	36 (6)	$p < 0.001$
Non-Hodgkin's Lymphoma	11 (3)	22 (8)	33 (6)	$p < 0.005$
Lung cancer	20 (6)	3 (1)	23 (4)	$p < 0.005$
Hodgkin's Lymphoma	10 (3)	11 (4)	21 (4)	$p = 0.072$
<b>Cardiovascular risk factors – n (%)</b>				
HTN	166 (50)	98 (37)	264 (44)	$p < 0.005$
DM	44 (13)	44 (16)	88 (15)	$p = 0.163$
Smoking	53 (16)	25 (9)	78 (13)	$p < 0.001$
BMI $\geq 30$	108 (33)	87 (33)	195 (33)	$p = 0.524$
DLP	52 (16)	80 (30)	132 (22)	$p < 0.005$
$\geq 2$ risk factors	131 (39)	94 (35)	225 (38)	$p = 0.142$
<b>Treatment – n (%)</b>				
Cardioprotective drugs	160 (48)	114 (43)	274 (92)	$p = 0.095$
Radiotherapy	145 (44)	162 (61)	283 (47%)	$p = 0.001$
Treated with anthracyclines + taxanes	151 (47)	106 (40)	257 (87)	$p = 0.151$
Treated with monoclonal antibodies + taxanes or platins	124 (37)	122 (45)	246 (83)	$p < 0.001$
<b>Developed cardiotoxicity – n (%)</b>	51 (15)	20 (7)	71 (24)	$p < 0.001$



**Table 1** Baseline demographic and clinical characteristics of both cohorts.

BMI: body mass index, DLP: dyslipidemia, DM: diabetes mellitus, DR: Dominican Republic, HTN: hypertension, US: United States.

**Figure 1** Central Illustration. Cardiovascular risk factors and rate of cancer therapy-induced cardiotoxicity.

**Legend:** BMI: body mass index, DLP: dyslipidemia, DM: diabetes mellitus, DR: Dominican Republic, HTN: hypertension, US: United States. \*  $p < 0.001$ .

	ODDS RATIO	95% CI	CI	p
<b>DR/US</b>	2.24	1.28	3.91	<0.004
<b>Hypertension</b>	1.35	0.76	2.40	0.295
<b>Diabetes mellitus</b>	1.43	0.71	2.87	0.311
<b>BMI ≥ 30</b>	1.16	0.68	1.96	0.579
<b>Tobacco use</b>	0.97	0.46	2.02	0.937
<b>Age ≥ 60 years</b>	0.65	0.36	1.17	0.157
<b>Chemo: Anthracyclines + Taxanes</b>	1.48	0.87	2.52	0.142
<b>Chemo: Trastuzumab + Taxanes or Platins</b>	1.05	0.61	1.82	0.837

Adherence to ASCO was evaluated by accounting for established pre-treatment preventive strategies, including CV evaluation and a baseline echocardiogram, with 100% compliance found in both groups (Table 3). In addition, 48 / 43% (p = 0.095) of patients were already on cardioprotective drugs (Angiotensin-converting enzyme inhibitors, Calcium channel blockers, Beta-blockers, Statins) before chemotherapy.

RECOMMENDATIONS	DR	US	p
<b>Pre-treatment preventive strategies to reduce risk</b>	<b>n = 330 (%)</b>	<b>n = 267 (%)</b>	
Cardiovascular evaluation	330 (100)	267 (100)	p = 0.47
Echocardiogram	330 (100)	267 (100)	p = 0.47
Already on cardioprotective drugs	160 (48)	114 (43)	p = 0.095
<b>Management during cancer treatment</b>			
Follow-up echocardiogram	180 (54)	99 (37)	p =< 0.001
>1 echo during treatment	38 (12)	50 (19)	p = 0.009
Use of biomarkers	152 (46)	39 (18)	p =< 0.001
Developed cardiotoxicity	51 (15)	20 (7)	p =< 0.001
Cardio-oncology clinic follow up	180 (54)	99 (37)	p =< 0.001
<b>Monitoring after cancer treatment</b>			
Cardio-oncology clinic follow-up	180 (54)	99 (37)	p =< 0.001
Surveillance echocardiogram	180 (54)	99 (37)	p =< 0.001

During cancer treatment, 54 / 37% (p =< 0.001) of patients were seen in the cardio-oncology clinic, and they all had follow-up echocardiograms as determined by cardiotoxicity risk according to ASCO guidelines recommendations. The remaining patients either received follow-ups at other centers or did not attend their planned visits. Follow-up studies were obtained at a mean of three months; some patients (12 / 19% p = 0.009) had more than one study performed if symptoms developed. There was sub-utilization of biomarkers since they were 46 / 18% (p =< 0.001) of the cases. After cancer treatment, all follow-up patients underwent surveillance echocardiograms and subsequent clinic visits.

## DISCUSSION

The most important findings of this study, comparing to the US cohort are: 1) Caribbean cohort cancer patients have a similar prevalence of CV risk factors; 2) they have twice the likelihood of developing drug-induced LV dysfunction, even though many are already taking ‘cardioprotective’ therapies; and 3) local cardio-oncology programs can achieve similar rates of adherence to guidelines as in the US cohort.

We consider that cardiac evaluation based on ASCO recommendations in the Caribbean region remain suboptimal, as established cardio-oncology programs are scarce in the area. Although the published literature suggests that some progress has been made in this regard,

**Table 2** Multivariate logistic regression analysis for cancer therapy-induced cardiotoxicity.

BMI: body mass index, CI: confidence interval, DR: Dominican Republic, US: United States.

**Table 3** Adherence to American Society of Clinical Oncology Guidelines.

DR: Dominican Republic, US: United States.

implementation and compliance with protocols geared towards early detection of CTx is still a challenge in developing nations, often due to physician's adherence, access to health care, and patient's lack of awareness [7, 8–10].

Our findings are similar to those in the limited case series published in Spanish literature [8–10]. In Uruguay, Camejo et al. evaluated 69 breast cancer patients treated with trastuzumab, 27% of whom developed CTx (LVEF reduction >10% to a value <55%) in a mean time of 9 months [8]. In Argentina, Santos et al. studied 888 breast cancer subjects treated with trastuzumab and detected a decline in LVEF >10% in 35% of the cohort over a mean follow-up of 48±12 months [10]. Compared to our series, the CTx rates were higher in both reports; however, the more extended follow-up period in the Santos series may have influenced their results. No data on myocardial deformation was reported in these papers. In addition to the well-recognized inaccuracies of EF measurement by 2D-echo in determining CTx, definitive comparisons cannot be made due to the lack of standardization of CTx criteria [11].

Armenian et al., found that the presence of two or more CV risk factors bestowed the highest risk of CTx (IRR 1.83–2.59) to those affected by lung or breast cancer [12]. In contrast, our results did not identify age >60 years, HTN, DM, BMI, tobacco, or chemotherapy protocols as predictors of CTx. Although the DR cohort had more hypertensive patients and the US cohort used more trastuzumab-based chemotherapy regimens, none of these parameters were identified as predictors, and the highest risk of cardiotoxicity was conferred to patient ethnic origin, that is, DR over the US. Whether these findings result from genetic predisposition or cultural or demographic variations, their true explanation rests unclear, indicating the need for further population-based and translational research.

Even though 50% of patients in both cohorts were already using 'cardioprotective' drugs prescribed for other reasons before initiating chemotherapy (mainly angiotensin-converting enzyme inhibitors, calcium channel blockers, beta-blockers for HTN), DR patients again had twice the likelihood of developing CTx. The benefit of these drugs in cancer populations is a topic of ongoing investigation [13–16]. Likewise, the evaluation of recovered ejection fraction in patients with cardioprotective drugs and/or detention of chemotherapy regimens was not included in this research. There was a higher use of anthracycline-based protocols in the DR cohort, however, several questions are still unanswered: if selected dose chemotherapy regimen, BMI-adjusted dose, cumulative anthracycline dose, type of cancer mutation, cancer staging, or patient's adherence to cardioprotective drug therapy influenced the resulting LV dysfunction. Risk stratification protocols and preventive strategies need to be pursued between oncology and cardiology services in order to reduce the rate of cardiotoxicity in the DR cohort.

Dominican women included in this series had a higher prevalence of CV risk factors than men, an interesting find since recent local surveys in the DR have shown otherwise [5]. Additionally, the overall prevalence of such risk factors in our cohort was twice as high as reported figures in the US cohort; again, this underscores the need for population-based initiatives aimed at risk factors modification and control [17].

Lastly, although biomarkers and echocardiography utilization varied between the two centers, compliance with ASCO recommendations was similar, particularly in outpatient follow-up. In the DR cohort, fewer patients underwent echocardiographic monitoring during follow-up, even as the guidelines were strictly followed.

Cardiac troponin plasma concentrations can predict CTx in patients treated with anthracyclines and trastuzumab, and NT-proBNP has been recognized as an independent predictor of all-cause mortality in cancer patients [2, 18, 19]. Although the importance of measuring biomarkers periodically cannot be overemphasized, it remains uncertain if their use in conjunction with echocardiography constitutes a cost-effective approach in nations with limited resources.

We recognize that as most referrals came from within the institutions involved in the study, this may represent a selection bias since treating physicians were theoretically in more contact with the investigators, threatening the generalizability of the findings. The analysis of other severe adverse events like coronary artery disease, arrhythmia, or venous thromboembolism induced by chemotherapy were out of the scope of this investigation. Similarly, regimen doses, cumulative anthracyclines dose, and the association of cancer types and treatment protocols with cardiotoxicity were variables not included in this study. We understand our results comprise



