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HFA-ICOS Risk Stratification for Trastuzumab-Related Cardiac Dysfunction in HER2- Positive Breast Cancer: A Cohort Study from Saudi Arabia

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Abstract

Background

Cancer survival rates have improved substantially with advances in cancer therapy; however, treatment-related cardiotoxicity has become a growing concern. Cancer therapy-related cardiac dysfunction (CTRCD) is a recognized adverse effect of anti-HER2 therapies, including trastuzumab. The Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) risk stratification tool was developed to predict CTRCD risk and guide clinical management. This study assessed the correlation between HFA-ICOS risk stratification and CTRCD incidence in patients receiving trastuzumab therapy at a tertiary care hospital in Saudi Arabia, and the overall incidence of CTRCD in this population.

Methods

This retrospective cohort study included 369 adult patients who received trastuzumab therapy at King Fahad Specialist Hospital, Dammam, from January to December 2023. HFA-ICOS risk scores were calculated at baseline, and CTRCD was assessed via serial echocardiography over 3–12 months. Associations between risk category and CTRCD were analyzed using Chi-square and Fisher's exact tests.

Results

Among 369 patients (mean age 53 ± 11 years; 96.7% female), baseline HFA-ICOS risk stratification classified 57.7% as low risk, 21.1% as medium, 14.6% as high, and 6.5% as very high risk. Overall CTRCD incidence was 10.6% (39/369). CTRCD prevalence increased sharply with risk category: 5.2% in low-risk, 5.1% in medium-risk, 18.5% in high-risk, and 58.3% in very high-risk patients (OR 25.71, 95% CI 9.33–70.82 for very high vs. low risk; $p < 0.001$). Diabetes mellitus (35.9% vs. 18.2%, $p = 0.04$) and hypertension (43.6% vs. 24.8%, $p = 0.018$) were significantly more common among patients who developed CTRCD. Seven patients (1.9%) developed clinically overt heart failure, of whom only one also met CTRCD criteria.

Conclusion

The HFA-ICOS risk stratification tool effectively predicts CTRCD risk in patients receiving trastuzumab therapy, with incidence rising sharply from low to very high-risk categories. These findings support risk-based cardiac surveillance strategies and highlight diabetes and hypertension as modifiable comorbidities warranting closer monitoring in high-risk patients.

Background

Cancer therapy-related cardiac dysfunction (CTRCD) is a recognized adverse effect of anti-HER2 therapies, including trastuzumab, and has become a growing focus within the emerging field of cardio-oncology as cancer survival has improved (1, 2) (3). CTRCD is defined by the 2022 ESC cardio-oncology guidelines based on LVEF, global longitudinal strain, cardiac biomarkers, and clinical criteria, varying between symptomatic and asymptomatic presentations (Fig. 1) (4).

CTRCD emerged as a clinical concern following the introduction of HER2-targeted therapy in 1988 (5). Unlike anthracyclines, which cause dose-dependent (Type 1) cardiotoxicity through direct cardiomyocyte injury, HER2 antagonists cause a dose-independent (Type 2) cardiotoxicity that is typically reversible, with asymptomatic LVEF decline occurring in up to 50% of patients (6) (7). A recent cohort study reported an overall CTRCD incidence of 8.7% (95% CI: 6.4%-11.5%) and incident heart failure in 1.6% among trastuzumab-treated patients, with lower rates of 6.3% and 0.9% among those not also receiving anthracyclines (8). These findings are broadly consistent with pooled trial data and real-world cohorts (9) (10), and with a separate study reporting asymptomatic LVEF decline in 9.4% of patients (11).

Several risk stratification approaches have been proposed, though most are limited to specific cancer subsets. The Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) tool, developed in 2020, stratifies patients into low, medium, high, or very high risk of CTRCD based on cardiovascular history, risk factors, biomarkers, age, and prior cardiotoxic treatment, and is endorsed by the European Society of Cardiology (Class IIa, Level of Evidence C) (12) (13).

Breast cancer is the most common malignancy in Saudi Arabia, comprising 17.3% of cases nationally and up to 20.7% regionally in the Eastern Province (14) (15). A recent systematic review identified 11 external validations of HFA-ICOS internationally, five in HER2-targeted breast cancer populations, but none in a Saudi Arabian or Gulf cohort (16). King Fahad Specialist Hospital in Dammam is a tertiary and quaternary oncology center that serves a catchment population of 2.1 million. This study assessed the performance of the HFA-ICOS score in predicting

CTRCD among patients treated with trastuzumab at this center, extending the tool's evidence base to a population not previously represented in the literature.

Methods

Objectives

The objective of this study is to assess the correlation between higher risk groups, as predetermined by the HFA-ICOS score, and the incidence of CTRCD. More specifically, this study aims to:

- Determine the proportion of patients on anti-HER2 therapy classified as very high risk for CTRCD by the ICOS-HFA calculator.
- Assess how well the risk stratification tool correlates with the actual development of CTRCD.
- Measure the total incidence of CTRCD among patients receiving anti-HER2 therapy.

Study Design

This study is a retrospective observational cohort study that examines consecutive patients who received Trastuzumab therapy from January 1, 2023, to December 31, 2023. The study was conducted at a single tertiary oncology center at King Fahad Specialist Hospital. Data were obtained from the hospital's electronic medical records.

Patient Population

The inclusion criteria for this study were all adult patients receiving Trastuzumab during the specified time period. The exclusion criteria included patients below the age of 18, those who did not receive HER2 antagonists, and those who received HER2 antagonists outside the specified time frame. Male patients with breast cancer were eligible for inclusion.

A total of 369 patients were included in the study. Baseline patient demographics and comorbidities were assessed, and the HFA-ICOS score was calculated for each participant. The data comprised patient characteristics such as age, gender, history of diabetes, hypertension, dyslipidemia, prior cardiomyopathy or heart failure, coronary ischemic disease, history of chronic kidney disease (CKD), and smoking history. These baseline characteristics were inputted into the HFA-ICOS calculator, which stratified patients into low, medium, high, or very high risk groups.

Follow-up for the incidence of CTRCD was assessed via serial transthoracic echocardiograms after the administration of Trastuzumab. Follow-up time varied, ranging from 3 months to 12 months post-treatment. This variability occurred because patients started therapy at different times throughout 2023, but data were collected during the same period (from February to March 2024).

Outcome Measures

The primary outcome measure in this study is the incidence of CTRCD and its correlation with the risk stratification group, as classified by the ICOS-HFA score.

Statistical Analysis

Statistical analyses were performed using SPSS version 25. Categorical variables were summarized as frequencies and percentages, and continuous variables as mean ± standard deviation. Group comparisons were conducted using chi-square or Fisher's exact tests as appropriate, and z-scores were used to assess the strength of association between risk stratification and CTRCD. A p-value of less than 0.05 was considered statistically significant. AI-assisted tools (Claude, Anthropic) were used during manuscript preparation to support language refinement and formatting; all scientific content, analysis, and conclusions are the authors' own.

Ethics Approval

This retrospective observational cohort study was approved by the Institutional Review Board (IRB) of King Fahad Specialist Hospital, Dammam, Saudi Arabia (approval number: CAR0003). All patient data were anonymized prior to analysis, with medical record numbers blinded to the research team to ensure that patient information remained unidentifiable.

Consent

Individual informed consent was waived by the Institutional Review Board of King Fahad Specialist Hospital, Dammam (approval number: CAR0003), given the retrospective, fully anonymized nature of the data, with medical record numbers blinded to ensure patient unidentifiability.

Results

Table 1 presents an analysis of various demographic, comorbidity, and clinical characteristics of patients who developed CTRCD (Yes, n = 39) versus those who did not (No, n = 330). In terms of comorbidities, Diabetes Mellitus and Hypertension were significantly associated with CTRCD. The prevalence of Diabetes was notably higher in the CTRCD group (35.9% vs. 18.2%, p = 0.04), and similarly, Hypertension was more common in the CTRCD group (43.6% vs. 24.8%, p = 0.018). However, Dyslipidemia (p = 0.66) and chronic kidney disease (p = 0.59) did not exhibit significant differences between the two groups.

Regarding risk factors, there were no significant differences in the prevalence of Obesity (35.9% vs. 33.0%, p = 0.74) or Smoking (0% vs. 1.2%, p = 1.00). In terms of cardiovascular conditions, Heart Failure, Myocardial Infarction, CMP, PCI, and Arrhythmia did not show significant differences, with p-values ranging from 0.30 to 1.00, indicating no strong association between these conditions and the development of CTRCD.

Table 1
Characteristics of Study Participants

Variables	Total (N = 369)	CTRCD Yes (n = 39)	CTRCD No (n = 330)	p-value
Gender				
Female	357 (96.7%)	38 (97.4%)	319 (96.7%)	0.59
Male	12 (3.3%)	1 (2.6%)	11 (3.3%)	
Age (Mean ± SD)	53.1 ± 11.0	52.0 ± 9.6	53.0 ± 11.0	0.0013*
Age (Median, IQR)	52 (45, 60)	51 (45, 58)	53 (46, 60)	0.0010*
Comorbidities				
Diabetes Mellitus (DM)	74 (20.1%)	14 (35.9%)	60 (18.2%)	0.04*
Hypertension (HTN)	99 (26.8%)	17 (43.6%)	82 (24.8%)	0.018*
Dyslipidemia (DLP)	40 (10.8%)	5 (12.8%)	35 (10.6%)	0.66
Chronic Kidney Disease (CKD)	14 (3.8%)	2 (5.1%)	12 (3.6%)	0.59
Risk Factors				
Obesity	123 (33.3%)	14 (35.9%)	109 (33.0%)	0.74
Smoking	4 (1.1%)	0 (0%)	4 (1.2%)	1.00
Cardiovascular Conditions				
Heart Failure (HF)	7 (1.9%)	1 (2.6%)	6 (1.8%)	0.30
Myocardial Infarction (MI)	4 (1.1%)	1 (2.6%)	3 (0.9%)	0.35
CMP	7 (1.9%)	0 (0%)	7 (2.1%)	1.00
PCI	5 (1.4%)	0 (0%)	5 (1.5%)	1.00
Arrhythmia	5 (1.4%)	1 (2.6%)	4 (1.2%)	0.40

The p-values were computed using Chi-square for categorical variables, and t-test for continuous variables

Table 2 reveals that as risk increases, so does age, with the mean age rising from 49.7 years in the Low-risk group to 63.0 years in the High-risk group. The prevalence of comorbidities, such as Diabetes, Hypertension, Dyslipidemia, and chronic kidney disease (CKD), also increases with higher risk. Smoking is most common in the Medium-risk group, while obesity is highest in both the Medium and Very High-risk groups. The prevalence of Heart Failure and Coronary Artery Disease is more prominent in the High and Very High-risk groups. Comparisons across risk groups were performed using the Chi-square test; where expected cell frequencies were less than 5, Fisher's exact test was used instead (indicated by † in Table 2).

Table 2
Patient Characteristics and Risk Stratification

Risk Category	N	Age	Female (%)	Diabetes (%)	Hypertension (%)	Dyslipidemia (%)	CKD (%)	Smoker (%)	Obesity (%)	Heart Failure (%)	Coronary Artery Disease (%)
Low Risk	213	49.7	97.7	8.0	12.2	4.2	1.4	0.0	24.4	0.0	0.0
Medium Risk	78	55.5	93.5	29.9	37.7	7.8	1.3	3.9	41.6	1.3	1.3
High Risk	54	63.0	98.1	51.9	64.8	37.0	14.8	0.0	50.0	5.6	9.3
Very High Risk	24	54.4	88.5	24.4	37.1	20.8	8.3	4.2	50.0	12.5	6.3
P-value*				< 0.001	< 0.001	< 0.001†	0.0006†	0.033†	0.0002	0.0008†	0.0011†

Table 3 shows a strong graded association between baseline risk category and CTRCD development. In the Low-risk group (N = 213), 11 patients developed CTRCD (5.2%), compared to 4 of 78 (5.1%) in the Medium-risk group, 10 of 54 (18.5%) in the High-risk group, and 14 of 24 (58.3%) in the Very High-risk group. Group-level z-scores indicate this association is highly significant for the Low, Medium, and High-risk categories ($p < 0.001$ for each), but not for Very High risk considered alone ($p = 0.117$), reflecting the small sample size at this tier rather than an absence of effect. To quantify the size of this association, odds ratios (relative to Low-risk as reference) are also reported in Table 3 (calculated from a model including risk category alone, since age is already an intrinsic component of HFA-ICOS scoring and gender showed insufficient variability in this cohort for stable estimation): Medium-risk carried no additional risk (OR 0.99, 95% CI 0.31–3.21), whereas High-risk (OR 4.17, 95% CI 1.67–10.43) and Very High-risk (OR 25.71, 95% CI 9.33–70.82) carried substantially and significantly elevated risk. The near-identical prevalence between Low- and Medium-risk patients suggests these two categories could potentially be merged for surveillance purposes, while the markedly elevated risk in the High and Very High-risk groups points to a clear need for closer cardiac monitoring.

Table 3
Analysis of HFA-ICOS Risk Stratification and CTRCD

		CTRCD		*z-score* (p-value)	OR (95% CI)
		Yes	No		
Risk Stratification	Low	11	202	-12.78 (.000001)	Reference
	Medium	4	74	-7.81 (.000000)	0.99 (0.31–3.21)
	High	10	44	-4.49 (.000001)	4.17 (1.67–10.43)
	Very High	14	10	0.61 (.1168999)	25.71 (9.33–70.82)

Figure 2 gives visual form to a pattern the numbers alone can understate: CTRCD risk does not climb gradually across the four HFA-ICOS categories, but stays essentially flat through low and medium risk before rising steeply beyond the medium-risk threshold, more than tripling at each successive step. In practical terms, the tool's real strength lies in its upper tiers, where it identifies a relatively small group of patients, roughly one in five in this cohort, who carry a disproportionate share of the cardiotoxicity burden. The wider confidence intervals at the high and very high-risk categories are a reminder that these estimates rest on fewer patients, and larger, multi-center cohorts would sharpen them further.

The univariate and multivariate logistic regression analyses reveal that Hypertension (HTN) is a significant predictor, with the multivariate analysis showing a 2.57-fold increase in the odds of CTRCD among hypertensive patients as shown in Table 4. Cardiomyopathy (CMP) also remains a strong predictor, with an odds ratio of 49.17, indicating a high likelihood of CTRCD in patients with this condition, even after adjusting for other variables. Risk stratification also remained an independent predictor after adjustment for comorbidities; see Table 3 for the risk-category-specific analysis. While heart failure (HF) and chronic kidney disease (CKD) exhibit strong associations in univariate analysis, they lose significance in the multivariate model, suggesting their effects may be influenced by other variables in the dataset. Overall, the findings underscore the importance of hypertension, cardiomyopathy, and high-risk stratification as the primary predictors of CTRCD, while highlighting the potential confounding effects of other conditions like HF and CKD.

In addition to CTRCD, seven patients (1.9%) developed clinically overt heart failure during follow-up. Of these, only one (14.3%) also met criteria for CTRCD, while the remaining six (85.7%) developed heart failure in the absence of formally defined CTRCD. Given the small number of

events, a risk-stratified analysis of heart failure incidence was not performed. This rate is comparable to a recent contemporary cohort study, which reported an incident heart failure rate of 1.6% among trastuzumab-treated patients (8).

Table 4
Univariate and Multivariate logistic regression analyses

Predictor	Univariate Analysis (OR [95% CI])	p-value	Multivariate Analysis (OR [95% CI])	p-value
Demographics				
Age_category (> 50)	1.25 [0.82–1.91]	0.298	-	-
Comorbidities				
DM	1.43 [0.66–3.12]	0.359	-	-
HTN	1.83 [0.92–3.65]	0.086	2.57 [1.02–6.48]	0.046*
DLP	0.93 [0.31–2.82]	0.901	-	-
CKD	3.66 [1.09–12.29]	0.036*	2.47 [0.53–11.49]	0.25
Obesity	1.28 [0.64–2.57]	0.473	-	-
Cardiac History				
HF	12.46 [3.36–46.19]	0.001*	2.71 [0.29–25.04]	0.378
CMP	59.86 [8.61-416.18]	< 0.001*	49.17 [5.12-471.94]	0.001*
Risk Factors				
RiskStratification_HIGHRISK	4.32 [1.87–9.98]	< 0.001*	3.85 [1.42–10.45]	0.008*

Discussion

A recent systematic review and meta-analysis pooling 11 external validations of the HFA-ICOS tool found that it consistently underestimates cardiotoxicity risk, with a pooled C-statistic of only 0.60 (95% CI 0.52–0.68) among HER2-targeted breast cancer populations (16). Observed event rates in that analysis were 12% in low-risk, 15% in medium-risk, 25% in high-risk, and 41% in very high-risk patients, all well above the tool's predicted thresholds of less than 2%, 2 to 9%, 10 to 19%, and 20% or more. Our findings both align with and extend this pattern. In the low, medium, and high-risk groups, the CTRCD rates we observed (5.2%, 5.1%, and 18.5%) were closer to the tool's predicted ranges than the pooled international estimates, suggesting the tool is better calibrated in this population at low to moderate risk. In the very high-risk group, however, our cohort showed a larger gap between predicted and observed risk than the pooled estimate. We observed 58.3% against a predicted threshold of 20% or more, compared with a pooled rate of 41%. This suggests that HFA-ICOS underestimates risk most, and with the greatest clinical consequence, at the extreme end of the risk spectrum. A recent cross-sectional study examined how HFA-ICOS classified risk in a Cameroonian breast cancer population, but it described baseline risk categories and their correlates rather than testing the tool's ability to predict observed CTRCD outcomes (17). Our study adds to this literature by combining risk stratification with structured follow-up and formal outcome validation in patients treated with trastuzumab for HER2-positive disease, the population in which HFA-ICOS has been studied most.

The results of this retrospective study highlighted a significant positive correlation between higher risk strata, as determined by the ICOS-HFA risk assessment score, and the incidence of CTRCD in patients receiving HER2 antagonists, thereby validating its use as a predictive tool for identifying patients at increased risk. Moreover, although the mechanisms underlying Trastuzumab-induced cardiotoxicity are unclear, it supports the hypothesis that HER2 antagonists may exert toxicity on cardiomyocytes. Despite the fact that the vast majority of the patient cohort were classified as the low-risk group based on the HFA-ICOS score, they had the lowest overall incidence of CTRCD. On the contrary, the very high-risk category, who had a smaller proportion of the total number of patients, had a strikingly high incidence of CTRCD upon follow-up, with 58% of the patients developing the complication. In this subgroup, the use of HER-2 antagonists potentially worsened myocardial damage, posing the higher incidence of CTRCD.

Various similar studies in the literature were conducted to validate the use of the HFA-ICOS score in predicting the incidence of CTRCD. A retrospective single centre observational study by Di Lisi et al. was carried out on 58 patients who had CML treated with TKIs for a median period of 43 +/- 31 months (18). The primary aim of this study was to evaluate the usefulness of the new HFA-ICOS risk assessment model compared to the Systematic Coronary Risk Evaluation (SCORE) charts of the European Society of Cardiology (ESC) in stratifying patients based on their risk of developing cardiotoxicity. Results showed that the HFA-ICOS risk assessment score was significantly more sensitive ($P < 0.01$) in identifying patients at higher risk of cardiotoxicity. A nomogram-based model for CTRCD prediction in HER2-positive breast cancer has similarly been proposed as an alternative individualized risk-assessment approach (19). Another retrospective study by Parra et al. evaluated

the effectiveness of the tool in identifying HER2 positive metastatic breast cancer patients at high risk for cardiotoxicity (20). Findings revealed a significant correlation between the very high-risk strata and the incidence of cardiotoxicity, with no significant difference in the incidence of cardiotoxicity between the high, medium, and low risk groups. Additionally, Tini et al. showed the validity of the risk assessment score in preventing adverse cardiovascular events in breast cancer patients, as it allowed for cancer treatment modification according to their allocated strata (21). Moreover, patients who were stratified as medium-to-high risk based on HFA/ICOS were more likely to receive cardioactive therapies.

Even though the HFA-ICOS risk assessment score incorporates various risk factors, some have been studied more extensively in the context of anti-HER2 therapy induced cardiotoxicity. One significant risk factor for CTRCD progression is elevated baseline cardiac troponins (cTn), considering its high specificity for cardiac injury and cardiomyocyte necrosis (22). One large study showed the role of cTnT and cTnI in predicting the likelihood of cardiac dysfunction in patients which showed that increased levels at baseline was associated with a 4-fold increased risk (23). Baseline left ventricular ejection fraction (LVEF) is an important factor in risk assessment for CTRCD. While LVEF remains a cornerstone of cardiac evaluation, its efficacy is typically enhanced when paired with additional echocardiographic variables to improve the sensitivity of risk prediction models (24). Additionally, conditions such as hypotension, renal impairment, infections, or systemic illnesses tend to confound cardiac biomarker findings by falsely elevating them. Nonetheless, troponins remain a valuable marker that helps predict incidence of CTRCD. Other risk factors that show a promising predictive value include baseline LVEF, cumulative concurrent anthracycline dose, and cardiovascular comorbidities, all of which warrant further investigation to better elucidate their roles in the development of cardiotoxicity.

Several limitations merit mention. Follow-up duration depended on when patients started trastuzumab, so later enrollees may not have had time for cardiotoxicity to develop before data collection, a length bias reported elsewhere too: Bouwer and colleagues found a median follow-up of 15 months (IQR 8–31) after trastuzumab (25), versus at least three months for most of our cohort. Even low-risk patients showed a residual CTRCD incidence of 5.2%, suggesting HFA-ICOS does not capture every contributing factor. Heart failure and CTRCD also overlapped only modestly, with just one of seven heart failure cases meeting CTRCD criteria, hinting at partially distinct mechanisms, given the small event count. Finally, we did not stratify by concomitant anthracycline exposure. Randomized trials with protocolized, limited dosing, including the NOAH trial (26–28) and Shen et al. (29), found concurrent trastuzumab-anthracycline well tolerated; real-world evidence, including a recent cohort, tells a different story, linking combined exposure to substantially higher CTRCD and heart failure rates (8). Differences in cumulative dose and monitoring intensity, rather than concurrent use itself, likely explain this gap (30, 31), an unaddressed confounder in our analysis Biomarker-based assessment (BNP, troponin) and strain-based imaging (global longitudinal strain) were not systematically incorporated into our CTRCD ascertainment; future studies should evaluate whether incorporating these measures alongside HFA-ICOS improves risk discrimination, particularly at the extremes of the risk spectrum.

Declarations

Ethics approval and consent to participate

This retrospective observational cohort study was approved by the Institutional Review Board (IRB) of King Fahad Specialist Hospital, Dammam, Saudi Arabia (approval number: CAR0003). Individual informed consent was waived by the same IRB given the retrospective, fully anonymized nature of the data, with medical record numbers blinded to ensure patient unidentifiability.

Consent for publication

Not applicable.

Clinical trial number

Clinical trial number: not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

MA conceived and designed the study, supervised its conduct, and drafted the original manuscript. SEMBE contributed to patient investigation. MAA and IAA contributed to data curation and patient investigation. MT and SM contributed to draft review and data curation. MBM performed the statistical analysis and critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data underlying this article were derived from institutional patient records at King Fahad Specialist Hospital, Dammam, and are not publicly available due to patient privacy and institutional data protection policies. All data were fully anonymized prior to analysis. De-identified data may be made available by the corresponding author upon reasonable request, subject to institutional approval.

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Figures

CTRCD		
Symptomatic CTRCD (HF)[a,b]	Very severe	HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation
	Severe	HF hospitalization
	Moderate	Need for outpatient intensification of diuretic and HF therapy
	Mild	Mild HF symptoms, no intensification of therapy required
Asymptomatic CTRCD	Severe	New LVEF reduction to <40%
	Moderate	New LVEF reduction by ≥10 percentage points to an LVEF of 40–49% *OR* New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND either new relative decline in GLS by >15% from baseline OR new rise in cardiac biomarkers[c]
	Mild	LVEF ≥ ***50%*** AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers[c]

Figure 1

Definition of CTRCD as per the 2022 cardio-oncology guidelines (4)

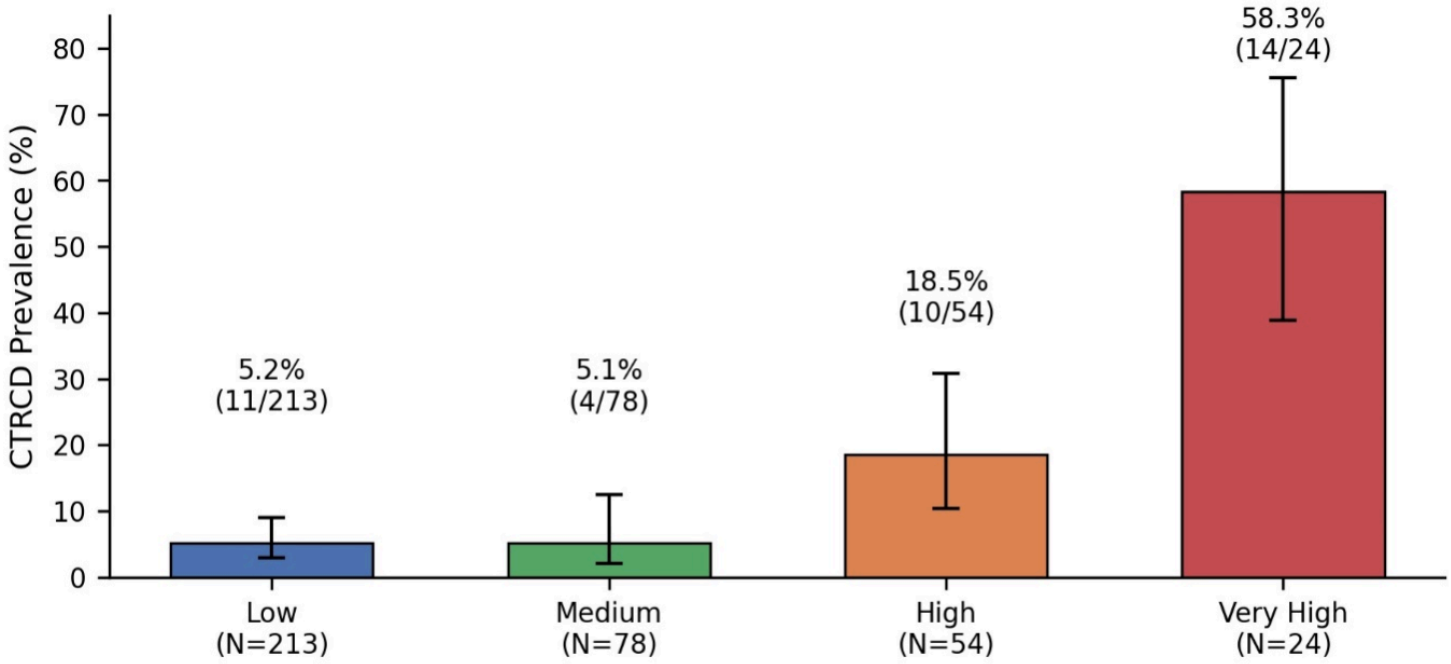


Figure 2

Prevalence of CTRCD by risk Category