

# **Evaluation of Risk Prediction Models to Identify Cancer Therapeutics Related Cardiac Dysfunction in Women with HER2+ Breast Cancer**

## **Supplementary Materials**

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**Supplemental Table S1.** Descriptions of the individual cardiotoxicity risk prediction models.

Risk Scores (Publication Year)	Total (n)	Score Components	Outcome/ Ascertainment	Internal Validation	External validation	Incidence of CTRCD in derivation cohort	Low Risk	Medium Risk	High Risk
<b>Romond et al./NSABP-31 (2012)</b>	947	Age LVEF Score = $[(7.0 + (0.04 \times \text{Age in years}) - (0.1 \times \text{Baseline LVEF})) \times 100] / (4.76)$	7-year Cardiac death or HF symptoms + LVEF decline (>10% decline to <55%, or >5% decline to below lower limit of normal) (MUGA)	Bootstrapping	No	Patients were not categorized into risk groups*	N/A	N/A	N/A
<b>Ezaz et al., (2014)</b>	1664	Age 67-74 = 0 points 75-79 = 1 points 80-94 = 2 points No chemotherapy = 0 points Non-anthracycline = 2 points Anthracycline = 2 points Diabetes mellitus = 1 point Hypertension = 1 point Coronary artery disease = 2 points Atrial Fibrillation/Flutter = 2 points Renal Failure = 2 points	3-year HF or cardiomyopathy/ ICD codes from administrative health data	Split sample (n=832)	No	Low risk n = 595 (72%), CTRCD in 86 (14.5%)  Medium risk n = 195 (23%), CTRCD in 51 (26.2%)  High risk n = 42 (5%), CTRCD in 18 (42.9%)	Cumulative 0-3 points = Low risk	Cumulative 4-5 points = Medium risk	Cumulative 6+ points = High risk
<b>HFA-ICOS Proformas (2020)</b>	Expert consensus	Age 65-79 = medium ≥80 = high LVEF 50-54% = medium LVEF < 50 % = high Anthracycline before Trastuzumab = medium Remote anthracycline exposure = medium Prior trastuzumab cardiotoxicity = very high Previous radiotherapy to left chest/mediastinum = medium Diabetes mellitus = medium Hypertension = medium Myocardial Infarction/previous coronary revascularization = high Stable angina = high Arrhythmia (Atrial fibrillation/flutter, Ventricular tachycardia/fibrillation) = medium Chronic Kidney Disease = medium Heart failure/cardiomyopathy = very high Severe valvular disease = high	N/A	N/A	No	Suggested incidence of CTRCD: Low risk <2%,  Medium risk 2-9%,  High risk 10-19%,  Very high risk >20%	Low risk = no risk factor OR one medium risk factor	Medium risk = medium risk factors totaling 2-4 points	High Risk = medium risk factors totaling ≥ 5 points OR any high risk factor  Very high risk = any very high risk factor

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Current/significant smoking history = **medium**  
Obesity (BMI > 30) = **medium**  
Elevated baseline troponin = **medium**  
Elevated baseline BNP/NT-proBNP  
= **medium**

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\* Note: incidence by risk group was not provided in the original publication, however, when we apply the tertiles identified in our study to the 37 patients with CTRCD in their study of them 5/37 (14%) were in the low risk group (CRS < 50), 14/37 (38%) in the medium risk group (CRS 51-64), and 18/37 (48%) in the high risk group (CRS ≥ 65). HF, heart failure; LVEF, left ventricular ejection fraction; NSABP-31, National Surgical Adjuvant Breast and Bowel Project B-31; ICD, international classification of diseases; HFA-ICOS, Heart Failure Association of the European Society of Cardiology-International Cardio-Oncology Society; BMI, body mass index; BNP, brain natriuretic peptide; NT-proBNP, N-terminal-pro hormone brain natriuretic peptide.

**Supplemental Table S2.** Comparison of the patient's characteristics for the 3 models based on the CTRCD risk category.

	NSABP-B31	Ezaz	HFA-ICOS Proforma
<b>LOW RISK</b>	N = 223	N= 577	N = 193
Age, years $\pm$ SD	47 $\pm$ 11	51 $\pm$ 11	49 $\pm$ 11
Anthracycline treatment, n (%)	191 (86)	514 (89)	171 (89)
Cumulative anthracycline dose, mg/m <sup>2</sup> $\pm$ SD	239 $\pm$ 62	266 $\pm$ 77	255 $\pm$ 73
Radiotherapy, n (%)	210 (94)	537 (93)	173 (90)
Diabetes, n (%)	14 (6)	16 (3)	1 (0.5)
Hypertension, n (%)	27 (12)	71 (12)	4 (2)
Dyslipidemia, n (%)	19 (9)	59 (10)	12 (6)
Coronary artery disease, n (%)	7 (3)	7 (1)	0 (0)
Heart Failure, n (%)	2 (1)	3 (0.5)	1 (0.5)
Atrial Fibrillation, n (%)	4 (2)	7 (1)	4 (2)
Baseline LVEF, %	70 $\pm$ 7	64 $\pm$ 7	65 $\pm$ 7
Cardiotoxicity (CREC), n (%)	40 (18)	141 (24)	30 (16)
Cardiotoxicity (ESC), n (%)	4 (2)	32 (6)	8 (4)
Cardiotoxicity (ASE), n %	26 (12)	93 (16)	22 (11)
<b>INTERMEDIATE RISK</b>	N = 204	N = 45	N = 404
Age, years $\pm$ SD	54 $\pm$ 11	61 $\pm$ 11	53 $\pm$ 11
Anthracycline treatment, n (%)	185 (91)	39 (86)	359 (89)
Cumulative anthracycline dose, mg/m <sup>2</sup> $\pm$ SD	263 $\pm$ 75	239 $\pm$ 67	271 $\pm$ 78
Radiotherapy, n (%)	189 (93)	39 (87)	379 (94)
Diabetes, n (%)	11 (5)	21 (47)	30 (7)
Hypertension, n (%)	36 (18)	33 (73)	83 (21)
Dyslipidemia, n (%)	30 (15)	20 (44)	55 (14)
Coronary artery disease, n (%)	4 (2)	7 (16)	8 (2)
Heart Failure, n (%)	2 (1)	1 (2)	1 (0.3)
Atrial Fibrillation, n (%)	6 (3)	3 (7)	4 (1)
Baseline LVEF, n (%)	64 $\pm$ 7	64 $\pm$ 7	64 $\pm$ 7
Cardiotoxicity (CREC), n (%)	50 (25)	9 (20)	109 (27)
Cardiotoxicity (ESC), n %	12 (6)	3 (7)	26 (6)
Cardiotoxicity (ASE), n %	38 (19)	8(18)	71 (18)
<b>HIGH RISK</b>	N=202	N = 7	N= 32
Age, years $\pm$ SD	60 $\pm$ 11	69 $\pm$ 11	60 $\pm$ 11
Anthracycline treatment, n (%)	182 (91)	6 (86)	29 (91)
Cumulative anthracycline dose, mg/m <sup>2</sup> $\pm$ SD	290 $\pm$ 84	226 $\pm$ 49	226 $\pm$ 65
Radiotherapy, n (%)	183 (92)	5 (71)	31 (97)
Diabetes, n (%)	16 (8)	4 (57)	9 (28)
Hypertension, n (%)	47 (23.5)	6 (86)	23 (72)
Dyslipidemia, n (%)	32 (16)	4 (57)	15 (47)
Coronary artery disease, n (%)	5 (2.5)	2 (29)	8 (25)
Heart Failure, n (%)	1 (1)	1 (14)	3 (9)
Atrial Fibrillation, n (%)	2 (1)	2 (29)	4 (13)
Baseline LVEF	58 $\pm$ 7	70 $\pm$ 7	64 $\pm$ 6
Cardiotoxicity (CREC), n (%)	61 (31)	1 (14)	12 (38)
Cardiotoxicity (ESC), n %	19 (10)	0 (0)	1 (3)
Cardiotoxicity (ASE), n %	38 (19)	1(14)	9 (28)

SD, standard deviation; NSABP-31, National Surgical Adjuvant Breast and Bowel Project B-31; HFA-ICOS, Heart Failure Association of the European Society of Cardiology-International Cardio-Oncology Society; LVEF, left ventricular ejection fraction; CREC, Cardiac Review and Evaluation Committee; ESC, European Society of Cardiology; ASE, American Society of Echocardiography

**Supplemental Table S3.** Comparison of the patient's characteristics between our cohort and NSABP31-CRS and Ezaz model. Available data in the original manuscript's are reported.

	All Patients	NSABP	EZAZ
	All Patients N=629	NSABP N= 947*	EZAZ N=1664
Age, years $\pm$ SD	52.4 $\pm$ 10.9	< 50 years, n= 485 50-59 years, n = 311 $\geq$ 60 years, n = 148	73.6 $\pm$ 5.3
Tumor Laterality, n (%)			
Left	341 (54)	354*	-
Right	268 (43)	590*	-
Bilateral	21 (3)	-	-
Stage, n (%)			
1	127 (20)	-	446 (27)
2	329 (52)	-	758 (46)
3	173 (28)	-	460 (28)
Hormone receptor positive (either ER/PR), n (%)	413 (66)	-	-
Post-Menopausal status, n (%)	309 (49)	-	-
Surgery (mastectomy or lumpectomy), n (%)	622 (99)	-	1664 (100)
Anthracycline received, n (%)	568 (90)	-	597 (36)
Cumulative anthracycline, mg/m <sup>2</sup> $\pm$ SD	272.4 $\pm$ 76	-	-
Radiotherapy, n (%)	493 (78)	-	949 (57)
Diabetes, n (%)	44 (7)	36^	325 (20)
Hypertension, n (%)	110 (18)	193^	1002 (60)
Dyslipidemia, n (%)	83 (13)	70^	981 (59)
Smoker (current), n (%)	46 (7)	374*	-
Smoker (Ex), n (%)	122 (19)	-	-
At least 1 CVRF, n (%)	402 (64)	-	590 (35)
Coronary artery disease, n (%)	16 (3)	-	60 (4)
Heart Failure, n (%)	5 (1)	-	-
Atrial Fibrillation, n (%)	12 (2)	-	90 (5)
Baseline LVEF, % $\pm$ SD	64 $\pm$ 7	$\geq$ 65%, n= 351 55-64%, n=473 50-54%, n=111	-
Imaging Modality, n (%)			
MUGA	440 (70)	-	-
Echo	189 (30)	-	-

(-) indicate this data was not reported in the original study

\* tables in original data do not add up to 947 patients and so there is some missing data from the original studies that was recorded and overall percentages are not reported

^ these were listed as medications for these co-morbidities and there could be under-representation of these co-morbidities

**Supplemental Table S4.** Summary of baseline characteristics of the whole cohort (stratified by ESC CTRCD definition)

	<b>CTRCD N= 35</b>	<b>No CTRCD N= 594</b>	<b>P Value</b>
Age, years $\pm$ SD	53 $\pm$ 11	52 $\pm$ 11	0.5778
Anthracycline treatment, n (%)	31 (89)	527 (89)	0.9783
Cumulative anthracycline dose mg/m <sup>2</sup> $\pm$ SD	262 $\pm$ 79	263 $\pm$ 76	0.9449
Radiotherapy, n(%)	28 (80)	465 (78)	0.8104
Diabetes, n (%)	2 (6)	38 (6)	0.8721
Hypertension, n (%)	5 (14)	104 (18)	0.6245
Dyslipidemia, n (%)	5 (14)	78 (13)	0.8445
Smoker (current)	2 (6)	43 (7)	0.7338
Smoker (Ex)	5 (14)	117 (20)	0.4314
At least 1 CVRF, n (%)	15 (43)	271 (46)	0.7495
Coronary artery disease, n (%)	0 (0)	17 (3)	0.6161
Heart Failure, n (%)	0 (0)	6 (1)	1.000
Atrial Fibrillation, n (%)	1 (3)	11 (2)	0.6727
Baseline LVEF, %	56 $\pm$ 7	64 $\pm$ 6	<b>0.0201</b>
<i>Imaging Modality, n (%)</i>			0.3497
MUGA	27 (77)	414 (70)	
Echo	8 (23)	180 (30)	

SD, standard deviation; CVRF, cardiovascular risk factor; LVEF, left ventricular ejection fraction; ESC, European Society of Cardiology; MUGA, multi-gated acquisition; Echo, echocardiography.

**Supplemental Table S5.** Summary of baseline characteristics of the whole cohort (stratified by ASE CTRCD definition)

	CTRCD N= 102	No CTRCD N= 527	P Value
Age, years $\pm$ SD	54 $\pm$ 11	52 $\pm$ 11	0.3912
Anthracycline treatment, n (%)	92 (90)	468 (89)	0.6806
Cumulative anthracycline dose mg/m <sup>2</sup> $\pm$ SD	275 $\pm$ 81	262 $\pm$ 76	0.1416
Radiotherapy, n(%)	90 (88)	413 (78)	<b>0.0223</b>
Diabetes, n (%)	5 (5)	32 (6)	0.6457
Hypertension, n (%)	22 (22)	88 (17)	0.2359
Dyslipidemia, n (%)	16 (16)	67 (13)	0.4168
Smoker (current)	8 (8)	38 (7)	0.8223
Smoker (Ex)	17 (17)	105 (20)	0.4463
At least 1 CVRF, n (%)	25 (25)	143 (27)	0.6049
Coronary artery disease, n (%)	2 (2)	14 (3)	0.6829
Heart Failure, n (%)	2 (2)	3 (1)	0.1475
Atrial Fibrillation, n (%)	5 (5)	10 (2)	0.0687
Baseline LVEF, %	63 $\pm$ 7	65 $\pm$ 7	<b>&lt;0.001</b>
<i>Imaging Modality, n (%)</i>			<b>0.049</b>
MUGA	63 (62)	377 (72)	
Echo	39 (38)	150 (28)	

SD, standard deviation; CVRF, cardiovascular risk factor; LVEF, left ventricular ejection fraction; ASE, American Society of Echocardiography; MUGA, multi-gated acquisition; Echo, echocardiography.

**Supplemental Table S6.** Proportion of patients who developed CTRCD with ASE and ESC CTRCD definitions stratified by risk categories for the 3 risk models.

<b>EZAZ</b>	<b>Total no. of patients</b>	<b>ASE CTRCD N = 102</b>	<b>ESC CTRCD N = 35</b>
<b>Risk categories</b>			
Low, n (%)	577	93 (16)	32 (6)
Medium, n (%)	45	8 (18)	3 (7)
High/, n (%)	7	1 (14)	0 (0)
P value <sup>†</sup>	-	0.949	-

  

<b>NSABP-31 CRS</b>	<b>Total no. of patients</b>	<b>ASE CTRCD N = 102</b>	<b>ESC CTRCD N = 35</b>
<b>Risk categories</b>			
Low, n (%)	223	26 (12)	4 (2)
Medium, n (%)	204	38 (19)	12 (6)
High, n (%)	202	38 (19)	19 (10)
P value <sup>†</sup>	-	0.067	<b>0.003</b>

  

<b>HFA-ICOS</b>	<b>Total no. of patients</b>	<b>ASE CTRCD N = 102</b>	<b>ESC CTRCD N = 35</b>
<b>Risk categories</b>			
Low, n (%)	193	22 (11)	8 (4)
Medium, n (%)	404	71 (18)	26 (6)
High, n (%)	27	6 (22)	1 (4)
Very high, n (%)	5	3 (60)	0 (0)
P value <sup>†</sup>		<b>0.001</b>	-

\*p values represent comparison between the ASE and ESC cardiotoxicity criteria, some p values not reported because of 0 values; <sup>†</sup>p value represents comparison between the 3 risk categories for that specific score and the respective CTRCD definition. CTRCD refers to cancer therapeutics associated cardiac dysfunction; NSABP-31, National Surgical Adjuvant Breast and Bowel Project B-31; HFA-ICOS, Heart Failure Association of the European Society of Cardiology-International Cardio-Oncology Society; ESC, European Society of Cardiology; ASE, American Society of Echocardiography



**Supplemental Table S7.** Incidence of CTRCD (CREC criteria) with the three models stratified by MUGA versus echocardiography. Percentages reported amongst entire individual risk groups.

EZAZ	Total no. of patients	Total MUGA (n = 440)	MUGA CREC CTRCD (n = 93)	Total ECHO (n = 58)	ECHO CREC CTRCD (n = 58)	P Value
<b>Risk categories</b>						
Low, n (%)	577	397 (69)	86 (22)	180 (31)	55 (31)	<b>0.021</b>
Medium, n (%)	45	36 (80)	6 (17)	9 (20)	3 (33)	0.264
High, n (%)	7	7 (100)	1 (14)	0 (0)	0 (0)	-

  

NSABP-31	Total no. of patients	Total MUGA (n = 440)	MUGA CREC CTRCD (n = 93)	Total ECHO (n = 58)	ECHO CREC CTRCD (n = 58)	P Value
<b>Risk categories</b>						
Low, n (%)	223	191 (86)	29 (15)	32 (14)	11 (34)	<b>0.001</b>
Medium, n (%)	204	140 (69)	32 (23)	64 (31)	18 (28)	0.417
High, n (%)	202	109 (54)	32 (30)	93 (46)	29 (31)	0.778

  

HFA-ICOS	Total no. of patients	Total MUGA (n = 440)	MUGA CREC CTRCD (n = 93)	Total ECHO (n = 58)	ECHO CREC CTRCD (n = 58)	P Value
<b>Risk categories</b>						
Low, n (%)	193	146 (76)	21 (14)	47 (24)	9 (19)	0.432
Medium, n(%)	404	266 (66)	62 (23)	138 (34)	47 (34)	<b>0.021</b>
High, n (%)	27	23 (85)	8 (35)	4 (15)	2 (50)	0.561
Very high, n (%)	5	5 (100)	2 (40)	0 (0)	0 (0)	-

CTRCD, cancer therapeutics associated cardiac dysfunction; CREC, Cardiac Review and Evaluation Committee; MUGA, multi-gated acquisition; Echo, echocardiography; NSABP-31, National Surgical Adjuvant Breast and Bowel Project B-31; HFA-ICOS, Heart Failure Association of the European Society of Cardiology-International Cardio-Oncology Society; ESC, European Society of Cardiology; ASE, American Society of Echocardiography. Some p values not reported because of 0 values.