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ORIGINAL RESEARCH

Extensive Cardiac Function Analyses Using Contemporary Echocardiography in Childhood Cancer Survivors

A DCCSS LATER Study

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ABSTRACT

BACKGROUND Childhood cancer survivors (CCS) are at risk for cardiotoxicity.

OBJECTIVES We sought to assess how cardiac dysfunction measurements in CCS overlap and are differentially influenced by risk factors.

METHODS This cross-sectional Dutch Childhood Cancer Survivor Study evaluated echocardiograms of 1,397 ≥5-year CCS and 277 siblings. Of CCS, n = 1,254 received cardiotoxic (anthracyclines/mitoxantrone/radiotherapy involving the heart region [RT_{heart}]) and n = 143 received potentially cardiotoxic (cyclophosphamide, ifosfamide, or vincristine) therapy. We assessed demographic, treatment-related, and traditional cardiovascular risk factors for cardiac dysfunction using multivariable logistic regression.

RESULTS CCS were a median of 26.7 years after diagnosis; 49% were women. Abnormal left ventricular ejection fraction (LVEF) (defined as <52% in men, <54% in women) occurred most commonly in CCS treated with anthracyclines and RT_{heart} combined (38%). Age/sex-specific abnormal global longitudinal strain (GLS) occurred most commonly in CCS treated with RT_{heart}, either with (41%) or without (38%) anthracyclines. Of CCS with normal LVEF, 20.2% showed abnormal GLS. Diastolic dysfunction grade ≥II was rare. Abnormal LVEF was mainly associated with female sex, anthracycline dose, and only in women, RT_{heart} dose. Abnormal GLS was associated with female sex, RT_{heart} dose, diastolic blood pressure, and only in women, anthracycline dose. Cyclophosphamide, ifosfamide, and vincristine were not associated with LVEF or GLS. Compared with siblings, CCS showed higher risk of abnormal LVEF (OR: 2.9; 95% CI: 1.4-6.6) and GLS (OR: 2.1; 95% CI: 1.2-3.7), independent of (potentially) cardiotoxic treatment-related and cardiovascular risk factors.

CONCLUSIONS Abnormal LVEF and GLS constitute complementary measures of systolic dysfunction among long-term CCS. Their diagnostic value may differ according to cardiotoxic exposures. Also, CCS have residual, unexplained risk of cardiac dysfunction. (Early Detection of Cardiac Dysfunction in Childhood Cancer Survivors, a DCOG LATER study; NTR7481) (J Am Coll Cardiol CardioOnc 2023;5:472–485) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Heart failure increases mortality in childhood cancer survivors (CCS) to 6-fold that of the general population.[1] Anthracyclines, mitoxantrone, and radiotherapy to the heart region (RT_{heart}) constitute treatment-related risk factors.[2,3] Echocardiographic surveillance of at-risk CCS is recommended to detect asymptomatic cardiac dysfunction before heart failure ensues.

The standard systolic function measurement, left ventricular (LV) ejection fraction (LVEF), has considerable measurement variability and is a late indicator of cardiac dysfunction.[4] Global longitudinal strain (GLS) may be more sensitive, with greater predictive value for subsequent heart failure and mortality.[5] In CCS, abnormal GLS is more prevalent than reduced LVEF and is also associated with cardiotoxic treatment exposure.[6,7] This suggests that abnormal GLS may detect cardiotoxicity earlier than LVEF, but the prognostic value of GLS for heart failure in CCS remains unknown.[8] Knowledge on how LVEF and GLS are related,[9] and whether they are differentially influenced by cardiotoxic treatments, may enhance the clinical interpretation of these measurements.

Specific gaps in knowledge exist for subgroups of CCS. Among these are the potential cardiotoxic effects of cyclophosphamide, ifosfamide, and vincristine,[3,10-12] and the controversial influence of sex.[2,3,6] Measurement of GLS may provide a more sensitive assessment of these risk factors. Finally, the residual risk of cardiac dysfunction compared with siblings, beyond the known cardiotoxic exposures, remains unexplored.

This cardiac substudy of the nationwide DCCSS (Dutch Childhood Cancer Survivor Study), LATER cohort, part 2 clinical visit and questionnaire study,[13] aimed to increase our understanding of cardiac dysfunction in long-term CCS, as defined by LVEF and GLS in relation to risk factors.

METHODS

STUDY POPULATION. We performed a nationwide, prospective, cross-sectional outpatient clinic evaluation of ≥5-year CCS, treated with potentially cardiotoxic (established or unknown) therapies before the age of 18 years, between January 1, 1963, and December 31, 2001.[13] Participants who received cardiotoxic therapy (anthracyclines, mitoxantrone, and/or RT_{heart}) were designated study arm 1 (unlimited inclusion). The exploratory, mutually exclusive, study arms 2 to 4 each consisted of a maximum 100 CCS who respectively received the potentially cardiotoxic agents cyclophosphamide, ifosfamide, or vincristine, without other cardiotoxic treatments. Analogous to previous studies, we analyzed the prevalence of abnormalities in subgroups according to their cardiotoxic exposure: only anthracyclines/mitoxantrone, only RT_{heart}, both RT_{heart} and anthracyclines/mitoxantrone, or potentially cardiotoxic agents (cyclophosphamide, ifosfamide, or vincristine). We included CCS with diagnosed cardiomyopathy or heart failure, but excluded pregnant CCS and heart transplant recipients. Sibling control subjects were recruited as the most suitable reference group, representing the general population and having a shared background.

ABBREVIATIONS AND ACRONYMS

CCS = childhood cancer survivors

CVRF = cardiovascular risk factors

GCS = global circumferential strain

GLS = global longitudinal strain

LV = left ventricle

LVEF = left ventricular ejection fraction

RT_{heart} = radiotherapy to the heart region

TBI = total body irradiation

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Unlike most reference cohorts, they were unselected and not necessarily without comorbidities. Eligible CCS and siblings visited our late-effects clinic once for usual care (including treatment-based cardiology surveillance) and/or research tests. The investigation conforms with the principles outlined in the Declaration of Helsinki. All participants signed informed consent for use of their data, and the medical ethics boards of all centers approved the study protocol.

DATA COLLECTION. Cardiotoxic exposures. Our central registry contained cancer diagnosis and treatment history, including imputed chemotherapy doses.[14] Anthracycline analogs were reported using a doxorubicin-equivalence ratio representing cardiotoxic potential.[15] Mitoxantrone, the more cardiotoxic anthraquinone, was considered separately.[15] All other chemotherapy doses were available as cumulative doses/m^2.

For each body compartment (eg, thorax, abdominopelvic, spine), the maximum prescribed radiotherapy dose to the smallest field was available.[14] To calculate RT_{heart} dose, we used the highest value of 100% of the prescribed thorax dose, 55% of the abdominopelvic dose, or 10% of the spinal dose (the latter 2 percentages were derived from pilot data [Supplemental Methods 1]). Finally, we summed 100% of the total body irradiation (TBI) dose, but dose-response analyses of RT_{heart} were corrected for the high fraction dose used in TBI.

Cardiovascular risk factors. Participants completed questionnaires on previous diagnoses of cardiomyopathy, myocardial infarction, hypertension, and diabetes (yes/no questions). Except myocardial infarction, these conditions are actively surveilled for and treated at our clinics. We validated these diagnoses against reported appropriate medication use. We separately noted lipid-lowering medication use, since dyslipidemia is not actively surveilled for. Any investigations following the study visit remained unrecorded, precluding analyses of newly diagnosed conditions. Considering the low prevalence and proactive treatment of hypertension and missing questionnaire entries, we also analyzed resting blood pressure, measured during the visit, as a more objective measurement available for the whole cohort. Because major surgery may affect body mass index, we measured waist circumference to assess abdominal obesity. A participant was considered to have ever smoked when having smoked ≥1 cigarette/week for ≥1 year.

Echocardiography. Two-dimensional echocardiograms were acquired using a comprehensive protocol.[16] Two core lab physicians (R.M., J.M.L.) performed offline structural and functional measurements, blinded from participant information. We calculated LVEF using Simpson's biplane method. Midwall myocardial strain was separately analyzed in vendor-independent software (2D CPA 1.4, TomTec). End-systolic midwall GLS was calculated from 3 apical views, and midventricular global circumferential strain (mid-GCS) from parasternal short-axis views.

Feasibility and reproducibility of our outcomes were previously published; intraclass correlation coefficients for interobserver variability were 0.85 for LVEF, 0.76 for GLS, 0.70 for mid-GCS, and 0.98 for lateral e'.[16] Qualitative references regarding myocardial strain concern the absolute values (−18% denotes worse function than −20%); positive correlations indicate worsening strain.

OUTCOME MEASURES. To determine the risk of cardiac dysfunction, the primary outcomes were defined as LVEF below sex-specific limits following international guidelines (men: <52%, women: <54%)[17]; GLS below age- and sex-specific reference values (Supplemental Methods 2)[18]; or LV diastolic dysfunction ≥grade II.[19] The combination of abnormal LVEF and abnormal GLS was analyzed because these measurements may corroborate each other. Secondary outcomes were continuous values of LVEF and GLS, mid-GCS and lateral e'. No corrections were performed for multiple testing because echocardiographic measurements are correlated.[20] All secondary outcomes were considered exploratory.

STATISTICAL ANALYSIS. Continuous values are presented as mean ± SD or median (range) where appropriate. Distributions of cardiac abnormalities are presented in bar charts. Echocardiographic measurements were compared between CCS and siblings, and different treatment groups, with Student's *t*-test or analysis of variance (continuous variables) and with Pearson chi-square or Fisher's exact test (categorical variables). No paired statistical analyses were performed, given that siblings and CCS were not matched in a 1:1 ratio.

Risk factors for primary outcomes in CCS were assessed in multivariable logistic regression models. We applied a mixed strategy for variable selection: known risk factors including established cardiotoxic treatment doses and traditional cardiovascular risk factors (CVRF) were considered "fixed" in our models, where variables remained in models regardless of significance, based on prior knowledge. Risk factor discovery for other potentially cardiotoxic therapies were considered "flexible," applying

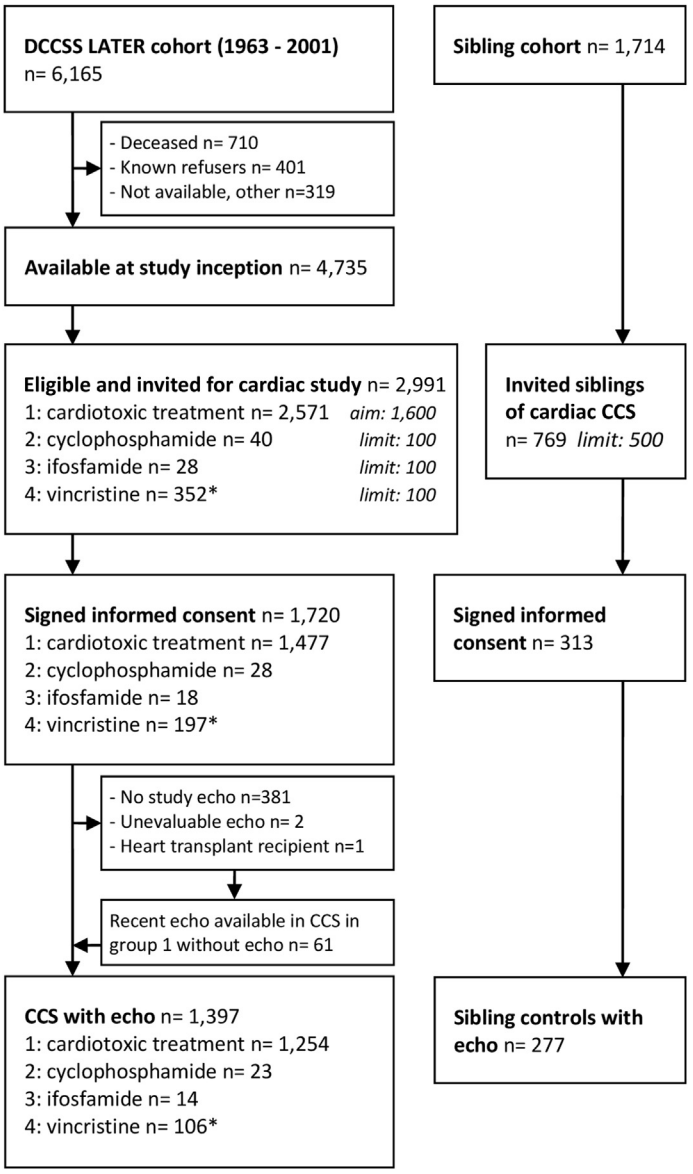
variable selection. The fixed model covariates included sex, age at diagnosis and age at echocardiography. Anthracycline dose was entered as a polynomial because of its known nonlinear association with systolic function.[10] Potential nonlinearity of other variables was tested in univariable analysis using quadratic and cubic polynomials, and confirmed in the final multivariable model using the chi-square test. Interactions between cardiotoxic exposures, and between cardiotoxic therapy dose with sex, were tested before adding CVRF to the model. Systolic/diastolic blood pressure and hypertension were tested for multicollinearity and strength of univariable associations before adding these to the multivariable models; diastolic blood pressure was finally included, given it had the strongest correlation. Subsequently, we added therapies that *potentially* could cause heart failure or ischemic heart disease[12] (administered in >5% of our cohort) (Supplemental Table 1) to these models in a stepwise fashion. Amongst others, these included cyclophosphamide, ifosfamide, and vincristine. Nonsignificant variables were again omitted from the models.

The risk of the primary outcome in CCS was then tested in models that included siblings. These were adjusted for all variables in the final model in CCS, except for age at diagnosis, which is not a relevant confounder in siblings. Siblings were assigned cardiotoxic therapy doses of "zero." We then repeated these analyses by excluding CCS unexposed to known cardiotoxic therapies, in order to confirm the potential residual cardiovascular risk in CCS exposed to cardiotoxic therapies.

The abovementioned "fixed" model variables were also used to assess associations of the continuous secondary outcomes in linear regression.

Logistic model results are presented as OR with 95% CI; linear model results as regression coefficient (β) with 95% CI. Two-sided P values <0.05 were considered significant. Analyses were performed in R (version 3.5.3, R Foundation for Statistical Computing).

FIGURE 1 Inclusion Flowchart



An **asterisk** indicates the study arm closed early after exceeding the predefined limit. CCS = childhood cancer survivors; DCCSS = Dutch Childhood Cancer Survivor Study.

RESULTS

PARTICIPANTS. Echocardiograms were available for 1,397 CCS and 277 siblings. **Figure 1** shows the inclusion flowchart. Baseline characteristics are presented in **Table 1**. Participants were more often women than nonparticipants (49% vs 40%). Among participants, cardiotoxic exposures differed between sexes (Supplemental Table 2). Median age of CCS at echocardiography was 34.5 years [range: 15.6-65.2 years], at a median of 26.7 years [range: 14.5-54.7 years] after cancer diagnosis; 49% were female. Siblings were slightly older and more often female (60% vs 49%). Of all CCS, 77.2% received anthracyclines (with or without RT_{heart}; median dose 180 mg/m^2 [range: 7.7-760 mg/m^2]); 29.5% received RT_{heart} (median dose 12 Gy [range: 0.4-99 Gy]). Cyclophosphamide, ifosfamide or vincristine were administered without other known cardiotoxic therapies in 143 CCS (10.2%). Self-

TABLE 1 Demographics and Baseline Characteristics of CCS, Grouped by Cardiotoxic Exposures, and Sibling Control Subjects

		CCS According to Cardiotoxic Exposure				
	All CCS (N = 1,397)	Only Anthracyclines/ Mitoxantrone (n = 839[a])	Only Radiotherapy to Heart Region (n = 152)	Radiotherapy to Heart Region and Anthracyclines/ Mitoxantrone (n = 260[a])	Potentially Cardiotoxic Therapy[b] (n = 143)	Siblings (n = 277)
Demography, diagnosis and treatment history						
Sex						
Male	720 (52)	440 (52)	74 (49)	139 (54)	64 (45)	112 (40)
Female	677 (49)	399 (48)	78 (51)	121 (47)	79 (55)	165 (60)
Age at cancer diagnosis, y	6.1 (0.1-17.9)	6.2 (0.1-17.9)	6.1 (0.1-17.0)	6.9 (0.3-17.9)	3.9 (0.2-17.3)	–
<5	595 (43)	347 (41)	67 (44)	97 (37)	82 (58)	–
5-9	396 (28)	238 (28)	51 (34)	71 (27)	35 (25)	–
10-14	317 (23)	196 (23)	28 (18)	71 (27)	22 (15)	–
15-18	89 (6.4)	58 (6.9)	6 (3.9)	21 (8.1)	4 (2.8)	–
Incidence year						–
1963-1969	12 (0.9)	0 (0)	12 (7.9)	0 (0)	0 (0)	–
1970-1979	168 (12)	47 (5.6)	74 (49)	21 (8.1)	26 (18)	–
1980-1989	421 (30)	243 (29)	32 (21)	98 (38)	46 (32)	–
1990-2001	796 (57)	549 (65)	34 (22)	141 (54)	71 (50)	–
Primary cancer diagnosis, ICCC-3						
Leukemias, myeloproliferative and myelodysplastic diseases	566 (41)	375 (45)	18 (12)	88 (34)	83 (58)	–
Lymphomas and reticulo-endothelial neoplasms	335 (24)	231 (28)	24 (16)	65 (25)	14 (9.8)	–
Central nervous system, intracranial and intraspinal neoplasms	45 (3.2)	3 (0.4)	33 (22)	2 (0.8)	7 (4.9)	–
Neuroblastoma and other peripheral nervous cell tumors	48 (3.4)	23 (2.7)	16 (11)	8 (3.1)	1 (0.7)	–
Renal tumors	167 (12)	41 (4.9)	44 (29)	64 (25)	18 (13)	–
Hepatic tumors	12 (0.9)	12 (1.4)	0 (0)	0 (0)	0 (0)	–
Bone tumors	118 (8.4)	93 (11)	3 (2.0)	21 (8.1)	1 (0.7)	–
Soft tissue and other extraosseous sarcomas	74 (5.3)	56 (6.7)	5 (3.3)	11 (4.2)	2 (1.4)	–
Other, incl. retinoblastoma, germ cell, trophoblastic, gonadal, melanomas and other malignant neoplasms	32 (2.3)	5 (0.6)	9 (5.9)	1 (0.4)	17 (11.8)	
Anthracycline exposure	1078 (77)	818 (98)	0 (0)	257 (99)	0 (0)	–
Anthracycline dose, exposed, mg/m^2	180 (7.7-760)	180 (7.7-760)	–	200 (25-720)	–	–
1-100	189 (18)	152 (19)	–	37 (14)	–	–
101-250	560 (52)	432 (53)	–	127 (50)	–	–
>250	324 (30)	230 (28)	–	92 (36)	–	–
Mitoxantrone exposure	75 (5.4)	55 (6.6)	0 (0)	20 (7.7)	0 (0)	–
Mitoxantrone dose, exposed, mg/m^2	40 (10-168)	44 (10-168)	–	21 (19-80)	–	–
RT to heart region, incl. total body	412 (30)	0 (0)	152 (100)	260 (100)	0 (0)	–
RT dose to heart region, exposed, Gy	12 (0.4-99)	–	13 (0.4-76)	9.9 (0.4-99)	–	–
0.1-15	261 (64)	–	80 (54)	181 (70)	–	–
15.1-30	95 (23)	–	53 (36)	42 (16)	–	–
>30	51 (13)	–	14 (9.5)	37 (14)	–	–
Total body irradiation	83 (6.0)	0 (0)	9 (5.9)	74 (29)	0 (0)	–
Stem cell transplant	137 (9.9)	36 (4.3)	10 (6.8)	82 (32)	8 (5.6)	–
Cyclophosphamide exposure	784 (56)	566 (68)	37 (24)	155 (60)	23 (16)	–
Ifosfamide exposure	211 (15)	116 (14)	4 (2.6)	77 (30)	14 (9.8)	–
Vincristine exposure	1172 (84)	716 (85)	103 (68)	244 (94)	106 (74)	–
Time since cancer diagnosis, y	27 (14-55)	25 (14-48)	40 (17-55)	27 (15-45)	28 (16-49)	–
Age at echocardiography, y	34 (16-65)	33 (16-61)	46 (21-65)	35 (17-59)	34 (17-64)	37 (16-59)
Questionnaire data						
Cardiomyopathy/ heart failure	47 (3.7)	27 (3.5)	3 (2.1)	17 (7.1)	0 (0)	0 (0)
Myocardial infarction	4 (0.3)	1 (0.1)	1 (0.7)	2 (0.8)	0 (0)	0 (0)
Hypertension	82 (6.4)	34 (4.5)	26 (18)	14 (6.0)	8 (6.0)	2 (0.9)
Diabetes	26 (2.0)	9 (1.2)	8 (5.5)	7 (3.0)	2 (1.5)	0 (0)
Lipid-lowering medication	56 (4.0)	19 (2.3)	17 (11.2)	16 (6.2)	4 (2.8)	1 (0.4)
Ever smoked >1 y	377 (30)	234 (31)	40 (28)	69 (29)	33 (25)	83 (37)
Incomplete medical history	191	119	17	39	16	92

Continued on the next page

TABLE 1 Continued

	All CCS (N = 1,397)	CCS According to Cardiotoxic Exposure: Only Anthracyclines/ Mitoxantrone (n = 839[a])	Only Radiotherapy to Heart Region (n = 152)	Radiotherapy to Heart Region and Anthracyclines/ Mitoxantrone (n = 260[a])	Potentially Cardiotoxic Therapy[b] (n = 143)	Siblings (n = 277)
Outpatient clinic data						
Waist circumference, cm	85 (59-144)	85 (60-139)	87 (63-133)	83 (59-135)	88 (65-144)	86 (62-124)
Systolic blood pressure, mm Hg	123 ± 16	121 ± 14	131 ± 18	122 ± 16	125 ± 18	120 ± 14
Diastolic blood pressure, mm Hg	75 ± 11	74 ± 10	78 ± 11	75 ± 11	75 ± 13	73 ± 10
Incomplete physical examination	44	31	3	8	2	2

Values are n (%), mean ± SD, or median (range). No *P* values are reported in Table 1 following the STROBE recommendations. [a]Three childhood cancer survivors (CCS) treated with anthracyclines but with missing radiotherapy exposure status could not be classified. [b]Either cyclophosphamide, ifosfamide, or vincristine without anthracyclines, mitoxantrone, or radiotherapy involving the heart region.
ICCC = International Classification of Childhood Cancer; RT = radiotherapy.

reported hypertension was present in 6.4% of CCS, and 3.7% used medication for a previously diagnosed cardiomyopathy.

PREVALENCE OF CARDIAC DYSFUNCTION. Table 2 summarizes the echocardiographic results according to cardiotoxic exposure. An abnormal LVEF was present in 24.2% of CCS vs 5.2% of siblings ($P < 0.001$). Mean LVEF was 56.1% ± 5.9% vs 59.6% ± 3.8%, respectively ($P < 0.001$). An abnormal GLS was present in 29.8% of CCS and 10.6% of siblings ($P < 0.001$). Mean GLS was −18.3% ± 2.4%) vs −20.1% ± 2.1%), respectively ($P < 0.001$).

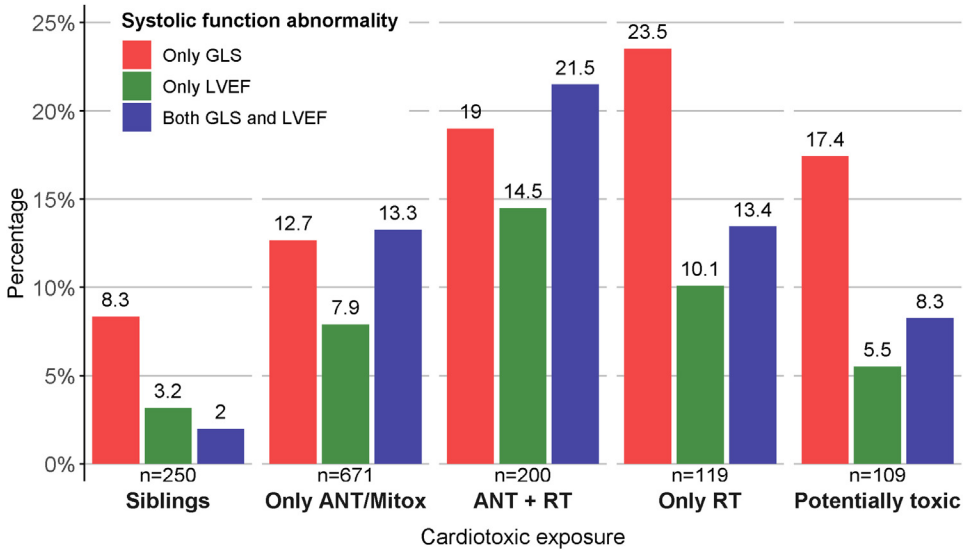
Abnormal LVEF was most prevalent in CCS who received anthracyclines and RT_{heart} combined (38%), whereas GLS abnormalities were particularly prevalent in CCS exposed to RT_{heart} with (41%) or without

TABLE 2 Echocardiographic Results in CCS, Grouped by Cardiotoxic Exposures, and Sibling Control Subjects

	Childhood Cancer Survivors: Only Anthracyclines/ Mitoxantrone (n = 839[a])	Only RT to Heart Region (n = 152)	RT to Heart Region and Anthracyclines/ Mitoxantrone (n = 260[a])	Potentially Cardiotoxic Therapy[b] (n= 143)	*P* Value Among CCS Groups	Siblings: Siblings (n = 277)	*P* Value CCS vs Siblings
Primary outcomes							
Abnormal LV ejection fraction	171 (22)	32 (23)	87 (38)	17 (13)	<0.001	14 (5.2)	<0.001
Missing	66	13	30	16		10	
Abnormal LV global longitudinal strain	175 (26)	46 (38)	84 (41)	29 (26)	<0.001	27 (10.6)	<0.001
Missing	160	30	54	30		23	
Abnormal LV ejection fraction + LV global longitudinal strain	89 (13)	16 (13)	43 (22)	9 (8.3)	0.008	5 (2.0)	<0.001
Missing	168	33	60	34		25	
LV diastolic dysfunction ≥grade II	4 (0.5)	2 (1.4)	7 (2.9)	1 (0.8)	0.014	0 (0)	0.15
Missing/indeterminate	33	8	18	11		3	
Secondary outcomes							
LV ejection fraction, %	56.2 ± 6.0	56.3 ± 5.1	54.2 ± 6.1	58.6 ± 4.8	<0.001	59.6 ± 3.8	<0.001
LV global longitudinal strain, %	−18.4 ± 2.4	−18.0 ± 2.2	−17.6 ± 2.4	−18.9 ± 2.4	<0.001	−20.1 ± 2.1	<0.001
Mid-LV global circumferential strain, %	−19.1 ± 3.4	−19.5 ± 3.5	−17.4 ± 3.5	−21.4 ± 3.2	<0.001	−21.2 ± 3.1	<0.001
LV lateral e′, cm/s	15 ± 4	12 ± 3	13 ± 3	15 ± 4	<0.001	16 ± 4	<0.001
LV lateral e′ <10 cm/s	72 (9.0)	37 (25)	38 (16)	15 (11)	<0.001	13 (4.8)	<0.001
LA end-diastolic volume index, mL/m^2	21 ± 6.5	20 ± 6.7	19 ± 6.8	23 ± 6.6	<0.001	23 (6.3)	<0.001
Mitral inflow E/A ratio	1.6 ± 0.6	1.3 ± 0.4	1.4 ± 0.5	1.6 ± 0.5	<0.001	1.6 ± 0.5	0.026
Mitral average E/e′ ratio	6.1 ± 2.1	8.2 ± 3.7	7.5 ± 2.9	6.2 ± 2.0	<0.001	5.6 ± 1.4	<0.001
Tricuspid regurgitation gradient, mm Hg	15.3 ± 6.4	18.5 ± 7.3	17.4 ± 7.2	14.4 ± 5.9	<0.001	15.1 ± 5.7	0.10
Diastolic dysfunction grade I, in presence of normal LVEF	0 (0)	1 (1.0)	0 (0)	1 (0.9)	0.068	5 (2.0)	0.006

Values are n (%) or mean ± SD. [a]3 CCS treated with anthracyclines but with missing radiotherapy exposure status could not be classified. [b]Either cyclophosphamide, ifosfamide, or vincristine without anthracyclines, mitoxantrone, or radiotherapy involving the heart region.
LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

FIGURE 2 Bar Chart of Echocardiographic Abnormalities per Cardiotoxic Exposure Group



Single and combined abnormalities are shown in separate bars, for all participants in an exposure group with a complete set of measurements. ANT = anthracyclines; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; Mitox = mitoxantrone; RT = radiotherapy to the heart region.

(38%) anthracyclines. Only 1.1% of CCS and no siblings had diastolic dysfunction ≥grade II ($P = 0.15$). A breakdown of prevalence in the "potentially cardiotoxic treatment" subgroup is provided in Supplemental Table 3.

Notably, 20.2% of CCS with a normal LVEF had an abnormal GLS, but 39.1% of CCS with an abnormal LVEF had a normal GLS. The combination of abnormal LVEF and abnormal GLS was most prevalent in CCS who received anthracyclines and RT_{heart} combined (22%). Distributions of abnormalities according to cardiotoxic exposure in CCS and siblings with complete measurements are shown in **Figure 2**. Abnormal GLS was noted as a more frequent solitary finding in CCS who received only potentially cardiotoxic treatment or only RT_{heart}, compared with CCS who received anthracyclines.

RISK FACTORS. In multivariable logistic regression analyses (**Table 3**, **Figure 3**), abnormal LVEF was associated with younger age at cancer diagnosis, female sex, higher cumulative anthracycline dose, high RT_{heart} fraction dose (TBI) and, only in female CCS, higher RT_{heart} dose. Abnormal GLS was associated with female sex, higher RT_{heart} cumulative and fraction dose, higher diastolic blood pressure (nonlinear), and only in female CCS, higher anthracycline dose. Nonlinearity in the association of low-dose RT_{heart} with both outcomes diminished when accounting for high fraction dose (TBI). No potentially cardiotoxic treatments, including cyclophosphamide, ifosfamide, and vincristine, were independently associated with either abnormal LVEF or abnormal GLS (Supplemental Table 1). The combination of abnormal LVEF and abnormal GLS was associated with younger age at diagnosis, female sex, all cardiotoxic therapies (including mitoxantrone), but not any CVRF.

In separate multivariable logistic regression models, CCS had an increased odds of abnormal LVEF (OR: 2.9; 95% CI: 1.4-6.6), abnormal GLS (OR: 2.1; 95% CI: 1.2-3.7), and combined abnormal LVEF and GLS (OR: 3.9; 95% CI: 1.3-16.9) compared with siblings, adjusting for demographic, cardiotoxic, and cardiovascular risk factors (**Central Illustration**, **Table 3**). Odds ratios for cardiotoxic exposures remained essentially unchanged. After excluding CCS without known cardiotoxic exposures, increased odds in CCS versus siblings were still observed for abnormal LVEF (OR: 3.0; 95% CI: 1.4-7.0), abnormal GLS (OR: 1.7; 95% CI: 0.94-3.3), and for abnormal LVEF and GLS combined (OR: 3.8; 95% CI: 1.2-16.6).

Linear regression models for the continuous endpoints of LVEF, GLS, mid-GCS and lateral e' are shown

TABLE 3 Multivariable Logistic Regression of Risk Factors for Abnormal LVEF and/or GLS

		Any Abnormal LVEF				Any Abnormal GLS				Both Abnormal LVEF and GLS			
	Unit/ Reference	OR	95% CI	*P* Value	n Events/ Group Total	OR	95% CI	*P* Value	n Events/ Group Total	OR	95% CI	*P* Value	n Events/ Group Total
Model in all CCS[a]													
Age at cancer diagnosis	1 y	0.95	0.91-0.98	0.006		0.98	0.97-1.02	0.25		0.93	0.88-0.98	0.006	
Age at echocardiography	1 y	1.01	0.99-1.03	0.54		0.99	0.96-1.01	0.20		1.00	0.97-1.03	0.85	
Female	Male	1.47	1.05-2.07	0.027	165/591	1.78	1.30-2.44	<0.001	175/517	2.22	1.46-3.40	<0.001	90/509
Cumulative anthracycline dose	50 mg/m^2	Nonlinear plot[b]		<0.001[c]		Nonlinear plot[b]		0.31[c]		Nonlinear plot[b]		<0.001[c]	
Cumulative mitoxantrone dose	10 mg/m^2	1.05	0.94-1.17	0.31		1.06	0.95-1.16	0.26		1.17	1.02-1.30	0.010	
Radiotherapy dose, heart region	10 Gy	1.08	0.87-1.33	0.17		1.35	1.16-1.58	<0.001		1.37	1.14-1.64	<0.001	
High fraction dose, TBI	no	2.23	1.26-3.90	0.005	27/80	2.67	1.47-4.86	0.001	32/65	2.59	1.20-5.26	0.011	13/65
Diastolic blood pressure[d]	10 mm Hg	1.00	0.86-1.16	0.97		Nonlinear plot[b]		0.009[f]		1.00	0.82-1.23	0.97	
Waist circumference	10 cm	1.14	0.99-1.31	0.075		1.07	0.93-1.23	0.35		1.15	0.95-1.38	0.14	
Diabetes with medication	None	2.35	0.85-6.24	0.089	10/24	2.74	0.97-8.14	0.060	12/21	3.01	0.93-8.91	0.053	6/21
Lipid-lowering medication	None	1.30	0.60-2.72	0.49	18/49	1.89	0.89-4.01	0.095	20/41	1.46	0.56-3.48	0.41	9/40
Ever smoked	Never	1.01	0.72-1.41	0.95	81/338	1.25	0.90-1.74	0.19	95/307	1.21	0.78-1.87	0.39	44/300
Radiotherapy dose* sex		Interaction plot[b]		0.007		–				–			
Cumulative anthracycline dose* sex		–				Interaction plot[b]		0.019[c]		–			
Model including CCS and siblings[e]													
Childhood cancer survivors	Siblings	2.91	1.44-6.55	0.005	308/1272	2.05	1.17-3.74	0.014	328/1102	3.92	1.31-16.9	0.030	157/1102

[a]Models included all CCS in the cohort: CCS exposed to known cardiotoxic therapies as well as CCS in the exploratory risk groups exposed to potentially cardiotoxic therapies vincristine, cyclophosphamide, or ifosfamide. None of the potentially cardiotoxic therapies were significant during stepwise addition; these were therefore not added to the final model. [b]Nonlinear and interaction terms are plotted in Figure 3. [c]*P* values for polynomial risk factors denote significance of the linear term, quadratic terms were nonsignificant. [d]Diastolic blood pressure was multicollinear to both the systolic blood pressure and hypertension variables. In univariable analyses, diastolic blood pressure was most related to all outcomes. Hypertension was not related to any outcome. [e]Models included all CCS and siblings in the cohort and were adjusted for all variables that were included in the models in CCS alone, except for age at diagnosis, which is not a confounder when assessing the risk in CCS versus siblings. ORs of other variables remained practically unchanged. [f]*P* <0.01 for quadratic terms.

GLS = global longitudinal strain; TBI = total body irradiation; other abbreviations as in Tables 1 and 2.

in Supplemental Table 4 and Supplemental Figure 1. A worsening in mid-GCS was associated with all cardiotoxic therapies, including mitoxantrone.

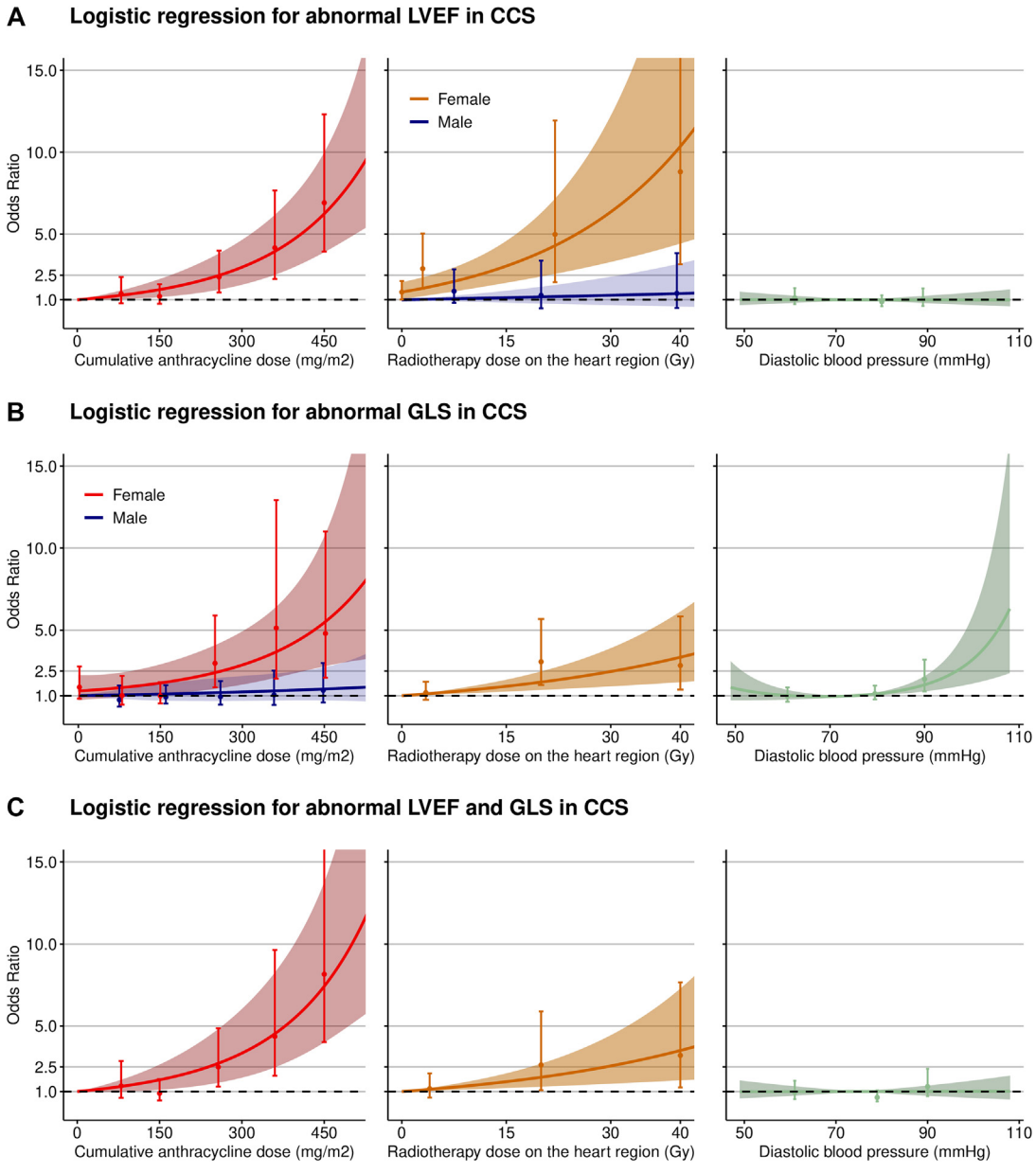
DISCUSSION

Our analysis focused on the prevalence and risk factors of cardiac dysfunction on echocardiography, defined as LVEF or GLS abnormalities compared with sex-specific normative values from healthy cohorts. Abnormal LVEF and GLS were highly prevalent in CCS compared with siblings, with abnormal GLS being the most prevalent abnormality. Both measurements do not seem interchangeable, because they identified different individuals and were associated with different risk factors. Abnormal LVEF was associated with increasing anthracycline dose, independent of sex, whereas higher RT_{heart} doses increased risk of abnormal LVEF only in women. Abnormal GLS was less clearly associated with anthracycline dose, but more with increasing RT_{heart} doses, despite the combination of abnormal LVEF and GLS again being associated with all cardiotoxic exposures.

Cyclophosphamide, ifosfamide, and vincristine were not associated with systolic dysfunction, although cardiac abnormalities were prevalent in CCS treated with potentially cardiotoxic treatments. In separate multivariable models, CCS had increased odds of abnormal LVEF (OR: 2.9) and abnormal GLS (OR: 2.1) compared with siblings, independent of demographic, known cardiotoxic, and cardiovascular risk factors.

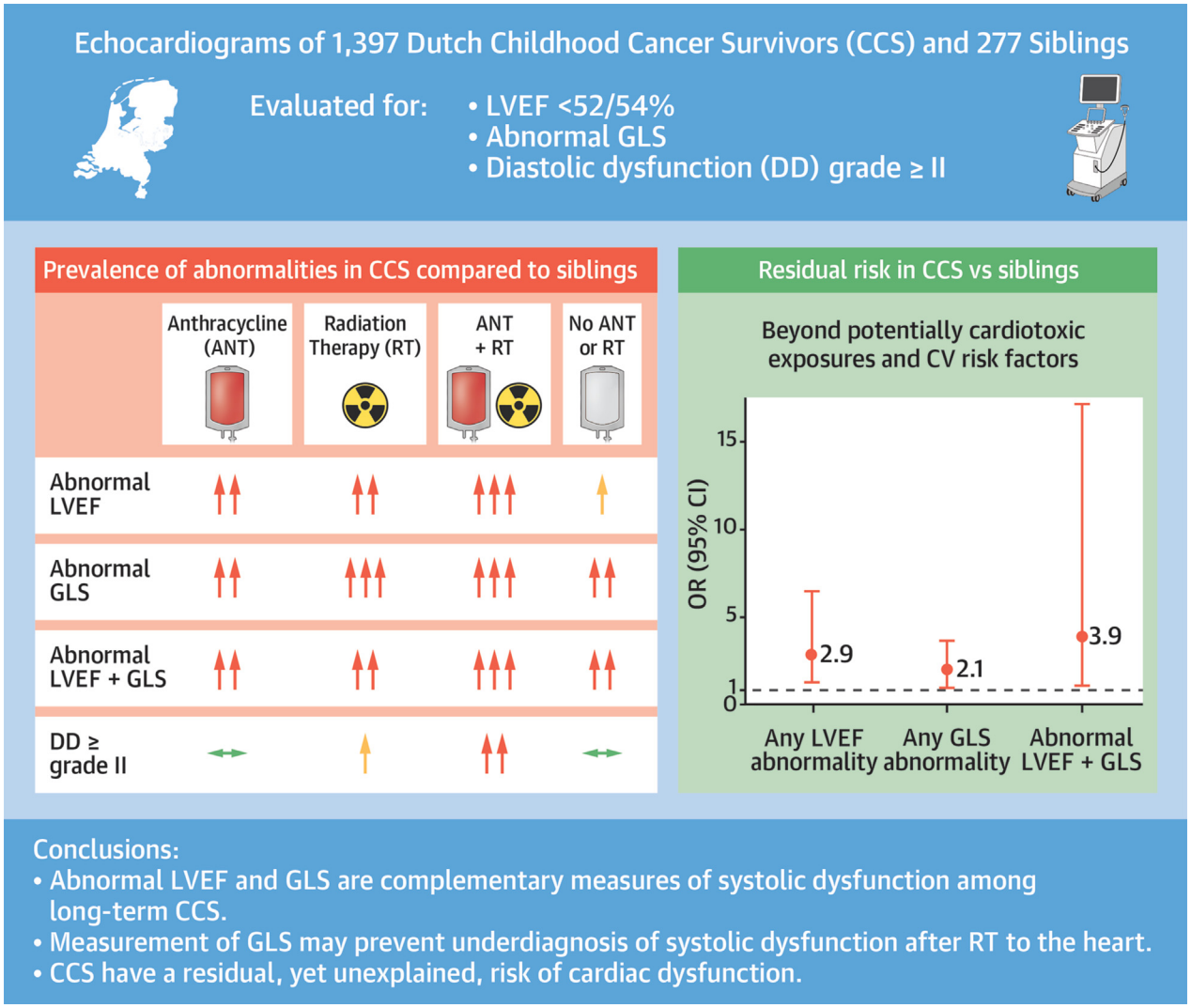
SYSTOLIC DYSFUNCTION. Prevalence of systolic dysfunction can only be interpreted in light of the risk factors present. Previous literature primarily interpreted the presence of abnormal GLS in CCS, despite a normal LVEF, as an early sign of systolic dysfunction.[7] In our cohort, abnormal GLS was also more prevalent than abnormal LVEF. However, the distribution of GLS and LVEF among CCS was not equal, but determined by different risk factors indicating different types of cardiac damage. These measurements seem, therefore, not interchangeable but complementary. The rate of normal GLS in CCS with abnormal LVEF complicates our understanding of GLS as a predictor of subsequent LVEF decline. Unavoidably, some contradictory measurements may be based on measurement errors around the lower limit of normal, with greater expected variation for

FIGURE 3 Plots of Nonlinear Associations and Interaction Terms for Abnormal LVEF and/or GLS



Plots depict nonlinear or interaction ORs for (any) abnormal LVEF **(A)**, (any) GLS **(B)**, and the combination of abnormal LVEF and GLS **(C)** in CCS in a multivariable logistic regression model. **Shaded areas** denote 95% CIs. **Dots and whiskers** indicate risk estimates for categorical risk factor variables and are plotted at the category median value of noncases. Abbreviations as in Figures 1 and 2.

CENTRAL ILLUSTRATION **The Dutch Childhood Cancer Survivor Study, Echocardiography Substudy**



Merkx R, et al. J Am Coll Cardiol CardioOnc. 2023;5(4):472–485.

The **left panel** shows prevalence of cardiac abnormalities in childhood cancer survivors compared with sibling control subjects; **green arrows** denote comparable prevalence, **yellow arrows** denote slightly elevated prevalence, and **red arrows** denote markedly elevated prevalence. The **right panel** shows the residual risk of cardiac abnormalities compared with siblings, after correction for demographics, cardiotoxic therapies, and cardiovascular risk factors. ANT = anthracyclines or mitoxantrone; CCS = childhood cancer survivors; CV = cardiovascular; DD = diastolic dysfunction; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; RT = radiotherapy to the heart region.

LVEF than GLS. Among all cardiotoxic exposures, cases were present where abnormal LVEF and abnormal GLS corroborated each other, probably indicating more severe cardiac dysfunction.

A cardiac geometry study supports the interpretation that GLS and LVEF represent different components of LV function because LVEF mainly depends upon circumferential rather than longitudinal shortening.[9] Furthermore, ventricular size confounds LVEF (biased high in smaller ventricles and vice versa).[9,21] Because irradiated hearts are generally smaller and show more concentric remodeling,[22,23] GLS may better indicate cardiac dysfunction in this subpopulation. Conversely, abnormal LVEF with normal GLS may be expected in a dilated phenotype, which may be more often seen after anthracyclines.

The interpretation of the combination of multiple systolic function measurements within an individual should be further elucidated. Meanwhile, measurement of both LVEF and GLS in clinic may prevent underdiagnosis of systolic dysfunction after RT_{heart}.

GCS measurement may provide useful insight into cardiac dysfunction mechanisms because it contributes more to LVEF than GLS.[9] However, varying normality thresholds in literature (~1.0 to 1.5 times the magnitude of GLS[18,24]) hamper a clinically useful definition of abnormality. In our linear regression analysis, mid-GCS showed stronger associations with anthracyclines and highly cardiotoxic mitoxantrone doses[15] than GLS. Thus, GCS may indeed contain important information, and there is a need for better definitions of normative values and investigation of its prognostic significance.

RISK FACTORS. Similar to our study, previous studies did not suggest an association between GLS with anthracycline dose,[7,25,26] or only determined associations with the highest doses.[27] In the St. Jude Lifetime Study, high-dose anthracyclines were mainly associated with abnormal LVEF, rather than abnormal GLS, whereas low-dose RT_{heart} influenced GLS, but not LVEF.[6]

The inclusion of mutually exclusive "reference groups" treated with either cyclophosphamide, ifosfamide, or vincristine, but no known cardiotoxic treatments, enabled us to more precisely assess the risk associated to these therapies. Our study confirms earlier negative results describing a lack of association of these therapies with echocardiographic-defined cardiac dysfunction in a study that included only high-risk CCS (treated with cardiotoxic therapies or high-dose cyclophosphamide/ifosfamide).[10] We recently showed that there was no dose-response relationship between vincristine and cardiac dysfunction in CCS without other cardiotoxic exposures.[28] Definitive exclusion of these therapies as cardiotoxic requires further study, for example, further exploration of our prior finding that low-dose cyclophosphamide has a nonlinear risk of heart failure.[3]

Sex has been a controversial risk factor in CCS. Heart failure studies in CCS reported either neutral findings or an increased risk in women,[2,3] whereas most echocardiography studies reported mixed results after not applying sex-specific thresholds.[6,7,29] Using well-established sex-specific cutoffs, we found that female CCS have a higher risk of abnormal LVEF and GLS, along with a female sex-dependent relationship with cardiotoxic treatment doses. Obviously, such analyses are impacted by the chosen thresholds, but testing a generic threshold for both sexes (ie, LVEF <53%) does not account for established sex differences.[17] Lipshultz et al[29] reported an interaction between anthracycline dose and female sex in CCS, using sex-specific contractility Z-scores; no reports addressed interactions of RT_{heart} dose with sex. Ionizing radiation affects both the macro- and microvasculature.[30] Estrogens may play an important role in the sex-specific risk of cardiotoxicity because they modulate tolerance of ischemia/reperfusion damage in female hearts.[31] Accordingly, premature ovarian failure in some CCS may negatively affect the response mechanism to radiation-induced vascular damage. The differential influence of cardiotoxic therapies on cardiac tissue according to sex needs further exploration.

Our cohort reported a low prevalence of CVRF. Abnormal GLS was related to current diastolic blood pressure, but not waist circumference. It remains unclear whether this association represents cardiac damage from hypertension, or only the load dependency of GLS. In the St. Jude Lifetime Study, traditional CVRF were prevalent, and GLS was associated with all components of the metabolic syndrome.[6] Also, CVRF explained much greater variance in GLS than cardiotoxic exposures.[32] A potential added value of GLS may therefore lie in identifying CCS in whom CVRF cause abnormal cardiac measurements and need more aggressive management. The influence of antihypertensive treatment on GLS needs exploration.

UNKNOWN RISK FACTORS. The sibling control group constitutes a strength of our cohort. CCS showed a high residual risk of systolic dysfunction compared with sibling control subjects, independent of established or potentially cardiotoxic therapy doses and CVRF. Our analyses included confirmation that doses of cyclophosphamide, ifosfamide, vincristine, and various other potentially cardiotoxic agents were not associated with systolic dysfunction.

Several confounders may explain a residual cardiovascular risk, including predisposing genetic variants and time-dependent effects. However, CCS unexposed to known cardiotoxic therapies also carry a risk of systolic dysfunction.[28,33] Risk factors to explore may include sepsis, intensive care unit admission, and steroid support during childhood cancer treatment, early cardiotoxicity, nephrotoxicity, systemic inflammation, lifestyle, and exercise capacity. The finding of GLS abnormalities in childhood cancer patients even before chemotherapy[34]

supports the hypothesis of still unknown, probably systemic, risk factors related to childhood cancer that should be further explored.

DIASTOLIC DYSFUNCTION. Evolving definitions hamper assessment and comparison of diastolic function in CCS populations. Our cohort showed very low prevalence of diastolic dysfunction ≥grade II, although more subtle diastolic function changes were detected. Lateral e', mostly representing myocardial stiffness, was related to age and RT_{heart} dose in the current and previous studies.[6,22] The St. Jude Lifetime Study also related diastolic dysfunction (grades I to III) to age and RT_{heart} dose.[6]

Of note, irradiated hearts are generally smaller,[22,35] which might justify different definitions of left atrial dilatation in CCS. Left atrial longitudinal strain may be superior to left atrial size in detecting elevated filling pressures and may be useful when the current diagnostic algorithm yields an indeterminate result.[36]

STUDY LIMITATIONS. The risk of survival bias in long-term follow-up cohorts is evident. We may have underestimated systolic dysfunction in CCS treated for cardiomyopathy. Multicollinearity of echocardiographic measurements with clinical heart failure prevented us from correcting for this phenomenon. Excluding such CCS would have skewed results toward a more healthy phenotype, whereas the opposite may apply to the current analyses. For eligible CCS per study arm, echocardiograms were deemed "missing at random" (data not shown). Heterogeneity within and between CCS cohorts warrants reproduction of our results regarding the sex interactions and residual risk for cardiac dysfunction of CCS versus siblings.

We analyzed prescribed RT_{heart} dose, which is not the absorbed dose. Nonlinearity of RT_{heart} dose-response relations diminished when correcting for high fraction dose (TBI), and this variable was associated with all cardiac outcomes. However, TBI recipients constitute a distinct subgroup of CCS, hampering attribution of risk solely to TBI. Currently, surveillance recommendations are lacking for CCS who received low-dose RT_{heart} in unconventional fractionation,[37] although irradiated volume and TBI-fraction dose are proposed cardiac risk factors.[38,39]

Although we used vendor-independent speckle tracking software, strain analyses require time and expertise. Many vendors implement semiautomated measurements to expedite its clinical use. Proposed simplified GLS thresholds of −18% (borderline) and −16% (abnormal) still require prognostic validation in CCS and are not sex-specific.[40] Three-dimensional LVEF measurement was not feasible in all participating centers.

CONCLUSIONS

Among long-term CCS, abnormal LVEF and abnormal GLS constitute complementary measures of systolic LV dysfunction, as they are affected differently by cardiotoxic treatments. GLS measurement may prevent underdiagnosis of systolic dysfunction after RT_{heart}. The prognostic value of GLS and GCS, as well as of combinations of (ab)normal LVEF and GLS within individual CCS, needs further investigation.

There may be sex-dependent contributions of cardiotoxic therapy doses. Because the risk of cardiac dysfunction in long-term CCS is not fully explained by demographics, cardiotoxic therapy doses, and traditional CVRF, future research should explore genetics, lifestyle factors, or additional cancer-related variables as potential risk factors for systolic dysfunction.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In long-term CCS, LVEF and GLS constitute complementary measures of systolic dysfunction. Measurement of GLS may prevent underdiagnosis of systolic dysfunction after RT_{heart}. Cyclophosphamide, ifosfamide and vincristine were not associated with systolic dysfunction. Compared to siblings, and even after accounting demographics, established or potentially cardiotoxic exposures, traditional cardiovascular risk factors, cardiac abnormalities were more prevalent in CCS.

TRANSLATIONAL OUTLOOK: The prognostic value of the combination of (ab)normal LVEF and GLS within an individual should be further elucidated. Further research should explore the residual risk of cardiac dysfunction in CCS that is not explained by demographic, cardiotoxic therapy doses and traditional cardiovascular risk factors.

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KEY WORDS **cancer survivors, cardiotoxicity, child, echocardiography, global longitudinal strain, left ventricular dysfunction**

APPENDIX **For an expanded Methods section as well as supplemental figure and tables, please see the online version of this paper.**