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ORIGINAL RESEARCH

A Biomarker-Based Diagnostic Model for Cardiac Dysfunction in Childhood Cancer Survivors

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ABSTRACT

BACKGROUND Childhood cancer survivors at risk for heart failure undergo lifelong echocardiographic surveillance. Previous studies reported the limited diagnostic accuracy of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) in detecting left ventricular (LV) dysfunction. However, potential enhanced diagnostic accuracy through the combination of biomarkers and clinical characteristics has been suggested.

OBJECTIVES The aim of this study was to develop and internally validate a diagnostic model that combines cardiac biomarkers with clinical characteristics for effectively ruling in or ruling out LV dysfunction in childhood cancer survivors.

METHODS A multicenter cross-sectional study included 1,334 survivors (median age 34.2 years) and 278 siblings (median age 36.8 years). Logistic regression models were developed and validated through bootstrapping, combining biomarkers with clinical characteristics.

RESULTS Abnormal NT-proBNP levels were observed in 22.1% of survivors compared with 5.4% of siblings, whereas hs-cTnT levels exceeding 10 ng/L were uncommon in both survivors (5.9%) and siblings (5.0%). The diagnostic models demonstrated improvement upon the addition of NT-proBNP and hs-cTnT to clinical characteristics, resulting in an increased C statistic from 0.69 to 0.73 for LV ejection fraction (LVEF) <50% and a more accurate prediction of more severe LV dysfunction, with the C statistic increasing from 0.80 to 0.86 for LVEF <45%. For LVEF <50% (prevalence 10.9%), 16.9% of survivors could be effectively ruled out with high sensitivity (95.4%; 95% CI: 90.4%-99.3%) and negative predictive value (97.5%; 95% CI: 94.6%-99.7%). Similarly, for LVEF <45% (prevalence 3.4%), 53.0% of survivors could be ruled out with moderate to high sensitivity (91.1%; 95% CI: 79.2%-100%) and high negative predictive value (99.4%; 95% CI: 98.7%-100%).

CONCLUSIONS The biomarker-based diagnostic model proves effective in ruling out LV dysfunction, offering the potential to minimize unnecessary surveillance echocardiography in childhood cancer survivors. External validation is essential to confirm these findings. (Early Detection of Cardiac Dysfunction in Childhood Cancer Survivors; A DCOG LATER Study; https://onderzoekmetmensen.nl/nl/trial/23641) (J Am Coll Cardiol CardioOnc 2024;6:236-247)

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Cardiovascular disease poses a major concern among the growing number of long-term childhood cancer survivors (CCS).[1,2] Approximately 11% of CCS treated with anthracyclines, mitoxantrone, and/or chest-directed radiotherapy develop heart failure within 40 years of their cancer diagnoses.[3] Lifelong echocardiographic surveillance is currently recommended to prevent or delay heart failure through the early detection of left ventricular (LV) dysfunction, with surveillance intervals determined on the basis of cumulative doses of anthracycline, mitoxantrone, and chest-directed radiotherapy.[4,5]

The role of cardiac biomarkers in the long-term surveillance of CCS remains uncertain. Biomarkers could potentially serve as a cost-effective triage test, helping determine whether to proceed with or delay echocardiography. If a blood biomarker test can effectively rule out LV dysfunction, echocardiography may be deferred until the next scheduled surveillance time point. Despite previous studies reporting limited diagnostic accuracy of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) in detecting LV dysfunction in long-term CCS,[6,7] leading to a recommendation against using cardiac biomarkers for surveillance in CCS,[4,5] several unresolved questions persist. First, although previous studies investigated cardiac biomarkers as a stand-alone diagnostic test for detecting LV dysfunction,[6] combining them with clinical information might improve diagnostic performance.[8] Second, studies among CCS have not investigated biomarker cutoff concentrations specific for ruling out or ruling in LV dysfunction, a potential factor in improving diagnostic performance.[6] Third, it remains unclear in CCS whether cardiac biomarkers might be more effective at diagnosing more significant LV dysfunction, a consideration acknowledged in a previous study in the general population.[9]

In the context of this cross-sectional multicenter study, we endeavored to develop and internally validate diagnostic models that integrated cardiac biomarkers with clinical characteristics. The primary aim was to ascertain their effectiveness in ruling in or ruling out LV dysfunction in CCS who had not previously received a diagnosis of cardiomyopathy.

ABBREVIATIONS AND ACRONYMS

CCS = childhood cancer survivor(s)

hs-cTnT = high-sensitivity cardiac troponin T

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

NPV = negative predictive value

NRI = net reclassification improvement

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PPV = positive predictive value

METHODS

STUDY POPULATION. We conducted a multicenter cross-sectional study involving CCS and their siblings as participants in the Dutch Childhood Cancer Survivor Study, specifically the LATER (Late Effects After Childhood Cancer) part 2 cardiology study (DCCSS LATER2 CARD). DCCSS LATER2 CARD is a multicenter study conducted across 7 pediatric oncology centers in the Netherlands, encompassing individuals diagnosed with malignancies before 18 years of age between January 1, 1963, and December 31, 2001. The study specifically focuses on individuals who, having been treated with cardiotoxic cancer treatments, are 5 years postdiagnosis.[10] Participants visited the outpatient clinic of each participating center between February 2016 and February 2020, undergoing questionnaires, physical examinations, blood sampling, and echocardiography.

For the present study, we included CCS treated with anthracyclines, mitoxantrone, and/or chest-directed radiotherapy, excluding those with previous diagnoses of cardiomyopathy to mirror a surveillance population. To align with the most recent

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surveillance guidelines,[5] which no longer recommend surveillance in low-risk CCS (defined as anthracycline dose <100 mg/m^2 and chest-directed radiotherapy dose <15 Gy), we conducted a secondary analysis excluding these low-risk CCS. Siblings of CCS served as control subjects. Participants who were pregnant, had histories of heart transplantation, or had severe congenital heart disease that could interfere with echocardiographic measurements of LV function were excluded from the study.

ETHICS. The study was approved by the medical ethics boards of all participating centers and included the storage of blood samples. Informed consent was obtained from all participants.

CLINICAL CHARACTERISTICS. Patient and cancer treatment characteristics were extracted from the central database of the study. The cumulative anthracycline or anthraquinone dose was calculated using doxorubicin equivalents.[11] The radiotherapy dose received by the heart was calculated following a standardized protocol (see Supplemental Methods). Medical history, use of cardiac medications, and cardiac symptoms were obtained from questionnaires. Participants were considered to have self-reported heart failure, hypertension, and diabetes if they also reported using medications for these conditions. A physical examination was conducted at the time of blood sampling to obtain data on body mass index, heart rate, and blood pressure.

BLOOD BIOMARKERS. NT-proBNP, hs-cTnT, and creatinine levels were measured in fasting serum samples at the Erasmus Medical Center in the Netherlands. Fasting serum samples were collected from participants within 1 year of the qualifying echocardiographic examination, with 89% obtained on the same day. After centrifugation at 3,000 × *g* for 10 minutes, samples were shipped on dry ice to the central biobank and stored at −80 °C.

The assay range for NT-proBNP was 5 to 35,000 ng/L (Cobas e601, Roche Diagnostics), and for hs-cTnT, it was 3 to 10,000 ng/L (Cobas e602, Roche Diagnostics). Biomarker values less than the limit of detection (NT-proBNP, n = 111; hs-cTnT, n = 543) were set at the limit of detection divided by the square root of 2. An abnormal NT-proBNP was defined as the 97.5th percentile value exceeding age- and sex-specific normal values in the Framingham Heart Study cohort obtained using the quantile regression method (Supplemental Table 1).[12] An abnormal hs-cTnT level was defined as ≥10 ng/L, in line with a previous study among CCS.[7] Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula.[13]

ECHOCARDIOGRAPHY. Two core laboratory physicians (R.M. and J.M.L.) independently measured echocardiographic parameters, with biplane LV ejection fraction (LVEF) serving as the main outcome. This evaluation took place in a core laboratory that was blinded to both blood biomarker results and patient characteristics.[14] The reproducibility of our echocardiographic outcomes has been previously published.[14] For biplane LVEF, the intraclass correlation coefficients for intraobserver variability and interobserver variability were 0.87 and 0.85, respectively. The upper agreement limit of biplane ejection fraction was +8%, and the lower agreement limit was −4.5%. We used the following definitions for LV dysfunction: LVEF <54% for female subjects and LVEF <52% for male subjects,[15] LVEF <50%, and LVEF <45%.

MISSING VALUES. Cardiac biomarkers had missing values, each constituting <5%. Cardiotoxic cancer treatment doses had minimal missing data (≤1%). Traditional cardiovascular risk factors, including self-reported history of hypertension, diabetes, dyslipidemia, and smoking, had missing data ranging from 8% to 10%. LVEF had a higher percentage of missing data at 17%. Supplemental Table 2 presents a comparison of characteristics of CCS with and without any missing data. We assumed these to be missing values to be random and used predictive mean matching for imputation, with the process repeated 20 times.[16] The imputation model included all variables considered in the diagnostic models, along with additional measures of LV function (fractional shortening, mitral annular plane systolic excursion) to improve LVEF imputations. Analyses were performed on each imputed data set, and the results were pooled using Rubin's rules.[16] We also compared these imputed results with those obtained through a complete case analysis.

STATISTICAL ANALYSES. Continuous biomarker concentrations are presented as median (Q1-Q3). Abnormal biomarker levels (yes or no) are reported as counts and percentages. Associations between cardiac biomarker concentrations and LVEF in CCS were visually represented through local polynomial regression fitting.

We established predefined criteria for ruling out (negative predictive value [NPV] ≥98% and sensitivity ≥90%) and ruling in (positive predictive value [PPV] ≥75% and specificity ≥90%) LV dysfunction. These criteria were based on previous studies focusing on the diagnosis of heart failure in dyspneic patients.[8,17] Findings in the 3 defined

categories of LV dysfunction were subsequently compared.

We calculated the diagnostic test accuracies, including sensitivity, specificity, PPV, and NPV, using multiple cutoff concentrations of NT-proBNP (within normal values based on age and sex,[12] ranging from 10 to 600 ng/L) and concentrations of hs-cTnT (ranging from 3 to 14 ng/L).

Next, we proceeded to develop and internally validate multivariable logistic regression models aimed at estimating the probability of 3 categories of LV dysfunction in CCS. The first model solely considered clinical predictors, including sex, age at diagnosis, age at study, anthracycline dose (including doxorubicin-equivalent dose of mitoxantrone), chest-directed radiotherapy dose, history of hypertension, hypercholesterolemia, diabetes, smoking, body mass index, heart rate, and systolic blood pressure at the time of blood sampling. A backward selection approach was applied with a significance threshold of 0.05, obtained using the pooled Wald test for multiple imputed data, considering variables occurring in more than 50% of imputed models to be included in the final clinical model.[16] Sex, age at diagnosis, age at study, and cardiotoxic treatments were not subjected to this backward selection process.

In the second model, we added NT-proBNP and hs-cTnT (continuous scale) to the clinical model and tested for improvement in model fit using the pooled Wald test. We also examined the impact on model fit when incorporating restricted cubic splines, allowing for a nonlinear association of biomarker levels with the outcome.[18] The C statistic, sensitivity, specificity, PPV, and NPV were calculated using optimal cutoffs for rule-in and rule-out derived from receiver-operating characteristic curve analysis. These results underwent internal validation through 500 bootstrap resamples in each of the imputed data sets, adjusting for optimism and calculating 95% CIs.

Calibration was evaluated by plotting the observed vs predicted risk for LV dysfunction in 10 groups, with calibration tested using the Spiegelhalter test ($P < 0.05$ indicates inadequate model calibration). The categorical net reclassification improvement (NRI) was calculated by adding cardiac biomarkers to the clinical model at the optimal cutoff for rule-out.[19] This metric quantifies the percentage of patients whose predicted risk category is correctly altered with the inclusion of cardiac biomarkers in the clinical model and is assessable for cases and noncases. All analyses were conducted using R version 4.2

TABLE 1 Characteristics of Participating Childhood Cancer Survivors and Siblings

	Survivors (n = 1,334)	Siblings (n = 278)
Female	625 (46.9)	166 (59.7)
Age at diagnosis, y	6.3 (3.2-11.3)	NA
Age at study, y	34.2 (28.5-41.5)	36.8 (29.1-43.7)
Primary cancer diagnosis		
Leukemias, myeloproliferative diseases, and myelodysplastic diseases	537 (40.3)	
Lymphomas and reticuloendothelial neoplasms	342 (25.6)	
CNS and miscellaneous intracranial and intraspinal neoplasms	43 (3.2)	
Neuroblastoma and other peripheral nervous cell tumors	50 (3.7)	
Retinoblastoma	0 (0.0)	
Renal tumors	150 (11.2)	
Hepatic tumors	12 (0.9)	
Bone tumors	112 (8.4)	
Soft tissue and other extraosseous sarcomas	71 (5.3)	
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	12 (0.9)	
Other malignant epithelial neoplasms and malignant melanomas	4 (0.3)	
Other and unspecified malignant neoplasms	1 (0.1)	
NA	0 (0.0)	
IGHG risk group		
Low risk	306 (22.9)	
Moderate risk	596 (44.7)	
High risk	432 (32.4)	
NA	0 (0.0)	
Anthracycline dose, mg/m^2		
No anthracyclines	202 (15.1)	
1-100	207 (15.5)	
100-250	603 (45.2)	
>250	302 (22.6)	
Missing	20 (1.5)	
Mitoxantrone dose, mg/m^2		
No mitoxantrone	1,258 (94.3)	
1-40	42 (3.1)	
>40	28 (2.1)	
Missing	6 (0.4)	
Chest-directed RT dose, Gy		
No chest-directed RT	896 (67.2)	
1-15	277 (20.8)	
15-30	99 (7.4)	
>30	52 (3.9)	
Missing	10 (0.7)	
Hypertension		
No	1,138 (85.3)	228 (82.0)
Yes	68 (5.1)	2 (0.7)
Missing	128 (9.6)	48 (17.3)
Diabetes		
No	1,183 (88.7)	231 (83.1)
Yes	27 (2.0)	0 (0.0)
Missing	124 (9.3)	47 (16.9)

Continued on the next page

TABLE 1 Continued

	Survivors (n = 1,334)	Siblings (n = 278)
Hypercholesterolemia		
No	1,152 (86.4)	227 (81.7)
Yes	44 (3.3)	1 (0.4)
Missing	138 (10.3)	50 (18.0)
Smoking		
No	859 (64.4)	140 (50.4)
Yes	364 (27.3)	83 (29.9)
Missing	111 (8.3)	55 (19.8)
BMI, kg/m^2	24.0 (21.6-26.9)	25.2 (23.0-27.8)
Systolic blood pressure, mm Hg	123.0 (114.0-134.0)	120.0 (112.0-131.0)
Diastolic blood pressure, mm Hg	76.0 (69.0-82.0)	74.0 (67.0-81.0)
Heart rate, beats/min	70.0 (62.0-79.0)	63.0 (56.7-70.1)
eGFR, mL/min/1.73 m^2	107.8 (92.4-125.8)	103.8 (89.5-123.2)
NT-proBNP, ng/L	42.3 (25.4-84.6)	33.8 (16.9-59.2)
Abnormal NT-proBNP for age and sex		
No	996 (74.7)	232 (83.5)
Yes	295 (22.1)	15 (5.4)
Missing	43 (3.2)	31 (11.2)
hs-cTnT, ng/L	4.0 (2.2-5.0)	3.0 (2.4-5.0)
Abnormal hs-cTnT (≥10 ng/L)		
No	1,214 (91.0)	233 (83.8)
Yes	77 (5.8)	14 (5.0)
Missing	43 (3.2)	31 (11.2)

Values are n (%) or median (Q1-Q3).

BMI = body mass index; CNS = central nervous system; eGFR = estimated glomerular filtration rate; hs-cTnT = high-sensitivity cardiac troponin T; IGHG = International Late Effects of Childhood Cancer Guideline Harmonization Group; NA = not applicable; NT-proBNP = N-terminal pro-B-type natriuretic peptide B; RT = radiotherapy.

(R Foundation for Statistical Computing). *P* values <0.05 were considered to indicate statistical significance.

RESULTS

STUDY POPULATION. Of the 6,165 CCS in the DCCSS LATER cohort, 2,986 CCS met the eligibility criteria for the LATER2 CARD study (Supplemental Figure 1). Of these CCS, 1,605 (54%) participated in the LATER2 CARD study. Although participants were more frequently female (48%) compared with non-participants (39%), no clinically relevant differences were observed between participants and non-participants in other patient and treatment characteristics (Supplemental Table 3). After excluding CCS with previous diagnoses of cardiomyopathy (n = 51) and CCS not treated with anthracyclines, mitoxantrone, or chest-directed radiotherapy (n = 220), 1,334 CCS were included in the present study. A total of 278 siblings served as control subjects (Supplemental Figure 1).

Characteristics of the included CCS and siblings are presented in **Table 1**. CCS were slightly younger (median age 34.2 years; Q1-Q3: 28.5-41.5 years), with fewer women among CCS compared with siblings (46.9% vs 59.7%; median age 36.8 years; Q1-Q3: 29.1-43.7 years).

CARDIAC BIOMARKERS IN CCS COMPARED WITH SIBLINGS. The median NT-proBNP concentration was higher in CCS compared with siblings (42.3 ng/L [Q1-Q3: 25.4-84.6 ng/L] vs 33.8 ng/L [Q1-Q3: 16.9-59.2 ng/L], respectively), and abnormal NT-proBNP levels for age and sex were more frequent among CCS compared with siblings (22.1% vs 5.4%) (**Table 1**). The median hs-cTnT concentration did not differ significantly in CCS (4.0 ng/L; Q1-Q3: 2.2-5.0 ng/L) compared with siblings (3.0 ng/L; Q1-Q3: 2.4-5.0 ng/L), and abnormal hs-cTnT levels (≥10 ng/L) were rare in both CCS (5.8%) and siblings (5.0%) (**Table 1**).

DIAGNOSTIC ACCURACY OF CARDIAC BIOMARKERS ONLY. Among the 1,334 CCS, 23.2% exhibited LVEF <54% (women) or LVEF <52% (men), 10.9% had LVEF <50%, and 3.4% had LVEF <45%. Visual inspection of local polynomial regression curves of both biomarkers with LVEF showed increasing NT-proBNP and hs-cTnT concentrations in CCS with lower LVEF, especially when LVEF decreased to <50% (Supplemental Figure 2). The diagnostic accuracy of abnormal NT-proBNP or abnormal hs-cTnT in isolation was insufficient to either rule out or rule in any category of LV dysfunction (**Table 2**), even when using lower cutoff concentrations for ruling out or higher cutoff concentrations for ruling in (Supplemental Table 4).

DIAGNOSTIC ACCURACY OF CARDIAC BIOMARKERS IN COMBINATION WITH CLINICAL CHARACTERISTICS. Clinical characteristics included in the final multivariable diagnostic model, determined through backward selection, comprised sex, age at diagnosis, age at study, anthracycline dose, mitoxantrone dose, chest-directed radiotherapy dose, and heart rate (see **Table 3**). For all 3 categories of LV dysfunction, adding NT-proBNP and hs-cTnT to the clinical characteristics significantly improved the diagnostic model compared with the model with clinical characteristics alone ($P < 0.05$, pooled Wald test) (**Table 3**).

The discriminatory power of the diagnostic model improved with the addition of cardiac biomarkers to clinical characteristics, resulting in an increase in the C statistic from 0.69 to 0.73 for LVEF <50% and from 0.80 to 0.86 for LVEF <45% (**Figure 1**, **Table 2**). The addition of cardiac biomarkers to clinical characteristics expanded the proportion of CCS that could be ruled out for LVEF <50% (from 9.7% to 16.9%) and LVEF <45% (from 34.6% to 53.0%), demonstrating high NPV and sensitivity (**Table 2**).

TABLE 2 Diagnostic Accuracy of Models Based on Cardiac Biomarkers and Clinical Characteristics to Detect Left Ventricular Dysfunction

	C Statistic	Cutoff	Ruled Out, %[a]	Sensitivity, %	Specificity, %	PPV, %	NPV, %
LVEF <52% in men, LVEF <54% in women (prevalence 23.2%)							
NT-proBNP	0.63 (0.59-0.66)	Age/sex[b]	77.0	35.2 (29.6-40.8)	80.7 (78.2-83.2)	35.5 (29.6-41.3)	80.5 (77.8-83.3)
hs-cTnT	0.55 (0.51-0.60)	10 ng/L	94.1	10.5 (6.8-14.1)	95.4 (94.1-96.8)	40.7 (28.8-52.7)	78.0 (75.3-80.6)
Clinical[c]	0.67 (0.64-0.71)	9.0%[d]	2.5	100 (98.6-100)	3.3 (0.1-5.1)	23.6 (22.6-24.6)	99.1 (91.8-100)
Clinical + NT-proBNP	0.70 (0.66-0.73)	9.0%[d]	2.8	99.7 (98.0-100)	3.5 (0.1-5.8)	23.6 (22.5-24.7)	96.6 (89.6-100)
Clinical + NT-proBNP + hs-cTnT	0.70 (0.67-0.73)	9.0%[d]	3.4	99.3 (97.4-100)	4.3 (0.2-7.0)	23.7 (22.6-24.9)	95.4 (89.3-100)
LVEF <50% (prevalence 10.9%)							
NT-proBNP	0.63 (0.58-0.69)	Age/sex[b]	77.0	44.9 (36.2-53.7)	79.7 (77.3-82.1)	21.3 (16.3-26.4)	92.2 (90.3-94.1)
hs-cTnT	0.64 (0.59-0.69)	10 ng/L	94.1	15.6 (9.2-22.1)	95.2 (94.0-96.5)	28.7 (17.8-39.6)	90.2 (88.3-92.1)
Clinical[c]	0.69 (0.64-0.74)	4.3%[d]	9.7	97.9 (93.0-100)	10.6 (4.8-18.1)	11.6 (10.7-12.5)	97.2 (94.0-100)
Clinical + NT-proBNP	0.72 (0.67-0.77)	4.3%[d]	15.1	95.3 (90.3-99.3)	16.4 (7.9-26.3)	12.1 (11.1-13.6)	97.0 (94.0-99.6)
Clinical + NT-proBNP + hs-cTnT	0.73 (0.68-0.78)	4.3%[d]	16.9	95.4 (90.4-99.3)	18.3 (9.1-29.0)	12.4 (11.3-13.3)	97.5 (94.6-99.7)
LVEF <45% (prevalence 3.4%)							
NT-proBNP	0.75 (0.65-0.84)	Age/sex[b]	77.0	65.0 (50.3-79.7)	78.5 (76.2-80.8)	9.7 (6.3-13.1)	98.4 (97.6-99.3)
hs-cTnT	0.75 (0.67-0.83)	10 ng/L	94.1	24.5 (10.9-38.0)	94.7 (93.5-96.0)	14.1 (5.9-22.4)	97.2 (96.3-98.2)
Clinical[c]	0.80 (0.73-0.86)	1.5%[d]	34.6	92.9 (83.1-100)	35.7 (28.7-44.0)	5.0 (4.2-5.6)	99.5 (98.7-100)
Clinical + NT-proBNP	0.85 (0.79-0.91)	1.5%[d]	49.8	91.7 (80.0-100)	51.2 (38.7-57.4)	6.2 (4.9-7.3)	99.5 (98.8-100)
Clinical + NT-proBNP + hs-cTnT	0.86 (0.80-0.91)	1.5%[d]	53.0	91.1 (79.2-100)	54.5 (42.9-61.2)	6.6 (5.2-7.8)	99.4 (98.7-100)

Values in parentheses are 95% CIs. All accuracy measures in the table are bootstrap optimism corrected. [a]Percentage of survivors ruled out for left ventricular dysfunction. [b]Abnormal NT-proBNP cutpoints defined by 97.5th percentile limit of normal by age and sex from the Framingham Heart Study (see Supplemental Table 1). [c]Clinical characteristics: sex, age at diagnosis, age at study, anthracycline dose (including doxorubicin-equivalent dose of mitoxantrone), chest-directed radiotherapy dose, and heart rate. [d]Predicted risk cutoff for left ventricular dysfunction from the multivariable logistic regression model maximizing the number of survivors ruled out while aiming for NPV ≥98% and sensitivity ≥90%.

LVEF = left ventricular ejection fraction; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table 1.

Net reclassification also improved with the addition of cardiac biomarkers to the clinical characteristics for LVEF <50% (NRI 6.50%; $P < 0.001$) and for LVEF <45% (NRI 13.80%; $P < 0.001$). This improvement was driven by appropriate reclassification of survivors without LV dysfunction (Table 4). The diagnostic models, combining cardiac biomarkers and clinical characteristics, were well calibrated for all 3 categories of LV dysfunction (Figure 2).

At the optimal rule-out predicted risk cutoff, determined by receiver-operating characteristic curve analysis, the diagnostic model incorporating clinical characteristics and cardiac biomarkers could rule out LVEF <54% (women) or LVEF <52% (men) in only 3.4% of survivors, achieving sensitivity of 99.3% (95% CI: 97.4%-100%) and NPV of 95.4% (95% CI: 89.3%-100%) (Table 2). In contrast, for ruling out LVEF <50%, the optimal rule-out predicted risk cutoff

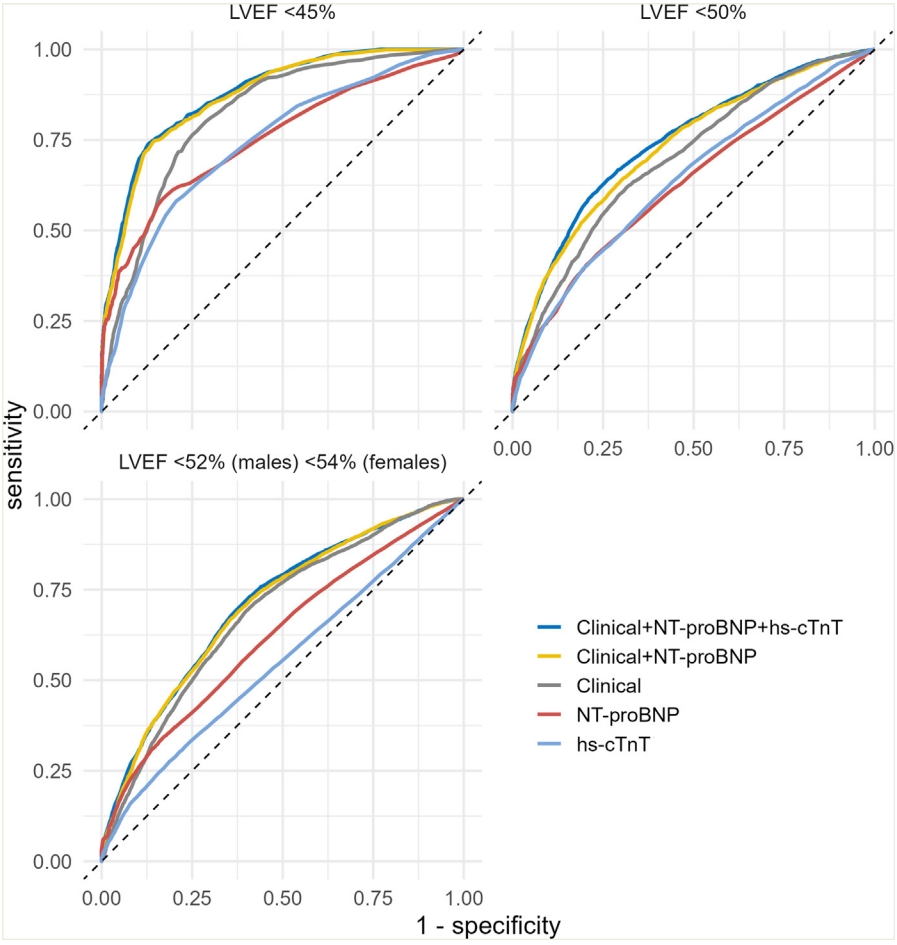
TABLE 3 Odds Ratios for Clinical Characteristics and Cardiac Biomarkers Included in the Full Diagnostic Model

		LVEF <52% (Men), LVEF <54% (Women)		LVEF <50%		LVEF <45%	
	Q1-Q3	OR	*P* Value	OR	*P* Value	OR	*P* Value
Female vs male	–	1.28	0.16	0.53	0.011	0.36	0.030
Age at diagnosis	3.2-11.3 y	0.85	0.32	0.90	0.63	0.94	0.89
Age at study	28.5-41.5 y	0.90	0.44	0.89	0.54	1.11	0.78
Anthracycline dose anthracycline dose (including doxorubicin equivalent dose of mitoxantrone)	87.5-240 mg/m^2	1.21	0.037	1.30	0.006	1.75	<0.001
Chest-directed RT dose	0.0-3.0 Gy	1.04	0.072	1.01	0.69	0.97	0.57
Heart rate	62.0-79.0 beats/min	1.86	<0.001	2.00	<0.001	2.40	0.001
NT-proBNP	25.4-84.6 ng/L	1.19	<0.001	1.20	<0.001	1.35	<0.001
hs-cTnT	2.2-5.0 ng/L	1.15	0.020	1.23	0.006	1.18	0.050

Odds ratios (ORs) are reported for the 75th percentile (Q3) vs the 25th percentile (Q1) for continuous variables. Intercepts of the models are −4.32 (LVEF <52% and LVEF <54%), −5.45 (LVEF <50%), and −8.93 (LVEF <45%). *P* values were obtained with the pooled Wald test for multiple imputed data.

Abbreviations as in Tables 1 and 2.

FIGURE 1 Receiver-Operating Characteristic Curves



Receiver-operating characteristic curves showing the discrimination of diagnostic models with cardiac biomarkers alone, clinical characteristics alone, and cardiac biomarkers combined with clinical characteristics for left ventricular dysfunction in childhood cancer survivors. hs-cTnT = high-sensitivity cardiac troponin T; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

of 4.5% demonstrated high sensitivity of 95.4% (95% CI: 90.4%-99.3%) and NPV of 97.5% (95% CI: 94.6%-99.7%), effectively ruling out LVEF <50% in 16.9% of survivors (Table 2). To rule out LVEF <45%, a predicted probability threshold of 1.5% ruled out 53.0% of survivors, with high NPV of 99.4% (95% CI: 98.7%-100%) and sensitivity of 91.1% (95% CI: 79.2%-100%). Notably, the lower 95% CI was less than our predefined sensitivity of 90% for rule-out (Table 2).

Although hs-cTnT significantly improved the overall performance of the diagnostic model, we were interested in whether a model comprising only clinical characteristics and NT-proBNP, excluding hs-cTnT, could effectively rule out LVEF <50% or LVEF <45%. As shown in Table 2, the sensitivity and NPV of this simplified model were comparable with those of the full model. However, the simplified model resulted in a slightly lower percentage of CCS being identified for having LVEF <50% (15.1% vs 16.9%) and LVEF <45% (49.8% vs 53.0%). Complete case analysis yielded comparable results for all 3 LV dysfunction definitions (Supplemental Table 5). The combined diagnostic model was not effective in confirming (ruling in) any of the 3 LV dysfunction definitions. This is evident because, at PPVs ≥75% and specificities ≥90%, <2% of survivors could be confirmed for LV dysfunction.

SECONDARY ANALYSIS IN MODERATE- AND HIGH-RISK CCS. In response to the recently updated cardiomyopathy surveillance guideline,[5] which no longer recommend echocardiographic surveillance in low-

risk CCS treated with low anthracycline doses (<100 mg/m^2) and/or low chest-directed radiotherapy doses (<15 Gy), we also tested the performance of the diagnostic model after excluding low-risk CCS. The results of this secondary analysis are presented in Supplemental Table 6. In moderate- and high-risk CCS (n = 1,028), the model continued to demonstrate its ability to rule out LVEF <50% in 11.0% of these cases, with high NPV of 97.3% (95% CI: 94.5%-100%) and high sensitivity of 97.5% (95% CI: 91.9%-100%). Additionally, LVEF <45% could be ruled out in 40.0% of these moderate- and high-risk cases, with high NPV of 99.3% (95% CI: 98.4%-100%) and high sensitivity of 92.9%, although with a wider 95% CI (82.5%-100%).

TABLE 4 NRI of the Full Clinical and Biomarker-Based Diagnostic Model Compared With the Clinical Model

	Cutoff	NRI Cases	NRI Noncases	NRI	P Value
LVEF <52% (men), LVEF <54% (women)	9.0%	−0.40%	1.50%	1.10%	0.078
LVEF <50%	4.5%	0.00%	6.50%	6.50%	<0.001
LVEF <45%	1.5%	−4.90%	18.60%	13.80%	<0.001

Clinical model includes sex, age at diagnosis, age at study, anthracycline dose, chest-directed radiotherapy dose, and heart rate. Biomarker-based model includes factors included in the clinical model, N-terminal pro-B-type natriuretic peptide, and high-sensitivity cardiac troponin T.

LVEF = left ventricular ejection fraction; NRI = net reclassification improvement.

DISCUSSION

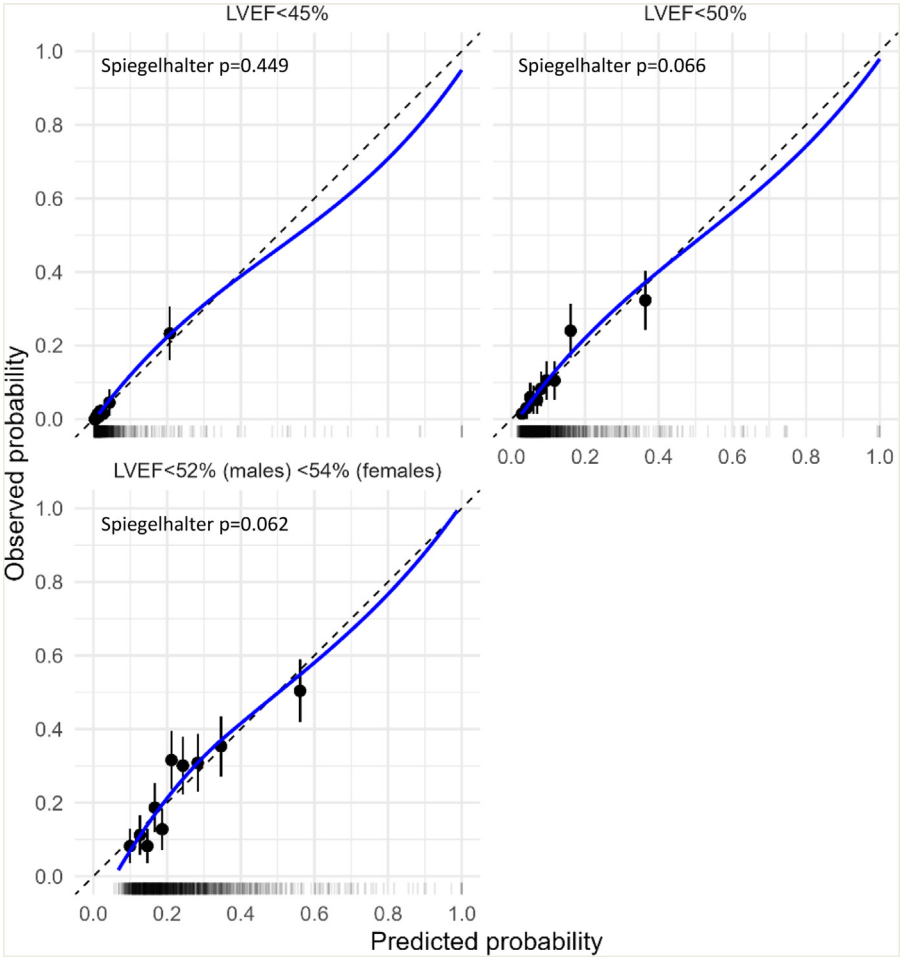
In this multicenter cohort study, we successfully developed and internally validated diagnostic models for 3 categories of LV dysfunction by combining clinical characteristics with cardiac biomarkers, namely, NT-proBNP and hs-cTnT, in adult survivors of childhood cancer. To our knowledge, our study is the first to demonstrate that the combination of cardiac biomarkers with clinical characteristics may be useful for the diagnosis of LV dysfunction in CCS. Pending validation in an independent cohort, our biomarker-based diagnostic model can be used for ruling out LVEF <50% in 16.9% of survivors, presenting an opportunity to defer echocardiography using evidence-based decision making (**Central Illustration**).

The diagnostic accuracy of NT-proBNP alone for LV dysfunction was found to be low, despite the finding that 22% of CCS treated with cardiotoxic therapies exhibited age- and sex-defined abnormal NT-proBNP levels at the age of 34 years, in contrast to 5% of siblings. This prevalence is in line with a previous report from the St. Jude Life cohort in CCS of similar age.[7] The observed high prevalence gained significance considering the association of abnormal NT-proBNP levels with cardiac mortality in CCS[7] and the general population.[20] We confirm the results of previous studies in CCS[6,7] and the general population,[9] indicating that natriuretic peptides as solitary predictors have limited diagnostic accuracy for ruling in or ruling out LV dysfunction on echocardiography. This definition includes LVEF <50% to <55% and/or fractional shortening <28% to <30%. Importantly, our study extends these findings in CCS by showing that higher or lower NT-proBNP cutoff concentrations are also ineffective for ruling in or ruling out LV dysfunction.

We found a higher prevalence of abnormal troponin T values (5.8%) than the previously reported 0.6% in CCS of similar age in the St. Jude Life cohort.[7] Nevertheless, abnormal hs-cTnT concentrations remained uncommon in CCS and were not significantly different from those in siblings. As CCS in our cohort were of comparable age with the St. Jude Life cohort, and abnormal troponin levels were not more prevalent in CCS compared with siblings, we postulate that this observation can be explained by the use of a high-sensitivity assay in our study. This assay provided greater precision, particularly around the troponin T concentrations near the cutoff level of 10 ng/L.[21] Although the diagnostic value of hs-cTnT for LV dysfunction was very limited in univariable analyses at any cutoff concentration, corroborating previous reports,[6,7,22] hs-cTnT demonstrated a significant association with LV dysfunction in the multivariable diagnostic model, thereby slightly improving its diagnostic performance.

Interestingly, modifiable cardiovascular risk factors such as hypertension, diabetes, and hypercholesterolemia were not identified as important predictors in the clinical model. This is likely due to the relatively low prevalence of these conditions in our cohort (hypertension, 5.0%; diabetes, 2.0%; hypercholesterolemia, 3.3%) compared with North American survivor cohorts such as the Childhood Cancer Survivor Study.[23] We found higher resting heart rate to be associated with abnormal LVEF. To our knowledge, this association has not been described before in CCS. In the general primary care population, higher heart rate was associated with future heart failure.[24] Thus, heart rate appears to be a useful and easily obtainable biomarker to include in diagnostic and prognostic models for (asymptomatic) cardiac dysfunction in CCS. Intriguingly, our analyses using non-sex-specific LVEF cutpoints revealed a seemingly higher risk for cardiomyopathy in men compared with women. Further investigation is warranted to thoroughly

FIGURE 2 Calibration Plots



Calibration plots showing agreement between observed and predicted risk for left ventricular dysfunction in childhood cancer survivors using the diagnostic model incorporating cardiac biomarkers and clinical characteristics. Model calibration was assessed using the Spiegelhalter test, where $P < 0.05$ indicates inadequate calibration. LVEF = left ventricular ejection fraction.

interpret and understand the implications of these findings, and the consideration of sex-specific thresholds deserves further study.

The multivariable diagnostic model, combining cardiac biomarkers with clinical characteristics to estimate the probability of LV dysfunction in CCS, proved valuable for ruling out LV dysfunction. Its performance was notably better for more severely abnormal LV function, similar to findings observed for NT-proBNP in the general population.[9] Although the diagnostic model could not accurately rule out LVEF <54% (women) or LVEF <52% (men), it effectively ruled out LVEF <50% in 16.9% of CCS. Despite our expectation that the model would excel in ruling out LVEF <45%, with NPV of 99.4%, the lower 95% CI for sensitivity (91.1%; 95% CI: 79.2%-100%) fell well below our predefined sensitivity of 90% required for rule-out. The wide CI likely stemmed from the low prevalence of LVEF <45% (3.4%), contributing to overfitting of the model. Future studies including a larger representation of survivors with LVEF <45% are needed to address this issue conclusively.

As for clinical use, both the model with clinical factors alone and the model combining cardiac biomarkers with clinical factors could serve as triage tests before conducting surveillance echocardiography, particularly for ruling out LVEF <50%. This approach substantially reduces the burden on both CCS and echocardiography laboratories. Although the

CENTRAL ILLUSTRATION **Biomarker-Based Model to Rule Out Cardiac Dysfunction in Childhood Cancer Survivors**

Childhood cancer survivors treated with cardiotoxic cancer treatment without a previous diagnosis of cardiomyopathy from the Dutch LATER CARD study (N = 1,334)

Outcomes

LVEF Outcome	Prevalence
<52% in males, <54% in females	23.2%
<50%	10.9%
<45%	3.4%

Diagnostic Test

Clinical model:	Sex, age at diagnosis, age at study, anthracyline dose, chest directed radiotherapy, HR
Full model:	Clinical + NTproBNP + hs-cTnT

	LVEF <52% in males, <54% in females	LVEF <50%	LVEF <45%
AUC clinical model only	0.67	0.69	0.80
AUC full model	0.70	0.73	0.86
Specificity full model	99.3%	95.4%	91.1%
NPV full model	95.4%	97.5%	99.4%
Ruled out clinical only	2.5%	9.7%	34.6%
Ruled out full model	3.4%	16.9%	53.0%

Leerink JM, et al. J Am Coll Cardiol CardioOnc. 2024;6(2):236–247.

In a cross-sectional cohort study including 1,334 childhood cancer survivors treated with anthracyclines and/or chest-directed radiotherapy, a diagnostic model combining cardiac biomarkers (N-terminal pro-B-type natriuretic peptide [NTproBNP] and high-sensitivity cardiac troponin T [hs-cTnT]) with clinical characteristics was useful in ruling out the presence of left ventricular ejection fraction (LVEF) <50% on echocardiography for 16.9% of the population, demonstrating high negative predictive value and sensitivity. The considered clinical characteristics include sex, age at diagnosis, age at study, anthracycline dose, chest-directed radiotherapy dose, and heart rate (HR). AUC = area under the receiver-operating characteristic curve; NPV = negative predictive value.

model with cardiac biomarkers and clinical factors showed superior diagnostic performance and a higher proportion of survivors ruled out for LVEF <50% compared with the clinical model (16.9% vs 9.7%), it is important to note the increased need for blood biomarker assessments if all survivors undergo this evaluation. Future studies could explore a 2-stage approach, reserving blood biomarker assessment for survivors with borderline results from the clinical only model to further refine the risk for LV dysfunction. The diagnostic model may have additional applications, such as ruling out LVEF <50% in cases in which LVEF cannot be obtained because of poor image acquisition (observed in 17% of our cohort) or in patients with borderline LVEF. Importantly, the recently updated International Late Effects of Childhood Cancer Guideline Harmonization Group cardiomyopathy surveillance guideline no longer recommends surveillance in low-risk survivors treated with anthracycline doses <100 mg/m^2 and/or

chest-directed radiotherapy doses <15 Gy.[5] Our secondary analysis indicated that the diagnostic model performed well, even after excluding the low-risk group, with respect to ruling out LV dysfunction. For ruling out LVEF <50%, it resulted in a reduction in the number of patients for whom echocardiography might be deferred, from 16.9% to 11.0%.

STUDY LIMITATIONS. The present study was prospectively designed, including a substantial number of CCS. Reliable LVEF measurements were ensured through a core laboratory, and the study was conducted across multiple centers in the Netherlands, improving the generalizability of the results. However, certain limitations of the study should be acknowledged.

First, 17% of CCS had missing biplane LVEF. To mitigate potential bias arising from these missing values, we used multiple imputation and compared the outcomes with a complete case analysis, revealing consistent results.

Second, the low prevalence of survivors with LVEF <45% (3.4%) may have contributed to overfitting in the diagnostic model for this specific threshold, as discussed earlier.

Third, although we conducted internal validation through bootstrapping, external validation of our findings is essential. Fourth, although we understand the potential limitations associated with the use of NRI, we present these as secondary analyses to further support our main findings.

Finally, we recognize a potential interest in the diagnostic accuracy of cardiac biomarkers for abnormalities in global longitudinal strain, diastolic dysfunction, and/or valve dysfunction. However, our primary focus on detecting LVEF stems from its current impact on the decision to initiate heart failure treatment in asymptomatic patients.[25]

CONCLUSIONS

Our study demonstrates the superiority of a diagnostic model that combines cardiac biomarkers with clinical characteristics, surpassing the utility of using either cardiac biomarkers alone or clinical characteristic alone. After external validation, this diagnostic model can be used to triage survivors for echocardiography, ruling out LVEF <50% in 16.9% of CCS.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In the cardiac surveillance of CCS at risk for heart failure, a diagnostic model incorporating NT-proBNP, hs-cTnT, and clinical characteristics proved superior to models using biomarkers alone or clinical characteristics alone. This comprehensive model ruled out LVEF <50% in 16.9% of survivors, achieving sensitivity of 95.4% and NPV of 97.5%.

TRANSLATIONAL OUTLOOK: With external validation, the diagnostic model could be used to reduce unnecessary surveillance echocardiograms in CCS.

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KEY WORDS **biomarkers, cardio-oncology, childhood cancer survivors, diagnostic accuracy**

APPENDIX **For supplemental methods, figures, tables, and references, please see the online version of this paper.**