Development and validation of risk prediction models for coronary heart disease and heart failure after treatment for Hodgkin lymphoma

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original reports

Development and Validation of Risk Prediction Models for Coronary Heart Disease and Heart Failure After Treatment for Hodgkin Lymphoma

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abstract

PURPOSE Previous efforts to predict absolute risk of treatment-related cardiovascular diseases (CVDs) have mostly focused on childhood cancer survivors. We aimed to develop prediction models for risk of coronary heart disease (CHD) and heart failure (HF) for survivors of adolescent/adult Hodgkin lymphoma (HL).

METHODS For model development, we used a multicenter cohort including 1,433 5-year HL survivors treated between 1965 and 2000 and age 18-50 years at HL diagnosis, with complete data on administered chemotherapy regimens, radiotherapy volumes and doses, and cardiovascular follow-up. Using cause-specific hazard models, covariate-adjusted cumulative incidences for CHD and HF were estimated in the presence of competing risks of death because of other causes than CHD and HF. Age at HL diagnosis, sex, smoking status, radiotherapy, and anthracycline treatment were included as predictors. External validation for the CHD model was performed using a Canadian cohort of 708 HL survivors treated between 1988 and 2004 and age 18-50 years at HL diagnosis.

RESULTS After a median follow-up of 24 years, 341 survivors had developed CHD and 102 had HF. We were able to predict CHD and HF risk at 20 and 30 years after treatment with moderate to good overall calibration and moderate discrimination (areas under the curve: 0.68-0.74), which was confirmed by external validation for the CHD model (areas under the curve: 0.73-0.74). On the basis of our model including prescribed mediastinal radiation dose, 30-year risks ranged from 4% to 78% for CHD and 3% to 46% for HF, depending on risk factors.

CONCLUSION We developed and validated prediction models for CHD and HF with good overall calibration and moderate discrimination. These models can be used to identify HL survivors who might benefit from targeted screening for CVD and early treatment for CVD risk factors.

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INTRODUCTION

Survival after Hodgkin lymphoma (HL) has greatly improved over time, with a current 5-year survival rate of 88%.[1] Several studies observed increased risks of cardiovascular morbidity and mortality for patients treated for HL.[2-8] Compared with the general population, risks (standardized incidence and mortality ratios) were three- to four-fold increased for coronary heart disease (CHD) and five- to seven-fold for heart failure (HF).[5,7-9] Mediastinal radiotherapy (RT) and anthracycline-induced cardiotoxicity appear to be the most important underlying causes of this increased risk.[2,4,7,10]

Accurate identification of patients at particularly high risk for cardiovascular disease (CVD) enables targeted cardiovascular surveillance and can thereby potentially prevent adverse events and improve quality of life in HL survivors.[11] Previous efforts to individually predict cancer treatment–related CVD have mostly focused on childhood cancer survivors[12,13] and cannot be directly translated to survivors of adolescent and adult cancers because absolute and relative risks of treatment-related CVD differ by age.[7] In addition, conventional cardiovascular risk factors, such as smoking, are very rare at the time of childhood cancer diagnosis,[14] but may influence the absolute risk of CVD in patients treated during adulthood. Therefore, our aim was to develop prediction models for CHD and HF to obtain absolute risks for adult 5-year survivors of HL and to internally and externally validate these models.

METHODS

Study Population

Our initial cohort comprised 2,584 patients who were age 18-50 years at HL treatment in one of five

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

What is the individual absolute risk of coronary heart disease (CHD) and heart failure (HF) in 5-year survivors of Hodgkin lymphoma? So far, no individual risk prediction models are available to assess treatment-related cardiovascular disease risk in adolescent and adult Hodgkin lymphoma survivors.

Knowledge Generated

Two separate prediction models were developed for CHD and HF, which were internally and externally validated with moderate to good discrimination and calibration. The models allow for an individual prediction of CHD or HF risk on the basis of treatment-related factors including sex, age at treatment, radiotherapy field or dose, anthracycline (dose), and smoking.

Relevance *(J.W. Friedberg)*

This validated model defines risk of coronary artery disease and congestive HF after treatment for Hodgkin lymphoma. Moving forward, these data may enable studies to refine screening recommendations for the prevention of these late adverse sequelae.*

*Relevance section written by JCO Editor-in-Chief Jonathan W. Friedberg, MD.

University Hospitals or Cancer Centers (The Netherlands Cancer Institute Amsterdam, Erasmus MC Cancer Institute Rotterdam, Leiden University Medical Center, Radboud University Medical Center Nijmegen, and University Medical Center Utrecht) in The Netherlands between 1965 and 2000 and who had survived ≥ 5 years after HL diagnosis. The selection of patients has been described previously.[4,7,15,16] From the medical records, data were collected on the date of birth and HL diagnosis; treatment, including salvage treatment (starting date, radiation fields and prescribed dose, chemotherapy (CT) regimens, and number of cycles); risk factors; date of most recent medical information; vital status; and cause of death. Over time, a wide variety of treatment regimens were used in the study population, which are described in the Data Supplement (online only). Information on mediastinal RT dose was not routinely abstracted for patients in two hospitals participating in the cohort. We excluded 1,151 patients because of missing data on RT dose (n = 1,024), anthracycline dose (n = 76), and/or smoking status (n = 244).

Outcome Definitions

Near-complete information on CHD or HF was obtained from hospital and GP medical records.[7] All events were defined and graded according to a slightly adapted version of the Common Terminology Criteria of Adverse Events, version 4.0 (all included events ≥ grade 3).[17,18] CHD included both myocardial infarction and angina pectoris (grade 3 defined as hemodynamically stable events, confirmed by electrocardiogram, laboratory, or imaging report), and HF included both congestive HF and cardiomyopathy (on the basis of the decreased ejection fraction). End points were the first CHD event irrespective of other prior cardiovascular events and the first HF event without other prior cardiovascular events, to exclude HF events occurring as a consequence of other CVDs. Data used in this study were obtained from the medical charts, and therefore, this study was exempt from IRB approval.

Statistical Analysis

Covariate-adjusted cumulative incidences for CHD and HF in the presence of competing risk of death because of other causes than CHD and HF were estimated using cause-specific hazard models.[19] Separate prediction models were developed for CHD and HF. Time at risk started 5 years after initial HL treatment and ended at CHD or HF diagnosis, date of last medical contact, or death. On the basis of literature and expert opinion, the following predictors for the prediction model for CHD were selected a priori: age at HL treatment, sex, mediastinal RT, and smoking at HL diagnosis. For predicting HF, the following predictors were selected: age at HL treatment, sex, mediastinal RT, and anthracycline-containing CT. Smoking status was evaluated in the HF models, but was not a significant predictor. For each outcome, two different models were developed: a simple model with categorical treatment variables (ie, no RT, mediastinal RT or mantle RT, and anthracycline-containing CT or no anthracycline-containing CT) and a model with cumulative prescribed radiation dose to the mediastinum and cumulative administered anthracycline dose. RT dose, obtained through original RT prescription sheets, simulation films, or clinical notes, was categorized as 0 Gy, ≤ 35 Gy, or > 35 Gy. Cumulative anthracycline dose was calculated by multiplying regimen-specific standard doses with the number of cycles that a patient received and categorized as 0, ≤ 210 mg/m^2, or > 210 mg/m^2. In addition, as a sensitivity analysis, we evaluated models with age and RT dose as continuous variables. The predicted cumulative incidences of CHD and HF were plotted over time, and values at 20 and 30 years were reported for several risk factor profiles. All models were based on complete-case analysis, leaving 1,433 patients in our development cohort.

The assumption of proportional hazards, examined with log minus log plots and Schoenfeld residuals, was fulfilled. Model performance was assessed by evaluating discrimination and calibration.[20] Discriminative ability was assessed by evaluating the area under the curve (AUC) at follow-ups of 20 and 30 years after HL diagnosis. AUC values range from 0 to 1, with higher values indicating a higher ability of the model to discriminate between patients who did and did not develop the event of interest.[21] The 95% CI for the AUC was the 2.5th-97.5th percentile of 1,000 bootstrap samples. To assess internal validity and to quantify potential overfitting in our models, we calculated the optimism in the AUC values through 10-fold cross-validation. Model calibration was then assessed by calculating the ratio of the expected and observed (E/O) numbers of CHD or HF (E/O ratio), overall and stratified by risk factors. Observed numbers of CHD and HF were calculated on the basis of cumulative incidences obtained with the Aalen-Johansen estimator to account for censored observations in the presence of competing risks. Expected numbers of CHD and HF were estimated using predicted cumulative incidences. The 95% CI for the ratio was calculated on the basis of a normal approximation of the natural logarithm of observed events.[22] An E/O value significantly smaller (or larger) than 1 indicates a model that underestimates (or overestimates) the risk. A more extensive description of the statistical analysis is provided in the Data Supplement.

External Validation

We validated our prediction models with a population-based cohort of Canadian HL survivors from the Opportunities to Reduce Cardiac Late Effects (ORaCLE) study.[23] Patients with HL were diagnosed between 1988 and 2004, identified through the Ontario Cancer Registry. Information on treatment, pretreatment cardiac function, and cardiac risk factors was obtained from the medical records. Information on CVD was obtained through linkage with hospital admission data or outpatient procedure claims data for CVD not requiring hospitalization. For the purpose of validation, patients who were age 18-50 years at diagnosis and survived $\geq$ 5 years after initial treatment were selected, leaving 708 patients (including 92 CHD events) with complete data for validation. To assess the external validity of our CHD model, we applied the coefficients from our development model to the ORaCLE data and examined the resulting AUC. Since only 13 HF events were observed in this sample, we could not validate our HF model.

RESULTS

Patient Characteristics of the Dutch HL Cohort

In total, 580 female and 853 male 5-year HL survivors were included in the development cohort (Table 1). The median age at diagnosis was 30.1 (interquartile range [IQR], 23.9-37.7) years. After a median follow-up since treatment of 24.3 (range, 5.1-49.4) years, 341 patients had developed CHD and 102 patients had developed HF. Patients were treated with a combination of RT and CT (61.5%), RT alone (27.4%), or CT alone (11.1%). After combining exposures from primary and salvage treatment, the median anthracycline dose was 210 (IQR, 200-280) mg/m^2 and the median RT dose to the mediastinum was 40 (IQR, 35-40) Gy.

Coronary Heart Disease Model

In our simple model, all a priori selected covariates were significant predictors of CHD (Table 2). Males, smokers, and patients with mediastinal or mantle field RT had a higher CHD risk in comparison with females, nonsmokers, and patients without RT, respectively. Moreover, CHD risk increased with age. In the model including RT dose categories, CHD risk rose with increasing RT dose. The AUC at 20 years after treatment was 0.73 (95% CI, 0.69 to 0.77) for the simple model and 0.74 (95% CI, 0.70 to 0.77) for the dose model. The AUCs at 30 years after treatment were similar: 0.73 (95% CI, 0.71 to 0.76) for the simple model and 0.73 (95% CI, 0.70 to 0.76) for the dose model (Table 2). AUC values on the basis of 10-fold cross-validation yielded similar results, ie, realized AUC values were all within the presented CIs. The overall E/O ratio at 30 years was 0.84 (95% CI, 0.76 to 0.93) for the simple model (Data Supplement) and 0.89 (95% CI, 0.80 to 0.98) for the dose model (Fig 1). Calibration plots at 20 years for the simple and dose model are shown in the Data Supplement. A model with continuous age and RT dose did not show better performance (results not shown).

Heart Failure Model

In our simple model, all covariates were significant predictors of HF, except for sex (Table 2). Predictors of HF were higher age at HL treatment, mediastinal or mantle field RT, and anthracycline-containing CT. The model including dose categories indicates that HF risk rises with increasing doses of RT and anthracyclines. The AUC at 20 years after treatment was 0.71 (95% CI, 0.64 to 0.79) for the simple model and 0.70 (95% CI, 0.64 to 0.72) for the dose model. Internal cross-validation yielded AUCs within the aforementioned CIs. The AUCs at 30 years after treatment were similar: 0.69 (95% CI, 0.64 to 0.75) for the simple model and 0.68 (95% CI, 0.62 to 0.74) for the dose model (Table 2). The overall E/O ratio at 30 years was 0.87 (95% CI, 0.73 to 1.04) for the simple model and 0.92 (95% CI, 0.77 to 1.10) for the dose model. Calibration plots are shown in the Data Supplement. A model with continuous age, continuous RT dose, and continuous anthracycline dose did not show a better performance (results not shown).

Risk Factor Profiles

We created risk tables showing the 30-year cumulative incidence of CVD for several risk factor profiles (CHD: Fig 2 and HF: Fig 3). For example, a male smoker who was treated with $>$ 35 Gy to the mediastinum at age 40 years has a risk of 67.4% (95% CI, 56.2 to 77.3) of developing CHD at age 70 years. By contrast, a female nonsmoker who did not receive mediastinal RT and was 40 years old at HL diagnosis has a risk of 9.5% (95% CI, 6.2 to 13.6) of CHD at

TABLE 1. Characteristics of 5-Year Hodgkin Lymphoma Survivors

Characteristic	Development Data Set Dutch HL Cohort (N = 1,433)	Validation Data Set Canadian ORaCLE Study (N = 708)
Age, years		
Median (IQR)	30.1 (23.9-37.7)	31.0 (25.0-38.0)
Sex, No. (%)		
Male	853 (59.5)	397 (56.1)
Female	580 (40.5)	311 (43.9)
Treatment period, No. (%)		
1965-1976	429 (29.9)	—
1977-1988	565 (39.4)	33 (4.7)
1989-2000	439 (30.6)	567 (80.1)
2001-2004	—	108 (15.3)
Radiotherapy, No. (%)		
No mediastinal RT	455 (31.8)	254 (35.9)
Mediastinal field	220 (15.4)	46 (6.5)
Full mantle field	758 (52.9)	408 (57.6)
Mediastinal RT dose, Gy, No. (%)		
Median (IQR)	40.0 (35.0-40.0)	35.0 (35.0-35.0)
≤ 35	283 (19.8)	401 (56.6)
> 35	695 (48.5)	53 (7.5)
CT, No. (%)		
No CT	393 (27.4)	130 (18.4)
Without anthracyclines	504 (35.2)	9 (1.3)
With anthracyclines	536 (37.4)	567 (80.3)
Anthracycline dose, mg/m^2[a]		
Median (IQR)	210.0 (200-280)	300.0 (210-300)
35-200, No. (%)	139 (9.7)	102 (14.8)
210-335, No. (%)	348 (24.1)	394 (57.3)
350-880, No. (%)	49 (3.4)	53 (7.7)
Smoking at HL diagnosis, No. (%)		
Yes	809 (56.5)	258 (36.4)
Cardiac events,[b] No. (%)		
No CHD or HF	1,011 (70.6)	616 (87.0)
CHD	341 (23.8)	92 (13.0)
HF	102 (7.1)	13 (1.8)
Follow-up since initial treatment, years		
Median (range)	24.3 (5.1-49.4)	13.1 (5.0-27.1)

Abbreviations: ABV, doxorubicin, bleomycin, and vinblastine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CHD, coronary heart disease; CT, chemotherapy; HF, heart failure; HL, Hodgkin lymphoma; IQR, interquartile range; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; RT, radiotherapy.

[a]Computed by multiplying the standard dose from a specific regimen with the number of cycles. Standard doses of anthracycline per regimen per cycle were 25 mg/m^2 at days 1 and 15 for ABVD and alternating MOPP-ABVD and 35 mg/m^2 at day 8 for hybrid MOPP-ABV. In the ORaCLE data, 18 patients had missing data on anthracycline dose. For two patients, there was missing information on the type of CT.

[b]These numbers do not add up to the total number of patients in the cohort because a patient could have had both CHD and HF.

age 70 years. Risks of developing HF were generally lower compared with the risk of CHD. CHD was more common in men than in women, whereas HF was more common in women. For example, a woman treated with > 35 Gy to the mediastinum and > 210 mg/m^2 cumulative dose of anthracyclines at age 40 years has a risk of 46.0% (95% CI, 27.4 to 65.9) of HF at age 70 years, whereas a man with the same risk factors has a risk of 39.9% (95% CI, 22.9 to

TABLE 2. Simple Model and Dose Model to Predict Coronary Heart Disease and Heart Failure in 5-Year HL Survivors (N = 1,433)

	CHD				HF			
No. of events	**Simple Model**		**Dose Model**		**Simple Model**		**Dose Model**	
CVD	341		341		102		102	
Deaths	425		425		568		568	

Risk Factor	**No.**	**HR**	**95% CI**	**HR**	**95% CI**	**No.**	**HR**	**95% CI**	**HR**	**95% CI**
Sex										
Female	104	1.00	Ref.	1.00	Ref.	53	1.00	Ref.	1.00	Ref.
Male	237	2.21	1.74 to 2.80	2.31	1.81 to 2.94	49	0.76	0.51 to 1.12	0.83	0.55 to 1.24
Age at HL treatment, years										
18-24	91	1.00	Ref.	1.00	Ref.	35	1.00	Ref.	1.00	Ref.
25-34	117	1.44	1.09 to 1.90	1.44	1.09 to 1.90	21	0.55	0.32 to 0.95	0.57	0.33 to 0.98
35-50	133	2.77	2.10 to 3.65	2.73	2.07 to 3.59	46	1.98	1.26 to 3.11	1.93	1.23 to 3.01
Radiotherapy field										
No mediastinal RT	38	1.00	Ref.	NA	NA	11	1.00	Ref.	NA	NA
Mediastinum	40	3.34	2.13 to 5.23	NA	NA	11	1.66	0.71 to 3.86	NA	NA
Mantle field	263	4.49	3.19 to 6.34	NA	NA	80	4.03	2.11 to 7.69	NA	NA
Mediastinal RT dose, Gy										
No mediastinal RT	38	NA	NA	1.00	Ref.	11	NA	NA	1.00	Ref.
≤ 35	85	NA	NA	3.52	2.40 to 5.17	22	NA	NA	2.64	1.28 to 5.48
> 35	218	NA	NA	4.74	3.34 to 6.72	69	NA	NA	3.66	1.91 to 7.01
Anthracyclines										
No		NA	NA	NA	NA	64	1.00	Ref.	NA	NA
Yes		NA	NA	NA	NA	38	2.86	1.85 to 4.44	NA	NA
Cumulative anthracycline dose, mg/m^2										
No anthracyclines		NA	NA	NA	NA	64	NA	NA	1.00	Ref.
≤ 210		NA	NA	NA	NA	21	NA	NA	2.13	1.26 to 3.59
> 210		NA	NA	NA	NA	17	NA	NA	2.73	1.56 to 4.69
Smoking at HL diagnosis										
No	120	1.00	Ref.	1.00	Ref.		NA	NA	NA	NA
Yes	221	1.37	1.09 to 1.72	1.37	1.09 to 1.73		NA	NA	NA	NA

Cohort	**AUC**	**95% CI**	**AUC**	**95% CI**	**AUC**	**95% CI**	**AUC**	**95% CI**
Dutch HL cohort (20-year)[a]	0.73	0.69 to 0.77	0.74	0.70 to 0.77	0.71	0.64 to 0.79	0.70	0.64 to 0.72
Dutch HL cohort (30-year)[a]	0.73	0.71 to 0.76	0.73	0.70 to 0.76	0.69	0.64 to 0.75	0.68	0.62 to 0.73
Canadian ORaCLE study (20-year)	0.73	0.68 to 0.80	0.74	0.68 to 0.79	NE	NE	NE	NE

Abbreviations: AUC, area under the curve; CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; HL, Hodgkin lymphoma; NA, not applicable: risk factor was not included in the model; NE, not estimable because of lack of events; Ref, reference category; RT, radiotherapy.

[a]AUC values on the basis of 10-fold cross-validation yielded similar results, ie, realized AUC values were all within the presented CIs.

58.2). By contrast, a man diagnosed with HL at age 40 years and not treated with mediastinal RT or anthracycline-containing CT has a 5.0% (95% CI, 2.3 to 9.1) risk of HF at age 70 years. Risk tables showing the 20-year cumulative incidence and 30-year risk tables on the basis of the simple models are shown in the Data Supplement. Graphs showing the cumulative incidences over time for different risk factor profiles are shown in Figure 4 (CHD) and the Data Supplement. For all models, cumulative incidences at specified follow-up intervals are provided as an online calculator on the medical prediction platform Evidencio.[24-27]

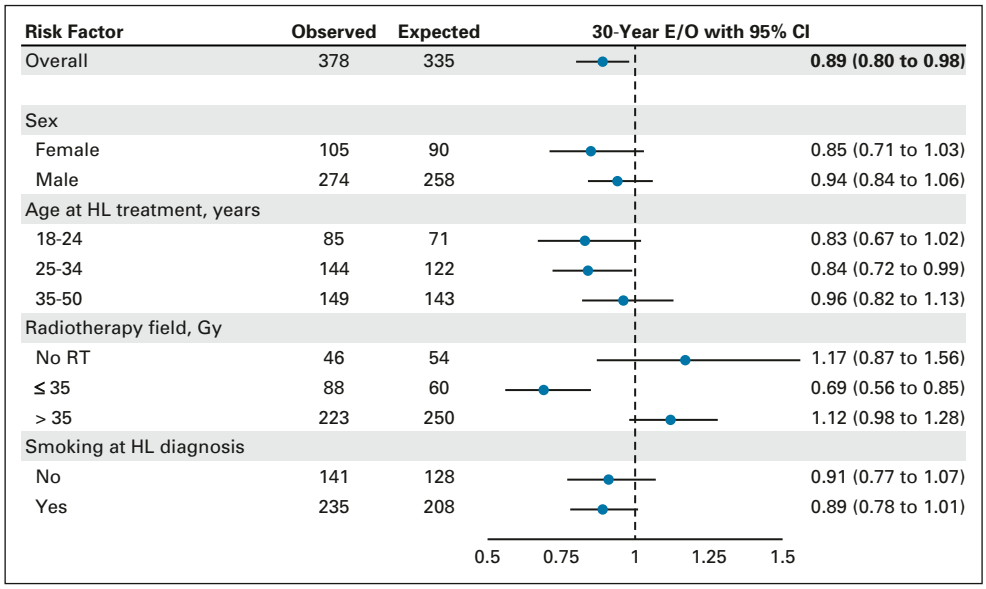
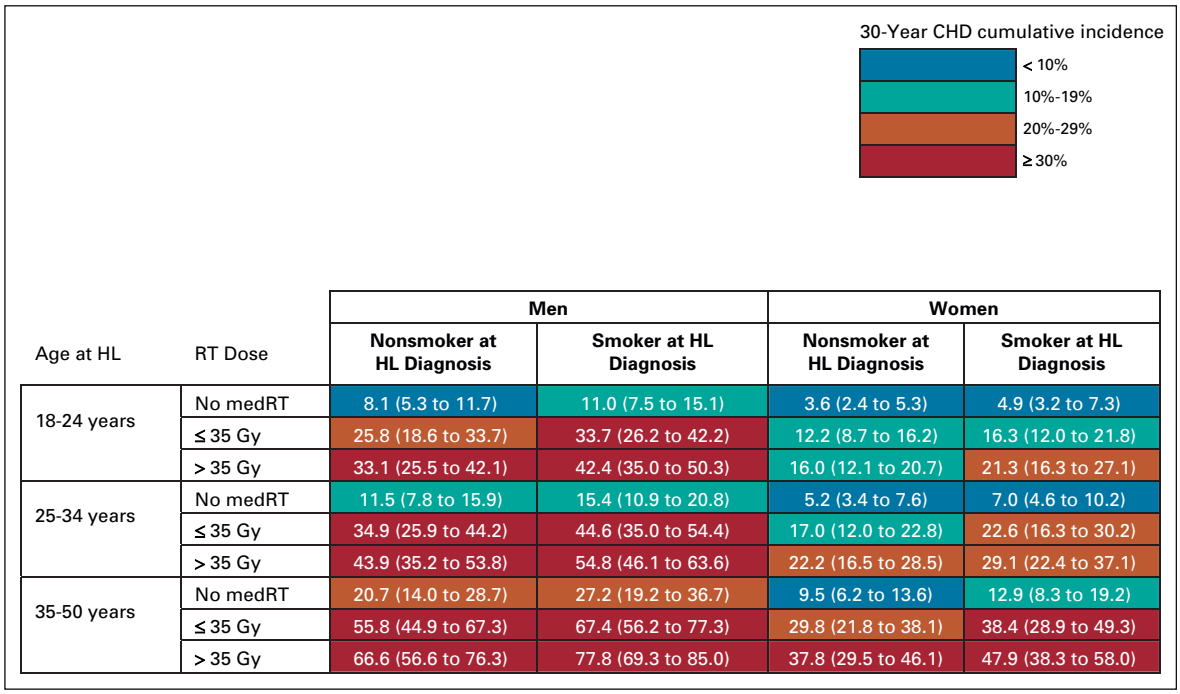


FIG 1. Calibration plot of the coronary heart disease dose model at 30 years in the Dutch cohort of HL survivors. Note that the observed number of events differs from those presented in Table 2 since they are calculated on the basis of cumulative incidences obtained with the Aalen-Johansen estimator to account for censored observations in the presence of competing risks. E/O, ratio of expected and observed numbers; HL, Hodgkin lymphoma; RT, radiotherapy.

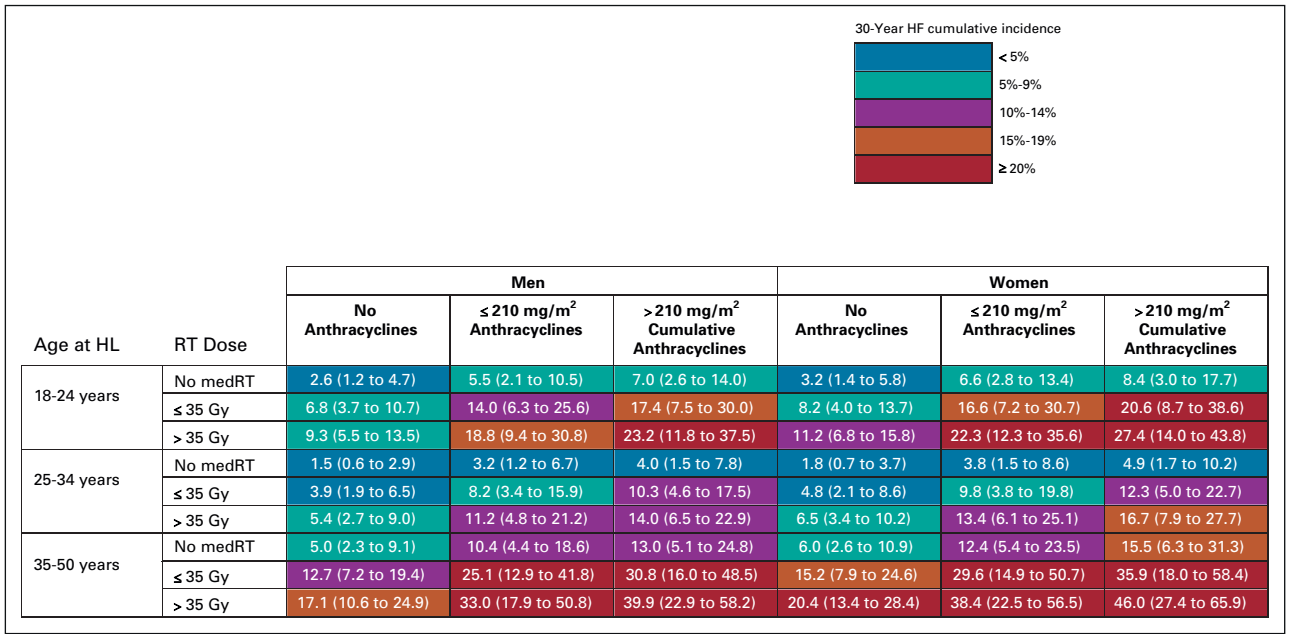
External Validation

In total, 311 female and 397 male 5-year HL survivors were included in the validation cohort (Table 1). The median age at diagnosis was 31.0 (IQR, 25.0-38.0) years; the median follow-up was 13.1 (range, 5.0-27.1) years. Patients were treated with a combination of RT and CT (52.9%), RT alone (18.5%), or CT alone (28.6%). After combining exposures from primary and salvage treatment, the median cumulative anthracycline dose was 300 (IQR, 210-300) mg/m^2 and the median RT dose to the mediastinum was 35 (IQR,



Age at HL	RT Dose	Men		Women	
		Nonsmoker at HL Diagnosis	Smoker at HL Diagnosis	Nonsmoker at HL Diagnosis	Smoker at HL Diagnosis
18-24 years	No medRT	8.1 (5.3 to 11.7)	11.0 (7.5 to 15.1)	3.6 (2.4 to 5.3)	4.9 (3.2 to 7.3)
	≤ 35 Gy	25.8 (18.6 to 33.7)	33.7 (26.2 to 42.2)	12.2 (8.7 to 16.2)	16.3 (12.0 to 21.8)
	> 35 Gy	33.1 (25.5 to 42.1)	42.4 (35.0 to 50.3)	16.0 (12.1 to 20.7)	21.3 (16.3 to 27.1)
25-34 years	No medRT	11.5 (7.8 to 15.9)	15.4 (10.9 to 20.8)	5.2 (3.4 to 7.6)	7.0 (4.6 to 10.2)
	≤ 35 Gy	34.9 (25.9 to 44.2)	44.6 (35.0 to 54.4)	17.0 (12.0 to 22.8)	22.6 (16.3 to 30.2)
	> 35 Gy	43.9 (35.2 to 53.8)	54.8 (46.1 to 63.6)	22.2 (16.5 to 28.5)	29.1 (22.4 to 37.1)
35-50 years	No medRT	20.7 (14.0 to 28.7)	27.2 (19.2 to 36.7)	9.5 (6.2 to 13.6)	12.9 (8.3 to 19.2)
	≤ 35 Gy	55.8 (44.9 to 67.3)	67.4 (56.2 to 77.3)	29.8 (21.8 to 38.1)	38.4 (28.9 to 49.3)
	> 35 Gy	66.6 (56.6 to 76.3)	77.8 (69.3 to 85.0)	37.8 (29.5 to 46.1)	47.9 (38.3 to 58.0)

FIG 2. Thirty-year cumulative incidence of CHD in 5-year male and female Hodgkin lymphoma survivors on the basis of the dose model. CHD, coronary heart disease; HL, Hodgkin lymphoma; medRT, mediastinal radiotherapy.



Age at HL	RT Dose	Men			Women		
		No Anthracyclines	≤ 210 mg/m² Anthracyclines	> 210 mg/m² Cumulative Anthracyclines	No Anthracyclines	≤ 210 mg/m² Anthracyclines	> 210 mg/m² Cumulative Anthracyclines
18-24 years	No medRT	2.6 (1.2 to 4.7)	5.5 (2.1 to 10.5)	7.0 (2.6 to 14.0)	3.2 (1.4 to 5.8)	6.6 (2.8 to 13.4)	8.4 (3.0 to 17.7)
	≤ 35 Gy	6.8 (3.7 to 10.7)	14.0 (6.3 to 25.6)	17.4 (7.5 to 30.0)	8.2 (4.0 to 13.7)	16.6 (7.2 to 30.7)	20.6 (8.7 to 38.6)
	> 35 Gy	9.3 (5.5 to 13.5)	18.8 (9.4 to 30.8)	23.2 (11.8 to 37.5)	11.2 (6.8 to 15.8)	22.3 (12.3 to 35.6)	27.4 (14.0 to 43.8)
25-34 years	No medRT	1.5 (0.6 to 2.9)	3.2 (1.2 to 6.7)	4.0 (1.5 to 7.8)	1.8 (0.7 to 3.7)	3.8 (1.5 to 8.6)	4.9 (1.7 to 10.2)
	≤ 35 Gy	3.9 (1.9 to 6.5)	8.2 (3.4 to 15.9)	10.3 (4.6 to 17.5)	4.8 (2.1 to 8.6)	9.8 (3.8 to 19.8)	12.3 (5.0 to 22.7)
	> 35 Gy	5.4 (2.7 to 9.0)	11.2 (4.8 to 21.2)	14.0 (6.5 to 22.9)	6.5 (3.4 to 10.2)	13.4 (6.1 to 25.1)	16.7 (7.9 to 27.7)
35-50 years	No medRT	5.0 (2.3 to 9.1)	10.4 (4.4 to 18.6)	13.0 (5.1 to 24.8)	6.0 (2.6 to 10.9)	12.4 (5.4 to 23.5)	15.5 (6.3 to 31.3)
	≤ 35 Gy	12.7 (7.2 to 19.4)	25.1 (12.9 to 41.8)	30.8 (16.0 to 48.5)	15.2 (7.9 to 24.6)	29.6 (14.9 to 50.7)	35.9 (18.0 to 58.4)
	> 35 Gy	17.1 (10.6 to 24.9)	33.0 (17.9 to 50.8)	39.9 (22.9 to 58.2)	20.4 (13.4 to 28.4)	38.4 (22.5 to 56.5)	46.0 (27.4 to 65.9)

FIG 3. Thirty-year cumulative incidence of HF in 5-year male and female Hodgkin lymphoma survivors on the basis of the dose model. HF, heart failure; medRT, mediastinal radiotherapy.

35-35) Gy. Compared with the development cohort, patients included in the validation cohort were more often treated with CT alone and received higher anthracycline doses.

Both our simple model and the model including dose categories were based on 92 CHD events in the validation cohort. Applying the coefficients obtained in our development cohort to the validation cohort yielded an AUC of 0.73 (95% CI, 0.68 to 0.80) for the simple model and an AUC of 0.74 (95% CI, 0.68 to 0.79) for the model including dose categories (Table 2). If we would have used the ORaCLE data set for model development, we would have obtained different HRs (Data Supplement).

DISCUSSION

We developed prediction models for CHD and HF risk after HL treatment, and validation showed good performance of our models. Subsets of HL survivors were at very high risk of CVD; even at an attained age of 50 years, the cumulative incidence of CHD exceeded 30% in some risk groups. The discriminative ability of the models predicting CHD and HF at 20 and 30 years after treatment was moderate (AUCs between 0.68 and 0.74), which was confirmed by external validation for the CHD model (AUCs between 0.73 and 0.74). Moreover, the models show moderate to good overall calibration (E/O ratios between 0.80 and 0.92).

We provide simple models for CHD and HF risk, without treatment dose, and more extensive ones including prescribed mediastinal radiation dose and anthracycline dose. We expected that incorporating dose information for RT and CT would yield a better predictive performance. However, adding prescribed dose information did not increase the discriminative ability of the models, and overall, our discriminative ability remained moderate. This has also been observed in other studies.[28] Sensitivity analyses including age and RT dose as continuous variables did not enhance discriminative ability, probably because of the relatively small variation in RT dose to the mediastinum (IQR, 35-40) in our development cohort. It is worth noting that almost all patients in our study were treated with parallel opposed fields, leading to a limited variation of radiation exposure of the heart. Contemporary RT policies including smaller radiation volumes, lower radiation doses, and modern RT techniques[29] will, however, result in lower radiation exposure of the heart and significant variation in actual heart dose across patients. Incorporating measures derived through radiation dosimetry, such as mean heart dose and the volume of the left ventricle receiving at least 5 Gy, might improve the predictive performance of our models.[30] Unfortunately, we were unable to test such a model because of unavailability of long-term follow-up data in recently treated patients and lack of dosimetry data for our entire cohort. Regarding calibration, our models provide an underestimation of CHD risk in our cohort. No significant deviation was observed for the overall calibration of the HF models. The performance of our models is similar to performance of previously published models for CHD and HF in cancer survivors.[12,13] Reassuringly, AUCs obtained through external validation of our CHD model were quite similar compared with the AUCs in our development cohort although differences exist between the two cohorts.

HL survivors can experience multiple cardiovascular events during follow-up.[7,31] Because HF can occur as a consequence of CHD or valvular disease, we only included HF events in patients without a prior CVD event. Because of this

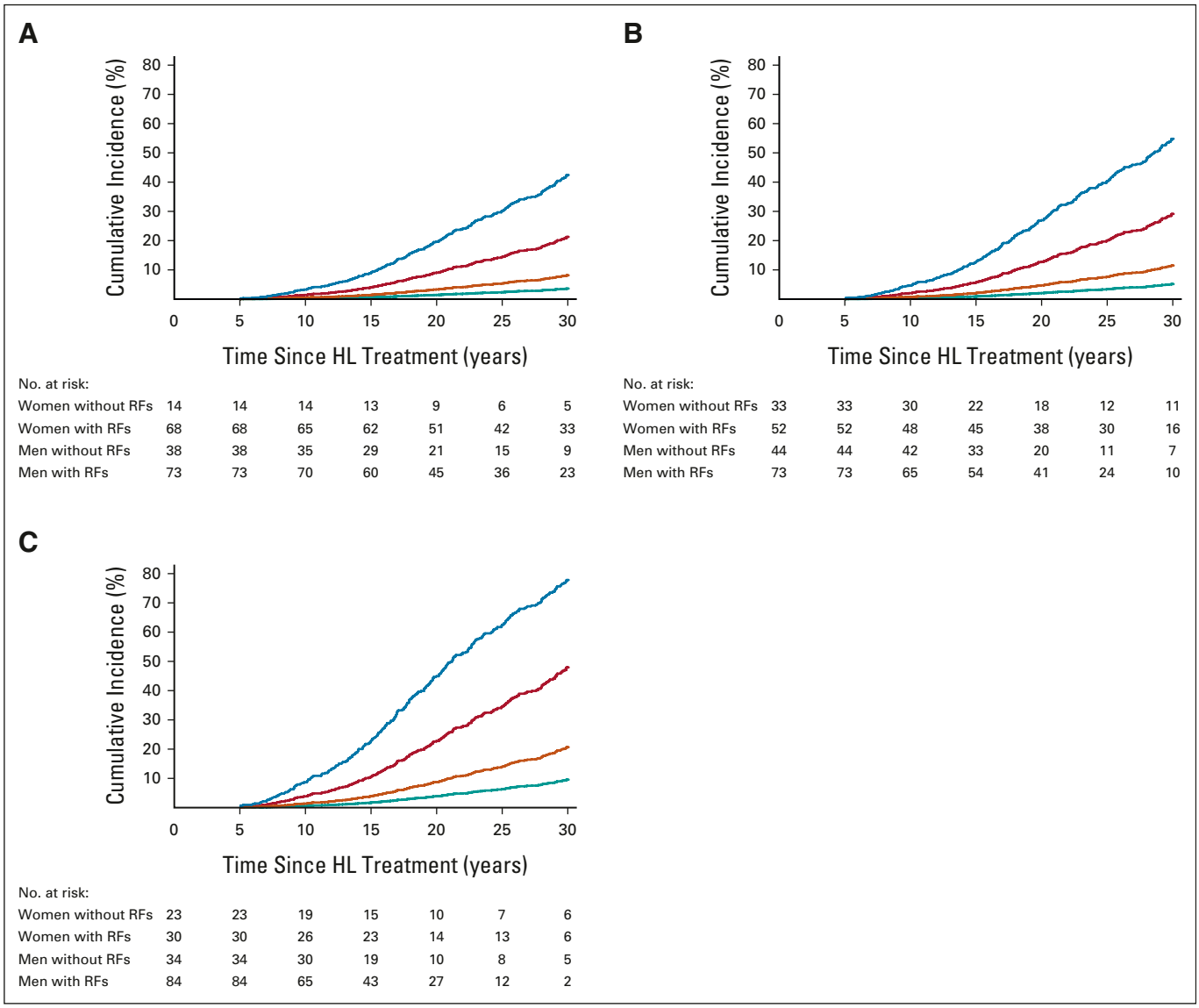


FIG 4. Cumulative incidence of coronary heart disease by risk group derived from the development cohort. Risk factors defined as smoking at HL diagnosis and mantle field radiotherapy. In all figures, the green/turquoise line represents a female, treated without mediastinal radiotherapy who did not smoke at diagnosis; the red line represents a female, treated with mantle field radiotherapy who smoked at diagnosis; the orange line represents a male, treated without mediastinal radiotherapy who did not smoke at diagnosis; the blue line represents a male, treated with mantle field radiotherapy who smoked at diagnosis. Cumulative incidence for patients between (A) 18 and 24 years, (B) 25 and 34 years, and (C) 35 and 50 years at HL treatment. HL, Hodgkin lymphoma; RF, risk factor.

choice, we might have underestimated the total burden from HF, but we deemed it more important to provide information about treatment-related risk to develop HF as a first cardiovascular event. This resulted in a further reduction of HF cases, limiting our ability to validate the HF model on the basis of the ORaCLE data. Furthermore, some of our 30-year cumulative incidence estimates for CHD are quite high (> 50%), also compared with our previous study by van Nimwegen et al.[7] However, that study was restricted to CHD events that occurred as a first CVD event, whereas we included all CHD events. It is also possible, however, that our models slightly overestimate the risk especially for high-risk patients. As it was not possible to externally validate the HF model, we recommend recalibrating this model before applying it in other settings. In addition, treatment of patients with HL differed between the development and validation cohort. The more recently treated patients in the validation cohort more often received (anthracycline-based) CT and less often RT. Despite these differences, discrimination of the CHD model in the ORaCLE data was comparable with that in the Dutch HL cohort. Since HL cohorts including adult patients with long-term follow-up on CVD incidence are scarce, using the ORaCLE data allowed for an external validation in a slightly different treatment setting.

In a recently published paper from the Childhood Cancer Survivor Study (CCSS) on prediction of CVD risk in childhood

cancer survivors, classical CVD risk factors such as diabetes, dyslipidemia, and hypertension were incorporated in the prediction models.[14] In our models, these factors were not included. Although information on risk factors in the Dutch cohort was collected through patient and general practitioner questionnaires at various time points during follow-up, the date at diagnosis of first report or assessment of these risk factors was often missing. Therefore, for many patients, we could not exclude the possibility that risk factor status was determined as a consequence of the occurrence of a CVD event, which would cause overestimation of the HRs associated with these risk factors. Such bias might have also occurred in similarly designed studies.[12-14] We did, however, include smoking status in our model for CHD, which resulted in a significant improvement of the model fit. Smoking was not taken into account in previous models[12-14] although it is an important predictor for CHD.[32] Incorporating more detailed information on smoking, such as the number of pack-years, may further increase our predictive ability in the future. Unfortunately, in two participating hospitals, data on prescribed RT dose were not collected. As we based our models on a complete-case analysis to be able to compare the performance of the simple and dose models, patients with missing RT dose were also excluded from the development set for the simple model. Characteristics of patients with and without RT dose information did not differ.

To our knowledge, our cardiovascular risk prediction models are the first that have been developed for survivors of adolescent and adult HL. Models based solely on well-known risk estimators for CVD, such as the Framingham Coronary Heart Disease Score, may greatly underestimate cardiovascular risk in our population, as they do not account for cardiotoxic cancer treatment exposures.[33] Previous risk prediction models to assess the risks of CHD and HF after cancer treatment were based on CCSS data.[12-14] Although treatment-related factors (mediastinal RT and anthracycline dose) included in these models largely correspond with our model parameters, HL-specific models covering a much wider age range are needed to predict CHD and HF risk after treatment for adolescent and adult HL. Our models show that age at HL treatment is an important predictor for subsequent CVD, in terms of both relative and absolute risks. Our models enable improved identification and counseling of HL survivors who may benefit from targeted screening for CVD and early treatment of risk factors, which could be incorporated in screening recommendations for the prevention of late adverse effects after treatment for HL. Existing prevention strategies already include lifestyle recommendations, such as smoking cessation.[11] We expect that more recent treatment changes over the past decade will result in significantly lower risks of late treatment effects. Therefore, future efforts should focus on incorporating cardiac radiation dosimetry to enable more personalized CVD risk prediction in recently treated patients and to tailor treatment options.

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DISCLAIMER

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