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Prediction of cardiovascular disease among hematopoietic cell transplantation survivors

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Key Points

- We identified distinct groups of HCT survivors at low, intermediate, and high risk of developing late-occurring CVD.
- The prediction model had good discrimination across outcomes and was validated in an external cohort of HCT survivors.

Cardiovascular disease (CVD) is a leading cause of late morbidity and mortality in hematopoietic cell transplantation (HCT) survivors. HCT-specific CVD risk prediction models are needed to facilitate early screening and prevention. In the current study, patients who underwent HCT at City of Hope (COH) and survived 1-year free of clinically evident CVD (N = 1828) were observed for the development of heart failure (HF) or coronary artery disease (CAD) by 10-years from index date (1 year from HCT). CVD occurred in 135 individuals (92 HF, 43 CAD). Risk prediction models were developed for overall CVD (HF and/or CAD) using COH-derived integer risk scores. Risk scores based on selected variables (age, anthracycline dose, chest radiation, hypertension, diabetes, smoking) achieved an area under the curve (AUC) and concordance (C) statistic of 0.74 and 0.72 for CVD; these varied from 0.70 to 0.82 according to CVD subtype (HF or CAD). A Fred Hutchinson Cancer Research Center case cohort (N = 580) was used to validate the COH models. Validation cohort AUCs ranged from 0.66 to 0.75. Risk scores were collapsed to form statistically distinct low-, intermediate-, and high-risk groups, corresponding to 10-year cumulative incidences of CVD of 3.7%, 9.9%, and 26.2%, respectively. Individuals in the high- and intermediate-risk groups were at 7.8-fold (95% confidence interval, 5.0-12.2) and 2.9-fold (95% confidence interval, 1.9-4.6) risk of developing CVD (referent group: low risk). These validated models provide a framework on which to modify current screening recommendations and for the development of targeted interventions to reduce the risk of CVD after HCT.

Introduction

Advances in hematopoietic cell transplantation (HCT) have led to a 10% improvement in survival each decade since the 1980s,[1] resulting in an estimated 200 000 HCT survivors alive in the United States today.[2,3] Despite these improvements, HCT survivors continue to have substantially higher mortality rates compared with the general population.[4-6] In particular, the risk of cardiovascular-related mortality is more than twice that of the general population,[5-7] and the magnitude of risk increases with time from HCT.[7] However, examining cardiovascular-related mortality alone underestimates the true burden of cardiovascular morbidity. HCT survivors have a fourfold higher risk of developing cardiovascular disease (CVD) compared with the general population,[7,8] adding to the already high burden of chronic health-related conditions in these survivors.[9] Among HCT survivors, median age at first cardiovascular event such as myocardial infarction is 53 years (range, 35-66 years),[10] much lower than would be expected in the general population (67 years).[11] This is likely due to pre-HCT cardiotoxic therapies (chest radiotherapy, anthracycline chemotherapy) and higher burden of potentially modifiable cardiovascular risk factors (CVRFs; hypertension, diabetes, dyslipidemia) in survivors after HCT.

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Table 1. Characteristics of the study cohorts

Cohort	City of Hope, N = 1828	Fred Hutchinson Cancer Research Center, N = 580
Population	Single US center; underwent a first HCT between 1 January 1995 and 31 December 2004; alive at 1-y post HCT; no history of CVD prior to HCT; follow-up censor date December 2012	Single US center; underwent any HCT between 1 January 1970 and 31 December 2010; alive at 1-y post-HCT; no history of CVD prior to HCT; follow-up censor date December 2012
Study design	Retrospective cohort	Retrospective case cohort
Cancer treatment information	Cumulative chemotherapy doses, radiotherapy fields and doses, no organ-specific dosimetry	Cumulative chemotherapy doses, radiotherapy fields and doses, no organ-specific dosimetry
Cardiovascular disease definition	Medical and death records; limited to CVD occurring ≥1 y post-HCT; heart failure (N = 92),* coronary artery disease (myocardial infarction, symptomatic coronary artery stenosis requiring intervention [N = 43])	Self-report†, hospital registry, medical, and death records; limited to CVD occurring ≥1 y post-HCT; heart failure (N = 56),* coronary artery disease (myocardial infarction, symptomatic coronary artery stenosis requiring intervention [N = 99])

CVD, cardiovascular disease; HCT, hematopoietic cell transplantation.
*Defined per the American Heart Association/American College of Cardiology guidelines.[59]
†Patients with self-reported CVD were reviewed against available hospital registry, medical, and death records prior to inclusion.

Given their increased risk for developing premature CVD, HCT survivors may benefit from customized and validated risk prediction models starting at a time when their level of engagement in post-HCT survivorship care is at its highest. As such, our goal was to use a large HCT survivor cohort with long-term follow-up to create clinically useful models that incorporate demographic, cancer treatment, and modifiable risk factor information available at the 1-year post-HCT time point to predict 10-year CVD risk with reasonable discrimination, and to validate our risk prediction model in an external cohort of HCT survivors. The development of a robust CVD risk prediction model for this population may help clinicians refine surveillance strategies for early detection and treatment of preclinical disease and to counsel patients at high risk for future events.

Methods

Primary study population

The cohort consisted of 1930 consecutive patients who underwent a first HCT for a hematologic malignancy at City of Hope (COH) between 1995 and 2004, and survived at least one year. Patients who refused participation (N = 32 [1.7%]), whose medical records were missing (N = 46 [2.4%]), had a history of CVD prior (N = 18 [0.9%]) or within 1 year of HCT (N = 6 [0.3%]) were excluded from the study; 1828 patients (95% of the cohort) were included in the analysis. Follow-up of the cohort was censored on 31 December 2012. Medical records served as the primary source of data for this study (Table 1). Details regarding methodology of patient tracking and data collection have been reported previously.[10,12,13]

Exposure and outcome definitions

Information pertaining to lifetime anthracycline chemotherapy (drug, cumulative dose) and chest radiation, as well as high-dose chemotherapy and radiation were captured using an established protocol. Cumulative anthracycline dose was calculated using an established cardiotoxicity risk score; cumulative dose of each agent was multiplied by a number that reflects its cardiotoxicity relative to doxorubicin (doxorubicin = 1, daunorubicin = 0.83, epirubicin = 0.67, idarubicin = 5, mitoxantrone=4).[14,15] Chest radiation included the following fields: mantle, mediastinal, or lung. Individuals who received a total of ≤200 cGy of radiation as part of conditioning were not considered as having received total body irradiation (TBI).

The study included only clinically validated CVRFs (hypertension, diabetes, dyslipidemia, and smoking) that were present at the 1-year post-HCT time point (index date). Patients who developed transient CVRFs, defined as resolving prior to the 1-year post-HCT time point, were considered as not having CVRF. Hypertension was defined per the National Heart, Lung and Blood Institute's Joint Committee criteria.[16] Thus, individuals ≥18 years of age with systolic blood pressure (BP) ≥140 mm Hg and/or diastolic BP ≥90 mm Hg or those <18 years of age with BPs >90th percentile for age on ≥2 consecutive visits, or individuals receiving treatment of hypertension were defined as having hypertension. Diabetes mellitus was defined according to the American Diabetes Association's criteria,[17] and included any 1 of the following: fasting plasma glucose ≥126 mg/dL, random plasma glucose ≥200 mg/dL, or receiving treatment of diabetes. Dyslipidemia was defined per the National Cholesterol Education Program,[18] and included any 1 of the following: fasting total cholesterol ≥240 mg/dL, low density lipoprotein ≥160 mg/dL, triglyceride ≥200 mg/dL, or treatment of dyslipidemia. Smoking history (ever/never) was obtained from medical records. Family history of CVD was not abstracted because it was not reliably documented in the medical records. Obesity was defined as body mass index ≥30 kg/m^2 at index date.

CVD was defined as coronary artery disease (CAD; myocardial infarction, symptomatic coronary artery stenosis requiring intervention) or heart failure (HF, per established guidelines)[19] developing after index date. If a patient developed pre-HCT CVD or CVD within the first year after HCT, they were not included in the risk prediction model. Patients who developed transient cardiac dysfunction due to a potentially reversible complication such as sepsis and subsequently had no evidence of cardiac dysfunction were considered not to have HF.

Statistical analysis

Univariate analyses were performed to compare demographics, diagnosis, pre-HCT cardiotoxic exposures (anthracyclines, chest radiotherapy), HCT type, conditioning-related exposures, and CVRFs at index date between patients who developed a first CVD and those who did not, using χ^2 for dichotomous or Student t tests for continuous variables. The time to CVD was computed starting

1 year post-HCT to the date of disease onset, date of last contact, or date of death, whichever came first. Cumulative incidence (CI) of CVD was calculated treating death as a competing risk, and Gray's test[20] was used to compare the CI of CVD, taking into consideration competing risk of death for left-censored data.[20]

Fine-Gray subdistribution proportional hazards models[21] were used to estimate the relationship between selected variables ($P < .1$ univariate analysis, literature review) and CVD, taking into consideration competing risk of death. Due to high collinearity between HCT type (autologous, allogeneic) and anthracycline dose, HCT type was not included in the final regression model. The final model included the following: age at index date (<30 [referent], 30-<50, ≥50 years), anthracycline dose (≤250 [referent], >250 mg/m^2),[22,23] hypertension (no [referent], yes), diabetes (no [referent], yes), smoking (never [referent], ever), and chest radiotherapy (none [referent], any). A simplified model was also developed that did not require knowledge about anthracycline dose (none [referent] vs any). Of note, obesity was not included in our models due to its high collinearity with hypertension and diabetes.

Regression coefficient estimates of covariates were converted to integers for ease of summing to calculate overall risk scores (rate ratios <1.3, 1.3 to 1.9, 2.0 to 2.9, and 3.0 to 4.9 corresponded to risk scores of 0, 1, 2, and 3, respectively) on the basis of published methods.[24,25] Competing risks proportional hazards regression with time from HCT as its time scale was used to estimate the risk scores' discriminatory and predictive power. Specifically, we examined the area under the receiver operating characteristic curve (AUC) at 10 years post-index date and the concordance (C) statistic (representing the weighted average AUC from the index date through 10 years).[26,27] Risk prediction models were developed for overall CVD using COH-derived integer risk scores. R package survivalROC (version 1.0.3),[26] was used to calculate AUCs and C-statistics for the entire cohort and by HCT type (allogeneic, autologous). SAS (version 9.4; SAS institute, Cary, NC) was used for the regression analysis. Risk scores were summed to create low-, intermediate-, and high-risk groups on the basis of the absolute risks (incidence at 10 years from index date). The risk categories were designed such that each group ideally would be significantly distinct from one another ($P < .05$).

The integer scores derived from the overall CVD model were used to determine separate AUCs for HF and CAD as a first event, and to determine the CI for each outcome as well as the subdistribution hazard ratios (HRs) for low-, intermediate-, and high-risk groups. Each of these events was considered a competing risk in the context of the other (eg, CAD was a competing risk in the HF analyses).

External validation cohort

We used a well-established retrospective case-cohort dataset to validate the overall CVD risk prediction model. The Fred Hutchinson Cancer Research Center (FHCRC) data set included 580 HCT survivors (155 cases; 425 randomly selected members of the overall cohort, representing 10% of the overall population) who underwent HCT between January 1970 and December 2010 (Table 1). The case-cohort study design was chosen because the FHCRC did not have complete pre-HCT chemotherapy and radiation information, and study resources did not allow for a review of the entire cohort.[28] Demographic and treatment characteristics, and how CVRFs and CVD were defined have been described elsewhere[29,30] and are included in Table 2. The AUC (at 10 years post index date) for CVD was then estimated for the entire cohort and by HCT type on the basis of the COH risk scores. Each individual was then categorized into appropriate COH-based risk grouping, and the resulting Fine-Gray sub-distribution HRs by risk category (low [referent], intermediate, high) were created, using Barlow's weighting method with robust standard errors to account for the case-cohort design.[31] C-statistics and cumulative incidence curves were not generated for the validation cohort given methodologic limitations introduced by the case-cohort sampling design. Stata (version 15; StataCorp, College Station, TX) was used for the validation analysis.

Both the COH and FHCRC follow-up protocols were approved by their institutional review boards, and informed consent was obtained according to the Declaration of Helsinki.

Results

Within the COH cohort, median follow-up from index date was 7.1 years (range, 0.1-18.6 years); for the 1,116 (61%) patients alive at last contact, it was 9.2 years (range, 0.1-15.9 years). Overall, the cohort provided 14 359 person-years of follow-up, with 87% of the cohort followed through December 2012 (if alive) or up to date of CVD diagnosis or death. Of the 1,828 survivors included in the discovery cohort, 1,271 (~70%) were followed until the onset of CVD, to their date of death, or ≥10 years (if alive) whichever came first. Among the 135 patients who developed CVD, 92 (68%) had HF as the first event and 43 (32%) had CAD as the first event, developing at a median 5.0 years and 7.6 years from index date, respectively.

The clinical characteristics of the COH cohort are summarized in Table 2. The majority of patients underwent autologous HCT (56.4%), and the most common indication for HCT was lymphoma (38.5%). TBI was used for conditioning in 53.5% of patients, 75.3% had received anthracycline chemotherapy and 5.3% had received chest radiotherapy prior to HCT. Patients who developed CVD were significantly more likely to be older (53.0 vs 44.2 years, $P <$ .001), have received high dose (>250 mg/m^2) anthracycline (48.1% vs 34.3%, $P = .001$), undergone autologous HCT (70.4% vs 55.3%, $P = .001$), to have hypertension (49.6% vs 26.3%, $P <$ .001) or diabetes (27.4% vs 9.5%, $P <$ .001) at 1-year post-HCT, and to have reported ever smoking (43.7% vs 29.5%, $P = .001$) compared patients who did not develop CVD.

A set of influential predictors available at the 1-year HCT survival time point were identified from which corresponding integer scores were created (Table 3). The resulting AUC and C-statistic for CVD at 10-years using COH-derived integer risk scores were 0.74 and 0.72, respectively. The AUC and C-statistic derived from the simplified model (no anthracycline vs any) were 0.73 and 0.71, respectively. Prediction estimates associated with the original regression coefficients were virtually identical to those associated with integer scores (within 0.01). Application of the COH-based CVD risk score to the external validation cohort (FHCRC) showed that the AUCs at 10-years were comparable (0.72) despite differences in demographics and treatment-related exposures (Table 2). Of note, when our general CVD model was applied to COH allogeneic and autologous HCT recipients, the AUC and C-statistics ranged from 0.80 to 0.77 for allogeneic recipients and 0.70 to 0.68 for autologous recipients. AUCs for FHCRC allogenic and autologous HCT recipients were 0.72 and 0.71 respectively.

Table 2. Demographic and clinical characteristics of ≥1-year survivors of HCT

Characteristics	Training data set COH, N = 1828	CVD, N = 135	No CVD, N = 1693	*P**	Validation data set FHCRC, N = 580
Sex, n (%)					
Male	1052 (57.5)	82 (60.7)	970 (57.3)	.44	319 (55.0)
Ethnicity/race, n (%)					
Non-Hispanic white	1142 (62.5)	93 (68.9)	1049 (62)		502 (86.6)
Hispanic	453 (24.8)	22 (16.3)	431 (25.5)		41 (7.1)
Other	233 (12.7)	20 (14.8)	213 (12.6)	.06	37 (6.4)
Age, y†					
Median (range)	45.0 (1.6-79.9)	53.0 (17.0-79.9)	44.2 (1.6-78.3)	<.001	45.0 (2.0-74.0)
<30, n (%)	407 (22.3)	9 (6.7)	398 (23.5)		131 (22.6)
30 to <50, n (%)	756 (41.4)	46 (34.1)	710 (41.9)		98 (16.9)
≥50, n (%)	665 (36.4)	80 (59.3)	585 (34.6)	<.001	351 (60.5)
Diagnosis, n (%)					
Acute leukemia	537 (29.4)	34 (25.2)	503 (29.7)		211 (36.4)
Chronic leukemia	241 (13.2)	13 (9.6)	228 (13.5)		124 (21.4)
Lymphoma	704 (38.5)	64 (47.4)	640 (37.8)		118 (20.3)
Other	346 (18.9)	24 (17.8)	322 (19.0)	.15	127 (21.9)
Anthracycline dose, mg/m^2					
Median (range)	180 (0-1116)	225 (0-528)	180 (0-1116)	.001	116 (0-972)
≤250 mg/m^2, n (%)	1183 (64.7)	70 (51.9)	1113 (65.7)		409 (70.5)
>250 mg/m^2, n (%)	645 (35.3)	65 (48.1)	580 (34.3)	.001	165 (28.4)
Anthracycline use, n (%)					
Yes	1376 (75.3)	111 (82.2)	1265 (74.7)	.05	327 (56.4)
Chest radiation, n (%)					
Yes	97 (5.3)	11 (8.1)	86 (5.1)	.13	47 (8.1)
HCT type, n (%)					
Autologous	1031 (56.4)	95 (70.4)	936 (55.3)		191 (32.9)
Allogeneic	797 (43.6)	40 (29.6)	757 (44.7)	.001	389 (67.1)
Conditioning regimen, n (%)					
Chemotherapy only	850 (46.5)	63 (46.7)	787 (46.5)		264 (45.5)
Chemotherapy + TBI	978 (53.5)	72 (53.3)	906 (53.5)	.97	314 (54.5)
Cardiovascular risk factors,† n (%)					
Hypertension	512 (28.0)	67 (49.6)	445 (26.3)	<.001	136 (23.4)
Diabetes	198 (10.8)	37 (27.4)	161 (9.5)	<.001	48 (8.3)
Dyslipidemia	600 (32.8)	52 (38.5)	548 (32.4)	.14	36 (6.2)
Smoking, ever	558 (30.5)	59 (43.7)	499 (29.5)	.001	217 (37.4)
Obesity (BMI ≥30 kg/m^2)	442 (24.2)	41 (30.4)	401 (23.7)	.081	114 (19.7)

BMI, body mass index.
*CVD vs no CVD in training data set.
†At index date (1 year from HCT).

The 10-year cumulative incidence corresponding to each integer value was created (Figure 1A). Summed risk scores that shared similar absolute rates were then grouped to form low- (≤3), intermediate- (4-5), and high- (≥6) risk groups. The 10-year cumulative incidence of CVD for low-, intermediate-, and high-risk individuals were 3.7%, 9.9%, and 26.2%, respectively (Table 4, Figure 1A); the proportion subsequent deaths due to CVD also increased by risk group (1.7% [low], 4.7% [intermediate], 11.5% [high]; supplemental Table 1) The hazard ratios of CVD for the intermediate- and high-risk groups were 2.9 (95% confidence interval, 1.5-4.2) and 7.8 (95% confidence interval, 5.0-12.2); low risk (referent [Table 4]). These risk groups were statistically distinct from one another ($P < .001$). The same classification strategy was used for the validation cohort, resulting in similar hazard ratios (HRs) for intermediate- (HR, 4.2 [95% confidence interval, 2.6-6.8]) and high-risk (HR, 8.0 [95% confidence interval, 4.7-13.6]) individuals, with the difference between these 2 risk groups also significantly different ($P = .007$).

Table 3. Multivariable regression analysis with associated hazard ratios for CVD, 95% confidence intervals, integer risk scores, and corresponding prediction models

Variable	Hazard ratio	95% confidence interval		*P*	Risk score*
Age, y					
<30	1.0				0
30 to <50	2.35	1.15	4.80	.019	2
≥50 y	4.00	1.98	8.08	<.001	3
Anthracycline dose					
≤250 mg/m^2	1.0				0
>250 mg/m^2	1.88	1.33	2.66	<.001	1
Hypertension					
No	1.0				0
Yes	2.03	1.42	2.90	<.001	2
Diabetes					
No	1.0				0
Yes	2.70	1.84	3.97	<.001	2
Smoking					
Never	1.0				0
Ever	1.39	0.99	1.96	.060	1
Chest radiation					
None	1.0				0
Any	1.92	1.07	3.43	.028	1

*Risk scores of 0, 1, 2, and 3 correspond to hazard ratios of <1.3, 1.3 to 1.9, 2.0 to 2.9, and 3.0 to 4.9, respectively.

In the COH cohort, the AUC and C-statistic for HF were both 0.70 (simplified model: AUC 0.70, C-statistic 0.69), while the AUC and C-statistic for CAD were 0.82 and 0.79 respectively (simplified model: AUC 0.79, C-statistic 0.76). Application of the COH-based risk score to the FHCRC cohort showed that the AUCs varied by outcome and there was reasonable discrimination (HF: 0.66; CAD: 0.75). In the discovery cohort, the low risk group tended to have cumulative incidences at 10 years of <5%, irrespective of outcome. For the high-risk group, the incidence of HF was 15.4% and the incidence of CAD was 10.8% at 10 years (Table 4; Figure 1B-C). Hazard ratios of HF and CAD for the various risk groups remained statistically distinct from one another ($P < .001$); Table 4.

Discussion

We used data from a large and well-characterized cohort of HCT survivors to develop a 10-year CVD risk prediction model, allowing us to identify a subset of high-risk survivors in whom the post-HCT CVD incidence exceeded 25%. We also identified a low-risk subgroup where the incidence of CVD was <5%. The discriminatory power of our model was consistent when applied to an external cohort of HCT survivors with different demographics and treatment-related exposures (eg, higher proportion of non-Hispanic whites, allogeneic HCT recipients, lower median anthracycline dose, treatment era), or when it was examined by HCT type (allogeneic: AUC 0.72-0.80, autologous: AUC 0.70-0.72), speaking to the overall robustness of the model. The data needed to produce the CVD risk estimates can be readily obtained from medical records, providing health practitioners an accessible platform through which to identify high-risk individuals. Information from this study can be used to further refine current late effects screening recommendations[32-34] and to develop tailored interventions to minimize the morbidity associated with CVD after HCT.

To our knowledge, this is one of the first CVD risk prediction models applicable to survivors of mostly adult-onset cancers. The findings from this study are in line with other CVD risk prediction models developed for both survivors of childhood cancer[24,25] and individuals without a history of cancer,[35-37] and where AUCs/C-statistics have ranged from 0.6 to 0.8. It is important to note, however, that risk prediction scores used for the general population typically start around age 30 years (approximately 25% of patients in both the discovery and validation cohorts were <30 years of age at the index date). These general population risk prediction scores may in turn underestimate the true magnitude of risk to a young population at high risk for CVD due to pre-HCT cardiotoxic exposures and post-HCT modifiable risk factors. Therefore, the models presented in our study are both practical and can have clinical utility for health care providers as well as long-term HCT survivors alike.

Among HCT-survivors, treatment-related exposures (eg, TBI-based conditioning) and post-HCT complications (eg, GVHD) contribute to a significantly higher prevalence of risk factors such as hypertension and diabetes compared with the general population.[7,13,38] Our model's 1-year post-HCT starting time point capitalizes on the so-called "teachable moment" effect,[39] where survivors, having survived one life-threatening disease, may be more motivated to try and prevent additional illness. This can be done in the form of early screening and aggressive management of hypertension or diabetes, or by survivors' adoption of a heart healthy lifestyle, incorporating diet modification and exercise to reduce long-term CVD risk.[40,41] Such strategies have been effective in the general population[42-44] and interventions are under way for other cancer survivor populations at high risk for developing CVD.[45-48] Future CVD risk-reduction strategies for HCT survivors will benefit from a personalized approach, taking into consideration the physical limitations associated with complications such as GVHD and the burden of other chronic health conditions that develop after HCT.[9,49,50]

We acknowledge that as in other risk prediction models, there may be variables that are unaccounted for in our models. This may be especially true for HF prediction, as the AUC and C-statistics were consistently lower for HF than for CAD (0.66 to 0.71 [HF] vs 0.75 to 0.82 [CAD]). We and others have shown that despite the strong association between certain variables (eg, anthracycline dose, age, hypertension) and post-HCT HF, there is marked inter-individual variability in risk that is not explained exclusively by these factors alone.[29,51,52] For example, susceptibility due to inherited genetic variations in pathways involved in anthracycline-related toxicity have been shown to account for up to 10% of the HF risk after HCT,[38,39] and may need to be accounted for in future risk prediction estimates. As for CAD, the long latency (~10 years) between HCT and CAD may necessitate longer follow-up of our cohort, allowing us to further refine our risk estimates. For all models, the use of continuous (age, anthracycline or chest radiotherapy dose) vs

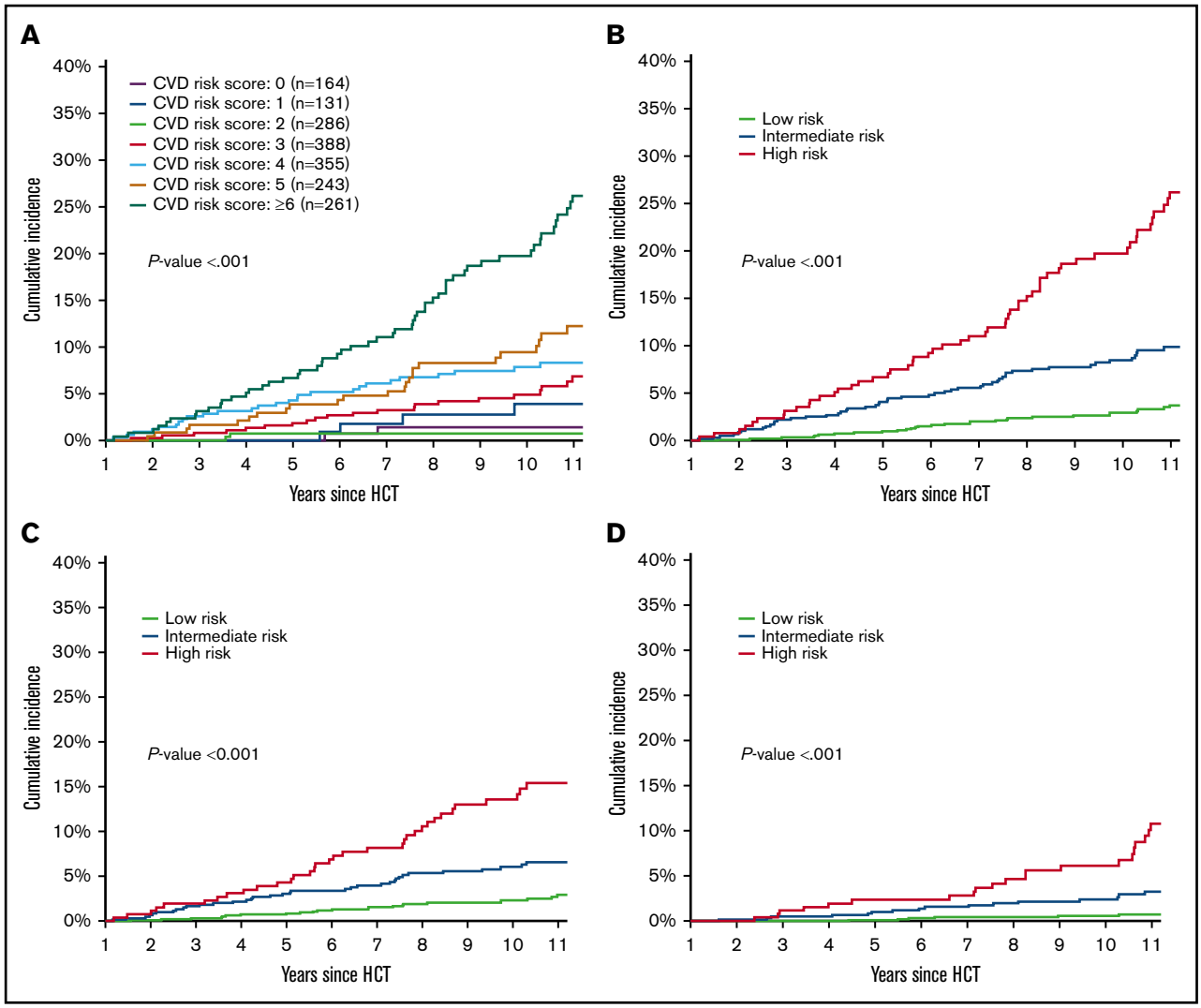

Figure 1. Ten-year cumulative incidence of cardiovascular disease. By integer risk score (A) and by risk groups (B). Cumulative incidence of heart failure (C) and coronary artery disease (D) by risk groups. Curves start at index date (1 year from HCT).

categorical variables may also improve risk prediction, although such changes could limit the ease of clinical application. However, knowledge about cumulative anthracycline dose did not impact the AUCs for either CVD or HF, and the low prevalence of chest radiotherapy in both cohorts made it unlikely that detailed radiation dosimetry information would have provided a meaningful improvement in either CVD or CAD prediction. Finally, chronic GVHD per se was not included in our risk prediction models. To our knowledge, the evidence supporting the association between chronic GVHD and CVD is mixed. We and others have shown that severity of chronic GVHD (eg, those requiring systemic immunosuppressive therapy) is often not a significant predictor of CVD in long-term HCT survivors, once modifiable risk factors such as hypertension, diabetes, and dyslipidemia are accounted for.[7,10,13,29] Some potential effect of chronic GVHD on CVD may be mediated by GVHD prophylaxis and treatment rather than GVHD itself. It is for this reason that we included the modifiable risk factors in the final regression model instead of GVHD.

The current study has some additional limitations. The information we had regarding modifiable risk factors was not ascertained via uniform in-person methods, as used by some population-based risk prediction models.[35-37] Despite this limitation, the discriminatory power of our model was similar to those routinely used in clinical practice for individuals without a history of cancer.[35-37] We were also unable to assess the role of other potential CVD risk factors, such as gonadal dysfunction, the duration and recency of tobacco exposure, lifetime corticosteroid exposure, as well as details regarding physical activity and family history of CVD. However, the health conditions included in the current study account for >70% of the attributable risk for cardiac[53,54] as well as arterial[55] disease in the general population, and provide the basis for the development of future models that may take into consideration the impact of both subclinical risk factors and lifestyle behaviors on long-term CVD risk after HCT. We also did not include family history of CVD in our models because it was not reliably documented in the medical records. It is worth noting that other major CVD risk scores for the general population (eg, Framingham risk score,[36,55]

Table 4. Classification of cardiovascular events and 10-year cumulative incidence and hazard ratios based on summed risk scores

	Risk score	No. events/no. at risk	CI (95% confidence interval), %*	*P*†	Hazard ratio (95% confidence interval)
All cardiovascular disease					
Low	≤3	29/969	3.7 (2.5-5.2)		1.0
Intermediate	4-5	51/598	9.9 (7.4-12.6)		2.9 (1.9-4.6)
High	≥6	55/261	26.2 (20.3-32.5)	<.001	7.8 (5.0-12.2)
Heart failure					
Low	≤3	23/969	2.9 (1.9-4.3)		1.0
Intermediate	4-5	35/598	6.6 (4.7-8.9)		2.5 (1.5-4.2)
High	≥6	34/261	15.4 (10.9-20.6)	<.001	5.8 (3.5-9.9)
Coronary artery disease					
Low	≤3	6/969	0.8 (0.5-1.9)		1.0
Intermediate	4-5	16/598	3.3 (1.9-5.2)		4.3 (1.7-11.0)
High	≥6	21/261	13.4 (10.8-15.8)	<.001	13.4 (5.4-33.1)

*At 10 years from index date (1-year post-HCT).
†The Gray k-sample test for equality of cumulative incidence functions.

American College of Cardiology/American Heart Association,[56] European Society of Cardiology[57]) do not include family history. Finally, we acknowledge that our models may not take into account changes in treatment that have occurred over the past decade, such as the greater use of molecular targeted agents, some of which have unique cardiotoxicity profiles.[58] Future studies will need to refine the current estimates, using contemporary cohorts of HCT survivors and taking into consideration the health-economic impact of early screening and prevention strategies in at risk survivors.

In conclusion, the major contribution of our CVD prediction models is that they combine established risk factors in a rational manner, allowing individualized risk prediction that extends beyond the current single risk factor-based approach that has characterized most survivorship surveillance guidelines. These validated models can be used to counsel HCT survivors at the beginning of their survivorship journey, providing health care practitioners with quantifiable CVD risk estimates to guide behavior modification and management of modifiable risk factors. For example, in survivors at high risk for CVD due to past exposure to cardiotoxic treatments (eg, high dose anthracycline, chest radiotherapy) and hypertension, aggressive management of systolic blood pressure may reduce the risk of future cardiovascular events, as shown in other high risk populations.[42-44] For others, with multiple risk factors, a more holistic approach may be necessary such as incorporating a heart healthy lifestyle (aerobic exercise, diet modification, smoking cessation, stress management) through partnerships with primary or subspecialty (eg, cardiology, endocrinology) providers. The growing population of long-term HCT survivors (estimated to be >500 000 in the United States by 2030)[3] makes the development of novel and personalized prevention strategies imperative, to ensure that these survivors live long and healthy lives well after completion of HCT.

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Authorship

Contribution: S.H.A. designed the research, collected and assembled the data, analyzed and interpreted the data, and wrote the paper; D.Y., F.L.W., and W.M.L. analyzed and interpreted the data, and contributed to the writing of the paper; J.B.T., L.C.A., A.G., S.J.F., and R.N. provided study participants, collected and assembled the data, and contributed to the writing of the paper; and E.J.C. designed the research, collected and assembled the data, analyzed and interpreted the data, and contributed to the writing of the paper.

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