Prediction of Low and Very Low Bone Mineral Density Among Adult Survivors of Childhood Cancer

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PURPOSE To develop and validate prediction models for low and very low bone mineral density (BMD) on the basis of clinical and treatment characteristics that identify adult survivors of childhood cancer who require screening by dual-energy x-ray absorptiometry.

PATIENTS AND METHODS White survivors of childhood cancer ($n = 2,032$; median attained age, 29.3 years [range, 18.1 to 40.9 years]) enrolled in the St Jude Lifetime Cohort (SJLIFE; development) and survivors treated at the Erasmus Medical Center (validation) in the Netherlands ($n = 403$; median age, 24.2 years [range, 18.0 to 40.9 years]) were evaluated with dual-energy x-ray absorptiometry to determine lumbar spine BMD and total-body BMD. Low and very low BMD were defined as lumbar spine BMD and/or total-body BMD z scores of -1 or lower or -2 or lower, respectively. Multivariable logistic regression was used to build prediction models; performance was assessed using receiver operating characteristic curves. Diagnostic values were calculated at different probabilities.

RESULTS Low BMD was present in 51% and 45% of SJLIFE and Dutch participants, respectively, and very low BMD was present in 20% and 10%, respectively. The model for low BMD included male sex (odds ratio [OR], 3.07), height (OR, 0.95), weight (OR, 0.98), attained age (OR, 0.97), current smoking status (OR, 1.48), and cranial irradiation (OR, 2.11). Areas under the curve were 0.72 (95% CI, 0.70 to 0.75) in the SJLIFE cohort and 0.69 (95% CI, 0.64 to 0.75) in the Dutch cohort. The sum of the sensitivity (69.0%) and specificity (64.0%) was maximal at the predicted probability of 50%. The model for very low BMD included male sex (OR, 3.28), height (OR, 0.95), weight (OR, 0.97), attained age (OR, 0.98), cranial irradiation (OR, 2.07), and abdominal irradiation (OR, 1.61), yielding areas under the curve of 0.76 (95% CI, 0.73 to 0.78; SJLIFE cohort) and 0.75 (95% CI, 0.67 to 0.83; Dutch cohort).

CONCLUSION Validated prediction models for low and very low BMD, using easily measured patient and treatment characteristics, correctly identified BMD status in most white adult survivors through age 40 years.

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INTRODUCTION

The survival rate of patients with childhood cancer has improved to more than 80% over the past several decades.¹ As a result of the increasing population of long-term survivors, recognition of late effects among survivors, including low bone mineral density (BMD) and subsequent risk of fractures, has increased.^{2,3} The prevalence of low BMD, generally defined as a BMD z score less than -1 , varies from 20% to 50% among survivors of acute lymphoblastic leukemia^{4,6} and from 40% to 60% among survivors of nonhematologic cancers.⁷⁻⁹ The prevalence of very low BMD (z score less than -2) ranges from 13% to 25% among survivors of pediatric cancer.^{4,7,9}

Adult survivors of childhood cancer are at risk for low BMD as a result of disturbances in bone metabolism during childhood or adolescence, which may inhibit

attainment of peak bone mass.¹⁰ These disturbances may develop as a consequence of the malignancy itself¹¹; as a result of the adverse effects of the cancer experience, such as altered dietary intake and reduced physical activity during and after cancer treatment¹²⁻¹⁴; or because normal bone mineral accretion is affected by corticosteroids and chemotherapeutic agents.^{6,15} In addition, BMD may be adversely affected as a result of gonadal failure after exposure to pelvic radiation or alkylating agents or as a result of hypothalamic-pituitary endocrinopathies after CNS irradiation.^{6,16} Finally, genetic susceptibility to developing BMD deficits may play a role.¹⁷

Low BMD is of concern because it may increase the risk of osteoporosis and fragility fractures.¹⁸ Multiple body sites can be used to measure BMD, including the hip, lumbar spine (LS), and total body (TB). Studies in

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noncancer populations have shown that depending on the site and severity, fractures can result in pain and temporary or permanent loss of function and may require hospitalization, rehabilitation, and after-hospital care, leading to a reduction in disability-adjusted life-years.¹⁹

The most widely validated technique to assess BMD is dual-energy x-ray absorptiometry (DXA).²⁰ However, DXA screening is not routinely recommended for all survivors because of concerns related to procedural financial costs and radiation exposure. Thus, it is important to identify subgroups of survivors at high risk of having low BMD who may benefit most from DXA screening, because survivors with low BMD may benefit from targeted interventions directed at improving bone health.²¹⁻²³

Although many studies have identified risk factors for low BMD among survivors of childhood cancer,^{6,24-26} no prediction model has been developed, and the optimal surveillance strategy for survivors at risk for low BMD has not been established. The aim of this study was to develop and validate clinically applicable prediction models that identify young adult survivors of childhood cancer at risk for low and very low BMD on the basis of individual patient characteristics and past cancer treatment.

PATIENTS AND METHODS

Study Population

St Jude Lifetime Cohort (development model). The development cohort consisted of participants in the St Jude

Lifetime Cohort Study (SJLIFE), a retrospective cohort study with ongoing prospective follow-up that includes periodic clinical assessments.^{27,28} To be eligible for this analysis, SJLIFE participants had to be between 18 and 40 years of age, be 10 years or more from diagnosis, have been treated for childhood cancer at St Jude Children's Research Hospital (Memphis, TN), have undergone DXA of both the LS and TB before June 30, 2016 ($n = 2,032$), and have reported their ethnicity as white (Fig 1). All participants underwent a core battery of testing that included DXA screening. This study was approved and conducted according to the standards of the institutional review board. Informed consent was obtained from all participants.

Dutch survivors (model validation). The Dutch survivors included a single-center cohort of 544 survivors of childhood cancer who visited the Long-Term Effects Registry (LATER) outpatient clinic between 2003 and 2008. All patients had been treated for childhood cancer at the Erasmus Medical Center–Sophia Children's Hospital (Rotterdam, the Netherlands) between 1965 and 2003 and had been finished with cancer treatment for at least 5 years. Among the 544 survivors attending the LATER clinic, 403 survivors (74.1%) who were between 18 and 40 years of age and who had been referred for DXA of the LS and TB according to the Dutch Children's Oncology Group long-term follow-up guidelines or at the discretion of the treating physician were included in this study (Fig 1). Survivors who underwent DXA screening tended to be older at both primary cancer diagnosis and at follow-up and were more

FIG 1. Flow diagram of study participants. DXA, dual-energy x-ray absorptiometry; LS, lumbar spine; SJLIFE, St Jude Lifetime Cohort; TB, total body.

likely to be treated with corticosteroids compared with survivors who did not undergo screening.⁶ Race and ethnicity of participants were not recorded. Informed consent was obtained from participants to use LATER clinic measurements for research purposes.

BMD Measurement

BMD of the LS (BMD_{LS}; L1 to L4) and TB (BMD_{TB}) were assessed using DXA (Hologic 4500 QDR fan array scanner [Hologic, Marlborough, MA] among SJLIFE participants and Lunar Prodigy or Lunar DPX-L [GE Healthcare, Madison, WI] among Dutch participants). z scores reflecting the number of standard deviations (SDs) that a BMD value of a survivor differs from the mean BMD of a healthy reference population were used to correct for age and sex. Low BMD was defined as a BMD_{LS} and/or BMD_{TB} z score of less than -1.0 . Very low BMD was defined as a BMD_{LS} and/or BMD_{TB} z score of less than -2.0 . z scores were used as end points instead of T scores because our analyses focused on a young adult population.²⁹

Predictors

Possible predictors of BMD status were selected based on previous reports showing an association with low BMD in survivors of childhood cancer^{7,15,16,25,30-34} or in the general population³⁵ and on the basis of the ease with which variables could be obtained in a late effects clinic or primary care setting. Patient characteristics included sex, age at diagnosis, and current smoking status (yes or no), as well as height (in centimeters), weight (in kilograms), and attained age at DXA examination (in years). Treatment factors included previous treatment (yes or no) with corticosteroids, methotrexate, alkylating agents, cranial irradiation, or abdominal irradiation (both including total-body irradiation). There were no missing data in the SJLIFE development cohort. In the Dutch validation cohort, each missing datum was replaced with its median value per sex (15.9% of the participants were missing height and weight; 15.6% were missing smoking status).

Statistical Analysis

The prediction models were developed using the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis criteria.³⁶ In the development cohort, univariable logistic regression was used to identify factors associated with an increased risk of low BMD. Factors associated with an increased risk of low BMD in the univariable analyses at $P < .20$ were included in multivariable analyses.

We created a prediction model for low BMD using backward multivariable logistic regression. All predictors that were associated with low BMD with $P < .05$ for the likelihood ratio test were included in the final model. A priori, we chose to include sex in the model because the decline in bone mass that occurs with aging differs by sex. We also included height because DXA provides a two-dimensional

assessment of a three-dimensional structure, consequently resulting in lower BMD z scores in short individuals.^{6,7,16,31} During model development, cumulative drug doses for methotrexate and alkylating agents, radiation dose to the hypothalamus-pituitary axis, and body mass index were considered but were not found to improve discrimination between survivors with and without low BMD above that of models in which treatments were dichotomized or in which height and weight replaced body mass index. The strength of the associations between the predictors and BMD was reported using β coefficients, odds ratios (ORs), and 95% CIs. Model performance was assessed using estimates of discrimination and calibration. Discrimination was evaluated by generating a receiver operating characteristic curve estimating the area under the curve (AUC), whereas calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit statistic. Sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) of the model were calculated at different cut points of predicted probabilities. The ability of the prediction model developed in the SJLIFE cohort to discriminate between participants with or without low BMD was assessed by calculating the AUCs of the same model in the Dutch validation cohort. Sensitivity analyses using only Dutch survivors with complete data were also performed.

A model for very low BMD was built and validated using the same methodology. A calculator to determine the predicted probability of low and very low BMD for an individual survivor is available online (<https://riskcalculator-bonemineraldensity-childhoodcancer.azurewebsites.net/>).

RESULTS

Cohort Characteristics

Survivors participating in SJLIFE, compared with survivors in the Dutch cohort, tended to be shorter (mean, 168.8 cm [SD, 10.2 cm] v 173.5 cm [SD, 9.1 cm], respectively; $P < .001$), heavier (mean, 79.5 kg [SD, 21.1 kg] v 71.0 kg [SD, 13.1 kg], respectively; $P < .001$), and older (median attained age, 29.3 years [interquartile range, 9.5 years] v 24.2 years [interquartile range, 9.2 years], respectively; $P < .001$; Table 1). Moreover, SJLIFE participants, compared with Dutch survivors, were more likely to be treated with an alkylating agent (56.5% v 50.6%, respectively; $P = .03$), cranial irradiation (33.9% v 22.5%, respectively; $P < .001$), or abdominal irradiation (21.7% v 6.5%, respectively; $P < .001$) and to smoke (24.4% v 17.9%, respectively; $P = .005$) and were less likely to have received methotrexate (53.9% v 60.5%, respectively; $P = .01$) or glucocorticoids (53.9% v 70.0%, respectively; $P < .001$). Median time between cancer diagnosis and DXA examination was 21.6 years (range, 10.4 to 40.6 years) for the SJLIFE cohort and 15.1 years (range, 5.1 to 39.8 years) for the Dutch survivors. Characteristics of Dutch survivors with complete values are listed in Appendix Table A1 (online only).

TABLE 1. Characteristics of Study Participants

Characteristic	SJLIFE Cohort (n = 2,032)		Dutch Cohort (n = 403)		P*
	Mean (SD; range)	No. of Participants (%)	Mean (SD; range)	No. of Participants (%)	
Childhood cancer diagnosis					< .001
Acute lymphoblastic leukemia		741 (36.5)		184 (45.7)	
Other leukemia		86 (4.2)		18 (4.5)	
Hodgkin lymphoma		205 (10.1)		46 (11.4)	
Non-Hodgkin lymphoma		150 (7.4)		50 (12.4)	
CNS tumor		265 (13.0)		23 (5.7)	
Renal tumor		122 (6.0)		48 (11.9)	
Neuroblastoma		98 (4.8)		16 (4.0)	
Soft tissue sarcoma		113 (5.6)		8 (2.0)	
Bone tumor		78 (3.8)		10 (2.5)	
Other		174 (8.6)		0 (0.0)	
Sex					.03
Male		1,075 (52.9)		237 (58.8)	
Female		957 (47.1)		166 (41.2)	
Height, cm	168.8 (10.2; 128.6-204.4)		173.5 (9.1; 145.5-196.0)		< .001
Weight, kg	79.5 (21.1; 31.7-171.0)		71.0 (13.1; 36.7-126.0)		< .001
Age at diagnosis, years	6.1 (9.1; 0-22.7)†		6.5 (8.3; 0-16.8)†		.97
Attained age, years	29.3 (9.5; 18.1-40.9)†		24.2 (9.2; 18.0-40.9)†		< .001
Current smoker					.005
Yes		496 (24.4)		72 (17.9)	
No		1,536 (75.6)		331 (82.1)	
Subsequent diagnosis‡					.19
Yes		198 (9.7)		48 (11.9)	
No		1,834 (90.3)		355 (88.1)	
Alkylating agent					.03
Yes		1,149 (56.6)		204 (50.6)	
No		883 (43.5)		199 (49.4)	
Methotrexate					.01
Yes		1,095 (53.9)		244 (60.5)	
No		937 (46.1)		159 (39.5)	
Glucocorticoid					< .001
Yes		1,095 (53.9)		282 (70.0)	
No		937 (46.1)		121 (30.0)	
Cranial irradiation§					< .001
Yes		688 (33.9)		91 (22.6)	
No		1,344 (66.1)		312 (77.4)	
Abdominal irradiation					< .001
Yes		441 (21.7)		26 (6.5)	
No		1,591 (78.3)		377 (93.5)	

Abbreviations: CNS, central nervous system; SD, standard deviation; SJLIFE, St Jude Lifetime Cohort.

* χ^2 *P* value for dichotomous covariates, two-sample independent *t* test *P* value for normally distributed continuous covariates, and Mann-Whitney *U* test *P* value for nonnormally distributed continuous covariates.

†Values are medians, with interquartile ranges and ranges in parentheses (nonnormally distributed).

‡Nonmelanoma skin cancer was excluded.

§Including total-body irradiation and excluding scatter radiation.

||Including pelvic radiation and total-body irradiation and excluding scatter radiation.

Low BMD was observed in 51.5% of the SJLIFE cohort and in 44.7% of the Dutch cohort. In the SJLIFE cohort, the prevalence of low BMD_{LS} was 25.1% (mean z score, -0.16; SD, 1.24), whereas low BMD_{TB} occurred in 48.0% of patients (mean z score, -0.94; SD, 1.25; Appendix Fig A1, online only). Among Dutch survivors, low BMD_{LS} occurred in 27.3% of patients (mean z score, -0.32; SD, 1.04), whereas low BMD_{TB} occurred in 37.0% of patients (mean z score, -0.51; SD, 1.10). Very low BMD occurred in 20.2% and 10.2% of participants in the SJLIFE and Dutch cohorts, respectively.

Prediction Model for Low BMD Among Adult Survivors

Results of univariable analyses in the SJLIFE development cohort are provided in Appendix Table A2 (online only). Backward multivariable logistic regression analysis identified male sex (OR, 3.07; 95% CI, 2.35 to 4.02), shorter height (OR, 0.95; 95% CI, 0.93 to 0.96), lower weight (OR, 0.98; 95% CI, 0.97 to 0.98), younger attained age (OR, 0.97; 95% CI, 0.96 to 0.99), current smoking status (OR, 1.48; 95% CI, 1.19 to 1.85), and cranial irradiation (OR, 2.11; 95% CI, 1.69 to 2.63) as predictors for low BMD (Table 2). The AUC of this model was 0.72 (95% CI, 0.70 to 0.75; Fig 2A). The Hosmer-Lemeshow goodness-of-fit test showed nonsignificant results in all steps of backward logistic regression, providing a χ^2 $P = .466$ in the final step.

The diagnostic values of the model are listed in Appendix Table A3 (online only). At relatively low cut points of predicted probability (eg, 20%), sensitivity was high (98.3%), whereas specificity was low (9.6%). At a cut point of 50%, the sum of sensitivity (69.0%) and specificity (64.0%) was highest, with 53.0% of the cohort predicted to have low BMD. The PPV was 67.0%, and the NPV was 66.1%. When this model was tested in the Dutch survivors, an AUC of 0.69 (95% CI, 0.64 to 0.75) was observed (Table 2, Fig 2A). Sensitivity was 50.6%, specificity was 77.6%, PPV was 64.3%, and NPV was 65.8% at a cut point of 50% among Dutch survivors. Sensitivity analyses limited to Dutch

survivors with complete data generated similar findings (AUC, 0.71; 95% CI, 0.66 to 0.77).

Prediction Model for Very Low BMD Among Adult Survivors

Univariable analyses of associations between patient and treatment factors and very low BMD are provided in Appendix Table A2. Male sex (OR, 3.28; 95% CI, 2.37 to 4.54), shorter height (OR, 0.95; 95% CI, 0.93 to 0.96), lower weight (OR, 0.97; 95% CI, 0.96 to 0.98), younger attained age (OR, 0.98; 95% CI, 0.96 to 1.00), cranial irradiation (OR, 2.07; 95% CI, 1.59 to 2.68), and abdominal irradiation (OR, 1.61; 95% CI, 1.23 to 2.11) were included in the model for very low BMD, yielding an AUC of 0.76 (95% CI, 0.73 to 0.78). In the validation cohort, the AUC of the model was 0.75 (95% CI, 0.67 to 0.83; Table 3; Fig 2B; Appendix Table A4, online only). Among Dutch survivors with complete data (sensitivity analyses), the AUC was 0.80 (95% CI, 0.71 to 0.88).

DISCUSSION

We developed and validated prediction models that can be used to identify young adult survivors of childhood cancer with a high probability of having low and very low BMD. Although a high prevalence of low BMD among survivors has been described in several studies,^{9,26} evidence-based guidance for surveillance of low BMD among survivors by DXA is limited. Screening guidelines for at-risk individuals have primarily been based on expert opinion, and it remains unclear which individual survivors will benefit most from DXA examination as part of the late effects surveillance program.³⁷⁻⁴⁰ The calculated AUC of the prediction model that we developed for low BMD was 0.72 in the development cohort, and for very low BMD, the AUC was 0.76. In the validation cohort, the AUCs for low and very low BMD were 0.69 and 0.75, respectively. This discriminatory power is similar to prediction models of fracture (FRAX; University of Sheffield, Sheffield, United Kingdom) in noncancer populations (AUC, 0.60 to 0.72)⁴¹⁻⁴³ and for other late effects such as cardiomyopathy and stroke among survivors of childhood cancer (AUC, 0.63 to 0.74).^{44,45} According to their AUCs, these models will provide a fair to good discrimination between adult survivors with normal, low, and very low BMD.⁴⁶ The availability of an online calculator will facilitate the clinical use of the models (Appendix, online only).

On the basis of the results from this study, we recommend DXA examination in a survivor at a predicted probability of low BMD of 50% or greater. At this cut point, the sum of sensitivity and specificity was highest in both cohorts (development cohort, 133%; validation cohort, 128%). We preferred a balance between sensitivity and specificity because, although low BMD is common among survivors and can cause significant morbidity, it is generally not life threatening and screening by DXA involves exposure to

TABLE 2. Multivariable Logistic Regression Model for Low BMD Among Adult Survivors of Childhood Cancer

Covariate	β (SE)	OR (95% CI)
β_0	10.91	
Sex	1.12 (0.14)	3.07 (2.35 to 4.02)
Height	-0.05 (0.01)	0.95 (0.93 to 0.96)
Weight	-0.02 (< 0.01)	0.98 (0.97 to 0.98)
Attained age	-0.03 (0.01)	0.97 (0.96 to 0.99)
Current smoker	0.39 (0.11)	1.48 (1.19 to 1.85)
Cranial irradiation	0.75 (0.11)	2.11 (1.69 to 2.63)

NOTE. Areas under the curve were 0.72 (95% CI, 0.70 to 0.75) in the St Jude Lifetime cohort and 0.69 (95% CI, 0.64 to 0.75) in the Dutch cohort.

Abbreviations: β , regression coefficient; β_0 , intercept; BMD, bone mineral density; OR, odds ratio.

FIG 2. Receiver operating characteristic curves of the prediction models for (A) low bone mineral density (BMD) and (B) very low BMD in the St Jude Lifetime Cohort (SJLIFE) development cohort and Dutch validation cohort.

low-dose radiation. We chose to focus our primary analysis on low BMD instead of very low BMD because in the general population most fractures occur among individuals with modest deficits in bone density⁴⁷ and because research supports that survivors experience significant comorbidities such as sarcopenia and peripheral neuropathies, which may further elevate their fracture risk.⁴⁸ For a survivor predicted to be at low risk on the basis of this model, DXA examination may be deferred until mid adulthood (eg, 40 years of age or older). We estimate that in services that follow current long-term follow-up guidelines (Children's Oncology Group, United Kingdom Children's Cancer Study Group, Scottish Intercollegiate Guidelines Network, and Dutch Children's Oncology Group), which recommend DXA screening either for all survivors at least once or for high-risk subgroups (eg, survivors who received cranial irradiation), that the number of DXA scans performed will either decrease slightly or stay the same on the basis of our recommendations. In services where implementation of our screening models may increase the

number of scans performed, the increased financial costs and clinical burden should be weighed against the benefit of detecting a greater number of survivors with BMD deficits.

Currently, most adult survivors of childhood cancer are younger than 50 years of age. Among survivors, the association between low BMD and fractures is not well established, and the validity of general BMD and fracture prediction tools has not been assessed.⁴⁹ Although our models were designed to predict low BMD and not fracture, they incorporate some of the same factors (ie, sex, height, weight, attained age, and smoking status) included in the widely used WHO fracture risk assessment tool FRAX, which was designed to predict the 10-year probability of osteoporotic fracture among the elderly.⁵⁰ However, unlike the FRAX tool, we found that younger survivors and males had a higher likelihood of having low BMD. A higher risk of low BMD among younger survivors may be explained by the fact that peak bone mass in the general population is not reached until an individual is in their mid-20s,⁵¹ and although the acquisition of bone mass can be delayed by cancer treatments, improvements in BMD can be observed among survivors many years after therapy.³⁰ This delay in bone maturation may occur more frequently among male survivors because males tend to attain their peak bone mass later than females in noncancer populations.⁵¹ Furthermore, the FRAX tool was developed for individuals older than 40 years, particularly postmenopausal women, whereas in our development cohort, the median age of survivors was 29 years.

Identification of low BMD among survivors of childhood cancer is important because several therapeutic options to remediate deficits exist. For survivors with low BMD, long-term follow-up guidelines for survivors recommend remediation of hormonal insufficiencies, optimization of calcium and vitamin D levels through diet or supplementation, weight-bearing exercise, and consideration of

TABLE 3. Multivariable Logistic Regression Model for Very Low BMD Among Adult Survivors of Childhood Cancer

Covariate	β (SE)	OR (95% CI)
β_0	9.98	
Sex	1.19 (0.17)	3.28 (2.37 to 4.54)
Height	-0.06 (0.01)	0.95 (0.93 to 0.96)
Weight	-0.03 (< 0.01)	0.97 (0.96 to 0.98)
Attained age	-0.02 (0.01)	0.98 (0.96 to 1.00)
Cranial irradiation	0.73 (0.13)	2.07 (1.59 to 2.68)
Abdominal irradiation	0.48 (0.14)	1.61 (1.23 to 2.11)

NOTE. Areas under the curve were 0.76 (95% CI, 0.73 to 0.78) in the St Jude Lifetime cohort and 0.75 (95% CI, 0.67 to 0.83) in the Dutch cohort.

Abbreviations: β , regression coefficient; β_0 , intercept; BMD, bone mineral density; OR, odds ratio.

pharmacologic intervention with bisphosphonates for survivors with fragility fractures or severe refractory BMD deficits.³⁷⁻⁴⁰ However, many of these recommendations are based on studies of older noncancer populations, and among survivors of childhood cancer, the efficacy of these interventions has varied across studies or has not been examined.^{21-23,52}

There are several important considerations when interpreting our results. First, selection bias may have occurred because participants included in the Dutch cohort received a DXA on the basis of physician referral, which may have led to a higher prevalence of BMD deficits and an unequal representation of cancer diagnosis subgroups. Second, data for certain risk factors known to be associated with low BMD or fracture, such as personal and family history of fractures, presence of hormonal insufficiencies, weight-bearing exercise, and alcohol consumption,^{14,50,53} were not available for all study participants and, therefore, could not be assessed. Inclusion of these data, as well as biochemical or genetic markers, may improve the

discriminatory power of future models.^{25,54,55} Third, because neither race nor ethnicity was recorded for Dutch participants, the ethnic backgrounds of participants may have varied between cohorts; nonetheless, the prediction models performed similarly across cohorts. Finally, our models were developed in white survivors; hence, they require validation in survivors of other races and ethnicities.

We created and validated prediction models for low and very low BMD of the LS and TB among adult survivors of childhood cancer through age 40 years based on easily obtainable predictors, including sex, height, weight, attained age, smoking status, and prior exposure to cranial and abdominal irradiation. Because these models identify most survivors with low BMD correctly, we consider their use a reasonable tool for personalized diagnostics and surveillance. For patients with confirmed deficits, targeted treatment directed at improving bone health and preventing fractures among this vulnerable population can be provided.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prediction of Low and Very Low Bone Mineral Density Among Adult Survivors of Childhood Cancer

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APPENDIX

Results of the Prediction Models for Fictitious Survivors

The use of the models in clinical practice can be shown using the following fictitious survivor descriptions. A 32-year-old nonsmoking female survivor with a height of 172 cm and a weight of 68 kg, who was diagnosed with a Wilms tumor at the age of 3 years and who was treated with chemotherapy and surgery, visits the outpatient late effects clinic. Entry of her clinical characteristics into the online calculator showed a probability of low bone mineral density (BMD) of 30% and of very low BMD of 7%. This individual would not be recommended to undergo dual-energy x-ray absorptiometry screening

because her predicted probability of low BMD is below the optimal cut point of 50%.

A 25-year-old male survivor of childhood cancer who smokes, is 175 cm tall, and weighs 62 kg visits the outpatient late effects clinic. He was diagnosed with pre-B cell acute lymphoblastic leukemia with central nervous system involvement at the age of 3 years and treated according to local acute lymphoblastic leukemia treatment protocols of that time, including prophylactic cranial irradiation. According to our models, his probabilities of low and very low BMD are 82% and 37%, respectively. In contrast to the previous survivor, he would be recommended to undergo dual-energy x-ray absorptiometry screening.

FIG A1. Distribution of (A) lumbar spine bone mineral density (BMD) z scores and (B) total-body BMD z scores in the St Jude Lifetime (SJLIFE) development cohort and Dutch validation cohort.

TABLE A1. Characteristics of Dutch Survivors of Childhood Cancer With Complete Values

Characteristic	Dutch Cohort (n = 339)	
	Mean (SD; range)	No. of Survivors (%)
Childhood cancer diagnosis		
Acute lymphoblastic leukemia		149 (44.0)
Other leukemia		16 (4.7)
Hodgkin lymphoma		36 (10.6)
Non-Hodgkin lymphoma		39 (11.5)
CNS tumor		23 (6.8)
Renal tumor		47 (13.9)
Neuroblastoma		14 (4.1)
Soft tissue sarcoma		6 (1.8)
Bone tumor		9 (2.7)
Other		0 (0.0)
Sex		
Male		199 (58.7)
Female		140 (41.3)
Height, cm	173.4 (9.65; 145.5-196.0)	
Weight, kg	71.2 (14.2; 36.7-126.0)	
Age at diagnosis, years	6.4 (10.0; 0-16.8)*	
Attained age, years	25.0 (10.0; 18.0-40.9)*	
Current smoker		
Yes		72 (21.2)
No		267 (78.8)
Subsequent diagnosis†		
Yes		42 (12.4)
No		297 (87.6)
Alkylating agent		
Yes		170 (50.1)
No		169 (49.9)
Methotrexate		
Yes		197 (58.1)
No		142 (41.9)
Glucocorticoid		
Yes		227 (67.0)
No		112 (33.0)
Cranial irradiation‡		
Yes		84 (24.8)
No		255 (75.2)
Abdominal irradiation§		
Yes		26 (7.7)
No		313 (92.3)

Abbreviations: CNS, central nervous system; SD, standard deviation.

*Values are medians, with interquartile ranges and ranges in parentheses (nonnormally distributed).

†Nonmelanoma skin cancer was excluded.

‡Including total-body irradiation and excluding scatter radiation.

§Including pelvic radiation and total-body irradiation and excluding scatter radiation.

TABLE A2. Univariable Logistic Regression Analysis for Low BMD and Very Low BMD in the SJLIFE Development Cohort

Covariate	Low BMD				Very Low BMD			
	Frequency of Low BMD (%)*	OR (95% CI)	β (SE)	P	Frequency of Very Low BMD (%)*	OR (95% CI)	β (SE)	P
Sex		1.11 (0.94 to 1.33)	0.11 (0.09)	.23		1.13 (0.91 to 1.41)	0.12 (0.11)	.26
Male	52.7				21.1			
Female	50.1				19.1			
Height, cm		0.96 (0.95 to 0.97)	−0.04 (< 0.01)	< .001		0.95 (0.94 to 0.96)	−0.06 (0.01)	< .001
First tertile	62.1				30.2			
Second tertile	50.5				18.1			
Third tertile	41.9				12.2			
Weight, kg		0.97 (0.97 to 0.98)	−0.03 (< 0.01)	< .001		0.96 (0.96 to 0.97)	−0.04 (< 0.01)	< .001
First tertile	64.3				32.2			
Second tertile	54.5				18.1			
Third tertile	35.6				10.2			
Age at diagnosis, years		0.96 (0.94 to 0.97)	−0.04 (0.01)	< .001		0.96 (0.94 to 0.98)	−0.04 (0.01)	.001
First tertile	52.8				21.2			
Second tertile	57.9				23.6			
Third tertile	43.7				15.7			
Attained age, years		0.97 (0.96 to 0.99)	−0.03 (0.01)	.001		0.98 (0.96 to 0.99)	−0.02 (0.01)	.009
First tertile	58.6				25.1			
Second tertile	48.4				17.9			
Third tertile	47.4				17.6			
Current smoker		1.42 (1.16 to 1.74)	0.35 (0.10)	.001		1.07 (0.83 to 1.37)	0.06 (0.13)	.61
Yes	58.1				21.0			
No	49.4				19.9			
Alkylating agent		1.23 (1.03 to 1.46)	0.20 (0.09)	.022		1.29 (1.03 to 1.61)	0.25 (0.11)	.025
Yes	53.7				21.9			
No	48.6				17.9			
Methotrexate		0.87 (0.73 to 1.04)	−0.14 (0.09)	.12		0.74 (0.59 to 0.92)	−0.31 (0.11)	.006
Yes	49.9				17.9			
No	53.4				22.8			
Glucocorticoid		0.85 (0.71 to 1.01)	−0.16 (0.09)	.066		0.75 (0.60 to 0.93)	−0.29 (0.11)	.008
Yes	49.6				18.0			
No	53.7				22.7			
Cranial irradiation		2.31 (1.91 to 2.79)	0.84 (0.10)	< .001		2.68 (2.15 to 3.34)	0.99 (0.11)	< .001
Yes	65.0				31.3			
No	44.6				14.5			
Abdominal irradiation		1.58 (1.28 to 1.96)	0.46 (0.11)	< .001		2.60 (2.05 to 3.30)	0.96 (0.12)	< .001
Yes	60.3				33.8			
No	49.0				16.4			

Abbreviations: β , regression coefficient; BMD, bone mineral density; OR, odds ratio; SJLIFE, St Jude Lifetime Cohort.

*For continuous variables, frequency of low and very low BMD is reported by tertile.

TABLE A3. Diagnostic Values of the Prediction Model for Low BMD at Different Cut Points for Predicted Probability

Cut Point Predicted Probability (%)	Frequency of Predicted Low BMD (%)	Sensitivity (%)	Specificity (%)	Σ (%)	PPV (%)	NPV (%)
10	99.3	99.8	1.3	101	51.8	86.7
20	94.4	98.3	9.6	108	53.6	84.1
30	85.1	93.6	23.9	118	56.6	77.9
40	70.6	83.6	43.2	127	60.9	71.2
50	53.0	69.0	64.0	133	67.0	66.1
60	34.6	48.9	80.6	130	72.8	59.8
70	18.9	29.3	92.0	121	79.5	55.1
80	7.9	12.9	97.5	110	84.4	51.3
90	1.6	2.8	99.7	103	90.6	49.1

Abbreviations: Σ , sum of sensitivity and specificity; BMD, bone mineral density; NPV, negative predictive value; PPV, positive predictive value.

TABLE A4. Diagnostic Values of the Prediction Model for Very Low BMD at Different Cut Points for Predicted Probability

Cut Point Predicted Probability (%)	Frequency of Predicted Low BMD (%)	Sensitivity (%)	Specificity (%)	Σ (%)	PPV (%)	NPV (%)
10	69.9	89.9	0.0	90	25.9	93.1
20	37.1	66.1	35.1	101	35.9	89.1
30	21.1	50.2	70.2	120	48.0	87.3
40	11.4	32.4	86.3	119	57.3	84.6
50	6.5	20.7	93.0	114	63.9	82.9
60	3.7	13.2	97.0	110	71.0	81.8
70	1.8	7.1	98.6	106	78.4	80.9
80	0.5	2.2	99.5	102	81.8	80.2
90	0.1	0.2	99.5	100	50.0	79.9

Abbreviations: Σ , sum of sensitivity and specificity; BMD, bone mineral density; NPV, negative predictive value; PPV, positive predictive value.