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ORIGINAL ARTICLE

Fracture risk prediction using FRAX in patients following hematopoietic stem cell transplantation

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Abstract

Summary We aimed to study the utility of the FRAX tool in predicting fractures in patient's receiving a hematopoietic stem cell transplantation (HSCT). Our results indicate that the FRAX tool has modest fracture predictive ability in patients greater than 50 years of age at the time of HSCT.

Purpose Identifying patients at high risk of osteoporotic fractures following HSCT is challenging. We aimed to evaluate the utility of the FRAX tool at the time of HSCT in predicting fractures following transplant.

Methods We conducted a retrospective chart review of adults (> 18 years) who underwent HSCT at MD Anderson Cancer Center from January 1, 2001, to December 31, 2010, and were followed until December 31, 2013, to identify osteoporotic fractures. Multivariate Cox regression models were built using FRAX score thresholds of low risk < 10%, medium risk 10 to 20%, and high risk > 20% probability of osteoporotic fracture.

Results We identified 5170 patients who had undergone HSCT, 10% of whom developed an osteoporotic fracture during a median follow-up of 3.2 years. In patients > 65 years of age, those with medium risk (hazard ratio (HR) 2.38, 95% confidence interval (CI) 1.27–4.47) and high risk (HR 3.41, 95% CI 1.73–6.75) had a greater probability of developing an osteoporotic fracture compared to those at low risk. Similar trends were seen in patients 50 to 65 years of age.

Conclusions In patients greater than 50 years, the FRAX tool has modest predictive ability and could be used to aid in preventive treatment decision-making at the time of transplant.

Keywords Fracture · Stem cell transplant · FRAX · Osteoporosis

Introduction

In the last couple of decades, the number of survivors following hematopoietic stem cell transplantation (HSCT) has been steadily increasing [1, 2], and more research is being conducted on complications following HSCT. Bone loss and its clinical manifestations—osteopenia, osteoporosis, and fragility fractures—are rapidly occurring, long-lasting, and common

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complications following HSCT [3]. Our previous research has shown that the incidence of fractures following HSCT is high and that these rates are significantly greater than the age- and sex-matched fracture rates in the general population [4]. Accurate fracture risk assessment can guide clinicians in identifying patients who are at high risk for fracture and may thus benefit from early pharmacological interventions. However, despite the common occurrence of bone loss and the increased post HSCT fracture incidence, identifying high-risk patients remains controversial. Bone mineral density (BMD) is a crucial determinant of fracture risk; however, it does not capture the non-skeletal determinants [5] and BMD evaluations are not performed routinely at the time of transplant. Furthermore, fractures can occur at BMD levels in the osteopenic and normal ranges, suggesting the need to identify other factors in fracture risk estimation [6, 7].

In the general population, the World Health Organization fracture risk assessment model (FRAX) is used to estimate a patient's 10-year probability of developing a hip fracture and a major osteoporotic fracture. The validity of the FRAX model in the non-transplant setting has been tested in several studies [8–10]. In one study of postmenopausal women, the FRAX model was useful for predicting incident vertebral fractures with an area under the curve (AUC) of the receiver operating characteristic (ROC) curve of 0.71 when femoral neck BMD was included and an AUC of 0.68 if femoral neck BMD was not included [8]. Another study in older women (> 65 years) showed similar results where FRAX was able to predict fractures with AUC = 0.75, AUC = 0.68, and AUC = 0.64 for hip, MOF, and clinical fractures, respectively [11]. However, the usefulness and validity of the FRAX model have not been evaluated at the time of HSCT, in predicting osteoporotic fractures following transplant. Furthermore, a large proportion of patients undergoing HSCT have multiple myeloma, a disease that is characterized by bone lesions that can lead to pathological fractures [12–14]. This increased risk of pathological fractures, coupled with HSCT, could translate into a higher risk of developing osteoporotic fractures. The difference in osteoporotic fracture risk in HSCT patients with and without multiple myeloma and the utility of the FRAX model in patients with and without multiple myeloma have not been comprehensively evaluated.

In addition, it is useful to note that bone loss prevention treatments that are currently available have been shown to be effective in maintenance of BMD and may also increase bone density [15]. However, preventative therapies are not free of side effects, and starting all HSCT patients on preventive therapy is not feasible. Therefore, the purpose of this study was to determine the utility of the FRAX model and assess the role of the individual clinical risk factors, at the time of HSCT in identifying patients who are at high risk of osteoporotic fracture following HSCT.

Patients and methods

Study design

We conducted a retrospective chart review of adult (> 18 years) patients who had undergone HSCT, as identified using billing information, at The University of Texas MD Anderson Cancer Center (UTMDACC, Houston, TX), from January 1, 2001, to December 31, 2010. Patients were considered to have entered the cohort at the time of HSCT. Patients who were suspected to have experienced a new osteoporotic fracture following HSCT were identified by reviewing all patients' electronic health charts and radiology records from the time of HSCT until December 31, 2013. Fractures that were identified concurrently with osteolytic lesions were excluded. Institutional review board approval was obtained before any data were collected for this study. The use of patient information complied with the Health Insurance Portability and Accountability Act, and sensitive patient data were protected in the data analysis.

Data collection

Information on the clinical variables included in the FRAX model, demographic factors, and comorbid conditions were obtained from patients' electronic health charts at baseline, defined as within 1 month prior to HSCT. Prior fracture and glucocorticoid use were assessed up to 1 year prior to HSCT. Secondary osteoporosis was assessed as a binary variable. It was defined as yes if the patient had one of the following disorders that are strongly associated with osteoporosis: type I (insulin-dependent) diabetes; osteogenesis imperfecta in adults; untreated long-standing hyperthyroidism, hypogonadism, or premature menopause (< 45 years); or chronic liver disease; otherwise, it was entered as no. Prior medical and surgical histories, as well as the presenting illness sections of each patient's electronic health record, were reviewed to identify conditions that are associated with secondary osteoporosis. Medication lists (for type 1 insulin-dependent diabetes) and laboratory findings (thyroid-stimulating hormone levels and T3 and T4 levels for untreated long-standing hyperthyroidism and luteinizing hormone, follicle-stimulating hormone, and testosterone levels for hypogonadism) were used to validate secondary osteoporosis status. Osteogenesis imperfecta, chronic malnutrition, and malabsorption were only documented if they were clearly identified and diagnosed in the clinical notes.

Information on the use of glucocorticoids prior to HSCT was obtained from the Department of Pharmacy Informatics. All glucocorticoids dispensed or billed up to 1 year prior to HSCT were evaluated. Patient's glucocorticoid use, alcohol intake, and smoking status were evaluated according to the definitions set forth in the FRAX model. The FRAX score

was calculated for each individual patient at the time of HSCT using The North American United States model specific for each race/ethnicity, i.e., Caucasian, Black, Hispanic, or Asian. The model to calculate the FRAX score and further details about the model can be found at http://www.shef.ac.uk/FRAX/. All data collection was completed independently by two research personnel.

Data analysis

The primary end point was time to fracture, which was defined as the day of HSCT until the day of osteoporotic fracture, as confirmed by chart review. The osteoporotic fracture-free survival function was estimated using the Kaplan-Meier method [16]. A two-sided log-rank test [17] was performed to test the differences in survival among risk groups defined by the clinical risk factors.

We built Cox regression models using the FRAX score risk groups (low risk < 10% [$n = 4138$], medium risk 10 to 20% [$n = 851$], and high risk ≥ 20% [$n = 181$]), the type of HSCT, and the underlying indication for HSCT in subgroups of patients < 50, 50 to 65, and ≥ 65 years at the time of HSCT. In addition to evaluation of the FRAX score while adjusting for underlying indication for HSCT and type of HSCT, we used Cox regression models to identify the independent risk factors involved in osteoporotic fracture development following HSCT. The stepwise selection method was used to determine the final risk models. Those who died before an osteoporotic fracture or who were lost to follow-up were considered censored. We also conducted a competing risk analysis (using sub-distribution hazard models), since death from any cause could be a competing event to preclude the occurrence of an osteoporotic fracture. Hazard ratios were estimated using the Fine and Gray method to compare the risk categories in the competing risk analysis [18].

To evaluate the performance characteristics of the FRAX model, we estimated the area under the receiver operating characteristic curve for censored data using the R package "survivalROC" found at https://CRAN.R-project.org/package=survivalROC. A two-sided p value of < 0.05 was considered statistically significant. All statistical analyses were performed using SAS software version 9.4 and R 3.3.1.

Results

We identified 5170 patients who had undergone HSCT from January 1, 2001, to December 31, 2010, at UTMDACC. Fifty-seven percent of patients were male, and 75% were white. The underlying indications for HSCT were multiple myeloma in 26% of patients and other hematological malignancies in 67%; other conditions, such as solid tumor, scleroderma, and amyloidosis, were the indications in 7%. Overall, a quarter of the patients had experienced a fracture prior to HSCT, and the vast majority (87%) had high glucocorticoid use prior to HSCT (Table 1).

Table 1 Overall baseline characteristics of HSCT recipients ($n = 5170$)

Characteristic	Result
Age (years)	50.1 ± 13.4
Male sex	2930 (57%)
Height (cm)	170.1 ± 10.0
Weight (kg)	82.3 ± 19.9
BMI (kg/m^2)	28.3 ± 5.9
Race	
White	3880 (75%)
Hispanic	703 (14%)
Black	449 (9%)
Asian	138 (2%)
Prior fracture	1282 (25%)
Prior high glucocorticoid use [a]	4478 (87%)
Rheumatoid arthritis	54 (1%)
Secondary osteoporosis	44 (< 1%)
High alcohol intake [b]	155 (3%)
Current smokers at HSCT	274 (5%)
Type of HSCT	
Autologous	2630 (51%)
Allogeneic	2540 (49%)
Indication for HSCT	
Multiple myeloma	1327 (26%)
Other hematological malignancies	3477 (67%)
Solid tumors and others [c]	366 (7%)
Myeloablative preparatory regimen	4155 (80%)

Data are mean ± SD or n (%)

BMI body mass index, *HSCT* hematopoietic stem cell transplant

[a] Patients were considered to have high glucocorticoid use if they had received glucocorticoids at the time of HSCT or if they had been exposed to oral glucocorticoids for more than 3 months at a dose of 5 mg of prednisolone daily or more (or equivalent doses of other glucocorticoids) prior to HSCT. They were considered to have low glucocorticoid use if they had not

[b] Patients were considered to have high alcohol intake if they had consumed three or more units of alcohol daily prior to HSCT; they were considered to have low use if they had not

[c] Others include hematological malignancies other than multiple myeloma and solid tumors

With a median follow-up of 3.2 years, 10% ($n = 527$) of patients developed an osteoporotic fracture. The fracture rate was 23% in patients with multiple myeloma and 6% in those without multiple myeloma. Overall, in patients who developed a fracture after HSCT, 20% occurred within the first 6 months and 37% occurred within the first year following the HSCT. The 10-year non-fracture rates, stratified by underlying malignancy, are shown in Table 2. Patients with a fracture prior to HSCT had lower 10-year non-fracture rates than

Table 2 Comparison of 10-year non-fracture rates in patients with and without multiple myeloma

Characteristic	Multiple myeloma		No multiple myeloma	
	10-year	*p* value	10-year	*p* value
Sex		0.436		0.059
Female	58		88	
Male	62		91	
BMI (kg/m^2)		0.483		0.261
Underweight	–		96	
Normal	55		90	
Overweight	58		89	
Obese	65		90	
Race		0.360		0.590
White	57		89	
Hispanic	62		89	
Black	73		91	
Asian	63		90	
Prior fracture		< 0.001		0.050
No	75		90	
Yes	54		86	
Prior glucocorticoid use [a]		0.530		0.047
Low	63		82	
High	60		90	
Rheumatoid arthritis		0.628		0.330
No	60		90	
Yes	–		89	
Secondary osteoporosis		0.574		0.704
No	–		90	
Yes	61		93	
Alcohol intake [b]		0.938		0.540
Low	61		90	
High	60		85	
Current smokers at HSCT		0.708		0.956
No	56		91	
Yes	61		89	
Type of HSCT		< 0.001		0.086
Autologous	61		90	
Allogeneic	47		89	
Preparatory regimen		0.212		0.213
Myeloablative	61		90	
Non-myeloablative	50		88	

BMI body mass index, *HSCT* hematopoietic stem cell transplant

[a] Patients were considered to have high glucocorticoid use if they had received glucocorticoids at the time of HSCT or had been exposed to 5 mg or more of prednisolone for more than 3 months (or equivalent doses of other glucocorticoids) prior to HSCT; otherwise, they were considered to have low glucocorticoid use

[b] Patients were considered to have high alcohol intake if they had consumed three or more units of alcohol daily prior to HSCT; otherwise, they were considered to have low use

did those who did not have a prior fracture, with and without multiple myeloma (with multiple myeloma: 54 vs 75%, respectively; $p < 0.001$; and without multiple myeloma: 86 vs 90%; $p = 0.05$). Similarly, multiple myeloma patients who had undergone allogeneic HSCT had lower 10-year non-fracture rates than did those who had undergone autologous HSCT (47 vs 61%; $p < 0.001$). In patients without multiple myeloma, those who had received high doses of glucocorticoids prior to HSCT did not demonstrate high rates of fracture following HSCT, than did those who received low doses of glucocorticoids prior to HSCT (non-fracture rates 90 vs 82%; $p = 0.047$).

Survival curves, estimated using the Kaplan-Meier method, are depicted in Fig. 1a, b. Patients without a fracture prior to HSCT and patients without multiple myeloma had lower fracture rates. We built multivariable models using the FRAX score, the underlying indication for receiving a HSCT, and the type of HSCT in patients stratified by age (< 50, 50 to 65, and ≥ 65 years of age at the time of HSCT; Table 3). In patients > 65 years of age, those with medium risk ($n = 226$) had 2.38 (95% confidence interval (CI) 1.27–4.47) times greater risk and patients with high risk ($n = 89$) had 3.41 (95% CI 1.73–6.75) times greater risk of osteoporotic fracture compared to those at low risk. In patients between 50 and 65 years of age, those with medium risk ($n = 613$) had 1.3 (95% CI 1.01–1.67) times greater risk and those at high risk ($n = 92$) had 1.9 (95% CI 1.21–2.94) times greater risk of osteoporotic fracture compared to those at low risk, while adjusting for the underlying indication and type of HSCT. In patients < 50 years, the FRAX score risk groups (medium risk $n = 12$ and high $n = 0$) were not statistically significantly related to osteoporotic fracture; however, patients with underlying multiple myeloma in this group had 4.12 (95% CI 3.03–5.60) times risk of developing a fracture compared to patients without multiple myeloma. To evaluate the performance characteristics of the FRAX model, we estimated the area under the curve for receiver operating characteristic curve at 10 years to be 0.66 (Fig. 2).

We fitted multivariable cause-specific Cox models considering all individual risk factors, including those of the FRAX tool. After controlling for all other variables, the risk of developing an osteoporotic fracture was 1.20 (95% CI 1.02–1.41; $p = 0.025$) times higher with every 20 years of increase in age at the time of HSCT and 1.24 (95% CI 1.05–1.48; $p = 0.013$) times higher for women than for men. Patients with a fracture prior to HSCT had 2.01 (95% CI 1.62–2.51; $p < 0.001$) times higher risk than did those without a prior fracture; patients who had undergone allogeneic HSCT had 1.57 (95% CI 1.20–2.05; $p = 0.001$) times higher risk than did those who had undergone autologous HSCT; and patients with multiple myeloma had 2.62 (95% CI 1.97–3.49; $p < 0.001$) times higher risk than did those without multiple myeloma. A subdistribution hazard model was fitted that considered death as a competing risk with the same variables as the model above.

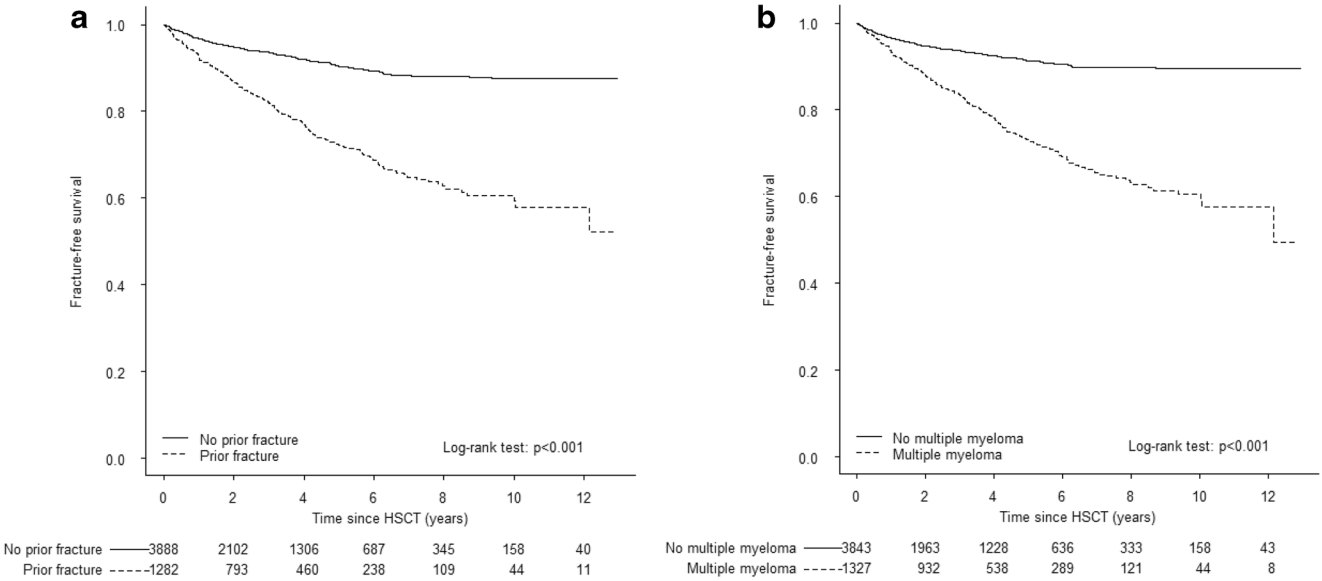

Fig. 1 **a** The Kaplan-Meier fracture-free survival curves for patients with and without fractures prior to HSCT. **b** The Kaplan-Meier fracture-free survival curves for patients with and without underlying multiple myeloma

Sex, prior fracture, and indication for HSCT had similar effect sizes and were statistically significantly associated with osteoporotic fracture. However, increasing age and type of HSCT were not significant predictors of osteoporotic fracture when death was considered as a competing risk (Table 4).

Table 3 Multivariable Cox proportional hazard regression models for osteoporotic fracture in patients stratified by age

Characteristic	HR	95% CI
Model 1 (age > 65 years)		
FRAX risk [a]		
Low	Ref	
Medium	2.38	1.27, 4.47
High	3.41	1.73, 6.51
Model 2 (age 50 to 65 years)		
FRAX risk [a]		
Low	Ref	
Medium	1.30	1.01, 1.67
High	1.89	1.21, 2.94
Type of HSCT		
Autologous	Ref	
Allogeneic	1.81	1.19, 2.75
Underlying indication		
No multiple myeloma	Ref	
Multiple myeloma	3.95	2.67, 5.85
Model 3 (age < 50 years)		
Underlying indication		
No multiple myeloma	Ref	
Multiple myeloma	4.12	3.03, 5.60

CI confidence interval, *HR* hazard ratio, *HSCT* hematopoietic stem cell transplant

[a] FRAX score risk categories low risk < 10%, medium risk 10 to 20%, and high risk ≥ 20%

To aid in the comparison, the same model was fit in patients with and without multiple myeloma (Supplemental Table 1). In patients with multiple myeloma, a prior fracture ($p < 0.001$) and allogeneic HSCT ($p < 0.001$) were associated with an increased risk of fractures while controlling for all other variables in the model. In patients without multiple myeloma, increasing age ($p = 0.002$) and female sex ($p = 0.017$) were associated with an increased risk of fractures while controlling for all other variables.

Because the FRAX model only captures the age effect in older patients, we performed a subgroup analysis by age using

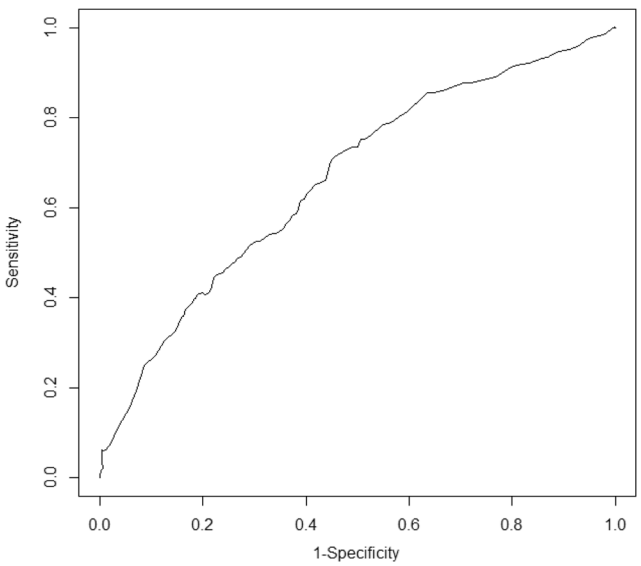

Fig. 2 Area under the curve for receiver operating characteristic curve at 10 years

Table 4 Multivariable Cox proportional hazard regression models for osteoporotic fracture in the entire cohort ($n = 5170$)

Characteristic	Cause-specific model			Sub-distribution hazard model		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age at HSCT (per 20 years)	1.20	1.02, 1.40	0.025	1.12	0.96, 1.32	0.152
Sex						
Male	Ref			Ref		
Female	1.24	1.05, 1.48	0.013	1.24	1.05, 1.47	0.014
Prior fracture						
No	Ref			Ref		
Yes	2.01	1.62, 2.51	< 0.001	1.88	1.52, 2.31	< 0.001
Type of HSCT						
Autologous	Ref			Ref		
Allogeneic	1.57	1.20, 2.05	0.001	1.05	0.80, 1.38	0.733
Indication for HSCT						
No multiple myeloma	Ref			Ref		
Multiple myeloma	2.62	1.97, 3.49	< 0.001	2.88	2.17, 3.83	< 0.001

HR hazard ratio, *95% CI* 95% confidence interval, *HSCT* hematopoietic stem cell transplantation

a cutoff of 40 years. Patients aged ≥ 40 years at the time of HSCT had similar results to those of the overall cohort (Supplementary Table 2). In contrast, while controlling for other variables in the model, patients aged < 40 years with multiple myeloma had 4.5 (95% CI 2.35, 8.77; $p < 0.001$) times higher risk of developing an osteoporotic fracture than did those without multiple myeloma, and patients with high consumption of alcohol prior to HSCT had 3.5 times (95% CI 1.10, 11.3; $p = 0.035$) higher risk than did those with low consumption of alcohol (Supplementary Table 3).

Discussion

We used several approaches to assess the performance of the FRAX model in predicting osteoporotic fractures following HSCT. Our results show that the FRAX model demonstrated modest discriminative ability for osteoporotic fracture prediction. Age, sex, fracture prior to HSCT, type of HSCT, and the underlying indication for HSCT are important considerations in evaluating osteoporotic fracture risk following HSCT. Patients with multiple myeloma had higher rates of fractures prior to HSCT than did those with no multiple myeloma (70 vs 9%). This higher initial rate of fractures prior to HSCT translated into a greater number of fractures after HSCT in patients with multiple myeloma (23%) than in those with no multiple myeloma (6%). There are two possible explanations for these higher pre- and post-HSCT fracture rates. First, multiple myeloma is characterized by osteolytic bone lesions, which are due to increased resorption of bone as a result of the upregulation of osteoclast activity that occurs in close proximity to myeloma cells [13, 14]. Second, multiple myeloma patients are usually older [19], and fractures are more common with age [20]. In our study, multiple myeloma patients had a higher median age (57 years, interquartile range 12), than did those without multiple myeloma (50 years, interquartile range 21).

With the growing number of survivors following HSCT [21, 22], the optimal and cost-effective management of bone health has become a priority. In 2006, a consensus panel comprising members of the Center for International Blood and Marrow Transplant Research, European Group for Blood and Marrow Transplantation, and American Society for Bone Marrow Transplantation developed guidelines for the screening and prevention of late complications in long-term survivors following HSCT [23]. The panel was reconvened in 2011, and the guidelines were updated [1]. The original guidelines recommended a dual-photon densitometry evaluation 1 year after HSCT in women and in those who had undergone prolonged treatment with corticosteroids or calcineurin inhibitors; the revised guidelines recommended a dual-photon densitometry evaluation for all patients 1 year after allogeneic HSCT, in addition to women and those at high risk of bone loss following HSCT. However, data from clinical practice on the utility and effectiveness of these guidelines are largely lacking. Furthermore, our study shows that a good proportion of patients (37% of those that fractured in our study) are at high risk of developing a fracture before the end of 1 year after their HSCT with risk factors identifiable at the time of HSCT; thus, waiting to evaluate bone health 1 year from HSCT may not be optimal. Additionally, we found that 25% of the study cohort patients had an osteoporotic fracture within 1 year prior to HSCT. This suggests that a significant proportion of patients have poor bone health and are at high risk of developing

fractures even prior to HSCT and this needs to be considered in future studies and guidelines for screening and prevention of bone loss in this patient population.

Our study evaluated the utility of the FRAX model and identified several risk factors for fracture development; however, our study has a few limitations. Not all elements of the FRAX model were evaluable. Information on parents with fractured hip was not retrospectively assessable from medical charts. Some of the components to diagnose secondary osteoporosis (osteogenesis imperfecta, chronic malnutrition, and malabsorption) were used only if they had been clearly diagnosed and documented in the clinical note. The added risk associated with these conditions may not have been captured completely in our study. Smoking and alcohol intake may have a dose-response relationship with fracture development, but this was not evaluable in our study. MD Anderson is a tertiary care center; patients may have been evaluated and treated for their fractures by their primary care doctor or at another institution. Thus, not all fractures following HSCT may have been evaluated, resulting in an underestimate of the fracture incidence in our population. Furthermore, it is noteworthy to mention that patients may have new or continued risk exposure following the HSCT such as high-dose steroid use for GVHD, reduced physical activity, and sarcopenia, which were not considered in this analysis.

Despite these limitations, our study has several strengths. This is the first study to evaluate the utility of the FRAX model at the time of HSCT to predict osteoporotic fractures during survivorship. MD Anderson is one of the largest cancer centers in the USA, and more than 500 HSCTs are performed each year, providing a rich source of data. Information on clinical variables was manually verified by two reviewers, and the likelihood that any exposure variables or outcomes were misclassified is low. Since approximately 50% of our study population died prior to developing a fracture, death was considered a competing risk, as simply censoring the patients who died would have led to a biased estimation.

Conclusion

Overall, in HSCT recipients, the FRAX model demonstrated modest discriminative ability in predicting osteoporotic fractures. In patients > 50 years, the FRAX model may serve as a useful prognostic tool in preventative treatment decision-making at the time of HSCT. The FRAX model is region specific and the results may not be globally applicable. Independent validation is needed, before routinely using the FRAX model to inform treatment decisions. Our findings also demonstrate that the risk factors for fracture differ by the underlying indication for HSCT. In patients without underlying multiple myeloma, increasing age and women are at a higher risk of fractures. Furthermore, a large proportion of patients experienced a fracture prior to the HSCT and are at an increased baseline risk of developing fractures following HSCT. Guidelines to screen bone health in HSCT patients should take into consideration the baseline risk in addition to the added risk following HSCT. Given the lack of research on highly effective screening methods, we recommend that all candidates for HSCT should have a comprehensive risk factor evaluation just before or at the time of HSCT.

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Compliance with ethical standards

Institutional review board approval was obtained before any data were collected for this study. The use of patient information complied with the Health Insurance Portability and Accountability Act, and sensitive patient data were protected in the data analysis.

Conflicts of interest None.

References

1. McClune B, Majhail NS, Flowers ME (2012) Bone loss and avascular necrosis of bone after hematopoietic cell transplantation. Semin Hematol 49(1):59–65. https://doi.org/10.1053/j.seminhematol.2011.10.007
2. Savani BN (2012) How can we improve life expectancy and quality of life in long-term survivors after allogeneic stem cell transplantation? Semin Hematol 49(1):1–3. https://doi.org/10.1053/j.seminhematol.2011.10.014
3. Schimmer AD, Minden MD, Keating A (2000) Osteoporosis after blood and marrow transplantation: clinical aspects. Biol Blood Marrow Transplant 6(2):175–181
4. Pundole XN, Barbo AG, Lin H, Champlin RE, Lu H (2015) Increased incidence of fractures in recipients of hematopoietic stem-cell transplantation. J Clin Oncol 33(12):1364–1370
5. Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359(9321):1929–1936. https://doi.org/10.1016/S0140-6736(02)08761-5
6. Schuit SC, van der Klift M, Weel AE, de Laet CE, Burger H, Seeman E, Hofman A, Uitterlinden AG, van Leeuwen JP, Pols HA (2004) Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam study. Bone 34(1):195–202

7. Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, Hochberg MC, Vogt MT, Orwoll ES, Study of Osteoporotic Fractures Research G (2005) Hip fracture in women without osteoporosis. J Clin Endocrinol Metab 90(5):2787–2793. https://doi.org/10.1210/jc.2004-1568
8. Donaldson MG, Palermo L, Schousboe JT, Ensrud KE, Hochberg MC, Cummings SR (2009) FRAX and risk of vertebral fractures: the fracture intervention trial. J Bone Miner Res 24(11):1793–1799. https://doi.org/10.1359/jbmr.090511
9. Kanis J, Johnell O, Odén A, Johansson H, McCloskey E (2008) FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporos Int 19(4):385–397
10. Trémollieres FA, Pouillès JM, Drewniak N, Laparra J, Ribot CA, Dargent-Molina P (2010) Fracture risk prediction using BMD and clinical risk factors in early postmenopausal women: sensitivity of the WHO FRAX tool. J Bone Miner Res 25(5):1002–1009
11. Ensrud KE, Lui LY, Taylor BC, Schousboe JT, Donaldson MG, Fink HA, Cauley JA, Hillier TA, Browner WS, Cummings SR, Study of Osteoporotic Fractures Research G (2009) A comparison of prediction models for fractures in older women: is more better? Arch Intern Med 169(22):2087–2094. https://doi.org/10.1001/archinternmed.2009.404
12. Callander NS, Roodman GD (2001) Myeloma bone disease. Semin Hematol 38(3):276–285
13. Giuliani N, Colla S, Rizzoli V (2004) New insight in the mechanism of osteoclast activation and formation in multiple myeloma: focus on the receptor activator of NF-kappaB ligand (RANKL). Exp Hematol 32(8):685–691. https://doi.org/10.1016/j.exphem.2004.03.015
14. Roodman GD (2004) Pathogenesis of myeloma bone disease. Blood Cells Mol Dis 32(2):290–292. https://doi.org/10.1016/j.bcmd.2004.01.001
15. Pundole X, Cheema HI, Petitto GS, Lopez-Olivo MA, Suarez-Almazor ME, Lu H (2017) Prevention and treatment of bone loss and fractures in patients undergoing a hematopoietic stem cell transplant: a systematic review and meta-analysis. Bone Marrow Transplant 52(5):663–670. https://doi.org/10.1038/bmt.2016.312
16. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53(282):457–481
17. Mantel N (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep Part 1 50(3):163–170
18. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94(446):496–509
19. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR (2003) Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 78(1):21–33. https://doi.org/10.4065/78.1.21
20. Cummings SR, Melton LJ (2002) Epidemiology and outcomes of osteoporotic fractures. Lancet 359(9319):1761–1767. https://doi.org/10.1016/S0140-6736(02)08657-9
21. Buchsel PC (2009) Survivorship issues in hematopoietic stem cell transplantation. Semin Oncol Nurs 25(2):159–169. https://doi.org/10.1016/j.soncn.2009.03.003
22. Niederwieser D, Baldomero H, Szer J, Gratwohl M, Aljurf M, Atsuta Y, Bouzas LF, Confer D, Greinix H, Horowitz M, Iida M, Lipton J, Mohty M, Novitzky N, Nunez J, Passweg J, Pasquini MC, Kodera Y, Apperley J, Seber A, Gratwohl A (2016) Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the Worldwide Network for Blood and Marrow Transplantation Group including the global survey. Bone Marrow Transplant 51(6):778–785. https://doi.org/10.1038/bmt.2016.18
23. Rizzo JD, Wingard JR, Tichelli A, Lee SJ, Van Lint MT, Burns LJ, Davies SM, Ferrara JL, Socie G (2006) Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, Center for International Blood and Marrow Transplant Research, and the American Society for Blood and Marrow Transplantation (EBMT/CIBMTR/ASBMT). Bone Marrow Transplant 37(3):249–261. https://doi.org/10.1038/sj.bmt.1705243