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FRAX is a robust predictor of baseline vertebral fractures in multiple myeloma patients

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A B S T R A C T

FRAX is a commonly used tool to evaluate patient fracture risk based on individual patient models that integrate the risks associated with clinical risk factors with or without bone mineral density (BMD) at the femoral neck. Retrospectively, factors identified by the FRAX scoring algorithm were used to predict the risk for vertebral compression fractures at baseline in newly diagnosed multiple myeloma patients. The data were derived from myeloma patients enrolled in Total Therapy Protocols (TT4 & TT5) between 8/2008 and 9/2017. FRAX scores were calculated and baseline PET and MRI imaging obtained. Univariate and multivariate logistic regression analyses determined the association between FRAX components and the existence of vertebral compression fractures, both pathologic and osteoporotic. The patient population had a median age of 61 years (43–76), 37% female, and 87% white. The median major osteoporotic score (MOS) and Hip fracture scores (HFS) for TT4 patients (low-risk myeloma) were 5.6 and 0.5, respectively, while median MOS and HFS for TT5 (high risk myeloma) patients were 6.2 and 0.7, respectively. The odds ratio for fracture at diagnosis in patients with elevated MOS (> 2), and HFS (> 4.5) was significant OR (1.48, 95% confidence interval (1.35,1.62)) and OR (1.61, 95% confidence interval (1.42, 1.81)), respectively. In sum, an elevated baseline FRAX score was highly predictive of baseline vertebral fractures in MM patients at presentation. In addition, patients with higher FRAX scores had significantly shorter survival in the low-risk (TT4) group but this survival effect was not seen in the high-risk (TT5) group. These findings suggest that FRAX assessment of baseline fracture risk is beneficial in MM patients to identify an individual patients' risk of vertebral fracture.

1. Introduction

It is estimated that approximately 30,280 new patients are diagnosed with multiple myeloma in annually [1]. Bone pathophysiology plays a key role in increasing morbidity in these patients, with osteolytic lesions being one of the major presenting features of the disease. In line with the extensive bone loss observed in myeloma patients, hip fractures, vertebral fractures and osteoporosis are serious and disabling complications [2].

Indeed, multiple myeloma is a plasma cell neoplasm in which the bone and bone marrow microenvironment has a been shown to exert major impact on the course of plasma cell survival [3]. For many years, the standard of care has involved a detailed musculoskeletal survey, considered essential for evaluating patients with bone fractures as well as to determine the extent of osteolytic lesions [4]. In 2014, the international myeloma working group included advanced imaging to aid in the assessment of bone lesions for newly diagnosed myeloma patients [5]. Those recommendations included bone MRI (magnetic resonance imaging) and PET (positron emission tomography) based on the premise that advanced imaging technology would be able to differentiate smoldering myeloma from active myeloma [5].

The early identification of bone disease in multiple myeloma is an important addition, as the extent of bone disease changes treatment course and guides the efficacy of preventive treatment interventions. In particular, prognosis is significantly worse for patients with more than three focal lesions post induction as detected by PET scan [6]. In this early identification scenario, there is a continued need to identify additional factors that may aid and/or enhance the earlier detection of bone disease. The FRAX score is a population-based computerized scoring system for predicting the 10 years risk of hip fracture and osteoporosis [7]. This scoring system was developed from population-based studies and uses common variables such as patient's age, weight, height, smoking status, alcohol consumption, and previous bone scan results when available [8].

At our Institution, Total Therapy (TT) protocols included ample information from frequent MRI's and PET scans. However, these

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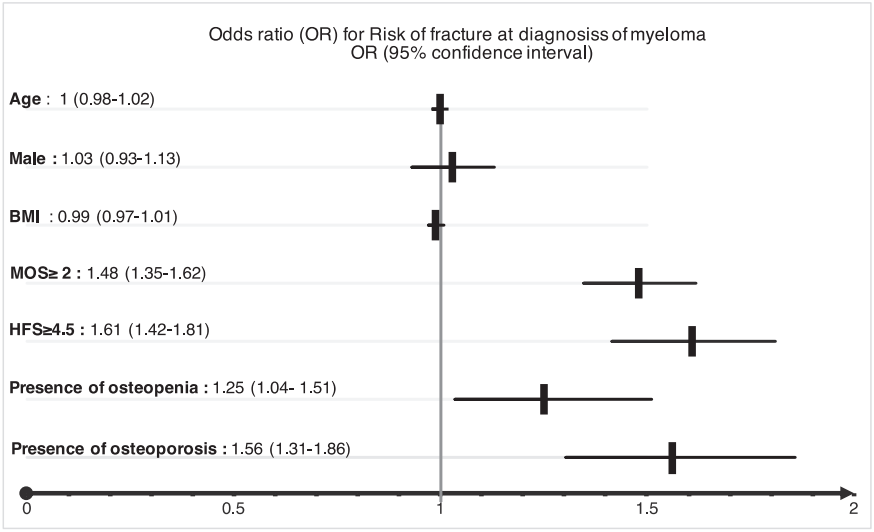

Fig. 1. Univariate analysis.
Forest plot for the odds ratio for fracture risk in newly diagnosed myeloma patients. MOS: Major Osteoporotic Score, HFS: Hip Fracture Score.

Table 1
Baseline characteristics for patients included in the study.

Baseline patient characteristics		
	TT4	TT5
Total number	357	75
Demographics		
Median age	61; range (30–76)	61; range (32–74)
Male	223	43
White	308	66
Black	41	9
FRAX modifiers		
Median weight (kg)	93; range(50–163)	93; range(55–120)
Median height (cm)	173; range(145–203)	169.5; range(155–191)
Smoking	45	10
Baseline fractures	167	36
Osteopenia	35	9
Osteoporosis	5	0
FRAX results		
Median MOS	5.6	6.2
Median HFS	0.5	0.7

advanced imaging resources is not available in routine oncology practice. Therefore, we propose that using a simple scoring system (FRAX) may be helpful for assessing the risk of fracture and provide insight into bone health for myeloma patients.

In this analysis, the baseline FRAX score of newly diagnosed myeloma patients was used to predict the future risk of fracture in newly diagnosed myeloma patients.

2. Methodology

With IRB approval, data from patients treated at the University of Arkansas for Medical Sciences (UAMS) Myeloma Institute for Research and Therapy (MIRT), between 8/2008 and 9/2017, under the Total Therapy protocol 4 (TT4) [9], and the Total Therapy protocol 5 (TT5) the details of which have been presented elsewhere [10] were interrogated. The TT4 protocol enrolled newly diagnosed transplant eligible patients with low risk multiple myeloma defined by gene expression profile (low GEP score < 0.66) [11], low LDH < 360 u/l and creatinine < 3 mg/dl. Whereas, the TT5 protocol enrolled newly diagnosed transplant eligible patients with high risk multiple myeloma defined by GEP risk score of ≥0.66 [11] or LDH ≥360 u/l or features of high risk such as Plasma Cell Leukemia or high risk Cytogenetics (i.e. t(4;14),t(14;16),t(14;20) or del(17p)).

Routine baseline MRI and PET scans were performed as part of the initial evaluation per protocol requirements. FRAX scores were calculated, for every patient individually at presentation. (https://www.sheffield.ac.uk/FRAX/index.aspx).

In this post hoc analysis, clinical reports from all PET scans and MRI's were reviewed. The presence of baseline fractures was assessed by musculoskeletal survey, whole body MRI and PET scan. Univariate analysis was used to determine the association between FRAX components and vertebral compression fractures. An optimal cutoff point was derived, using the area-under-the-curve (ROC) methodology based on ROCR package in R [12]. Based on ROC, we chose the best cutoff to predict survival difference for Major Osteoporotic Score (MOS), and for Hip Fracture Score (HFS). The best cut-off point was determined as 2 for MOS and 4.5 for HFS. Also, MOS and HFS were tested as a component of the survival analysis for both high risk and low risk myeloma patient groups [13].

3. Results

In this analysis, 432 patients were identified (median age, 61 years old range (43–76); 37% female, median height 173 cm, median weight 93 kg and 87% are white. In the cohort, fractures were identified in 203 patients at baseline. Median MOS and HFS for TT4 patients were 5.6 and 0.5, respectively, while median MOS and HFS for TT5 patients were 6.2 and 0.7, respectively. Multivariate logistic regression confirmed age, race, sex, BMI, major osteoporotic score, and hip fracture score did not significantly correlate with the presence of fractures at baseline (Fig. 1). The calculated Odds ratio for having a baseline fracture at diagnosis of myeloma for low MOS score (score < 2) was 0.67, and the odds ratio for baseline fractures for low HFS (score < 4.5) was 0.62 (Table 1).

Interestingly, the presence of vertebral fractures at diagnosis of multiple myeloma was not associated with poor outcomes (p-value 0.585).

In the standard-risk disease group (TT4), high FRAX scores (MOS > 4.5 & HFS > 2) were directly correlated with significantly worse progression free (PFS) and overall survival (OS) (Figs. 2 & 3).

For standard-risk disease, MOS lower than or equal to 4.5 was consistent with 3-years OS of 94.1% vs. 79.3% (p-value < 0.001) and 3-years PFS of 85.4% vs 73% (p-value < 0.001). HFS lower than or equal to 2 was consistent with OS of 87.9% vs. 67.1% (p-value < 0.001) and 3-years PFS of 81.5% vs. 54.7% (p-value < 0.01).

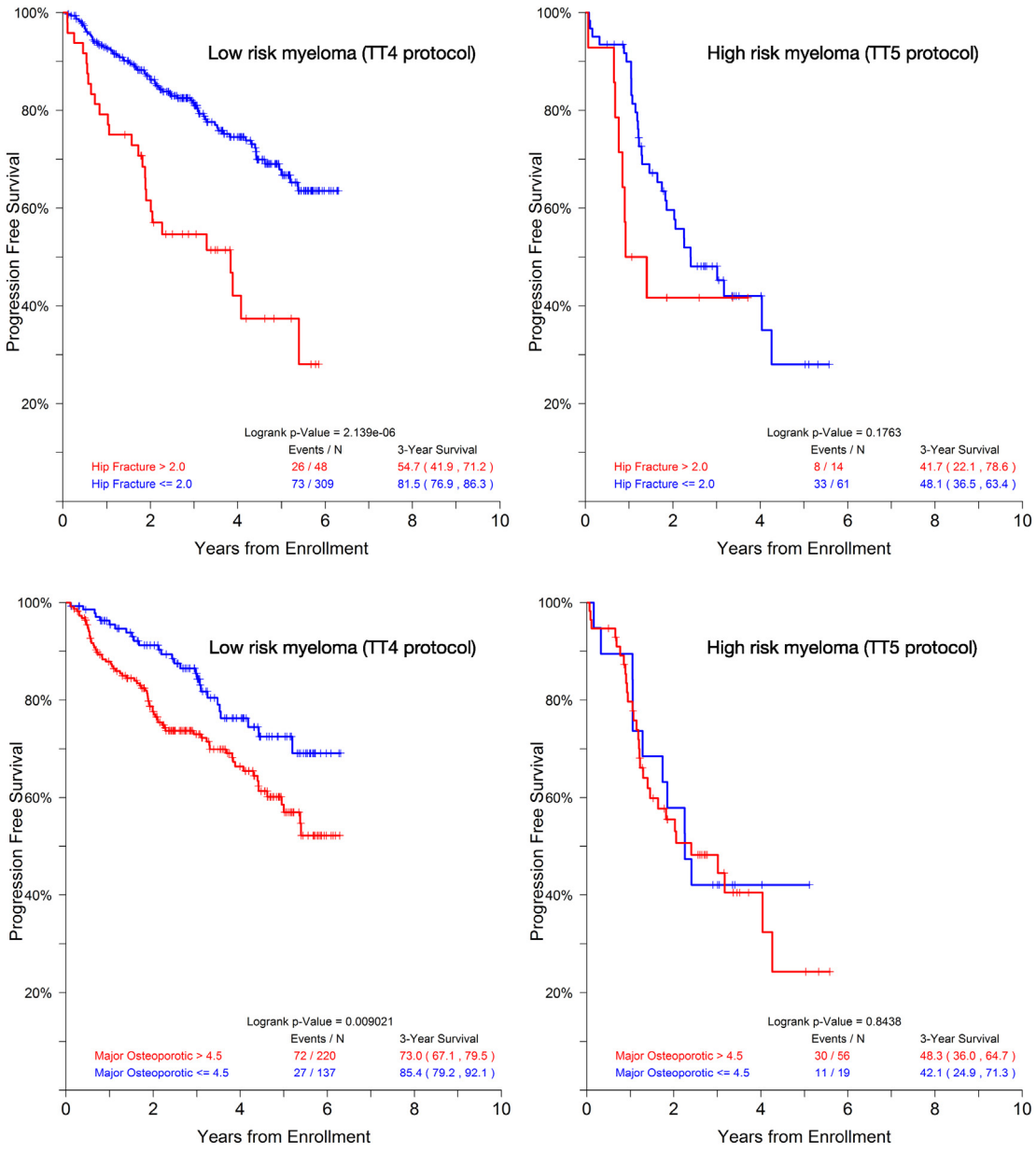

Fig. 2. Progression Free Survival Analysis.
Kaplan-Meier plots for progression free survival comparing high vs low scores of both FRAX scores (Hip Fracture Score, Major Osteoporotic Score) in the setting of newly diagnosed multiple myeloma low risk disease and high risk disease.

For high-risk disease, MOS lower than or equal to 4.5 was consistent with 3-years OS of 78.6% vs. 68.2% (p-value < 0.15) and 3-years PFS of 48.1% vs 41.7% (p-value < 0.17). HFS lower than or equal to 2 was consistent with OS of 71.6% vs. 68.8% (p-value 0.9) and 3-years PFS of 42.1% vs. 48.3% (p-value = 0.84). Interestingly, the significant overall and progression free survival correlation was not observed in the high risk patient group (TT5).

4. Discussion

Previous studies have demonstrated a fundamental role for altered bone pathology in myeloma bone disease and progression [3]. Asynchronous bone turnover (in which there is an increased osteoclastic activity without a proportional increase in osteoblastic activity,) is commonly encountered in multiple myeloma. Osteoclastogenesis and bone resorption are hyper stimulated predominantly due to the dysregulation of three TNF family members: RANK, its ligand (RANKL), and decoy receptor osteoprotegerin (OPG), making increased bone resorption a major driver of myeloma progression [14–17].

Any reduction in osteoclastic activity results in improved bone pain scores, decreased hypercalcemia and the delayed progression of osteolytic lesions [17–19]. Patients with a good response to current chemotherapy tend to also report improved bone mineral density (BMD) [20]. Therefore, bisphosphonate therapy is considered the standard of care for bone disease in multiple myeloma patients. Indeed, a recent Cochrane analysis called for the need to further investigate the effects of those drugs in myeloma patients [21]. All patients enrolled in the TT protocols at the UAMS Myeloma Institute for Research and Therapy received treatments with either zoledronic acid or pamidronate and proteasome inhibitors as part of the standard of care treatment.

Vertebral fractures are one of the most common manifestations of osteoporosis, and are defined by a loss of bone mass, microarchitecture and strength [22]. The majority of these fractures (about two-thirds)

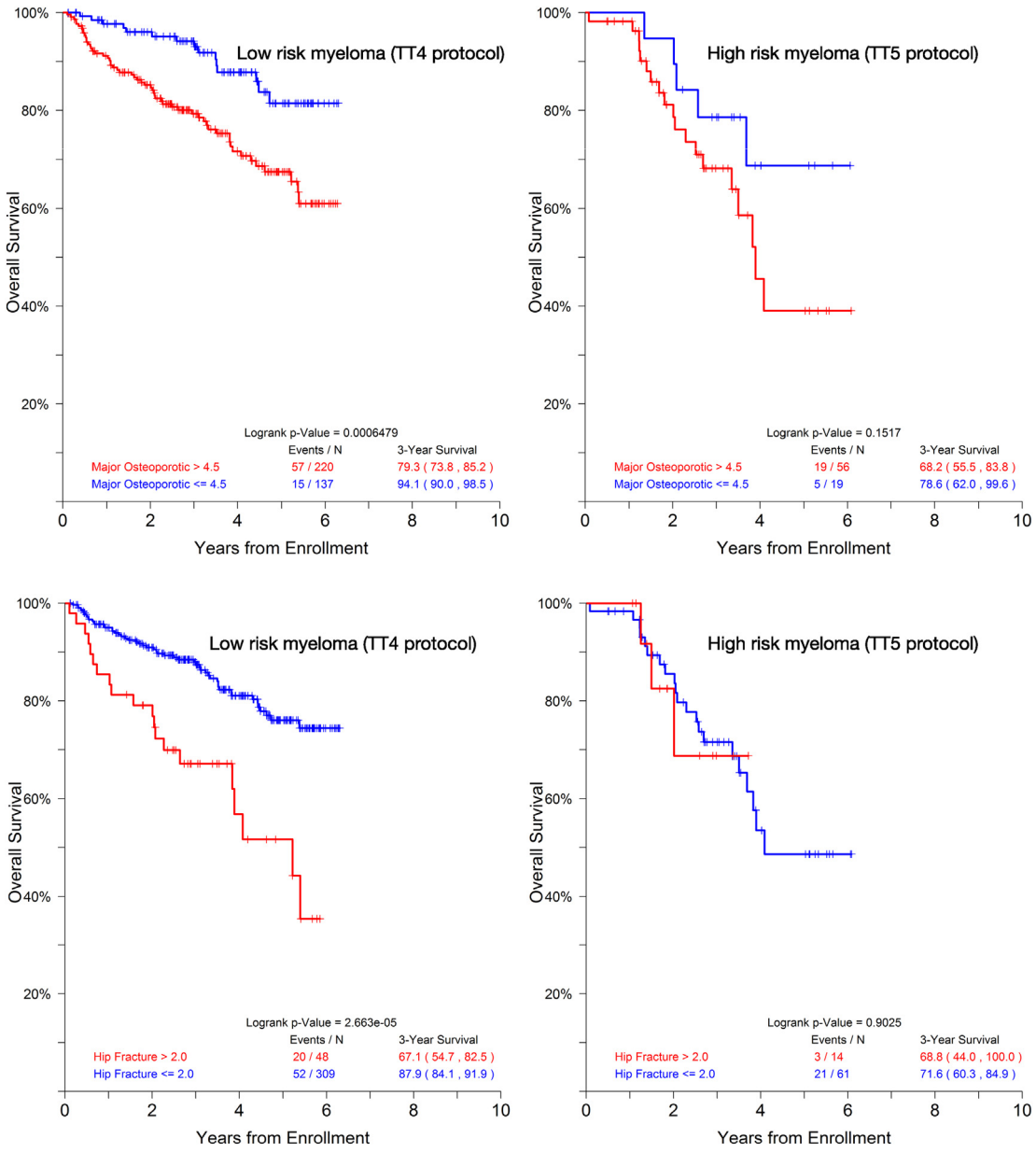

Fig. 3. Overall Survival Analysis.
Kaplan-Meier plots for Overall Survival comparing high vs. low scores of both FRAX scores (Hip Fracture Score, Major Osteoporotic Score) in the setting of newly diagnosed multiple myeloma low risk disease and high risk disease.

are asymptomatic; hence it remains significantly underdiagnosed [23]. TT protocols mandated screening of all newly diagnosed myeloma patients with a musculoskeletal survey, MRI and CT-PET, at presentation. Therefore, screening this myeloma patient population at presentation allowed us to capture the presence of asymptomatic vertebral fractures, in addition to more clinically apparent fractures at other sites.

In the standard-risk myeloma setting (TT4 defined as low GEP score (< 0.66) [11], low LDH $<$ 360 u/l and creatinine $<$ 3 mg/dl), the high FRAX scores (both MOS & HFS) were significantly more likely to predict the co-existence of spinal fractures than those with low FRAX score. These data underscore the knowledge that bone pathology plays a major role in myeloma progression. Furthermore, MOS & HFS predicted overall survival and progression free survival for myeloma (Figs. 2, 3).

Despite the significant ability of FRAX scores to predict bone disease in standard-risk myeloma, the same scores were less predictive in the setting of high-risk myeloma (TT5 defined as GEP risk score (≥ 0.66) [11] or LDH $\geq$ 360 U/L or features of high risk such as Plasma Cell Leukemia or high risk Cytogenetics (i.e. t(4;14),t(14;16),t(14;20) or del (17p)). In the setting of high-risk myeloma, high FRAX scores did not significantly predict PFS or OS (Figs. 2, 3). This interesting finding likely reflects the current lack of effective chemotherapies to control the underlying activity of aggressive plasma cells and/or the already advanced myeloma bone disease in these patients that is the limitation of the FRAX calculation. However, despite the inability of FRAX to predict patient survival, median survival for high risk myeloma remains approximately two years [6].

Interestingly, patient benefits from significant osteoclast inhibition are more prominent in patients with standard-risk disease compared to the high-risk disease group. These results are entirely consistent with a Finnish study [24], that reported on bisphosphonate treatment for high risk myeloma patients, defined as patients with $<$ 50% response to anti-myeloma therapy, in which treatment with the bisphosphonate clodronate did not delay the progression of osteolytic lesions.

It is important to recognize the limitations of the FRAX score. The

tool does not reflect biological or genetic factors contributing to bone health for any specific disease or malignancy, rather FRAX generates a population-based score. The score does not account for certain individual risk factors such as prior smoking history, which can affect bone density, vision problems which may increase the risk of falls and therefore fractures, neurological problems, prior falls, as well as the previous use of medications such as bisphosphonates or the presence of malignancy. However, the FRAX tool, while not perfect, is an effective method to familiarize myeloma patients with the importance of maintaining their bone health at diagnosis and beyond. As such, the patient educational opportunity is important clinically and relevant in a disease setting where skeletal related events can significantly compromise patient quality of life.

These studies demonstrate that the FRAX score was highly predictive of the risk of vertebral fractures at diagnosis in patients with multiple myeloma. Patients with a high FRAX score had vertebral fractures, as diagnosed by PET or MRI. This significant correlation supports the idea that the calculation of a FRAX score, at diagnosis, is an effective and useful clinical tool for evaluating patients with multiple myeloma (and potentially other malignancies that impact the skeleton) and provides new insight into the prediction of patient survival in the setting of standard-risk disease, where detailed skeletal imaging studies may be limited.

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