Journal of Bone Oncology 33 (2022) 100421

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Research Paper

Prediction of vertebral fractures in cancer patients undergoing hormone deprivation therapies: Reliability of who fracture risk assessment tool (frax) and bone mineral density in real-life clinical practice

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ARTICLE INFO

Article history:
Received 26 December 2021
Revised 4 March 2022
Accepted 5 March 2022
Available online 9 March 2022

Keywords:
Bone mineral density
Breast cancer
FRAX score
Fractures
Hormone deprivation therapy
Osteoporosis
Prostate cancer
Vertebral fractures

ABSTRACT

Background and Objective: Prediction of fractures in cancer survivors exposed to hormone-deprivation therapies (HDTs) is a challenge since bone loss is rapid and severe, and determinants of fractures in this setting are still largely unknown. In this study we investigated reliability of the WHO Fracture Risk Assessment Tool (FRAX) and bone mineral density (BMD) to identify subjects developing vertebral fractures during HDTs.

Design: Five-hundred-twenty-seven consecutive subjects (429 females with breast cancer, 98 males with prostate cancer; median age 61 years), under HDTs for at least 6 months, were evaluated for vertebral fractures by a radiological and morphometric approach, in relationship with FRAX score, body mass index (BMI), BMD, age and duration of HDTs.

Results: Vertebral fractures were found in 140 subjects (26.6%) and spine deformity index was significantly associated with duration of HDTs (rho 0.38; $p < 0.001$). Only in females, vertebral fractures were significantly associated with FRAX score for major fractures [OR 1.08; $P < 0.001$]. The best cut-off of FRAX score for major fractures, as calculated by receiving operating characteristic (ROC) analysis was 6.35%. In males, however, vertebral fractures were significantly and independently associated with BMI $\geq$ 25 Kg/m^2 (OR 17.63; $P < 0.001$), BMD T-score below −1.0 SD at any skeletal site (OR 7.79; $P < 0.001$) and gonadotropin-releasing hormone agonists (GnRHa) plus abiraterone treatment (OR 11.51; $P = 0.001$).

Conclusions: FRAX and BMD may be useful for predicting vertebral fractures in subjects undergoing HDTs, but the thresholds seem to be lower than those used in the general population. High BMI is a determinant of vertebral fractures in males under HDT.

1. Introduction

Skeletal fragility is an important clinical issue in women with early-stage breast cancer and men with non-metastatic prostate cancer. Cancer treatments, such as gonadotropin-releasing hormone agonists (GnRHa) and chemotherapy-induced ovarian failure in premenopausal women, aromatase inhibitors (AIs) in postmenopausal women, and antiandrogens in men with non metastatic prostate cancer cause bone loss with high risk of fragility fractures [1].

Vertebral fractures occur in a remarkable number of subjects exposed to hormone deprivation therapies (HDTs) especially when the diagnosis is performed by a radiological and morphometric approach [2,3]. However, prediction of fractures in this clinical

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https://doi.org/10.1016/j.jbo.2022.100421
2212-1374/

setting is a challenge since bone loss induced by cancer therapies is more rapid and severe than primary osteoporosis and determinants of fractures in this setting are still largely unknown [4].

Current guidelines propose to use bone mineral density (BMD) and the WHO Fracture Risk Assessment Tool (FRAX) for identifying cancer patients at higher risk of fractures to be treated in primary prevention with bone active drugs [5]. This approach is commonly adopted in management of primary osteoporosis [6], but its reliability in subjects with secondary osteoporosis is still unclear [4,7]. Moreover, it is unknown whether males with prostate cancer and females with breast cancer have different risk of fractures when exposed to HDTs.

In this study, reflecting the real-life clinical practice, we investigated the accuracy of FRAX algorithm and BMD in identifying breast and prostate cancer survivors who developed vertebral fractures during HDTs.

2. Materials and methods

This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [8]. Participation was offered to consecutive patients with hormone receptor-positive breast cancer or castration-sensitive prostate cancer attending two tertiary referral centers of Northern Italy (IRCCS Humanitas Research Hospital, Rozzano-MI- and ASST Spedali Civili di Brescia, Brescia) from March 1st 2019 to June 30th 2021. All participants were assessed one time, during HDT. The database was locked on July 31st 2021 and data analysis was completed by October 20th 2021. The inclusion criteria were: 1) hormone receptor-positive breast cancer or castration-sensitive prostate cancer with indication for estrogen or androgen deprivation therapies, respectively; 2) age $\geq$ 40 years; 3) duration of HDT $\geq$ 6 months; 4) written informed consent. Exclusion criteria were: 1) bone metastases; 2) treatment with bone-active drugs (except for calcium and vitamin D) at study entry; 3) spinal surgery; 4) stage IV-V renal insufficiency; 5) liver disease with Child-Pugh classes B-C.

Among 740 consecutive subjects with hormone receptor-positive breast cancer or castration-sensitive prostate cancer, 213 were excluded (210 were on treatment with bone-active drugs, two had bone metastases and one subject had renal insufficiency), whereas 527 individuals (429 females, 98 males; median age 61 years, range 40–89) were enrolled in the study.

As primary aim, we investigated whether the assessment of FRAX score can identify subjects with vertebral fractures during HDTs. As secondary aims, we explored: 1) the association between BMD and vertebral fractures; 2) the differences in prevalence and determinants of vertebral fractures between males with prostate cancer and females with breast cancer exposed to HDTs.

The study was approved by the Ethics Committee of IRCCS Humanitas Research Hospital and ASST Spedali Civili di Brescia and all included patients gave their consent to use the clinical and biochemical data for research purposes.

2.1. Assessment of vertebral fractures

Vertebral fractures were detected by a quantitative morphometric assessment using DXA (Hologic Inc) images (97 cases) [9] or conventional spine X-rays radiographs (430 cases) [10]. Six points were manually marked on each vertebral body to describe the vertebral shape. Anterior (Ha), middle (Hm), and posterior (Hp) vertebral heights were measured and height ratios (Ha/Hp, Ha/Hm, Hm/Hp) were calculated for each vertebra from T4 to L4. According to the quantitative morphometry method [11], the fractures were defined as mild, moderate, and severe based on height ratio decreases of 20–25%, 25–40%, and more than 40% respectively. Spine deformity index (SDI) was calculated by summing the score of each vertebral fracture assigned on the basis of the grade of fracture (score 1, 2, or 3 for mild, moderate, and severe fractures, respectively) [12]. Assessment of vertebral fractures was performed by two observers in each center and FRAX results were kept from them. In 64 fractured subjects (19 females with breast cancer and 45 males with prostate cancer), vertebral fractures and SDI were retrospectively evaluated also at diagnosis of cancer, before starting HDTs.

2.2. DXA measurement of BMD

All enrolled subjects were evaluated by DXA (Hologic Inc) at lumbar spine, femoral neck and total hip. BMD was expressed as T-score, comparing the results with those obtained in a gender-matched Caucasian population at the peak of bone mass [13]. A T-score less than or equal to – 2.5 SD at any skeletal site was defined as osteoporosis, whereas osteopenia was defined as a T-score between – 1 and – 2.5 SD. Fractured vertebrae were excluded from measurement of lumbar spine BMD.

2.3. Assessment of FRAX score

The fracture risk was assessed by the FRAX tool (FRAX® tool) using the online calculator (https://www.shef.ac.uk/FRAX) with the information collected at study entry. The calculation of FRAX score was performed including BMD values of subjects and considering HDTs as a cause of secondary osteoporosis. The results of morphometric analysis were not included in the FRAX analysis. Subjects with major osteoporotic fracture risk $\geq$ 20% were defined as high-risk [5,14].

2.4. Assessment of body mass index (BMI)

BMI was defined by the individual's weight in kilograms divided by the square of their height in meters. Overweight and obese were defined by BMI 25–30 Kg/m^2 and $\geq$ 30 Kg/m^2, respectively.

2.5. Statistical analyses

Data were described as number and percentage if categorical, or mean, standard deviation, and range if continuous. Difference between groups were explored with chi squared test if categorical, or Mann Whitney test, if continuous. Adherence to Gaussian distribution was verified with Shapiro-Wilks test. Association between SDI and duration of HDTs was assessed by Spearman's test. Associations of vertebral fractures with possible risk factors were explored with logistic regression analysis, separately for each gender. All independent factors with a *P* value under 0.10 were then submitted to a multivariate logistic regression analysis.

Variables in each final multivariate analysis were presented in the final tree, and the odds ratios (ORs) were presented for each root. BMI was dichotomized over and under 25 Kg/m^2 for reasons of data presentation.

The receiving operating characteristic (ROC) analysis was performed to assess the best cut-off of FRAX score for major fractures to identify females with vertebral fractures.

A p under 0.05 was considered as significant. All analyses were made with Stata15.

3. Results

3.1. Overall population

In the whole population, mean BMD T-scores were −1.22 ± 1.43 SD (range from −5.3 to + 4.9), −1.31 ± 1.04 SD (range from −5.0 to + 3.8) and −1.02 ± 1.02 SD (range from −4.7 to + 3.4) at lumbar spine, femoral neck and total hip, respectively. Osteoporosis and osteopenia at any skeletal site were diagnosed in 132 (25.1%) and 290 (55.0%) subjects, respectively. At this time, the mean FRAX score for major fractures was 8.2 ± 6.6% (range: 1–66), being ≥ 20.0% in only 37 subjects (7.0%).

The mean duration of HDTs was 39.1 ± 27.4 months (range: 6–120). Vertebral fractures were diagnosed in 140 subjects (26.6%) and the mean SDI was 2.2 ± 2.0 (range: 1–12). Prevalence of vertebral fractures was not significantly different among subjects stratified for duration of HDTs' quartiles (Fig. 1). However, in fractured individuals, SDI was significantly associated with duration of HDTs (rho 0.38; $p < 0.001$). In 64 fractured subjects (45 males and 19 females) in whom baseline assessment of vertebral fractures was retrospectively performed, 11 had prevalent vertebral fractures and 53 were without fractures before starting HDTs. In 9 out of 11 individuals with pre-existing vertebral fractures, SDI increased during HDTs.

The prevalence of vertebral fractures was significantly higher in males with prostate cancer as compared to females with breast cancer [45 (45.9%) vs. 95 (22.1%); $P < 0.001$], although the latter frequently had more osteoporosis compared to males [121 (28.2%) vs. 11 (11.2%), $P < 0.001$]. No significant difference in FRAX score for major fractures ≥ 20% was found between breast and prostate cancer patients [27 (6.3%) vs. 10 (10.2%), P = 0.172] (Fig. 2).

Stratifying all subjects for BMD and FRAX categories, prevalence of vertebral fractures was not significantly different between osteopenia and osteoporosis [86/290 (29.7%) vs. 37/132 (28.0%), $P = 0.733$] and between FRAX score for major fractures ≥ 20% and FRAX score for major fractures 10–20% [44/101 (43.6%) vs. 18/37 (48.6%), $P = 0.595$]. However, the prevalence of vertebral fractures was significantly lower in subjects with normal BMD values (i.e., T-score > -1.0 SD) compared to subjects with BMD T-score below −1.0 SD [17/105 (16.2%) vs. 123/422 (29.1%), $P = 0.007$], and in those with FRAX score for major fractures < 10% compared to subjects with FRAX score ≥ 10% [78/389 (20.2%) vs. 62/138 (44.9%), $P < 0.001$].

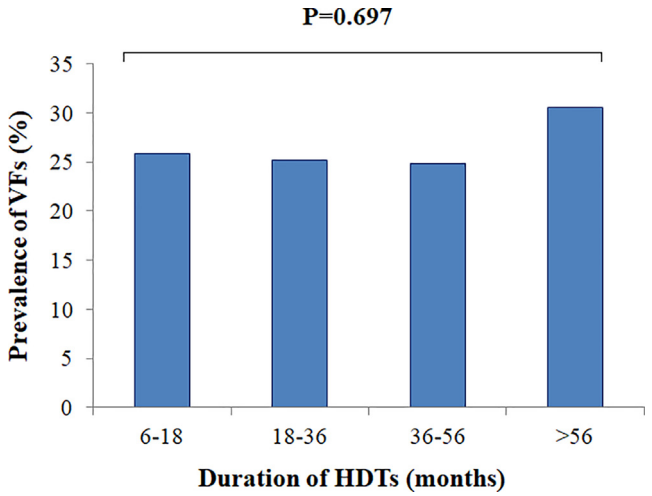

Fig. 1. Prevalence of vertebral fractures (VFs) in 527 subjects (429 females with breast cancer and 98 males with prostate cancer) stratified for quartiles of hormone-deprivation therapies (HDTs) duration.

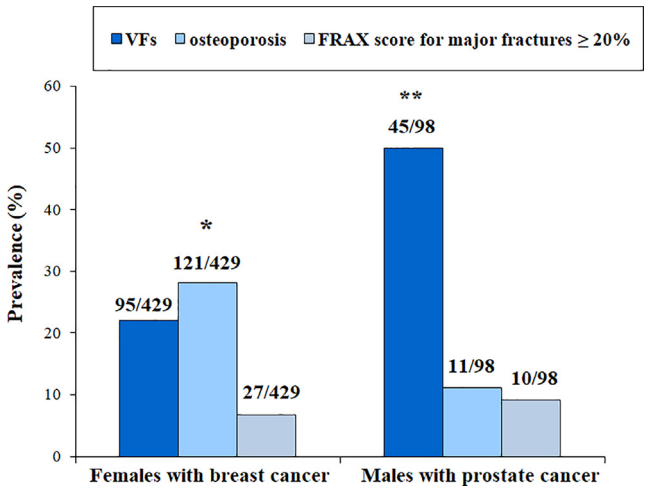

Fig. 2. Prevalence of total vertebral fractures (VFs), densitometric diagnosis of osteoporosis and FRAX score for major fractures ≥ 20 in 429 females with breast cancer under estrogen-deprivation therapies and 98 males with prostate cancer under androgen-deprivation therapies. *, $P < 0.001$ vs. males; **, $P < 0.001$ vs. females. The P values were derived from chi squared test.

3.2. Breast cancer patients

Four-hundred-thirteen females with breast cancer were treated with AIs (43 in combination with GnRHa), whereas 16 subjects were treated with GnRHa plus tamoxifene. Vertebral fractures were assessed on DXA (97 cases) or conventional spine X-rays radiographs (332 cases). Ninety-five females (22.1%) showed vertebral fractures during HDTs, which were moderate/severe and multiple in 34 (7.9%) and 32 (7.4%) cases, respectively. The prevalence of fractures was not significantly different between evaluations on DXA or conventional spine X-rays radiographs [18/97 (18.6%) vs. 77/332 (23.2%); $P = 0.333$]. Moreover, the prevalence of vertebral fractures was not significantly different between females treated with AIs (either alone or with GnRHa) and those treated with GnRHa plus tamoxifene [91 (22.0%) vs. 4 (25.0%); $P = 0.762$]. The mean duration of estrogen-deprivation therapies was 38.8 ± 27.1 months (range 6–120). Among 19 women with baseline vertebral morphometry retrospectively assessed, only one had pre-existing vertebral fractures before starting HDTs.

In univariate logistic regression analysis, vertebral fractures during HDTs were significantly associated with BMD T-score lower than −1.0 SD and FRAX score for major fractures (Table 1). Only FRAX score for major fractures entered in the multivariate model (OR 1.08; 95% CI 1.04–1.12; $P < 0.001$), due to collinearity of FRAX score with age and BMD. FRAX score for major fractures maintained a significant and independent association with vertebral fractures even when the analysis was restricted to either moderate/severe or multiple fractures (i.e. subjects with SDI ≥ 2; OR 1.06; 95% CI 1.03 = 2–1.11; $P = 0.007$). In the ROC analysis for FRAX major score (**supplemental** Fig. 1), the area under the curve was 0.638 and the best cut-off was 6.35%, with sensitivity and specificity of 62.0% and 61.9%, respectively.

3.3. Prostate cancer patients

Among the 98 males with prostate cancer, 46 (46.9%) were treated with GnRHa alone, 27 (27.6%) with GnRHa plus androgen receptor blocking drug and 25 (25.5%) subjects with GnRHa plus abiraterone. Vertebral fractures were assessed on conventional spine X-rays radiographs in all 98 males. Forty-five males (45.9%) showed vertebral fractures, which were moderate/severe in 21

Table 1
Determinants of vertebral fractures in breast cancer patients treated with estrogen deprivation therapies. Results of univariate and multivariate logistic regression analyses. *, the lowest BMD value at lumbar spine, femoral neck or total hip was considered.

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	OR	95% CI	P	OR	95% CI	*P* value
N = 429						
Age	1.02	1.00–1.05	0.073			
BMI	0.99	0.94–1.04	0.609			
BMD T-score < -1.0 SD at any skeletal site*	3.05	1.27–7.32	0.012			
FRAX score for major fractures	1.08	1.04–1.12	<0.001	1.08	1.04–1.12	<0.001
AIs	1.18	0.37–3.74	0.779			
Duration of HDTs	1.00	1.00–1.01	0.409			

AIs, aromatase inhibitors; BMD, bone mineral density; BMI, body mass index; C.I., confidence interval; FRAX, WHO Fracture Risk Assessment Tool; HDT, hormone deprivation therapies; OR, odds ratio; SD, standard deviation.

(21.4%) and multiple in 14 (14.3%) cases. The prevalence of vertebral fractures was significantly ($P = 0.009$) higher in males treated with GnRHa plus abiraterone (18/25; 72.0%) as compared to those treated with either GnRHa alone (18/46; 39.1%) or GnRHa plus anti-androgen (9/27; 33.3%). The mean duration of androgen-deprivation therapies was 40.4 ± 29.0 months (range: 9–120). The prevalence of total and either multiple or moderate/severe vertebral fractures (i.e., SDI $\geq$ 2) was significantly higher in overweight and obese males compared to males with BMI below 25 Kg/m^2 (Fig. 3). Among 45 males with baseline vertebral morphometry retrospectively assessed, 10 had pre-existing vertebral fractures and SDI increased in 8 of them during HDTs.

In univariate logistic regression analysis, vertebral fractures during HDTs were significantly associated with BMD T-score lower than −1.0 SD, higher BMI, FRAX score for major fractures and treatment with GnRHa plus abiraterone (Table 2). In the multivariate analysis, BMI $\geq$ 25 Kg/m^2 (OR 17.63; 95% CI 4.88–63.73; $P < 0.001$), BMD T-score lower than −1.0 SD (OR 7.79; 95% CI 2.48–24.50; $P < 0.001$) and treatment with GnRHa plus abiraterone (OR 11.51; 95% CI 2.78–47.69; $P = 0.001$) maintained a significant and independent association with vertebral fractures. The model including FRAX score for major fractures was less robust (data not shown). When the analysis was restricted to either moderate/-severe or multiple fractures (i.e. subjects with SDI $\geq$ 2), only BMI $\geq$ 25 Kg/m^2 maintained a significant and independent association with vertebral fractures (OR 24.68; 95% CI 2.80–217.74; $P = 0.004$).

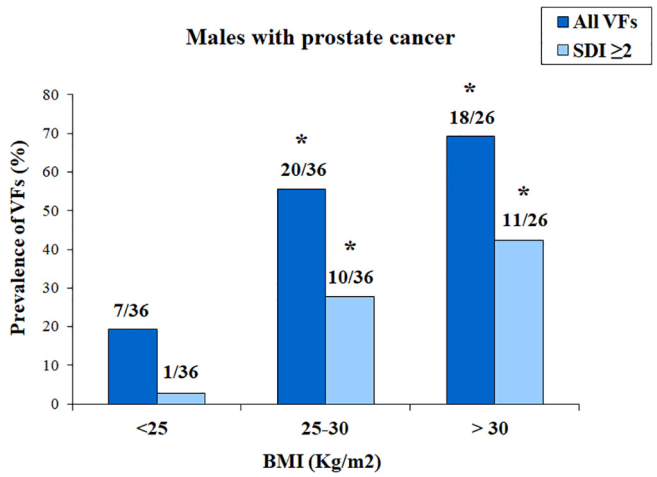

Fig. 3. Prevalence of total vertebral fractures (VFs) and multiple/moderate/severe VFs [i.e., those with spine deformity index (SDI) $\geq$ 2] in 98 males with prostate cancer under androgen-deprivation therapies and stratified for body mass index (BMI). *, $P < 0.001$ vs. BMI < 25 Kg/m^2. The *P* values were derived from chi squared test.

Fig. 4 shows the final tree model. Thirty-eight out of 45 subjects with vertebral fractures (84.4%) had BMI $\geq$ 25 Kg/m^2. The prevalence of vertebral fractures resulted to be high even when BMD T-score was > -1.0 SD. Moreover, BMI was $\geq$ 25 Kg/m^2 in 15 out of 18 subjects (83.3%) who showed vertebral fractures during treatment with GnRHa plus abiraterone. In subjects with BMI < 25 Kg/m^2, the cases with vertebral fractures were few making it impossible to evaluate statistically significant differences among the roots.

4. Discussion

In males with prostate cancer under androgen deprivation therapy, vertebral fractures were shown to be independently associated with BMI $\geq$ 25 Kg/m^2, BMD lower than −1.0 SD and treatment with GnRH agonists plus abiraterone. However, in females with breast cancer receiving either GnRHa or AIs, vertebral fractures were associated only with FRAX score for major fractures.

Guidelines for management of osteoporosis in cancer survivors exposed to HDTs did not discriminate between males with prostate cancer and females with breast cancer [5]. Moreover, the recommendations in this setting have been mainly based on BMD measurement and historical assessment of clinical fractures [5,15]. In this study, we had the opportunity to evaluate, in real-life clinical practice, the prevalence and determinants of vertebral fractures, i.e. the most frequent complication of osteoporosis [16], in a large heterogeneous population of males with prostate cancer and females with breast cancer under HDTs. Interestingly, prevalence of radiological vertebral fractures was remarkably high in males with prostate cancer under androgen-deprivation therapy, with a rate that was comparable to other forms of secondary male osteoporosis at high risk of fractures [17]. This finding might be dependent on a selection bias related to low awareness of skeletal fragility in this clinical setting [18]. As a matter of fact, one could argue that only subjects with clinically relevant vertebral fractures attended our outpatient bone clinics. Consistently, prevalence of moderate/severe fractures was higher in fractured males with prostate cancer as compared to fractured females with breast cancer. Another possible explanation of high fracture rate in our males with prostate cancer was treatment with abiraterone that was performed in a large number of subjects. Indeed, our study confirmed that abiraterone was an independent risk factor for fragility fractures [19]. In clinical practice, abiraterone is given in combination with prednisone 5 mg either once or twice daily to correct cortisol deficiency and prevent excessive production of mineralcorticoids induced by selective inhibition of 17α-hydroxylase and C17,20-lyase [20]. However, this corticosteroid regimen combined with abiraterone is an over-treatment of cortisol deficiency and this approach could cause detrimental effects on skeletal health [21]. In studies involving subjects with either adrenal insufficiency or

Table 2
Determinants of vertebral fractures in prostate cancer patients treated with androgen deprivation therapies. Results of univariate and multivariate logistic regression analyses. *, the lowest BMD value at lumbar spine, femoral neck or total hip was considered.

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	OR	95% C.I.	P	OR	95% C.I.	*P* value
N = 98						
Age	1.05	1.00–1.10	0.072			0.168
BMI ≥ 25 Kg/m2	6.56	2.49–17.32	<0.001	17.63	4.88–63.73	<0.001
BMD T-score < -1.0 SD at any skeletal site*	4.36	1.82–10.42	0.001	7.79	2.48–24.50	<0.001
FRAX score for major fractures	1.07	1.00–1.45	0.038			
GnRHa plus abiraterone	4.38	1.62–11.84	0.004	11.51	2.78–47.69	0.001
Duration of HDTs	1.01	1.00–1.02	0.182			

BMD, bone mineral density; BMI, body mass index; C.I., confidence interval; FRAX, WHO Fracture Risk Assessment Tool; GnRHa, gonadotropin-releasing hormone agonists; HDT, hormone deprivation therapies; OR, odds ratio, SD, standard deviation.

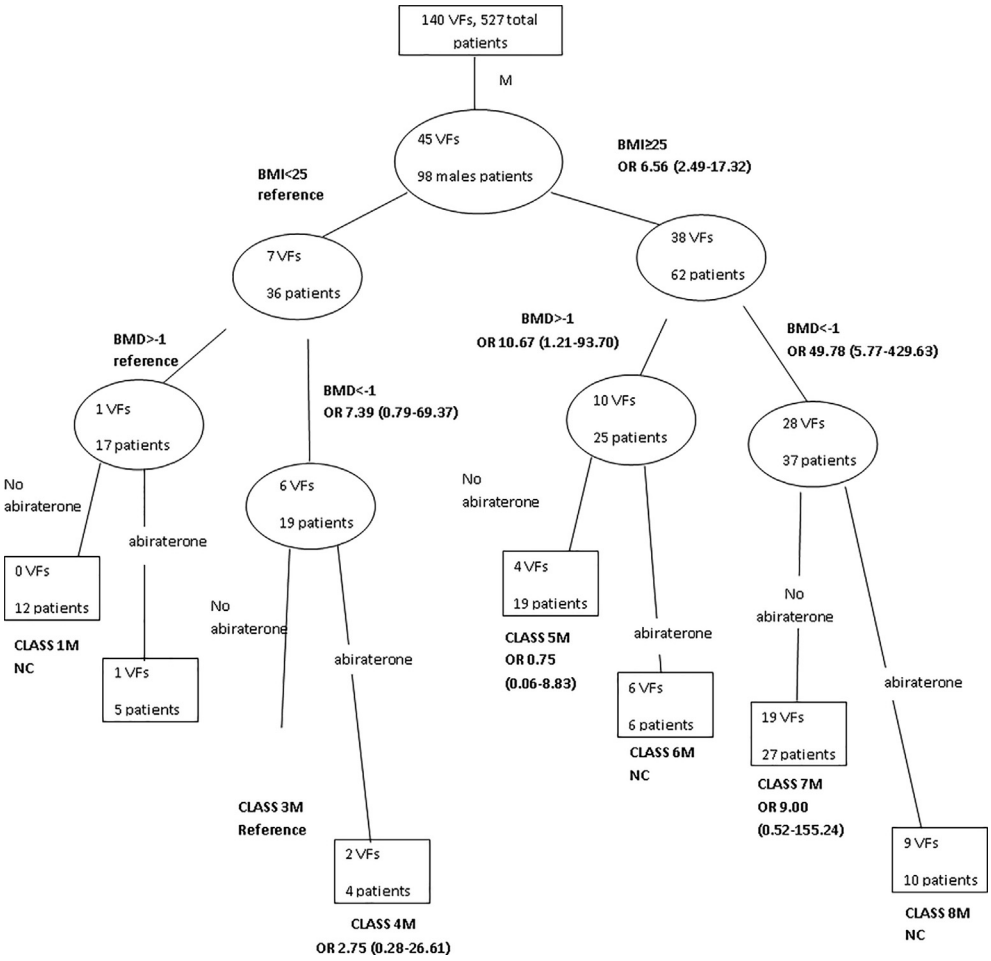

Fig. 4. Risk of vertebral fractures (VFs) in subgroups of male (M) subjects with prostate cancer under androgen-deprivation therapies, stratified for body mass index (BMI), bone mineral density (BMD) and abiraterone therapy. The odds ratio (OR) and 95% confidence intervals were reported in each root when the number of subjects and the events permitted the statistical analyses.

congenital adrenal hyperplasia, use of prednisone in place of either hydrocortisone or cortisone acetate was associated with bone loss and an increase in fracture risk [22,23]. In our population , most subjects who developed vertebral fractures during abiraterone therapy were either overweight or obese possibly reflecting the concomitant effects of glucocorticoids and androgen-deprivation therapies on body composition and skeletal health [24].

In the general population, low BMI is a well-recognized risk factor for fractures while higher BMI might have a beneficial effect [25,26]. In our subjects under androgen-deprivation therapy for castration-sensitive prostate cancer, most of vertebral fractures occurred in overweight or obese cases. Although our study did not provide information on body composition of enrolled subjects, one could argue that higher BMI might reflect the existence of sarcopenic obesity induced by androgen-deprivation therapy possibly contributing to skeletal fragility in this clinical setting [27]. From this point of view, high BMI and increased body fat mass are markers of unfavorable outcome in subjects with prostate cancer [28]. An association between body fat mass and vertebral fractures was already reported in women under treatment with AIs [29], especially when low lean body mass concomitantly decreased [30]. In our population of females with breast cancer under HDT,

vertebral fractures were not associated with higher BMI, likely because in most overweight or obese cases, lean body mass did not decrease in relationship with maintained androgen secretion during estrogen-deprivation therapies [4].

FRAX algorithm was developed to predict an individual's 10-year probability of major osteoporotic fracture and hip fracture from readily assessed clinical risk factors and optional BMD [14]. Use of FRAX in clinical practice informs the definition of fracture probability at which to recommend treatment – termed the intervention threshold. Several guidelines have recommended that a fixed probability threshold of 20% for a major osteoporotic fracture be used as an intervention threshold [31]. Although initially developed for use in the general population, there is increasing interest in the application of FRAX to subjects with secondary osteoporosis [5,32]. A recent study suggested that FRAX algorithm might overestimate risk of clinical fractures at the time of initiation of AIs [7], likely because women with estrogen receptor positive breast cancer could have baseline lower fracture risk than the general population in relationship with their frequently higher BMI [33] and BMD [34]. In our population of women with breast cancer under estrogen deprivation therapies, FRAX score for major fractures was significantly associated with radiological vertebral fractures irrespective of BMD and age. This finding would suggests that FRAX score can predict fractures even when BMD is not considered in the algorithm [7,35]. However, in our study, accuracy of FRAX in identifying subjects with vertebral fractures was less than acceptable as defined by ROC analysis, since about 40% of fractured women were missed using this algorithm. Moreover, FRAX appeared to underestimate the risk of radiological vertebral fractures since fractures were detected in a large number of subjects with FRAX score for major fractures lower than the threshold of 20%. Indeed, in our population, the best threshold for predicting vertebral fractures was in the range (i.e. < 10%) that is, generally, considered at low risk of fragility fractures, in several clinical contexts [32].

FRAX algorithm was proposed as a reliable tool for predicting fractures also in men undergoing androgen-deprivation therapies [36–40]. In our population, the accuracy of FRAX in identifying subjects with vertebral fractures resulted to be lower than BMI and BMD. This finding may be dependent on the fact that stratification of fracture risk was performed only during androgen-deprivation therapy, when drug-induced alterations in body composition, likely, led to change the relative impact of BMI in the calculation of FRAX score.

The diagnostic value of BMD is limited in most cases of secondary osteoporosis in which bone quality is altered more than bone quantity [41]. Bone loss induced by HDT is more rapid and severe than that occurring in post-menopausal osteoporosis and primary male osteoporosis [42]. Noteworthy, HDT causes not only decrease in bone mass but also early alterations in trabecular and cortical bone microarchitecture with consequent deterioration in bone quality occurring independently of decrease in BMD [43–45]. The mechanisms responsible for these skeletal effects and for the differences between hormone deprivation therapy-induced skeletal fragility and primary osteoporosis have not been completely understood, although abnormalities in body composition as well as alterations in skeletal hormone signals might play a role [4,46]. Consistently, fractures were reported in a large number of males and females exposed to HDTs even in the context of normal or low-normal BMD [2,47]. In our population, vertebral fractures developed in several subjects with BMD values in the range of osteopenia and a T-score BMD threshold of −1.0 SD was accurate for identifying males with castration-sensitive prostate cancer at higher risk of radiological vertebral fractures during androgen-deprivation therapy, independent of age, FRAX score, BMI and type of HDT. Also in women with breast cancer under estrogen-deprivation therapies, BMD T-score lower than −1.0 SD resulted to be associated with higher risk of vertebral fractures in univariate logistic regression analysis. These findings support the concept that in subjects exposed to HDTs, the threshold of BMD for predicting fractures should be increased compared to the general population [15].

This study has several limitations. The lack of detailed background data before starting HDTs and cross-sectional design did not allow for a definition of the timing of fracture development during follow-up and the causal relationship between HDTs and vertebral fractures. However, the prevalence of vertebral fractures in our study population was comparable to that already reported in similar clinical contexts of osteoporosis [2,3,47]. Moreover, the close relationship between duration of HDTs and SDI was suggestive of a direct role of hormone therapies in the pathogenesis of vertebral fractures. Consistently, in the longitudinal analysis retrospectively performed in a subgroup of subjects with available baseline spine images, most of subjects with pre-existing vertebral fractures showed a progression of fractures during HDTs. In this study we didn't assess the clinical effects of vertebral fractures. However, it is noteworthy that a remarkable number of our patients had multiple or moderate/severe multiple fractures frequently associated with back pain and impaired quality of life [48]. However, there is also evidence that radiological vertebral fractures could be clinically relevant even when asymptomatic owing to predisposition to develop further fractures [49]. The assessment of vertebral fractures was not centralized and two methods were used for diagnosis of fractures. However, as already demonstrated by others [50], we did not find differences between assessment of vertebral fractures on DXA and spinal radiographs images. DXA measurement of BMD and calculation of FRAX score were performed during HDTs, precluding the calculation of the performance of these diagnostic tools at the start of hormone therapies. We didn't use diagnostic tools evaluating bone microstructure and quality that can improve the prediction of fractures in the context of normal BMD values or osteopenia [43–45,47,51,52]. We excluded from the study subjects receiving bone-active drugs who were possibly those at higher risk of fragility fractures. This selection, likely, led to underestimate the true prevalence of vertebral fractures and reduce overall predictive accuracy of diagnostic tools investigated in the study. A further limitation of this study was the heterogeneity of the study's population as it including both males and females exposed to various HDTs. In this context, reflecting the real-life clinical practice, we found that combination therapy with GnRHa plus tamoxifene was associated with a risk of vertebral fractures which was not different from that associated with AIs.

Besides the limitations, the results of this study might have clinical implications by improving the therapeutic-decision making in individuals with HDT-induced skeletal fragility [53]. The progression of SDI in subjects with pre-existing vertebral fractures reinforces the concept that these fractures should be proactively and early diagnosed in cancer survivors starting HDTs [53]. Some guidelines suggest an universal treatment of subjects under HDTs [54], whereas others indicate to treat only subjects with high FRAX scores and/or low BMD [5,15]. The results of our study suggests that therapeutic thresholds of BMD and FRAX score could be different than those used in post-menopausal osteoporosis and primary male osteoporosis [6,31] and those indicated by guidelines for cancer survivors under HDTs [53]. Moreover, high BMI was shown to be an independent risk factor for multiple and moderate/severe vertebral fractures in males exposed to androgen-deprivation therapy, providing a further rationale for including this parameter in the risk assessment. This observation suggests to study body composition in the diagnostic work-up of subjects with prostate cancer.

Author contributions

G. Mazziotti and A.G. Lania had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Mazziotti received consultancy fees from Novartis, Ipsen, Eli Lilly and lecture fees from Amgen and Abiogen, outside the submitted work. Dr. Vena received grants from IBSA Pharmaceutical outside the submitted work. Dr. Zucali reports receiving, outside the submitted work, personal fees for an advisory role, speaker engagements and travel and accommodation expenses from Merck Sharp & Dohme (MSD), Astellas, Janssen, Sanofi, Ipsen, Pfizer, Novartis, Bristol Meyer Squibb, Amgen, Astrazeneca, Roche, and Bayer. Dr. Torrisi received research grants from Pfizer, consultancy fees from MSD and lecture fees from Pfizer, Eli Lilly, EISAI and Genomic Health outside the submitted work. Dr. Lania received grants from Pfizer and consultancy fees from Ipsen, outside the submitted work. Dr Berruti reports receiving grants and personal fees from Janssen Cilag, grants and personal fees from Astellas, and personal fees from Bayer outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbo.2022.100421.

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