Original Article

Majority of hip fragility fractures among older people can be predicted by a DXA examination: an updated analysis of literature results and empirical Chinese data with a focus on the validation of the newly proposed osteofrailia criterion for men

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Background: How different gender-specific bone mineral density cutpoint T-scores are associated with different hip fragility fracture (FFx) prediction sensitivity has not been well studied. This article presents an updated analysis of hip FFx prediction among older people by a dual-energy X-ray absorptiometry (DXA) measure, using literature results and our own Chinese data.

Methods: We systematically searched literature reports on DXA T-score results measured at the timepoint of a hip FFx. With osteoporotic fractures in women (MsOS) and in men (MrOS) Hong Kong studies, at baseline 2,000 Chinese women (mean: 72.5 years) and 2,000 Chinese men (mean: 72.3 years) were recruited. Female participants were followed up for 8.8±1.5 years, and 69 FFx were recorded. Male participants were followed up for 9.9±2.8 years, and 63 hip FFx were recorded.

Results: Ten articles published femoral neck (FN) and/or total hip (TH) T-score at the timepoint of a hip FFx with separated females' or males' T-score data. We estimated that, if a DXA exam were taken shortly before the FFx accident, females' FN, females' TH, males' FN, or males' TH T-scores on average predicted 66.9%, 70.4%, 66.5%, and 67.8% of the hip FFx. For the MsOS and MrOS Hong Kong studies, a combination of baseline FN and TH T-score predicted >50% of the cases with a follow-up hip FFx. A combination of baseline FN T-score, TH T-score, lumbar spine T-score, and spine fracture-like deformity assessment predicted 68.1% of the female cases with a follow-up hip FFx, and 63.4% of the male cases with a follow-up hip FFx.

Conclusions: If a DXA scan is regularly performed, approximately 70% of the hip FFx incidents can be predicted for older women and men.

Keywords: Dual-energy X-ray absorptiometry (DXA); T-score; fracture risk; hip fractures; osteoporosis diagnosis

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Introduction

Osteoporosis is a systemic skeletal disease characterised by a reduction in bone mass and qualitative skeletal changes that cause an increase in bone fragility and a higher fracture risk. The clinical significance of osteoporosis lies in the occurrence of fragility fractures (FFx), and the most relevant fracture site is the hip. Because hip FFx typically necessitates hospitalization, data on their incidence is more reliable than data on other types of fractures. According to the criteria set by the 1994 World Health Organization (WHO) Study Group, the T-score is defined as: $(BMD_{patient} - BMD_{young\ adult\ mean})/SD_{young\ adult\ population,}$ where BMD is bone mineral density and SD is the standard deviation (1). For a variety of reasons, including differences in X-ray energy generation, bone edge detection algorithms, region of interest placement, and methods of calibration, BMD by dual-energy X-ray absorptiometry (DXA) in g/cm^2 differs among DXA manufacturers. To avoid the confusion that would result from instrument-specific numerical BMD cutpoint values, the T-score concept was proposed, whereby each patient's value is compared with a young normative database generated on the same device. Although BMD is recognized as a continuous risk factor for fracture (i.e., no natural fracture threshold exists), operational ranges for the T-score were proposed for epidemiologic purposes. When the femoral neck (FN) is measured in adult Caucasian women, a cutpoint value of patient BMD of 2.5 SD below the young adult mean BMD results in a prevalence of osteoporosis for those aged ≥50 years of about 16.2%, the same as the lifetime risk of hip FFx for Caucasian women (1). This definition is the cornerstone of densitometric osteoporosis (DOP) classification. However, it has been frequently cited that one of the limitations of BMD measurement is '*the majority of fragility fractures occur at non-osteoporotic BMD (T-scores >–2.5)*, *compromising its role as a screening tool*' (2-7).

We have recently conducted literature analyses and showed that, for older women, the majority of hip FFx occurs among the DOP population (8). For female hip FFx, the notion that the majority of fractures occur at non-osteoporotic BMD (T-scores >–2.5) was partially derived from a few prospective epidemiology studies of older populations, where BMD was measured at baseline, rather than at the timepoint when a hip FFx occurred (9,10). A closer look at these reports suggests it is likely when hip FFx actually occurred, >50% of the study participant patients were with FN DOP (8). A few prospective epidemiology studies of older population also showed that >50% study participants with hip FFx during the follow-up already had DOP at baseline (11-13).

Following the 1994 WHO definition, DOP prevalence among a specific population should be in proportion to its relative osteoporotic fracture risk with Caucasian female data as reference (1,14,15). It is well noted that the total hip (TH) T-score tends to measure higher than FN T-score, then if TH T-score is solely considered (rather than the lower of FN or TH T-scores) and T-score DOP cutpoint of ≤–2.5 is used, then DOP will be under-diagnosed (16). For men, we recently described that older men suffer from hip FFx at FN or TH T-score approximately 0.5–0.6 higher than older women, thus we proposed a new category of low BMD status, osteofrailia, for older Caucasian men with T-score ≤–2.0 (T-score ≤–2.1 for older East Asian men) who are likely to suffer from hip FFx (16). Moreover, we noted that, due to the lower prevalence of FFx, the T-score cutpoint values for East Asians should be adjusted, rather than using the Caucasian values (14,15,17).

Based on the considerations noted above, in this article we present an updated analysis of hip FFx prediction among older people by a DXA measure, using literature results and our own Chinese data. We argue that, if DXA is applied appropriately, the majority of hip FFx among older population can be predicted.

Methods

Estimations with literature data on the sensitivity of hip region DXA to predict short-term hip FFx

The recent literature research results described were re-used in this study (8,16,18). We systematically searched literature reports on DXA T-score results measured at the timepoint of a hip FFx. We aimed to only include studies concerning the contralateral FN/TH DXA BMD measured right after the time of fracture, and we only included reports with data for female patients and male patients described separately. Additional exclusion criteria were (I) articles concerned with patients group-wise under a specific anti-osteoporotic treatment regime; (II) articles concerned with specific types of patients such as those with diabetes mellitus type 2; (III) articles only concerned with hip re-fracture patients; (IV) articles concerned with atypical femur fracture; (V) articles concerned with femoral head subchondral insufficiency fracture; and (VI) study cohorts with fewer than ten cases. For articles from East Asia, we only included studies which used a local or an East Asian gender-specific BMD reference to calculate the T-score. We were able to identify 12 studies in English that reported both women's and men's

Table 1 Various T-score cutpoint values applied in this study

Populations	Only FN T-score	FN or TH T-score	only TH T-score[#]	LS T-score
Caucasian females	≤–2.5[a]	The lowest ≤–2.5	≤–2.2[c#]	≤–2.5
East Asian females	≤–2.7[b]	The lowest ≤–2.7	≤–2.4[d]	≤–3.7[b]
Caucasian males	≤–2.0[c]	The lowest ≤–2.0	≤–1.7[e]	≤–2.0 (tentative)[g]
East Asian males	≤–2.1[c]	The lowest ≤–2.1	≤–1.8[f]	≤2.5 (tentative)[h]

[#], TH T-score is usually measured approximately 0.3 higher than FN T-score. When TH T-score is reportedly alone, the osteoporosis threshold should be 0.3 higher than FN T-score. [a], according to 1994 WHO definition (1). [b], see (15). [c], osteofrailia threshold, ≤–2.0 for Caucasian males and ≤–2.1 for East Asian males, see (16). [d], –2.4 is 0.3 higher than -2.7, see (16). [e], –1.7 is 0.3 higher than –2.0, see (16). [f], ≤–1.8 is 0.3 higher than –2.1, see (16). [g], tentatively ≤–2.0, as conventional LS osteoporosis T-score of –2.5 is the same as FN osteoporosis T-score of –2.5, see discussion in (16). [h], we have estimated that, Chinese male LS osteoporosis T-score of –3.2 is equivalent to Caucasian male LS osteoporosis T-score of –2.5 (15), thus, East Asian male LS osteofrailia T-score should be lower than Caucasian male LS osteofrailia T-score of –2.0, an East Asian male LS osteofrailia T-score of –2.5, approximately being equal to 3.2*(2/2.5), is taken and tested in this study. Caucasian LS T-scores are not actually used in this study, they are listed in this table for reference. TH, total hip; FN, femoral neck; LS, lumbar spine.

FN and/or TH T-score data separately (19-30). The report of Wilson *et al.* (29) had been noted to be an outlier [see (16)] and thus excluded. All included Caucasian data were from Europe or Turkey.

The estimation was based on the reported T-score data (mean, number of cases, SD or 95% confidence interval) and assuming the normal distribution of T-score measures. The report of Yeo *et al.* (30) only described mean values and range and was thus further excluded. The first question was: if a hip region DXA measure were taken shortly before the FFx accident, how many percentages of the hip FFx could be predicted? For this, the reported T-score data at the timepoint of hip FFx were used, and the DOP thresholds are listed in *Table 1*. The second question was: if a hip region DXA measure were taken 1 year before the FFx accident, how many percentages of the hip FFx could be predicted? For this, an approximate assumption was made that, both FN and TH T-score of the patients would be 0.02 higher than the values at the FFx timepoint value (Appendix 1) (31,32).

Chinese studies on the sensitivity of DXA examination to predict future hip FFx

Osteoporotic fractures in women (MsOS) and in men (MrOS) Hong Kong studies represent the first large-scale prospective cohort studies conducted on bone health in East Asians. At baseline, 2,000 Chinese men and 2,000 Chinese women ≥65 years were recruited from the local communities from August 2001 to March 2003, to determine the relationship between anthropometric, lifestyle, medical, and other factors with BMD measured at the hip and spine. The subjects had a baseline mean age of 72.3 years (range, 65–92 years) for men and 72.5 years (range, 65–98 years) for women. The recruitment criteria were structured so that the study results would represent similarly aged community-dwelling ethnic Chinese men and women in Hong Kong. All subjects were able to walk without assistance, without bilateral hip replacement, and have the potential to survive the duration of primary study for at least 4 years as judged by their pre-existing medical status. Men and women of similar age and from the same community-based population were investigated using the same methodology, thereby enabling a comparison of the results for men and for women. At baseline, BMD at the hip and lumbar spine (LS, L1–L4) was measured by Hologic QDR-4,500 W densitometers (Hologic, Inc., Waltham, MA, USA). Local reference data were used for the T-score calculation (33). Left lateral thoracic and LS radiographs were also obtained.

In addition to the primary studies of four years, in an observational manner, female participants were followed up for a total 8.8±1.5 years, and 69 FFx (fracture age: 82.0±5.9 years) were recorded. Male participants were followed up for a total of 9.9±2.8 years, and 63 hip FFx (mean fracture age: 82.5±5.7 years) were recorded. For these hip FFx patients, their baseline FN T-score, TH T-score, and LS T-score were extracted. As an alternative to DXA image-based vertebral fracture assessment (VFA), their spine radiographs were evaluated for osteoporotic-like vertebral fractural deformity (OLVF) (34,35). OLVF sum score (OLVFss) is a biomarker of spine bone strength. For each vertebra, according to the extended semi-quantitative VFA scheme, a score of 0, –0.5, –1, –1.5, –2, –2.5, and –3 was assigned for

Table 2 Prediction sensitivity of hip FFx when a hip region DXA measure is taken, and FN T-score or hip T-score is considered (not both considered)

Data source	Sex	n	FN				Hip			
			T-score	SD	*Prediction-1*	*Prediction-2*	T-score	SD	*Prediction-1*	*Prediction-2*
Li *et al*. (19)	Female	268					–3.10	0.98	75.5%	74.6%
	Male	92					–2.60	1.29	71.2%	71.2
Zhu *et al*. (20)	Female	28	–3.8	1.4	87.5%	85.7%				
Gani *et al*. (21)	Female	350	–3.22	0.89	72.8%	72.0%	–3.09	1.01	76.1%	75.6%
	Male	162	–2.73	0.90	76.5%	75.6%	–2.43	0.97	72.5%	72.5%
Lee *et al*. (22)	Female	819	–2.87	0.92	60.8%	59.8%				
	Male	271	–2.02	1.12	46.9%	46.4%				
Ho *et al*. (23)	Female	167					–2.67	1.055	64.1%	63.5%
	Male	72					–2.23	1.212	58.3%	58.3%
Di Monaco *et al*. (24,25)	Female	350	–2.8	0.90	60.6%	60.0%	–2.5	1.00	62.3%	60.0%
	Male	80	–2.4	0.80	77.5%	75.6%	–2.0	0.90	61.3%	60.0%
Schnabel *et al*. (26)	Female	22	–2.61	0.61	53.0%	51.5%				
Cesme *et al*. (27)	Male	20	–2.15	0.86	65%	65%	–1.81	0.79	70%	68.3%
Vlachos *et al*. (28)	Female	51					–2.76	0.90	73.9%	71.9%
	Male	19					–2.09	1.37	73.6%	73.6%

Prediction-1, assuming the DXA was taken shortly before the FFx accident. *Prediction-2*, assuming DXA was taken one year before the FFx accident, and the FN T-score or hip T-score is assumed to be on average 0.02 higher than the value measured at the time of the hip FFx incident. The report of Yeo *et al.* (29) only described mean values and range, thus their data could not be actually analysed; however, a favorable result could be anticipated with their reported FFx mean FN and TH T-score of –3.2 and –2.6 for female patients, and –2.6 and –1.9 for male patients. FN, femoral neck; TH, total hip; FFx, fragility fracture; DXA, dual-energy X-ray absorptiometry; SD, standard deviation.

no OLVF or OLVF of <20%, 20% to <25%, 25% to <33%, 33% to <40%, 40% to <67%, and ≥67% vertebral height loss, respectively (34). Two adjacent minimal OLVFs were assigned as –0.5, and three adjacent minimal OLVFs were assigned to be –1. The OLVFss is calculated by summing up the scores of vertebrae T3 to L5. For Chinese women, OLVFss ≤–1.5 suggests this subject being osteoporotic (36); for Chinese men, OLVFss ≤–2.5 suggests this subject being osteoporotic (35,37). Various combinations of DXA T-score and OLVFss were used to test their sensitivity and positive prediction value for hip FFx prediction.

Relative relevance of FN osteoporosis threshold and osteofrailia threshold among older Chinese men

For imperfect tests, the selection of a cutpoint value is always a compromise of mutual constrain of sensitivity and specificity. To capture the majority of FFx in males, we proposed osteofrailia category with FN T-score ≤2.1 for East Asians (16). Conventionally, osteoporosis criterion (FN T-score ≤–2.7 for East Asians) has been applied (15). With MrOS Hong Kong follow-up results, we tested the relationship between various baseline FN T-score groupings and the related percentage of hip FFx incidents during follow-up. Moreover, with a random selection of 802 cases with FN T-score ≤0.5 from MrOS Hong Kong study, we tested the relationship between various baseline FN T-score groupings and severity of OLVFss (baseline measures).

Results

Ten published articles with FN and/or TH T-score at the timepoint of a hip FFx were analysed, and the results are shown in *Table 2* and *Figure 1*. If a hip region DXA measure were taken shortly before the hip FFx accident (*prediction-1*), females' FN, females' TH, males' FN, or males' TH T-score osteoporosis/osteofrailia cutpoints on average predicted 66.9%, 70.4%, 66.5% and 67.8% of the hip FFx. If the DXA was taken 1 year before the hip FFx accident and assuming the T-scores were all 0.02 higher (*prediction-2*), the prediction sensitivities were only slightly inferior to *prediction-1* results (*Table 2*).

For the MsOS and MrOS Hong Kong studies, *Table 3* shows a baseline hip region DXA (a combination of FN and TH T-score) predicted >50% of the cases with a follow-up hip FFx. *Table 4* shows a combination of baseline hip region

DXA, LS DXA and OLVFss predicted 68.1% of the female cases with a follow-up hip FFx, and 63.4% of the male cases with a follow-up hip FFx. For females, LS <–3.7 predicted 23.2% of the follow-up hip FFx with a positive predictive value of 5.5%. For males, LS <–2.5 and –2.2 predicted 27.0% and 30.2% of the follow-up hip FFx with positive predictive values of 8.85%, and 6.86% respectively. Baseline LS T-score alone was inferior to hip region T-scores in prediction hip FFx. Baseline OLVFss was more useful for female patients' FFx prediction than for male patients' FFx prediction (*Table 4*, *Figure 2*).

For the Chinese men in MrOS Hong Kong study, *Figure 3* shows that when baseline FN T-score was higher than –2.1, then hip FFx prevalence was low during the follow-up period. After the baseline FN T-score was lower than –2.1,

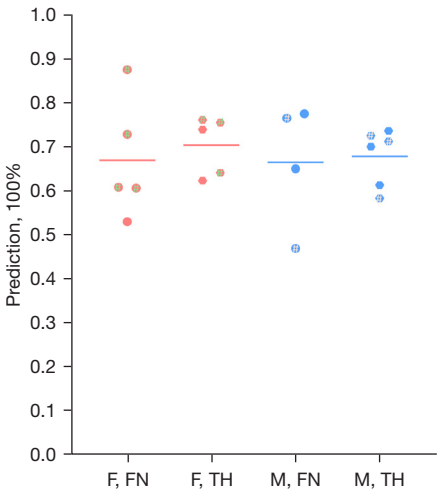

Figure 1 Hip FFx prediction sensitivity with the data shown in *prediction-1* of *Table 2*, assuming DXA was taken shortly before the hip FFx accident. Data are from Li *et al.* (19), Zhu *et al.* (20), Gani *et al.* (21), Lee *et al.* (22), Ho *et al.* (23), Di Monaco *et al.* (24,25), Schnabel *et al.* (26), Cesme *et al.* (27), Vlachos *et al.* (28). Each dot represents one study, and East Asian data marked with #. Bars: mean values, with each study giving an equal weight (i.e., sample size for each study was not weighted). F, females; M, males; FN, based on femoral neck T-score; TH, based on total hip T-score; FFx, fragility fracture.

Table 4 Sensitivity using various DXA T-scores and OLVFss, MrOS and MsOS Hong Kong studies follow-up results

Criteria	Sensitivity	
	Females	Males
FN or TH ≤–2.7, or LS ≤–3.7, or OLVFss ≤–1.5	47/69 (68.1%)	
OLVFss ≤–1.5	30/69 (43.5%)	
FN or TH ≤–2.1, or LS ≤–2.5, or OLVFss ≤–2.5		40/63 (63.4%)
OLVFss ≤–2.5		27/63 (27.0%)

OLVFss, osteoporotic-like vertebral fractural deformity sum score; FN, femoral neck T-score; TH, total hip T-score; LS, lumbar spine T-score; DXA, dual-energy X-ray absorptiometry; MrOS, osteoporotic fractures in men; MsOS, osteoporotic fractures in women.

Table 3 Sensitivity and positive prediction values using various DXA T-score thresholds, MrOS and MsOS Hong Kong studies follow-up results

Criteria	Females		Males	
	Sensitivity	Positive prediction values	Sensitivity	Positive prediction values
FN ≤–2.7	33/69 (47.8%)	33/337 (9.79%)		
FN or TH ≤–2.7	35/69 (50.7%)	35/437 (8.01%)		
FN or TH ≤–2.7, or LS ≤–3.7	36/69 (52.2%)	36/546 (6.59%)		
LS ≤–3.7	16/69 (23.2%)	16/291 (5.50%)		
FN ≤–2.1			29/63 (46.0%)	29/306 (9.47%)
FN or TH ≤–2.1			34/63 (54.0%)	34/358 (9.50%)
FN or TH ≤–2.1, or LS ≤–2.5			38/63 (58.5%)	38/424 (8.96%)
LS ≤–2.5			17/63 (27.0%)	17/192 (8.85%)
LS ≤–2.2			19/63 (30.2%)	19/277 (6.86%)

FN, femoral neck T-score; TH, total hip T-score; LS, lumbar spine T-score; DXA, dual-energy X-ray absorptiometry; MrOS, osteoporotic fractures in men; MsOS, osteoporotic fractures in women.

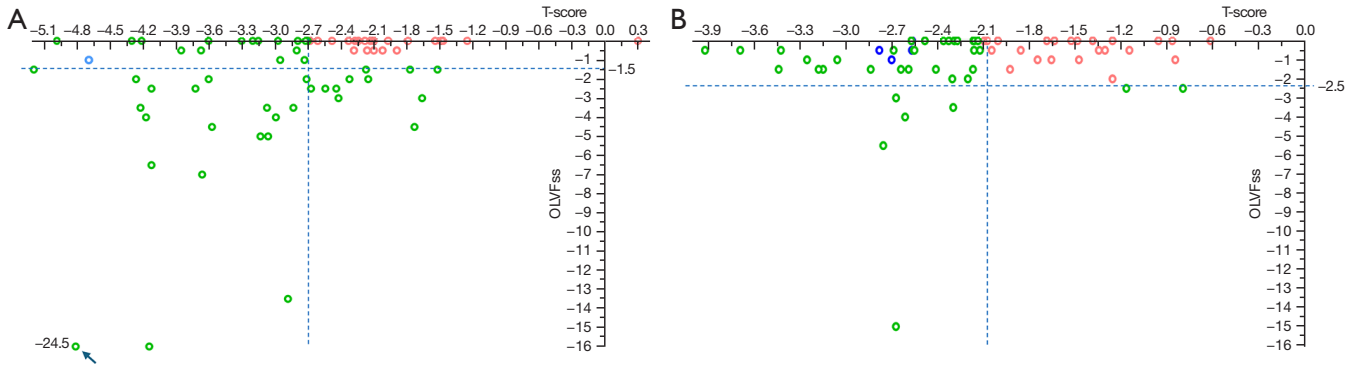

Figure 2 MsOS (A) and MrOS (B) Hong Kong studies, prediction of hip FFx during the follow-up period based on a combination of baseline measures of FN T-score, TH T-score, LS T-score, and OLVFss. Only the cases with a follow-up hip FFx are presented. (A) For the X-axis, cases with FN T-score ≤2.7 were firstly selected and presented; after that, if FN T-score was >2.7, the cases with TH T-score ≤2.7 were selected and presented, then LS T-score ≤3.7 were selected and presented if both FN and TH was >2.7. For the remaining cases did not meet these criteria, the FN T-scores were presented. The sample principle as in (A) was applied in (B). Osteoporotic/osteofrailia cases by either FN T-score or TH T-score ≤2.7 (≤−2.1 for males), or LS T-score ≤3.7 (≤−2.5 for males) or OLVFss (≤1.5 for females and −2.5 for males) are labeled as green (based on FN T-score or TH T-score) or blue (based on LS T-score). Non-osteoporotic/osteofrailia cases are labeled as red. Blue dotted lines: demarcation for osteoporosis threshold for women or osteofrailia threshold for men. OLVFss, osteoporotic-like vertebral fractural deformity sum score; FN, femoral neck; LS, lumbar spine; TH, total hip; FFx, fragility fracture; MrOS, osteoporotic fractures in men; MsOS, osteoporotic fractures in women.

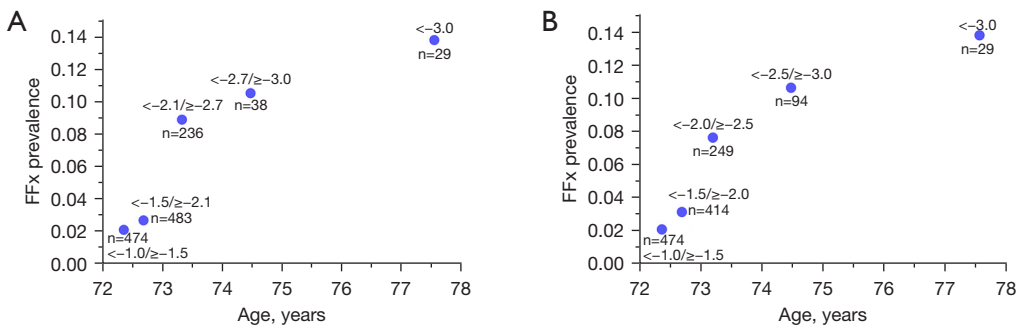

Figure 3 Hip FFx prevalence (Y-axis) among Chinese men associated with various groupings (A,B) of baseline FN T-score (blue dots). Data are from MrOS Hong Kong study follow-up results for males (n=1,260 cases with FN T-score <−1). X-axis is the mean age for each FN T-score grouping. FFx, fragility fracture; FN, femoral neck; MrOS, osteoporotic fractures in men.

hip FFx prevalence increased substantially. After the FN T-score was lower than −2.7, hip FFx prevalence increased further but only relatively slightly. Note that FN T-score ≤−2.1 predicted 46.0% (29/63) of male hip FFx cases, while FN T-score ≤−2.7 predicted only 15.9% (10/63) of male hip FFx cases (16). Therefore, the hip FFx prediction sensitivity analysis did not suggest a −2.7 (or −2.5) to be a favorable threshold. *Figure 4* shows that, with FN T-score decreased from −2.0 to −3.0, there was not an accelerated increase in OLVF severity, though a lower FN T-score is associated with an overall higher OLVF severity (i.e., lower OLVFss values). However, *Figure 4* suggests the possibility of an accelerated increase in OLVF severity after the FN T-score was lower than −3.0, and this was consistent with the data in *Figure 3* that FN T-score lower than −3.0 (together with a more advanced age) was associated with a further elevated hip FFx risk.

Discussion

Among all FFx, hip fracture incurs the greatest morbidity, mortality, and costs. Though the prevalence of hip FFx is

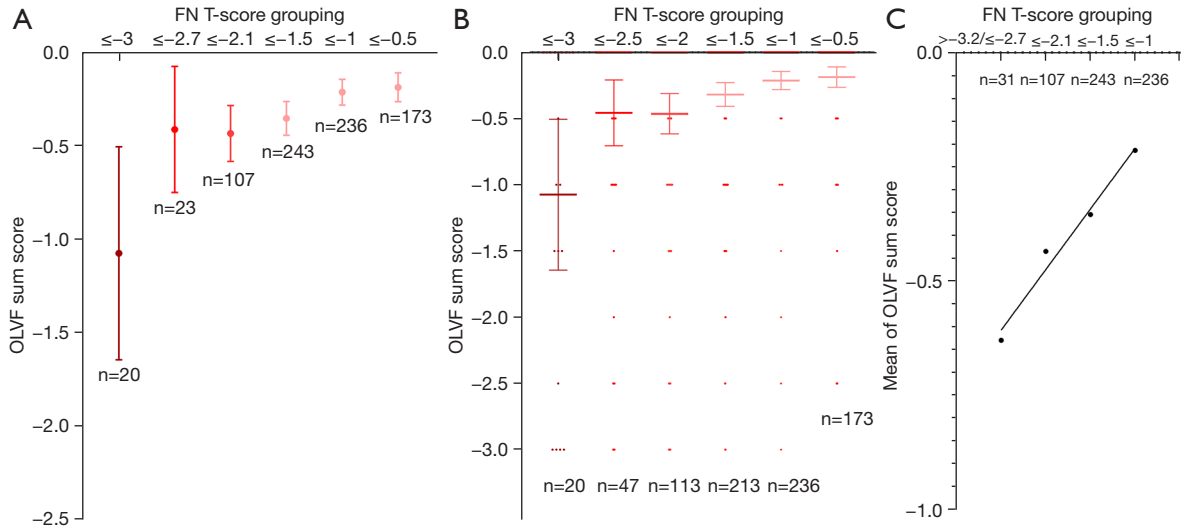

Figure 4 Relationships between various groupings of FN T-score (X-axis) and the severity of OLVFss (Y-axis) among Chinese men. Data are from MrOS Hong Kong study baseline data for males with FN T-score ≤−0.5 (total n=802 cases). (A,B) Mean and 95% confidence interval with scatter plot; (C) a linear fitting is taken. FN, femoral neck; OLVFss, osteoporotic-like vertebral fractural deformity sum score; MrOS, osteoporotic fractures in men.

lower among men than among women, multiple reports described that, once hip FFx occurs, the post-fracture mortality is substantially higher among men than among women (38-41). In addition, some studies suggest that males tend to suffer from hip FFx at a younger age than females [reviewed in (16)]. Thus, it is important to identify hip FFx high risk populations both for females and for males. Other 'major osteoporotic fractures' include those of distal forearm and proximal humerus and vertebral. However, traumatological literature shows that distal forearm, proximal humerus and vertebral fractures can also occur in young subjects with normal bone strength and with low energy trauma (35,42-46). For example, Lindau *et al.* (42) and Brogren *et al.* (43) described that, among young subjects, a notable portion (approximately 30%) of the distal forearm fractures was due to low energy trauma. Wong (44) and Rose *et al.* (45) described that, among young subjects, a notable portion (also approximately 30%) of the humeral fractures was due to low energy trauma. It has been well documented that low-energy trauma induced vertebral deformities are common among young subjects with normal bone strength (35,46). Compared with the cases of hip fracture, distal forearm fracture occurs at 'younger' age and 'higher' BMD (8,47). Compared with the cases with hip fracture, distal forearm fracture and proximal humerus are more likely to be associated with a 'higher' energy level (*Figure 5*). A fall involving a hip fracture is also associated with a larger 'contact surface' than a fall involving the distal forearm, and also the hip region has more soft tissues and muscles functioning as a cushion. While it is not necessary that all low-energy trauma among older population are osteoporotic fractures, hip fractures are most likely to be associated with a lower energy level, and low-energy induced hip fracture suggests that the bone strength is indeed much compromised. Thus, our working hypothesis is that *in vivo* imaging would likely be able to detect such a weakness of the femur.

In this study, *Figure 1* shows, if a hip region DXA was performed shortly before a hip FFx, then by either FN T-score *or* TH T-score, approximately 68% of the hip FFx could be predicted. Then, if a combination of FN T-score *and* TH T-score was applied, we can postulate that approximately >70% of the hip FFx might be predicted (see the related results in *Table 3*). *Table 2* further shows that, if a hip region DXA was performed 1 year prior to the hip FFx incident, a combination of FN T-score and TH T-score might still be able to predict 70% of the hip FFx incidents. *Figure 1* also suggests that, with cutpoints of T-scores used in *Table 1*, the percentages of prediction were broadly comparable for females' data and males' data, and for the FN data and TH data, tentatively suggesting the agreement among various T-score cutpoints applied in the

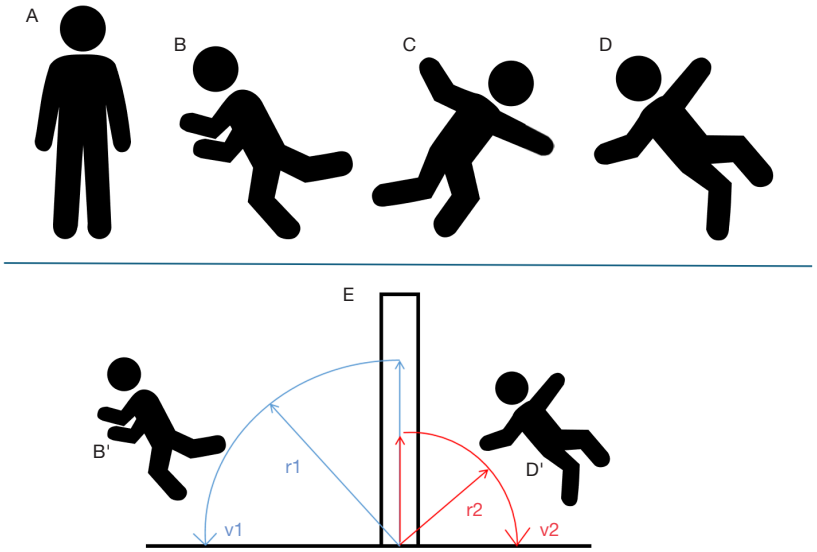

Figure 5 Compared with cases with hip fracture, distal forearm fracture is more likely associated with a 'higher' trauma energy level. (A) A standing person; (B,C) a fall will lead to a distal forearm (wrist) hitting the ground; (D) a fall will lead to a buttock hitting the ground. The net external force equals the change in momentum of a system divided by the time over which it changes. If we assume that the angular velocity is the same for a forward fall (B,C) as for a backward fall (D), since the radius r1 > r2, velocity at the impact with the ground for a forward fall (v1) will be larger than that for a backward fall (v2, v1 > v2) (E). In addition, due to the buffering of muscle and fat at the buttock, the impact time for backward fall (t2) will be larger than that of forward fall (t1, t1 < t2). Thence, the impact force for a forward fall (B', F1 = v1/t1) will be larger than that of backward fall (D', F2 = v2/t2). Reused with permission from (8).

current study. There is evidence that hip region quantitative computed tomography (QCT) is able to satisfactorily predict hip FFx only when gender-specific volumetric BMD thresholds are applied (48,49).

In this study, *Table 3* shows, for Chinese females, FN T-score alone, a combination of FN and TH T-scores, and a combination of FN, TH, and LS T-scores, can predict 47.8%, 50.7%, and 52.2% hip FFx during the 8-year observation; for Chinese males, FN T-score alone, a combination of FN and TH T-scores, and a combination of FN, TH, and LS T-scores, can predict 46.0%, 54.0%, and 58.5% during the 8-year observation. These results are likely consistent with the results in *Table 2* and *Figure 1*, as results in *Table 3* were from a long observation period. As expected, the prediction of hip FFx by only LS T-score was inferior to those of hip region DXA. For male's results, the results in *Table 2* suggest the cutpoint value of LS ≤–2.5 may be favored over LS ≤–2.2, considering the compromise between sensitivity and the positive prediction value. LS T-score of –2.5 in Chinese men would be equivalent to QCT BMD of 68 mg/mL according to our earlier analysis (14,50). *Table 4* further shows, a combination of hip region DAX, LS DAX, and OLVF assessment can predict 68.1% of the hip FFx for females and 63.4% of hip FFx for males during the 8-year observation period. *Table 3* shows OLVF analysis contributed better to females' hip FFx prediction than to males' hip FFx prediction. We have also reported that, in Chinese men, OLVF at baseline did not predict vertebral radiographical FFx during 4-year follow-up (51).

Compared with FN/TH DXA, LS DXA is inferior in predicting hip FFx which is the most important FFx. Thus, LS BMD defined DOP and hip BMD defined DOP have different clinical relevance, with hip BMD defined DOP being more clinically relevant. Currently spine QCT is more commonly conducted due to its conveniency than hip QCT, the prediction power (sensitivity and positive prediction value) of spine QCT for hip FFx shall require further studies.

In this study, the positive predictive value for hip DXA is slightly less than 10% for both Chinese women and men (*Table 3*). The current guidelines recommend that postmenopausal women and older men should be diagnosed as with osteoporosis if there is 3% or more 10-year risk for hip fracture. Positive predictive value of around 10% for FN T-score ≤2.1 for Chinese men reaches the treatment threshold (52). Note that, the relevance

of a positive predictive value is related to intervention regimens. For example, if a drug is effective, safe, and low cost, then a lower positive predictive value will be more acceptable. In the meantime, further studies to increase the sensitivity and specificity of a diagnostic imaging method for predicting hip FFx should be pursued. One simple and practically feasible approach is to improve the BMD reference database and to use a higher quality local BMD reference database (14,15,53). T-score estimation is very sensitive to the value of $SD_{\text{young adult population}}$. It has been noted that many East Asian BMD databases included relatively few participants, particularly in the young adult group, a factor that is critical in determining the statistical accuracy of the $SD_{\text{young adult population}}$ (14,15). With T-score definition being: $(BMD_{\text{patient}} - BMD_{\text{young adult mean}})/SD_{\text{young adult population}}$, to construct reliable BMD databases it is more important to sample a large number of representative young subjects. Northern Europeans and Mediterranean Europeans may better use region-specific BMD references. The hip fracture incidence rates are the highest in the Scandinavian countries particularly those of Norway, Denmark, Sweden, and Iceland, while lower among Southern Europeans (54,55). Lucas *et al.* (55) predicted that, the maximum hip fracture incidence rate (per 100,000 subjects) is 1,389.8 for Swedish women and 1,089.7 for Danish women (742.4 for Swedish men, 551.1 for Danish men), 376.0 for Portuguese women and 420.0 for Spanish women (156.9 for Portuguese men, and 195.0 for Spanish men). Among Scandinavian countries, the Finns have lower hip FFx risk. Lucas *et al.* (55) predicted that, the maximum hip fracture incidence rate was 649.5 for Finn women and 429.8 for Finn men.

Figure 3 shows that, while Chinese men with FN T-score of less than –3.0 were associated with an elevated hip FFx prevalence, there was no advantage in selecting –2.7 cutpoint value (or –2.5) over selecting –2.1 cutpoint, i.e., no advantage in substantially improved specificity at the cost of lower sensitivity. *Figure 4* also shows, while a lower FN T-sore was overall associated with lower OLVFss score, subjects with FN T-score of less than –3.0 were associated with accelerated lower OLVFss. Therefore, FN T-score ≤–3.0 might suggest '*severe*' osteoporosis among Chinese men.

There are many limitations to this study. With the literature analysis, annual loss of 0.02 T-score for hip region DXA measure was an estimation for average older populations (Appendix 1), there might be some BMD 'fast losers' among hip FFx patients. However, the results in *Tables 3,4* did not disagree with the results in *Table 2* at a group level. In the Hong Kong follow-up studies, the proportion of male hip FFx patients relative to female patients was high. It is possible that after the female participant was informed of being osteoporotic with their baseline T-scores, they might have taken some measures to lower future FFx risk, while male participants would not be informed of being osteoporotic when their baseline T-score was between –2.5 (i.e., the conventional osteoporosis cutpoint) and –2.0. If a study participant was informed that he or she was osteoporotic and then this participant took measures to lower future FFx risk, this might lower the incidences of hip FFx during the observation period, thus leading to a lower sensitivity and a lower positive predictive value for the results in *Tables 3,4*, than it would be if it was a natural experiment without any intervention. However, it was known to us that regular formal medication was not common among our study participants during the 8-year follow-up observation. Another issue is that some participants had died during the observation period. If the participants who would develop FFx had died in a higher proportion than the participants who would not develop FFx during the observation period, then the sensitivity and the positive predictive value of baseline DXA would have been under-estimated. When the Hong Kong study participants were recruited, one of the recruit criteria was that they would survive the duration of primary study for at least 4 years as judged by their pre-existing medical status. In addition, none of the participants recruited had hip fracture history before the enrolment, though the recruit criterion was that they should be '*without bilateral hip replacement*'. There was thus the possibility that our participants were somewhat healthier than the general community population. If so, then our positive predictive value might have been again underestimated. However, as a part of the Asian Osteoporosis Study (AOV), spine radiographs were compared with age-matched Thais and Indonesians in community settings, and it was noted that our Chinese participants had higher prevalence and severity of spine degenerative changes and spine fractural deformities, suggesting our participants might not be overrepresented by participants with much better bone heath (56,57). Positive predictive value is related to the observation period and FFx prevalence in a population. It is well known that, for both females and males, the hip FFx prevalence among Chinese is only half of that those of their Caucasian counterparts (15). If we extrapolate the value in the Hong Kong studies to predict older Caucasians, the positive predictive value would be higher for older Caucasians. Yet another limitation is while we were able

to register the hip FFx incidents during the observation period, the trauma energy levels were not always well defined. Johansen *et al.* (58) estimated that, for subjects aged over 80 years, 4% of hip fractures could be due to high energy trauma. It is possible that if a small portion of our cases had high energy trauma and we were able to exclude these cases, then the DXA diagnostic performance might be further slightly improved.

In conclusion, if DXA scan is regularly performed for at-risk populations, with proper selection of cutpoint T-score values, approximately 70% of the hip FFx incidents can be predicted for older women and men. Our results support regular DXA scan screening for at-risk subjects. OLVF analysis may benefit hip FFx prediction more for females than for males. While osteoporosis remains relevant as an epidemiological concept, there might be no particular benefit in maintaining the osteoporosis threshold for diagnostic DXA-screening for the at-risk older male population.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-2568/coif). Y.X.J.W. serves as the Editor-in-Chief of *Quantitative Imaging in Medicine and Surgery*. J.F.G. serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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