Mini-Review

For older women, the majority of hip fragility fractures and radiographic vertebral fragility fractures occur among the densitometrically osteoporotic population: a literature analysis

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Abstract: It has been frequently cited that '*the majority of fragility fractures (FF) occur at non-osteoporotic bone mineral density (BMD)*'. For the reports with T-score measured around the time of a hip fracture, we conducted a systematic literature search in December 2022, and resulted in 10 studies with five for Caucasian women and five for East Asian women. Femoral neck (FN) T-score was reported in five Caucasian studies and three East Asian studies, three of five Caucasian studies had a mean T-score ≤–2.5, and one study had the majority of their patients measuring a mean T-score ≤–2.5. All three East Asian studies reported a mean FN T-score ≤–2.7. Total hip T-score was reported in two Caucasian studies and three East Asian studies, the two Caucasian studies both had a mean T-score ≤–2.5, and all three East Asian studies had a mean T-score ≤–2.6. A new literature search conducted in April 2024 results in additional three studies, with results being consistent with the data described above. A trend was noted that 'younger' patients suffer from hip fractures at a 'higher' T-score. For the highly cited articles where the notion the majority of FF occur at non-osteoporotic BMD was derived from, authors reported prospective epidemiological studies where BMD was not measured at the timepoint of hip fracture, instead, BMD was measured at the study baseline. These epidemiological studies suggest that >50% of hip fractures likely occur in women with an osteoporotic FN or hip T-score. However, a pattern was seen that older men suffer from hip fracture at a notably higher T-score than older women. For the cases of radiographic vertebral FF, despite varying criteria being used to classify these FFs, the majority of female patients had spine densitometric osteoporosis. Literature shows, compared with the cases of hip fracture, distal forearm fracture occurs at a 'younger' age and 'higher' BMD, suggesting distal forearm fracture is more likely associated with a 'higher' trauma energy level.

Keywords: Bone mineral density (BMD); osteoporosis; hip fracture; osteoporotic vertebral fracture; prevalence

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Introduction

It has been frequently cited that one of the limitations of bone mineral density (BMD) measurement is that '*the majority of fragility fractures (FF) occur at non-osteoporotic BMD (T-scores >–2.5)*', compromising its role as a screening tool (1-8). We have recently conducted literature analyses and noticed that, for older women, the majority of hip FF and radiographic vertebral FF occur among the densitometric osteoporosis (DOP) population. The literature analyses are divided into three parts: (I) clinical studies when BMD was measured at the timepoint when a hip fracture occurred; (II)

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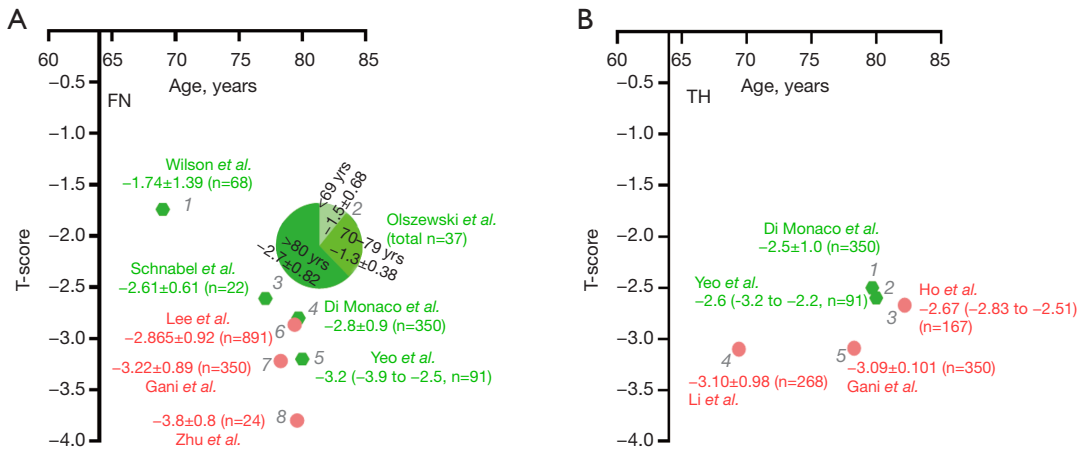

Figure 1 Distribution of T-scores of female patients with proximal femur fracture. Caucasian data in green color, East Asian data in pink color. (A) FN data, (B) TH data. A1: Wilson *et al.* (10); A2: Olszewski *et al.* (11); A3: Schnabel *et al.* (12); A4 and B1: Di Monaco *et al.* (13); A5 and B2: Yeo *et al.* (14); A6: Lee *et al.* (15); A7 and B5, [Gani *et al.* (16), non-diabetic group n=350, though the title of the article suggests only patients with severe osteoporotic hip fracture, however, according to the methodology and the T-score values, they included all low energy hip fracture patients]; A8: Zhu *et al.* (17); B3, Ho *et al.* (18); B4: Li *et al.* (19). In the study of Olszewski *et al.*; in total there were 37 patients, and the patients were divided into three age groups: <69 years (n=4, T-score =−1.5±0.68), 70–79 years (n=10, T-score =−1.3±0.38), and >80 years (n=23, T-score =−2.7±0.82). FN, femoral neck; TH, total hip.

prospective epidemiology studies of hip fracture population, where BMD was not measured at the timepoint when a hip fracture occurred; (III) retrospective or prospective studies of BMD status of radiographic vertebral FF patients, where the BMD was not known precisely when the radiographic vertebral FF occurred. In this article, we describe our literature search results.

Dual-energy X-ray absorptiometry (DXA) BMD T-score at the timepoint when a hip FF occurred

As described in detail earlier (9), on Dec 13th 2022, two structured literature searches on https://pubmed.ncbi.nlm.nih.gov/ were conducted using the keywords combination of '((hip OR femur OR femoral) AND fracture) AND T-score', and '(BMD OR T-score) AND hip fracture AND (Chinese OR Korean OR Japanese)'. The intention was to search literature for both Caucasians and East Asians. These searches generated 1,558 results and 492 results respectively. We aimed to include studies concerning DXA BMD measured around the time of fracture. Excluding 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; (VI) study cohorts with fewer than 10 cases. For articles from East Asia, we only included the studies which used a local or an East Asian BMD reference to calculate the T-score. Finally, the search resulted in ten articles that reported women's data as shown in *Figure 1* (9-19).

All Caucasian data are from Europe, and we assume that most of their older patients were Caucasians. East Asian studies were from South Korea, Singapore, Hong Kong, and China mainland. For the femoral neck (FN) T-score, three of five Caucasian studies have a mean T-score ≤−2.5, and the Caucasian study of Olszewski *et al.* (11) had the majority of their patients measuring a mean T-score ≤−2.5 (*Figure 1*). For the Caucasian study of Wilson *et al.* (10) where the mean T-score was only −1.74, this study has the feature that their study subjects were younger than most of the other studies, and this is consistent with the data of Olszewski *et al.* where 'younger' patients tended to have a 'higher' hip fracture T-score (*Figure 1*). All three East Asian studies reported a mean FN T-score ≤−2.7. For the total hip T-score, the two Caucasian studies both had a mean T-score ≤−2.5, and all three East Asian studies had a mean T-score ≤−2.6. Note that, when an East Asian BMD reference is used, the DOP cutpoint values for the T-score of FN and total hip have been recommended to be ≤−2.7

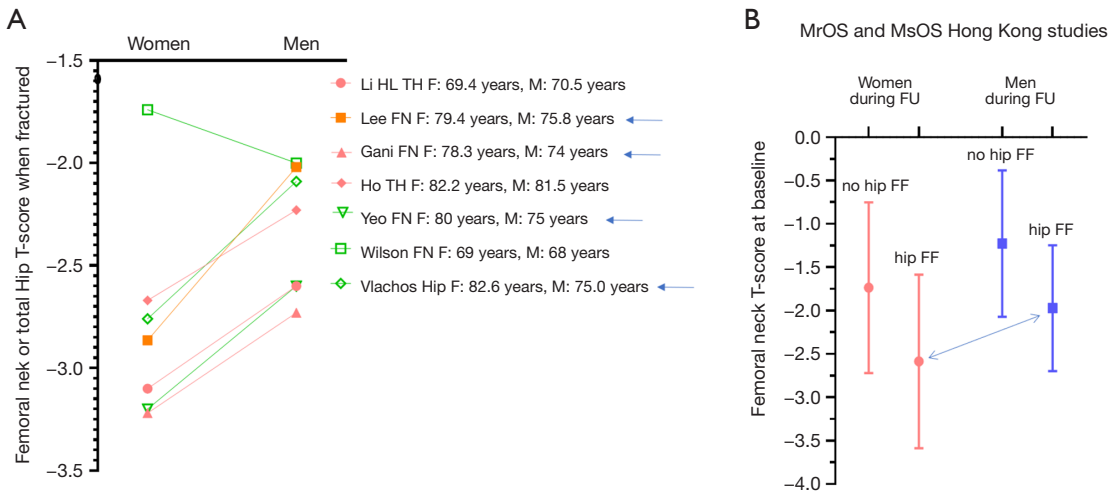

Figure 2 A comparison of FN or TH T-score of female patients and male patients. (A) Acute proximal femur fracture cases. Data are from Wilson *et al.* (10), Yeo *et al.* (14), Lee *et al.* (15), Gani *et al.* (16), Ho *et al.* (18); Li *et al.* (19), and Vlachos *et al.* (21). This graph was initially presented in (9). Except the data of Wilson *et al.*, all other six groups' data show a higher FN or TH T-score in men than in women. Yeo *et al.* and Gani *et al.* also presented TH T-score, with a similar trend shown in this graph. Arrow: male patients were younger in 4 out of 6 studies. Caucasian data in green color and East Asian data in pink color. (B) MrOS and MsOS Hong Kong studies. These are prospective studies with FN T-score measured at baseline. One thousand and nine hundred Chinese women (baseline age: 72.5 years) were followed up for 8.82±1.49 years, and 69 hip fracture were recorded. One thousand nine hundred and twenty-three Chinese men (baseline age: 72.3 years) were followed up for 9.94±2.77 years, and 63 hip fracture were recorded. The mean baseline T-score for the men with hip fracture during the follow-up was 0.61 higher than that of women with hip fracture during follow-up (blue line with double arrow heads). The mean age fracture was 82.5 years for men and 82.0 years for women. Therefore, a pattern was seen that older men suffer from hip fracture at a notably higher T-score (about 0.5–0.6 higher) than older women. The reason for this trend could be due to (I) male patients were involved with a 'higher' trauma energy level, (II) male patients tended to be younger in the study listed in graph (A); (III) osteoporosis T-score threshold for male patients should be defined higher than that of female patients. TH, total hip; FN, femoral neck; MrOS, Osteoporotic Fracture in men; MsOS, Osteoporotic Fracture in women; FF, fragility fractures; FU, follow-up.

and ≤–2.6, respectively, for Chinese women (20). Strictly speaking, unless the T-scores of the patients were normally distributed, it cannot be confirmed that a mean T-score of ≤2.5 means ≥50% of the patients were osteoporotic. However, as shown in *Figure 1*, the mean T-score value of a few studies was far below –2.5, and a few studies had relatively large sample sizes.

With the same method as stated above, on 15th April 2024, an additional literature search was conducted, and newer articles published after December 2022 were reviewed with three related articles identified. Vlachos *et al.* (21) prospectively studied DXA measurement for 70 Greek patients with hip FF in an emergency department. Among the patients, 51 were women and 19 were men, with a mean age of 82.59±7.14 years and 75.00±11.30 years, and a femoral T-score of –2.76±0.90 and –2.09±1.3, respectively (mean femoral T-score for both women and men: –2.58±1.08). Note that, the results of Vlachos *et al.* suggest men suffer from hip FF at a higher T-score than that of women, which is consistent with our earlier observation (9) (*Figure 2*). Therefore, the results of mixed male patients and female patients would have a higher T-score than the results for female patients only. Li *et al.* (22) enrolled Chinese 269 patients (82 males, 187 females) aged 78.4±7.2 years with FN fracture. FN T-score was –2.5±0.8, which was slightly higher than the ≤–2.7 DOP threshold recommended for Chinese women (20). However, it is highly likely that, if there were only female patients, then the mean FN T-score would be lower. Che *et al.* (23) conducted a retrospective analysis of 168 Korean patients who underwent surgical treatment for either an intertrochanteric or FN fracture, with intertrochanteric fracture patients (n=92, 61% females) having a mean FN T-score of –2.85±1.02 and FN fracture patients (n=76, 58% females) having a mean FN T-score

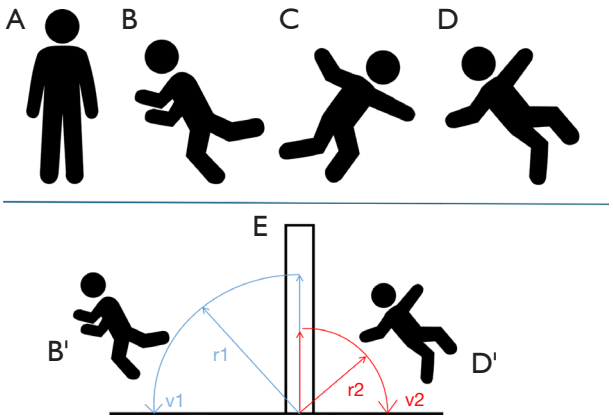

Figure 3 Compared with cases with hip fracture, distal forearm fracture is more likely associated with a 'higher' trauma energy level. (A) A standing person; (B,C) a fall will lead to a distal forearm (wrist) hitting the ground; (D) a fall will lead to a buttock hitting the ground. The net external force 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 (t, 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).

of −2.93±0.97. It is unclear whether East Asian women BMD reference T-score was used for the calculation of FN T-score. However, with these T-scores, it is likely that even a Caucasian BMD reference was used, their patients would have DOP after the adjustment with an East Asian BMD reference and if their cohort only included female patients.

Distal forearm fracture is more likely associated with a 'higher' trauma energy level

During our literature review, we also noticed that, compared with the cases of hip fracture, distal forearm fracture occurs at 'younger' age and 'higher' BMD, suggesting that distal forearm fracture is more likely associated with a 'higher' energy level.

Boschitsch *et al.* (24) described the results of a large retrospective analysis with 99,399 women referred to a menopause and osteoporosis clinic for BMD measurements. The mean age was 56.08 years (range, 40–98 years), and 78,283 women (78.8%) were younger than 65 years. A total of 6,540 patients (6.6% of the total study population) reported having suffered one or more FF in the past (and also reported the date of fracture). Of these, 3,070 (3.1% of the total population or 47% of fractured patients) had experienced an FF of the distal forearm (82%) or the hip (18%). The distal forearm was the predominant fracture site of all FF sites, and with 69.8% occurring in women aged <65 years and 30.2% occurring in women aged ≥65 years. For DOP (T-score ≤−2.5), the lower of either the spine or the hip T-scores was used for classification. Among the distal forearm fracture cases, 0.30% (756/2,518) had normal BMD, 34.91% (879/2,518) had osteopenia, and 35.07% (883/2,518) had DOP.

In the study of Boschitsch *et al.* (24), patients with hip fracture were older than those with distal forearm fracture (68.5±10.9 *vs.* 64.7±10.49 years). Among all hip fracture cases, 16.3% (90/552) patients had normal BMD, 27.36% (151/552) had osteopenia, and 56.34% (311/552) had DOP. For patients <65 years, similar proportions of hip FF occurred in women with normal (32.9%), osteopenic (35.2%) and osteoporotic (31.9%) BMD. These hip FF data are consistent with *Figure 1*. While among general female populations, most hip FF occur in later 70 years and early 80 years (9, 21) (*Figure 1*), the data of Wilson *et al.* (10) and Olszewski *et al.* (11) also suggested 'younger patients' suffer hip fracture at a 'higher' T-score.

A pattern noted in the study of Boschitsch *et al.* (24) is that, compared with the cases of hip fracture, distal forearm fracture occurred at a younger age and with higher BMD. With this study, the ratio of the distal forearm fracture to hip fracture is 4.56 (2,518/552, patients mean age: 64.7 years for distal forearm fractures and 68.5 for hip fractures), this ratio is much higher than other studies focusing on older patients (25-27). Also note that, in the study of Boschitsch *et al.*, when both a forearm fracture and a hip fracture occurred in one patient, then this distal forearm patient was counted as a hip fracture patient. We argue that not all their distal forearm fractures were typical osteoporotic fractures. Compared with the cases with hip fracture, distal forearm fracture is more likely to be associated with a 'higher' energy level (*Figure 3*). It is likely that, for some forearm fractures, trauma energy would be close to the upper limit of 'low energy trauma' which is defined as the energy level of a fall from standing height or less. 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. Hayhoe *et al.* (26) studied the proportions of hip, wrist, and clinical vertebral fractures for a UK population (n=3,678, mean age: 70.4±3.3 years) and a Hong Kong population (n=1,979, mean age: 72.4±5.0 years). In the UK cohort, hip fractures accounted for the largest proportion of fractures (56.8% in men and 52.6% in women); and wrist fractures made up the smallest proportion, particularly in men (9.1% in men and 20.7% in women). By contrast, in the Hong Kong cohort wrist fractures accounted for the largest proportion (42.9% in men and 57.9% in women); hip fractures made up 37.7% in men and 19.8% in women. Hip fracture rate was significantly higher in UK women relative to Hong Kong women (8.24 *vs.* 2.67 per 1,000 person-years). Clinical vertebral FF rate was also higher in the UK women relative to Hong Kong women (4.14 *vs.* 1.94 per 1,000 person-years). By contrast, the wrist fracture rate was lower in the UK women relative to HK women (3.12 *vs.* 4.22 per 1,000 person-years). In a study comparing Hong Kong older female population (n=200, mean age: 74.1 years) and age-match Italian Caucasian older female population (n=200), it was also noted that despite much higher hip fracture rate (10% for Italians, 0% for Chinese) and radiographic vertebral FF rate among Italians (46% for Italians, 26.5% for Chinese), forearm fracture rate was higher among Chinese women than among Italian women (11.5% *vs.* 6.5%) (27). It has been well noted that, compared with Caucasians, Chinese women and men have an overall much lower FF prevalence (20,28). The relatively higher wrist fracture rate among Chinese women cannot be fully explained by bone fragility, some of the wrist fractures among Chinese women were likely not osteoporotic fracture, the same as the distal forearm fractures in the 'relatively young' patients in the study of Boschitsch *et al.* (24).

Lashin and Davie (29) studied a total of 186 British women over 50 years consecutively referred with distal forearm fracture over one year without exclusion criteria. The 50–64, 65–74, and ≥75 years age group had FN T-scores of −1.02±1.0, −1.35±1.07, and −1.36±1.08, respectively, according to a local BMD database. Eight percent, 10%, and 28% had DOP according to NHANES III (the Third National Health and Nutrition Examination Survey of USA) BMD database. Lashin and Davie concluded that women with wrist fracture under 65 years are unlikely to have BMD low enough to merit treatment and do not require routine scanning. Treatment of women over 75 years with wrist fracture without DXA measure results in overtreatment. Jung *et al.* (30) studied 260 Korean female patients with distal radius fractures, with controls being age-matched Korean women without FF. Patients were divided into three groups by age: group 1 (50–59 years, patient n=71, control n=599), group 2 (60–69 years, patient n=93, control n=894), and group 3 (70–79 years, patient n=42, control n=313). While the BMD values in groups 2 and 3 were lower than those of controls, these differences were not statistically significant. FN BMD was significantly lower in group 1 than those of control (P<0.001), but not the lumbar spine (LS) BMD. In none of the three groups, the prevalence of LS or FN DOP was higher among the patient group than the control group.

DXA T-score status of hip FF patients: prospective epidemiological studies

It appears that the notion that the majority of FF occurs at non-osteoporotic BMD largely derives from a few highly cited epidemiological studies (31-34). In this article, we analyse these highly cited studies.

For the majority of prospective epidemiological studies, BMD was not measured at the timepoint of hip fracture, instead BMD was measured at the study baseline. At the actual timepoint of fracture during the follow-up, the BMD value would likely be lower than the baseline value. Wainwright *et al.* (31) reported the incident fracture cases recorded during five years' follow-up in the Study of Osteoporotic Fractures (SOF) with 6,252 women aged ≥65 years at baseline. During 5 years of observation, 243 participants experienced a new hip fracture. Among the women with incident hip fracture, the median age at baseline was 77 years (range, 67–95 years). The mean time of observation from BMD measurement to fracture was 2.8±1.4 years. Approximately 46.1% (112/243) had hip DOP at baseline. In a further follow-up of the SOF reported by Hillier *et al.* (32), over 10 years 368 hip fractures were observed. Among these 368 cases, 178 (48.4%), 176 (47.8%), 14 (3.8%) were observed in baseline osteoporotic, osteopenic, and normal FN BMD subjects. For the data of Wainwright *et al.*, if the analysis is restricted to the hip FF cases identified during the first 2 years of follow-up, then 51% of the 76 hip fracture cases had baseline hip DOP. It is highly likely that >50% of all hip FF cases described by Wainwright *et al.* and Hillier *et al.* actually had hip DOP when the fracture occurred. In our osteoporotic fractures in women (MsOS) Hong Kong study [materials see (33), T-scores re-calculated with local Hong Kong women BMD reference], 1,900 Chinese women were followed up for 8.82±1.49 years, and 69 hip fractur were

recorded. The mean baseline age was 76.34±4.93 years and the mean baseline FN T-score was –2.59±1.00 for the subjects who suffered hip fracture (n=69), and the mean baseline age was 72.39±5.22 years and the mean baseline FN T-score was –1.74±0.98 for the subjects did not suffer hip FF (n=1,931). 52.2% of the subjects with hip FF during the follow-up had a T-score ≤–2.5 at baseline. It is highly likely that the majority patents had a T-score ≤–2.7 (i.e., the recommended DOP threshold for Chinese women) when the hip fracture occurred.

Some other epidemiological studies reported most of the cases with hip fracture occurred during the follow-up had DOP at baseline (34-36). Sanders *et al.* (34) reported the incident fracture cases recorded during two years' follow-up in the Geelong Osteoporosis Study. Of 1,224 women aged >50 years and sustained fractures, the median age of fracture was: 73 years for pelvis fracture, 78 years for hip fracture, 70 years for rib fracture, 71 years for clinical vertebral fracture, 72 years for upper arm fracture, 65 years for foot fracture, 70 years for Colles fracture, 68 years for other forearm fracture, 67 years for ankle fracture, 68 years for lower leg fracture, and 65 years for other fracture grouped. DOP was defined according to LS and/or FN T-score. The prevalence of baseline DOP was highest among women with hip and pelvic fractures (71% and 80%, respectively). The proportion of women with clinical vertebral FF having baseline DOP was 65%. The proportion of women with forearm fracture having baseline DOP was 41% thus being low, which is consistent with the discussions above. The Rotterdam study of Schuit *et al.* (35) included 3,357 women aged ≥55 years and examined the relationship between baseline FN BMD and fracture incidence. After a mean follow-up time of 6.8±2.3 years, 211 hip FFs were recorded, with 63.8%, 31.0%, and 5.2% observed in baseline osteoporotic, osteopenic, and normal BMD subjects. Schott *et al.* (36) reported a study of older French population, with 7,698 women aged ≥75 years followed-up for two years. During the follow-up, 154 women suffered a hip fracture. The baseline mean FN T-score was –2.90 for those who suffered a hip fracture, and –2.32 for those who did not suffer a hip fracture. 75.3% of the hip fracture subjects had a baseline FN DOP.

The analyses in the paragraphs above suggest that, the majority of hip fractures occur in the female population with DOP. However, hip FF in 'younger' women (e.g., <70 years) likely occur with a non-osteoporotic T-score (7,10,11,24). This can be at least partially due to that, around of the age of later 70 years old and early 80 years old, around 35% the female population have hip DOP. On the other hand, before 69 years, only around 5% of the female population have hip DOP. The proportion of US Caucasian women with hip DOP is estimated to be 3.9%, 8.0%, 24.5%, and 47.5%, for the age bands of 50–59, 60–69,70–79, ≥80 years, respectively (37,38).

BMD status of radiographic vertebral FF patients

For radiographic vertebral FF, till now most of the reports did not use a diagnosis criterion which allow reliable inter-study comparison (39). We routinely use the term 'osteoporotic-like vertebral fracture (OLVF)' to reflect the uncertainty of radiographic vertebral FF during the diagnosis procedure (40). In our recent approach (41,42), for each vertebra in an older woman, a score of 0, –0.5, –1, –1.5, –2, –2.5, and –3 is assigned for no OLVF or OLVF of <20%, ≥20–25%, ≥25–33%, ≥33–40%, ≥40–67%, and ≥67% vertebral height loss, respectively. An OLVF sum score (OLVFss) is calculated by summing up the scores of vertebrae T1 to L5. If osteoporosis prevalence is estimated according to the lowest of FN, total hip, or LS T-scores, statistically, for older women, a radiographic vertebral FF is considered to be existent when OLVFss ≤–1. If osteoporosis prevalence is estimated according to FN T-score only, a radiographic vertebral FF is considered to be existent when OLVFss ≤–1.5 (42). In one study, our own results suggest majority of Italian Caucasian women with radiographic vertebral FF had DOP (42) (*Figure 4*).

There have also been numerous other reports that 'radiographic vertebral FF' occurs in DOP women. A random selection of eight studies on radiographic vertebral FF is shown in *Figure 5* (43-50). *Figure 5A* is a prospective study with baseline spine quantitative computed tomography (QCT) measure, while *Figure 5B-5H* are cross-sectional studies. All these 8 studies show most of the subjects with radiographic vertebral FF had LS DOP, or mean LS DXA T-score below –2.5, or a mean QCT BMD below 80 mg/mL for Caucasian women and a mean QCT BMD below 45 mg/mL for Japanese and Chinese women [45–50 mg/mL is our recommended QCT LS BMD threshold for classifying DOP among East Asian women (51,52)], despite varying criteria were used to classify radiographic vertebral FF including Genant semi-quantitative approach, algorithm-based qualitative approach, and morphometric approach. This trend appears to be more apparent with QCT results than the DXA results. Moreover, we anticipate that, statistically,

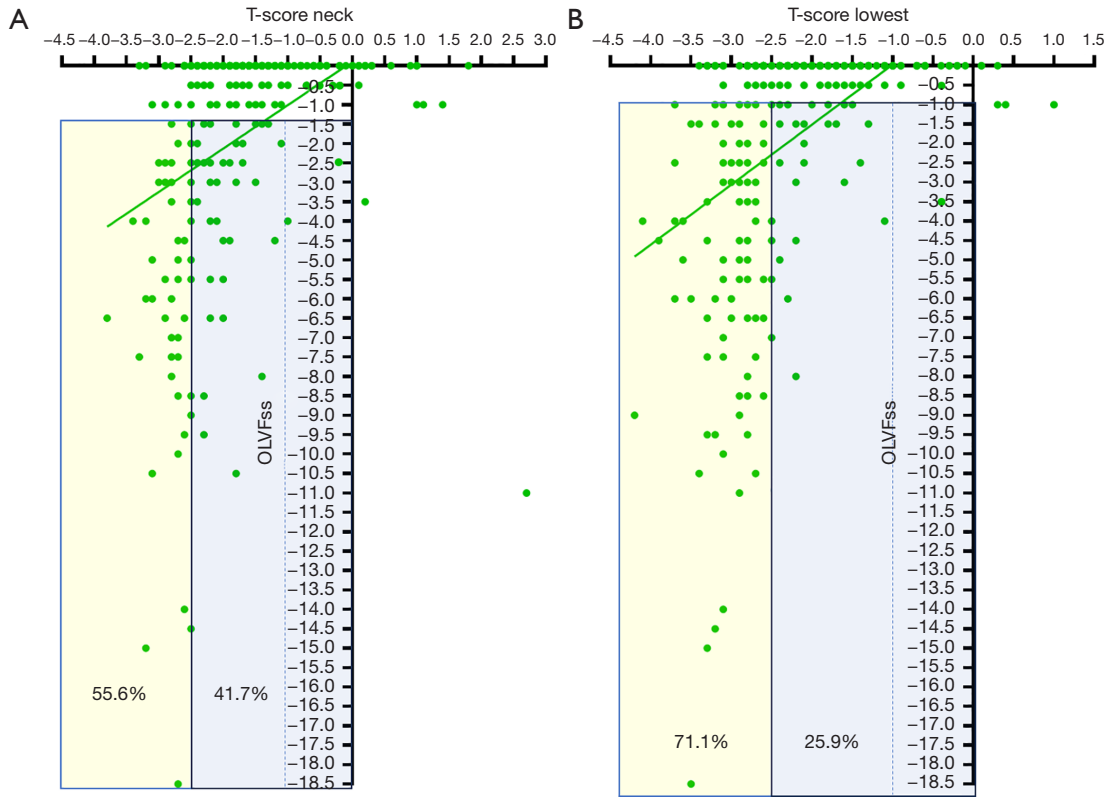

Figure 4 The correlation between OLVFss and femoral neck T-score (A) or lowest T-score of femoral neck, total hip, or lumbar spine T-scores (B). In A, radiographic vertebral FF is statistically diagnosed when OLVFss is ≤–1.5. Approximately 55.6% of the vertebral FF cases have femoral neck densitometric osteoporosis. In B, radiological vertebral FF is statistically diagnosed when OLVFss is ≤–1.0. 71.1% of the vertebral FF cases have densitometrical osteoporosis considering the lowest T-score. Of 301 women, 80 cases had DXA densitometric osteoporosis according to femoral neck T-score ≤–2.5, among them 85% (68/80) had OLVFss ≤–1.0, and 75% (60/80) had OLVFss ≤–1.5. Moreover, 135 cases had densitometric osteoporosis according to the lowest T-score ≤–2.5, among them 71% (96/135) had OLVFss ≤–1.0, and 62.2% (84/135) had OLVFss ≤–1.5. Data from Wáng *et al.* (42), with in total 301 Italian community Caucasian women (mean age: 73.6±6.1 years). OLVFss, osteoporotic-like vertebral fracture sum score; FF, fragility fractures; DXA, dual-energy X-ray absorptiometry.

some of these labelled vertebral FFs could have been false positive cases, as vertebral fracture-shaped deformities including endplate depression can exist even in subjects of normal bone strength (53,54). As osteophyte, endplate sclerosis, etc, will artificially increase spine DXA measure, LS BMD is probably better measured with QCT. In the study of Löffler *et al.* (43) (*Figure 5A*), the mean LS DXA T-score was –2.2±1.8 (QCT BMD: 56.7±31.6 mg/mL, i.e., osteoporotic value) for subjects had incident vertebral FF during follow-up (median: 2.6 years), and DXA T-score –1.6±1.7 (QCT BMD: 93.3±41.7 mg/mL) for subjects did not have incident vertebral FF during follow-up. In the study of Paggiosi *et al.* (46) (*Figure 5E*), for DXA measure, the mean LS T-score was –2.39±0.12 for group 1 (with low DXA BMD, T-score ≤–1 plus with radiographic vertebral FF), –2.2±0.13 for group 2 (with low DXA BMD without radiographic vertebral FF), and +0.24±0.12 for group 3 (normal DXA BMD without radiographic vertebral FF), respectively; whereas QCT LS BMD was 71.84±38.09 mg/mL (i.e., osteoporotic value) for group 1, 97.59±23.44 mg/mL for group 2, and 123±22.26 mg/mL for group 3, respectively. *Figure 5C,5D* also show that QCT allows a better identification of radiographic vertebral FF subjects with LS DOP. However, it should be noted that the precise BMD status was not known when these radiographic vertebral FFs occurred.

Note that as described above, in the Geelong Osteoporosis Study where the incident fracture cases were recorded during two years' follow-up, the proportion of women with clinical vertebral FF having baseline

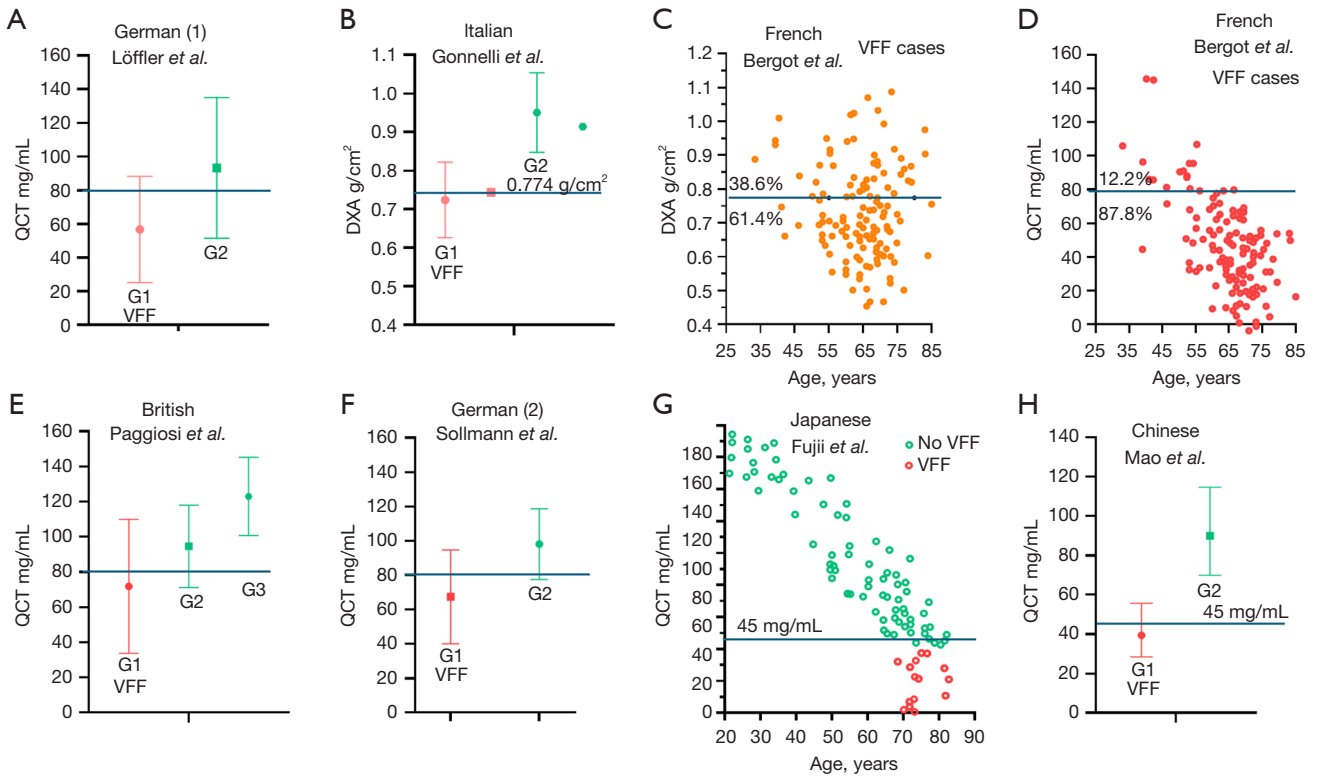

Figure 5 The majority of older women with radiographic VFF are densitometrically osteoporotic for lumbar spine. (A) A German prospective study of 84 patients aged 50 years and older (67 being female, mean age unspecified but likely to be around 70 years, assumed predominantly Caucasians). Over a median follow-up of 2.6 years, 16 (19%) sustained an incident VFF. Patients with incident VFF had a lower mean QCT spine BMD of 56.7±31.6 mg/mL than patients without incident VFF with a mean QCT spine BMD of 93.3±41.7 mg/mL. (B) An Italian cross-sectional study of 304 postmenopausal women (age 58.8±5.5 years). Subject with VFF had a spine DXA BMD of 0.724±0.098 g/cm^2, while those without VF had a BMD of 0.951±0.103 g/cm^2. Red squares denote the threshold to diagnose spine osteoporosis (0.774 g/cm^2), and green dot denotes the population mean for older Italian women (43). All data in B refer to Hologic scanners. (C) For spine DAX measure and (D) for spine QCT measure are from one cross-sectional study of French Caucasian women. (C) shows 61.4% of the subjects with VFF are in the DXA osteoporotic range, while 38.6% are not in DXA osteoporotic range. The threshold to diagnose osteoporosis is also considered to be 0.774 g/cm^2 (Hologic scanner, 50). (D) shows 87.8% of the subjects with VFF are in the QCT spine osteoporotic range, while 12.2% are not in QCT spine osteoporotic range. (E) is an UK cross-sectional case-control study for age-matched postmenopausal women with and without VFF (assumed predominantly Caucasians). G1: subjects (n=39, mean: 68.9 years) with low DXA BMD (T-score ≤–1) plus with VFF. G2: subjects (n=34, mean: 69.9 years) with low DXA BMD without VFF. G3: subjects (n=37, mean: 68.9 years) with normal DXA BMD without VFF. (F) is a study of a mixed-sex group of 88 German men and women (the majority being female, mean age unspecified but likely to be around 70 years, assumed predominantly Caucasians). 69 patients had VFF (G1), and 19 patients did not have VFF (G2). (G) 91 Japanese women of varying ages, with 20 of them having VFF. (H) Chinese women with VFF (G1, n=198, age mean: 68.0 years; range, 61.0–75.0 years) and sex- and age-matched controls without VFF (G2, n=198). For Caucasian women, the spine QCT threshold to classify osteoporosis is 80 mg/mL. For East Asian women, a threshold of 45 mg/mL is used to classify osteoporosis. Results of (A,B,E,F) are expressed as mean and standard deviation. Results of (H) are expressed as mean and ranges. German data-1 (A) re-plotted from Löffler *et al.* (44). Italian data (B) re-plotted from Gonnelli *et al.* (45). French data (C,D) re-plotted from Bergot *et al.* (46). UK data (E) re-plotted from Paggiosi *et al.* (47). German data-2 (F) re-plotted from Sollmann *et al.* (48). Japanese data (G) re-plotted from Fujii *et al.* (49). Chinese data (H) re-plotted from Mao *et al.* (50). QCT, quantitative computed tomography; VFF, vertebral fragility fracture; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry.

osteoporosis was 65% (34).

Results of a random selection of other recent reports

During the course of our literature search, we also read some articles which are related, but not strictly in line with our search criteria. A few recent results of these articles are listed below.

Li *et al.* (55) investigated the fracture predictive value of QCT-based trabecular BMD of thoracic vertebrae derived from coronary artery calcium scan for hip fractures in the Multi-Ethnic Study of Atherosclerosis (MESA), a nationwide multi-center cohort included 6814 people from six medical centers across the USA. At baseline participants had a mean age of 62.2±10.2 years, and 52.8% were women, 27.6% of participants (n=1,883) had osteoporosis (T-score ≤–2.5). Over a median follow-up of 17.4 years, in non-osteoporotic participants, 174 had radiographic moderate to severe compression vertebral fractures and 21 had hip fracture. In osteoporotic participants, 171 had radiographic moderate to severe compression vertebral fractures, and 50 had hip fracture. However, this was a mixed-sex cohort, authors used a T-score derived from thoracic vertebrae CT scan, and the baseline osteoporosis prevalence defined by the QCT approach appears to be quite high.

Oteo-Álvaro *et al.* (56) described a retrospective case-control study using data in a Spanish hospital bone metabolism unit. All patients (n=955) were referred to rule out metabolic bone diseases, and divided into two groups defined by the presence or absence of an FF after the age of 50 years (case group n=326, and control group n=629). The case group had a mean age of 69.8±10.5 years and 87.7% were females. The most frequently recorded FF were clinical vertebral fractures (66.26%), followed by distal radius (18.09%), proximal humerus (9.81%), and hip fractures (7.67%). The mean LS T-score was –2.6, and the mean FN T-score was –2.2. Considering distal radius (18.09%) likely suffers from facture at a higher T-score, it is likely that, if we excluded male patients and those with distal radius fracture, the majority of remaining female patients would have DOP.

Marchasson *et al.* (57) reported a French study with patients after recent FF. For their non-obese patients (n=577, 78.5% women; mean age 74.5±11.4 years), the fracture sites included: vertebrae 48.9%, hip 20.8%, pelvis 8.3%, proximal humerus 6.6%, wrist 7.6%, ankle/leg 4.8%. Forty-nine and a half percent (245/495) of these patients had DOP. For their (total) patients, 22.4% had anti-osteoporosis medication, 23.3% did not have BMD measured and some of the missing data were due to the presence of bilateral hip prostheses (thus the lowest BMD cases might had been excluded). With these factors considered, it is highly likely that the majority of their non-obese female FF patients had DOP.

Kapetanović *et al.* (58) reported a study with 100 postmenopausal Bosnian women aged between 55 and 75 years, with 50 of them having FF and 50 without FF. Osteoporosis (≤–2.5, either LS or proximal femur) was detected in 80.0 % (40/50) of the FF group, and 16% (8/50) of the control group. However, the sample size of this study was very small.

Sornay-Rendu *et al.* (8) studied the radius bone microarchitecture with high-resolution peripheral computed tomography (HR-pQCT) in their OFELY study postmenopausal women without low BMD. At the year-14 follow-up study, bone microarchitecture was measured in addition to areal DXA BMD. Among the year-14 follow-up study subjects, 166 (29%) women (age: 65±8 years) had normal BMD with T score ≥–1 at the LS, FN, and total hip. During a median of 15 years of further follow-up, 46 of those women sustained incident FF, including 19 women with a major FF (clinical spine, forearm, proximal humerus, hip). Women who sustained FF did not differ for age, falls, or areal BMD, compared with the women without incident FF, but they had significant impairment of volumetric densities, cortical area and thickness, and estimated failure load at the radius compared with the women without incident FF. Thus, even in women with normal areal BMD, FFs are associated with the deterioration of bone microarchitecture.

In conclusion, for older women, the majority of hip FF and radiographic vertebral FF occur among the population with DOP. Trends were noted that 'younger' patients suffer hip FF at a 'higher' T-score, and older men suffer from hip fracture at a notably higher T-score than older women. It is likely that not all distal forearm fractures among older women are truly osteoporotic fractures. Distal forearm fractures should be classified as a special FF category which tend to occur at a 'higher' T-score. The analyses in this article further emphasize the clinical importance of diagnostic imaging for osteoporosis care.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-227/coif). Y.X.J.W. serves as the Editor-in-Chief of *Quantitative Imaging in Medicine and Surgery*. The author has no other conflicts of interest to declare.

Ethical Statement: The author is 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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