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PERSPECTIVE

Quantitative CT lumbar spine BMD cutpoint value for classifying osteoporosis among older East Asian women should be lower than the value for Caucasians

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Abstract
For Caucasian women, the QCT (quantitative CT) lumbar spine (LS) bone mineral density (BMD) cutpoint value for classifying osteoporosis is 80 mg/ml. At the age of approximate 78 years, US Caucasian women QCT LS BMD population mean is 80 mg/ml, while that of Chinese women and Japanese women is around 50 mg/ml. Correlation analyses show, for Chinese women and Japanese women, QCT LS BMD of 45 mg/ml corresponds to the dual-energy X-ray absorptiometry cutpoint value for classifying osteoporosis. For Chinese and Japanese women, if QCT LS BMD 80 mg/ml is used as the threshold to classify osteoporosis, then the specificity of classifying subjects with vertebral fragility fracture into the osteoporotic group is low, whereas threshold of 45 mg/ml approximately achieve a similar separation for women with and without vertebral fragility fracture as the reports for Caucasian women. Moreover, by using 80mg/ml as the cutpoint value, LS QCT leads to excessively high prevalence of osteoporosis for Chinese women, with the discordance between hip dual-energy X-ray absorptiometry and LS QCT measures far exceeding expectation. Considering the different bone properties and the much lower prevalence of fragility fractures in the East Asian women compared with Caucasians, we argue that the QCT cutpoint value for classifying osteoporosis among older East Asian women will be close to and no more than 50 mg/ml LS BMD. We suggest that it is also imperative the QCT osteoporosis classification criterion for East Asian male LS, and male and female hips be re-examined.

Keywords Osteoporosis · Bone mineral density (BMD) · Quantitative CT · Asians · Chinese

Introduction

Osteoporosis is a systemic skeletal disease characterised by a reduction in bone mass (measured by bone mineral density: BMD) and qualitative skeletal changes that cause an increase in bone fragility and a higher fracture risk. The clinical significance of osteoporosis lies in the fragility fractures (FF) that occur. Dual-energy X-ray absorptiometry (DXA) is the current standard technique for measuring BMD. 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 DXA in g/cm^2 differs substantially 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. 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. Quantitative CT (QCT) for BMD measurement can be performed on any CT scanner with the use of a calibration phantom and dedicated analysis software (such as Mindways Software, Inc., Austin, USA). Calibration phantoms are required to transform the attenuation measured in Hounsfield units into BMD value (in mg/

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mL). The patient and phantom are commonly examined at the same time, which is termed as simultaneous calibration. Compared with DXA technique, QCT has a number of advantages. QCT is less susceptible to degenerative changes of the spine than DXA. Osteophytes and facet joint degeneration, as well as soft tissue calcifications, do not significantly increase BMD in QCT [1–3]. QCT provides trabecular bone measurements, which are more sensitive to monitoring changes with some diseases and therapies. Patients who are undergoing therapies that have a high impact on bone metabolic activity, such as parathyroid hormone and corticosteroids, may be better monitored with QCT. QCT also has advantages for patients with unusual body size or obesity. Disadvantages of QCT include the higher radiation dose, limited applicability of the WHO T-score criteria for the diagnosis of osteoporosis, and overall less experience with fracture prediction and treatment initiation with QCT compared with DXA [1–3].

Due to different bone structural properties and the much lower incidence of fragility fractures in the Chinese population compared with Caucasians [4, 5], we have recently recommended that, to diagnose osteoporosis using DXA with Chinese BMD reference ranges, the cutpoint T-score value for lumbar spine BMD for Chinese women should be -3.7 rather than the WHO cutpoint of -2.5 recommended for Caucasians [6–8]. Numerous studies have demonstrated that the skeleton of East Asians has microstructural and mechanical advantages [5]. For example, Walker et al. [9] reported that postmenopausal Chinese women have a higher trabecular plate-to-rod ratio and greater whole bone stiffness, translating into greater trabecular mechanical competence. Boutroy et al. [10] reported that, compared with Caucasians, both pre- and postmenopausal Chinese women had greater cortical thickness, cortical tissue mineral density, and reduced cortical porosity at both the radius and tibia. For the spine, compared with older Caucasian women, older Chinese women were less likely to have disc space narrowing, thoracic spine hyper-kyphosis, vertebral osteoarthritic wedging, Schmorl nodes defect, and degenerative spondylolisthesis [11, 12]. Almost all of the published results comparing East Asians and Caucasians show nearly all fragility fracture prevalences, including hip fracture, vertebral fracture, humerus fracture, and wrist fracture, are no more than half that of older Caucasians, both for men and women (reviewed in [7, 8], Fig. 1).

For Caucasian women (and men), the QCT lumbar spine (LS) BMD cutoff value for osteoporosis has been recommended to be 80 mg/ml [1, 13]. The same QCT criterion has also been commonly applied to East Asian populations [14–19]. With the proposed revision of the DXA LS T-score for East Asians in mind, in this article we discuss the most suitable QCT LS BMD cutpoint value for classifying osteoporosis among older East Asian women. Caucasian data will be used as reference, as the densitometric definition of osteoporosis was initially developed based on Caucasian fragility fracture profiles, and there are more validation studies available for Caucasians. We argue that an appropriate QCT LS BMD cutpoint value for classifying osteoporosis among older East Asian women is close to and no more than 50 mg/ml, which is substantially different from the value for Caucasians. Note that, for directly measured LS and hip DXA areal BMD, older East Asian women facture at a much lower BMD than that of Caucasians [7, 20].

Evidence supports a much lower QCT lumbar spine BMD threshold for classifying osteoporosis among older East Asian women than the value for Caucasians

The first line of evidence is based on population aging data. The population mean LS BMD and the related DXA T-score and QCT measure all decrease with age. Fig. 2 shows that, at the age of approximately 78 years, for US Caucasian women, the population mean LS T-score is -2.5 (i.e., the DXA cutpoint value for classifying osteoporosis), and if T-scores in this group are normally distributed, then half of them will have densitometric osteoporosis. At the same age, the LS T-score for Chinese women is -3.7 which is the recommended threshold to diagnose osteoporosis for Chinese women [7, 8]. By the age of 78 years, for US Caucasian women, the population mean QCT LS BMD is 77 mg/ml [21], consistent with the current QCT densitometric osteoporosis diagnosis threshold of 80 mg/ml. In contrast, for East Asian women at the same age, the QCT LS BMD has decreased to 54 g/ml (Fig. 2C) for Chinese women and 48 g/ml (Fig. 2D) for Japanese women, according to the data of Li et al. [14] and Fujii et al., respectively [22]. On the other hand, if a QCT LS BMD of 80 mg/ml is used as the cutpoint value to classify osteoporosis, then at the age of around 64 years, around half of the Chinese and Japanese female population of this age group will be classified as osteoporotic, which is known to be untrue [7, 8]. Note that, at the age of 78 years, the fragility fracture risk of Chinese and Japanese women is still lower than Caucasian women of the same age. Therefore, the data in Fig. 2 suggest that, for older East Asian women, the cutpoint for the QCT LS BMD definition of osteoporosis equivalent to the older Caucasian women's threshold of 80 mg/ml is likely no more than 50 mg/ml.

The second line of evidence is based on the analyses demonstrated in Fig. 3. As shown in Fig. 3A, Lin et al. [15] compared QCT and DXA studies in 501 patients (395 females and 106 males, mean age: 71.3 and 67.6 years, respectively). Their data shows that 50 mg/ml QCT LS BMD corresponds to a DXA T-score of approximately of -3.3, whereas 80 mg/ml QCT LS BMD corresponds to a

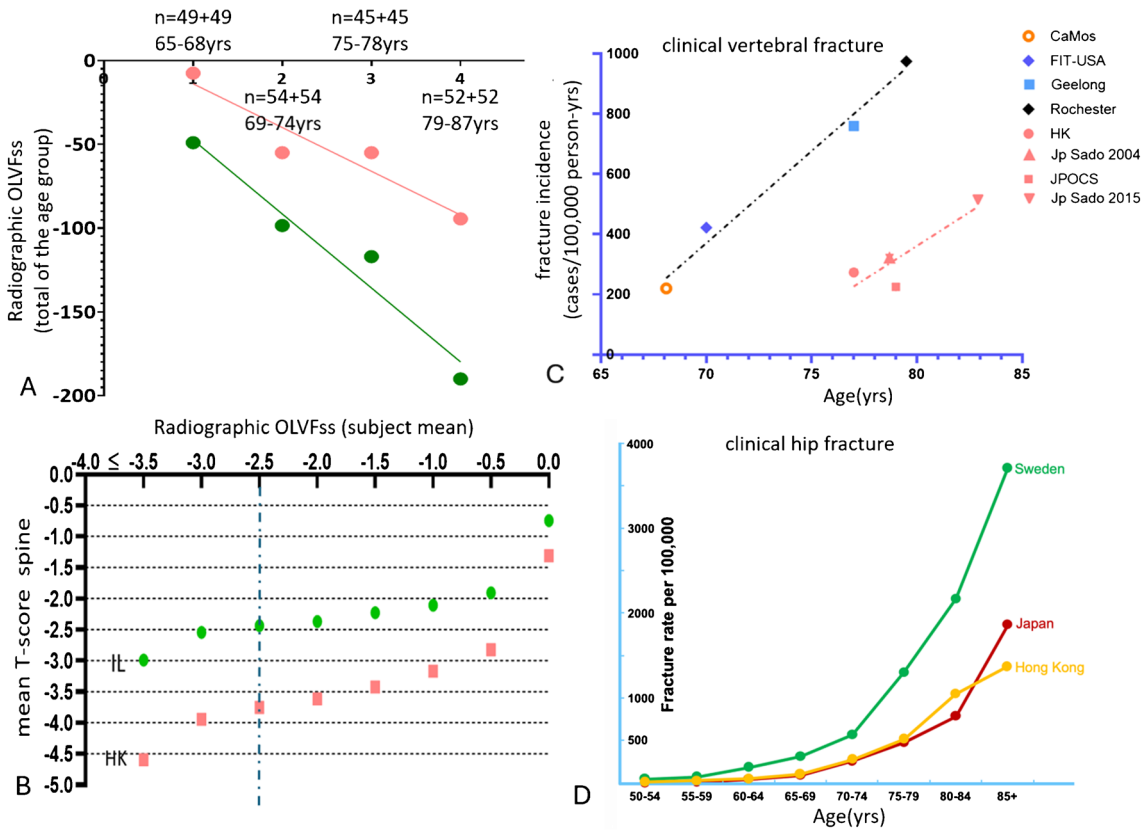

Fig. 1 Much lower fragility fracture risk of East Asian women relative to Caucasians women. A: Osteoporotic-like vertebral fracture sum score (OLVFss) of four age groups of Hong Kong (HK) Chinese women and Italian (IL) Caucasian women (population-based and age-matched data, n = 200 pairs). Each vertebra on spine radiograph was assigned a score of 0, -0.5, -1, -1.5, -2, -2.5, and -3 for no radiographic OLVF or OLVFs of < 20%, 20 ~ 25%, ≥ 25% ~ 1/3, ≥ 1/3 ~ 40%, ≥ 40% ~ 2/3, and ≥ 2/3 vertebral height loss, respectively. OLVFss for each subject was calculated by summing the scores of all vertebrae from T4 to L5. Light red balls/lines: Chinese subjects; green balls/lines: IL subjects. Lines denote linear fit. The term OLVF is used because radiograph can only suggest the diagnosis of fragility fracture while the diagnosis is not with certainty. Less severe OLVF is noted for Chinese than for Italians. N = 49 + 49 means there are 49 Chinese subjects and 49 Italian subjects in this age group. B. Relationship between OLVFss and mean lumbar spine T-score for older Chinese women and Italian Caucasian women (IL, n = 301, age: 73.6 ± 6.1 years, in green dots; HK, n = 512, 74.0 ± 7.2 years, in pink squares). Vertical line suggests that, when OLVFss is -2.5, the equivalent lumbar spine T-score is -2.44 for Italians and -3.75 for Chinese. C: Much lower clinical vertebral fragility fracture incidences are noted for East Asians than for Caucasians. The dotted black and orange lines in B indicate linear fits. D: Much lower clinical hip fracture prevalence among Chinese and Japanese women relative to Swedish Caucasian women. A: Data are from Wang et al. Arch Osteoporos. 2021;16:174. B: Data from Wang et al. Arch Osteoporos. 2023;18:1. C: Data are from Osteoporotic fracture in women HK study; Sakuma et al. J Bone Miner Metab 2008;26:373–378 (Japan Sado 2004), Imai et al. J Bone Miner Metab 2019; 37:484–490 (Japan Sado 2015); Kamiya et al. Maturitas.2019;130:13–20 (JPOCS); Sanders et al. Osteoporos Int 1999;10:240–7 (Geelong study); Cooper et al. J Bone Miner Res 1992;7:221–7 (Rochester study); Fink et al. J Bone Miner Res 2005;20:1216–22 (FIT-USA study), and Papaioannou et al. Osteoporos Int 2005;16:568–78 (CaMos study). D: data from Bow et al. Osteoporos Int 2012 23:879–85 (Hong Kong data); Hagino et al. Bone 1999; 4:265–270 (Japanese data), and Kanis et al. Osteoporos Int. 11:669–674 (Swedish data)

DXA T-score of approximately of -0.7. Note that we recommended cutpoint DXA T-score values for classifying osteoporosis of -3.7 for Chinese women and -3.2 for Chinese men. The data in Fig. 3B/C are from Yu et al. [23], who studied 24 women aged between 70–79 years using both LS QCT and DXA. The mean (± 1 SD) QCT BMD was 69.84 ± 20.14 mg/ml, and the DXA BMD was 0.912 ± 0.20 g/cm^2. This study shows a value of 49.7 mg/ml (i.e., 69.84 minus 20.14) by QCT was equivalent to a value of 0.712 g/cm^2 (i.e., 0.912 minus 0.20) by DXA. Following the Chinese BMD reference range study of Cheng et al. [24], we recommended that the DXA LS BMD threshold to diagnose osteoporosis is 0.674 g/cm^2 [7, 8], which would be close to 45 QCT mg/ml. According to the results of Yu et al. shown in Fig. 3B/C, a QCT LS BMD of 80 mg/ml is equivalent to a DXA LS BMD > 1.0 g/cm^2, well above the threshold for classifying osteoporosis using DXA [7]. Further supportive evidence comes from a study published by Uemura et al. [18]. They studied 59 patients (mean age: 66.3 years, 18 males, 41 females) with both LS QCT and DXA. Fig. 3D shows the

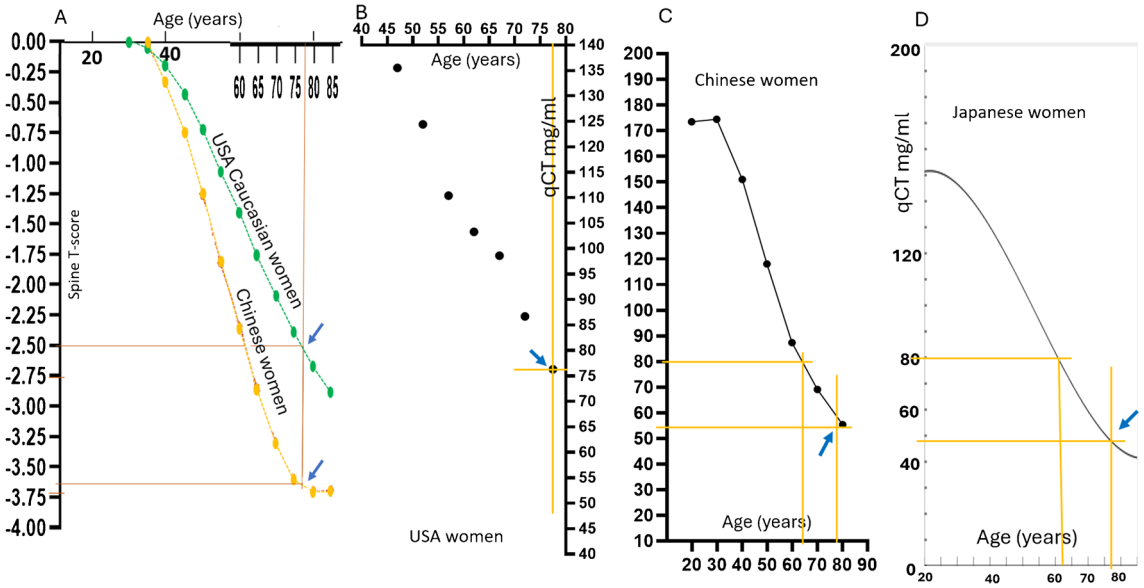

Fig. 2 Following aging of Chinese, Japanese, and American women, the population mean lumbar spine (LS) DXA T-score and QCT BMD decrease. A: at the age of approximately 78 years, the mean LS T-score decreases to -2.50 (arrow) for US Caucasian women and -3.65 (arrow) for Chinese women. B: at the age of 78 years, the mean QCT LS BMD of US women (non-black women, assumed predominantly Caucasians) decreases to approximately 77 mg/ml (arrow). C: at the age of 78 years, the mean QCT LS BMD of Chinese women decreases to approximately 54 mg/ml (arrow). D: at the age of 78 years, the mean QCT LS BMD of Japanese women decreases to approximately 48 mg/ml (arrow). For both Chinese and Japanese women, the mean QCT LS BMD is 80 mg/ml at the age of around 64 years. DXA data re-plotted from Wu et al. Calcif Tissue Int 2003;73:122–132 (Chinese women) and Looker et al. J Bone Miner Res 12:1761–1768 (US Caucasian women). QCT data re-plotted from Block et al. J Bone Miner Res. 1989;4:249–57 (US women), Li et al. Chin J Osteopros. 2019;25:1257–1272 (Chinese women), and Fujii et al. Bone Miner. 1989;6:87–94 (Japanese women)

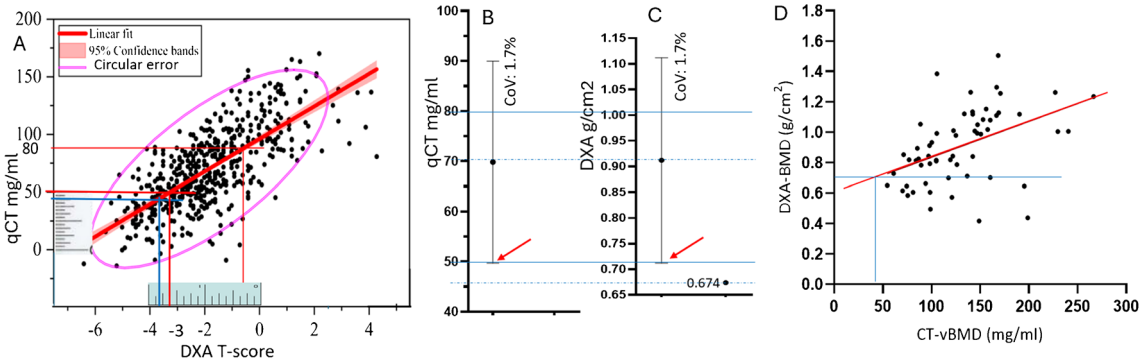

Fig. 3 Correlations of QCT lumbar spine (LS) BMD readings and DXA BMD readings for Chinese and Japanese. A: data for Chinese 501 patients (395 females and 106 males, mean age: 71.3 and 67.6 years, respectively) measured with both LS QCT and DXA. This graph shows that 50 mg/ml QCT LS BMD corresponds to a DXA T-score of approximately -3.3, and 44 mg/ml QCT LS BMD corresponds to a DXA T-score of approximately -3.7, whereas 80 mg/ml QCT LS BMD corresponds to a DXA T-score of approximately -0.7. B and C: 24 Chinese women (age: 70–79 years) were measured with both LS QCT (B, BMD data presented in mean and standard deviation) and DXA (C). The measurement precision (coefficient of variation: CoV) was the same (i.e., 1.7%) for QCT and DXA. The blue line shows that 50 mg/ml (arrow) by QCT is approximately equivalent to a BMD of 0.71 g/cm^2 (arrow) by DXA. 0.674 g/cm^2 is the DXA BMD cutpoint value for osteoporosis [7], which tentatively corresponds to QCT BMD value around 46 mg/ml (dotted line). D: Data of 59 Japanese patients (mean age: 66.3 years, 18 males, 41 females) measured with both LS QCT and DXA. The red line is the linear regression line. The Pearson *r* is 0.45 in D which indicates only moderate data fitting quality. Blue lines show that approximately 45 mg/ml QCT BMD corresponds to a DXA BMD of 0.7 g/cm^2. Chinese data in A was adapted and reused with permission from Lin et al., BMC Geriatr. 2023;23:231. For the X-axis, as the initial T-score value used a Caucasian BMD reference, the T-score values presented in this graph were readjusted and approximated according to Lo et al. (Osteoporos Int. 2016;27:3477–84) and Wang et al., (Skeletal Radiol 2024;53:409–417). Chinese data in B and C were re-plotted from Yu et al., Osteoporos Int. 1999;9:179–87. Japanese data (D) was re-plotted from Uemura et al. Arch Osteoporos. 2023;18:22

plot of LS DXA BMD vs. QCT BMD. It demonstrates that a QCT BMD of approximately 45 mg/ml corresponds to a DXA BMD of around 0.7 mg/cm^2, which is close to the cutpoint value for classifying osteoporosis [7]. Therefore, according to the data from these three studies, the QCT LS BMD threshold for diagnosing osteoporosis is likely to be 45 mg/ml.

The third line of evidence is that, for Chinese and Japanese, if a QCT LS BMD threshold of 80 mg/ml is used to classify osteoporosis, then the specificity of classifying subjects with vertebral fragility fracture (VFF) into the osteoporotic group is low (i.e., too many subjects without VFF will be classified into the osteoporotic group). Caucasian results for older populations have consistently shown that, in densitometrically osteoporotic women, the majority will have VFF while only a small proportion do not have VFF, whereas in densitometrically non-osteoporotic women, the majority do not have VFF while a small proportion have VFF. Fig. 4A shows data from a population-based study of Italian Caucasian women with a mean age of 74.1 years. If a DXA T-score $\leq$ -2.5 is used as the cutpoint value to classify osteoporosis, in the osteoporotic group, 86.2% of cases had VFF, while 38.8% of cases with VFF were in the non-osteoporotic group [25, 26]. In contrast, in Fig. 4B, if QCT LS BMD 80 mg/ml is used as the threshold to classify osteoporosis in the Chinese population-based study of Li et al. [14] (1304 males, mean age approximately 62.4 years; 2166 females, mean age approximately 61.5 years), 69.4% of osteoporotic cases did not have VFF, resulting in a very low specificity for VFF. Fig. 4C and D show two case–control studies for age-matched females with and without VFF from the UK and China, respectively. The UK women's study (Fig. 4C, QCT LS BMD data shown as the mean and standard deviation, mean age: 68.9 years, assumed predominantly Caucasians) suggests that most of the subjects with VFF are in the QCT osteoporotic range, while most of the subjects without VFF are not in the osteoporotic range. The Chinese women's study (Fig. 4D, QCT LS BMD data in mean and range, mean age: 68.0 years) suggests that, if the cutpoint value is < 80 mg/ml, a much higher portion of subjects without VFF are in the QCT osteoporotic range. A revision of the cutpoint value to 45 mg/ml would approximately achieve a similar separation of subjects with and without VFF as those shown in Fig. 4C, E, and F. Fig. 4E is a study of French Caucasian women, which demonstrates that 87.8% of the subjects with VFF are in the QCT osteoporotic range, while 12.2% are not in osteoporotic range. Fig. 4F is a study of a mixed-sex group of German men and women (assumed age: 70 years and predominantly Caucasians), where the majority (but not all) of the subjects with VFF are in the QCT osteoporotic range and the majority of the subjects without VFF are in the non-osteoporotic range. In Fig. 4G, if QCT LS 80 mg/ml is used as the cutpoint value to classify osteoporosis in Japanese women [22], then only 31.5% of cases in this osteoporosis group have VFF; if the cutpoint value is 45 mg/ml, then 88.8% of cases have VFF, which is more consistent with Caucasian data.

The fourth line of evidence is that, if 80 mg/ml is used as the cutpoint value, LS QCT leads to an excessively high prevalence of densitometric osteoporosis. In the Chinese population-based study of Li et al. [14] with 3420 community men and women aged > 40 years (characteristics described above, mean age around 62 years), the 80 mg/ml cutpoint value led to 28.5% of the study participants having osteoporosis, while only 33.2% had normal BMD (38.3% had osteopenia). In another Chinese study published by Li et al. [27], 140 postmenopausal women (age: 63.2 ± 8.1 years) underwent LS QCT and LS and hip DXA. The hip DXA-based osteoporosis prevalence was 12.9%, which can be reasonable [7]. However, the LS QCT-based osteoporosis prevalence was 46.4%, with the discordance between the hip DXA and LS QCT measures far exceeding expectations. Based on the initial WHO definition, the prevalence of densitometric osteoporosis is extrapolated from fragility fracture prevalence, and considering the relative low fragility fracture prevalence among Chinese women as compared with Caucasian women [4, 6, 7], the reported QCT osteoporosis prevalences in the above two studies were unreasonably high. In an analysis based on US data, Wright et al. [28] reported that DXA densitometric osteoporosis prevalence was 5.1%, 8.0%, 16.4%, and 26.2% for the age bands of 50–59 years, 60–69 years, 70–79 years, and ≥ 80 years of mixed gender and race, and the overall osteoporosis prevalence for Caucasian women (≥ 50 years) was 15.8%.

Discussion and conclusion

We admit that there are limitations to our arguments. With QCT, calibration precision, CT parameters, the use of single-slice QCT covering multiple vertebrae or volumetric measurement with spiral CT, region of interest (ROI) placement (which commonly includes trabecular bone while excluding cortex and vertebral posterior elements), etc. will all affect the final QCT reading. However, studies have demonstrated that the disagreements between various QCT measurements are usually minor [18, 29, 30]. The studies of Uemura et al. [18] and Yu et al. [23] are limited by their small sample sizes. The quality of data fitting for the study of Uemura et al. [18] is not optimal. The classification based on radiological VFF in Fig. 4 could be associated with reader subjectivity for milder VFF. Despite these limitations, the analyses in this article consistently show that the QCT LS BMD 80 mg/ml cutpoint value for

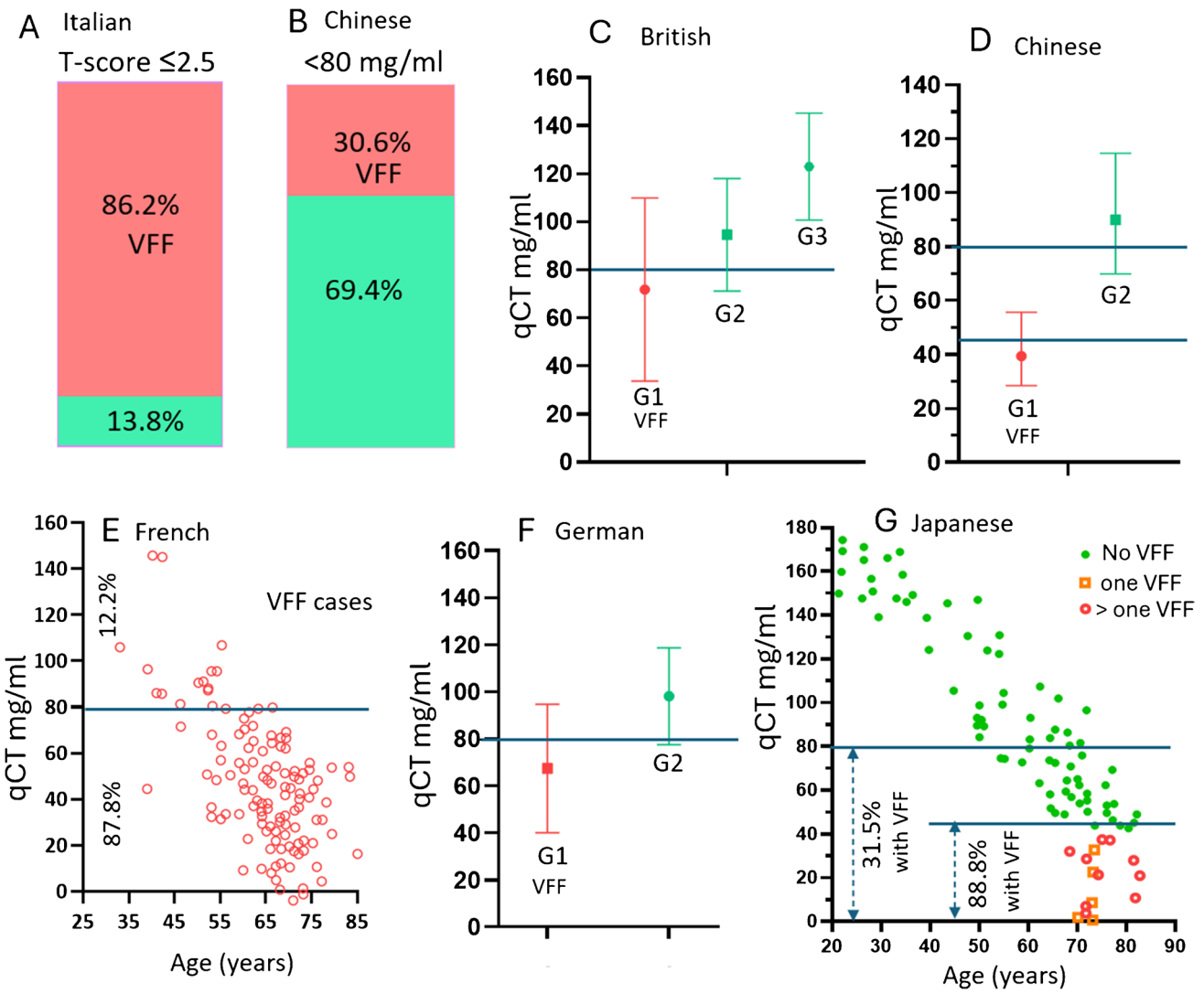

Fig. 4 DXA or QCT lumbar spine (LS) BMD cutpoint values for classifying osteoporosis with reference to radiological vertebral fragility fracture (VFF) status in the study participants. A: If a DXA T-score ≤ -2.5 is used as the cutpoint value to classify osteoporosis among 200 Italian community Caucasian women (mean age: 74.1 years), in the osteoporotic group (n = 58), 86.2% of cases had VFF and 13.8% did not. B: Data for a Chinese population sample (1304 males, mean age approximately 62.4 years; 2166 females, mean age approximately 61.5 years). If 80 mg/ml is used as the cutpoint value to classify osteoporosis, 30.6% of the osteoporotic group (n = 975 in the osteoporotic group) had VFF, and 69.4% did not. C: A UK study of postmenopausal women. 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. QCT results are the mean and standard deviation (estimated from the reported standard error). D: 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). QCT results are expressed as means and ranges. E: 123 French Caucasian women of varying ages with VFF. F: 88 mixed-sex German male and female patients (the majority being female, mean age unspecified but likely to be around 70 years). QCT results are expressed as the mean and standard deviation. 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. Italian data (A) re-plotted from Wang et al. Arch Osteoporos. 2021;16:174 and Wang et al. Arch Osteoporos. 2022;18:1. Chinese data in B re-plotted from Li et al. Chin J Osteopros. 2019;25:1257–1272. UK data (C) re-plotted from Paggiosi et al. Osteoporos Int. 2020;31:667–675; Chinese data in D re-plotted from Mao et al. J Orthop Translat. 2018;16:33–39. French data (E) re-plotted from Bergot et al. Calcif Tissue Int. 2001;68:74–82. German data (F) re-plotted from Sollmann et al. J Bone Miner Res. 2022;37:1287–96. Japanese data (G) re-plotted from Fujii et al. Bone Miner. 1989;6:87–94

classifying osteoporosis in East Asians is set too high. Instead, our analyses suggest that a more suitable cutpoint value would be closer to 45–50 mg/ml, though this article does not aim to propose a final cutpoint value. Since Chinese, Korean, and Japanese women have similar, though may not exactly the same, BMD and fragility fracture

profiles [8, 31, 32], we believe the arguments in this article likely to be broadly applicable to older East Asian women. We suggest that it is also imperative that the QCT osteoporosis classification criterion for East Asian male LS and male and female hips be re-examined. For example, in one study of a convenient sample of Chinese male patients (n = 313; age: 79.6 ± 7.2 years) who had both LS QCT and LS and hip DXA measures, Xu et al. [33] reported that the hip DXA-based osteoporosis prevalence was 9.9%, whereas the LS QCT-based osteoporosis prevalence was 45.1%, with the discordance between the hip DXA and the LS QCT results also far exceeding expectation.

Earlier epidemiological studies frequently described the paradoxical phenomenon that 'the densitometrical osteoporosis prevalence among Asians is high, but the FF prevalence among Asians is low' [34–36]. For classifying osteoporosis prevalence among East Asians, it is essential to optimize a QCT BMD threshold based on ethnic-specific bone property and FF profile among East Asians. This will allow a more meaningful comparison of disease burden between East Asians and Caucasians and allow comparable medication intervention thresholds for East Asians and Caucasians. Considering the different bone properties and the much lower incidence of fragility fractures in the East Asian women compared with Caucasians, the most suitable QCT cutpoint value for classifying osteoporosis among older East Asian women is likely to be 45–50 mg/ml LS BMD.

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Declarations

Conflicts of interest A.G. is a Shareholder of BICL, LLC and Consultant to Pfizer, ICM, TrialSpark, TissueGene, Coval, Medipost, and Novartis. Other authors declare no competing interests.

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