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REVIEW

Fragility fracture risk prediction using quantitative magnetic resonance and Vertebral Bone Quality scoring beyond density

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Abstract

Fragility fractures represent a significant global health burden, with osteoporosis affecting over 500 million individuals and contributing to nearly 9 million fractures annually. Conventional diagnosis relies on dual-energy X-ray absorptiometry (DEXA) to measure bone mineral density (BMD), yet BMD alone explains only part of fracture risk. Many fractures occur in patients without osteoporosis by DEXA criteria, underscoring the limitations of bone quantity-based assessment. Advances in imaging and biomarker research highlight the

importance of bone quality, microarchitecture, and marrow composition in fracture prediction. Quantitative magnetic resonance imaging (MRI) techniques - including T1ρ, T2 mapping, proton density fat fraction, and diffusion-weighted imaging - offer non-invasive insights into collagen integrity, proteoglycan content, water distribution, and marrow adiposity. These parameters correlate with trabecular deterioration and cortical porosity, enhancing risk stratification beyond BMD. Similarly, Vertebral Bone Quality (VBQ) scoring, derived from routine T1-weighted MRI, provides a practical surrogate for bone quality by quantifying vertebral marrow signal intensity relative to cerebrospinal fluid. Modified VBQ improves accuracy by minimising posterior vertebral artefacts, demonstrating stronger correlation with DEXA T scores and trabecular microarchitecture. Studies show VBQ predicts vertebral fragility fractures independently of BMD, with sensitivity exceeding 90% and discriminatory ability comparable to the fracture risk assessment tool and trabecular bone score. Integration of quantitative MRI and VBQ/modified VBQ into predictive models, supported by artificial intelligence, enables opportunistic, radiation-free screening and more precise fracture risk assessment. Together, these advanced imaging biomarkers represent a paradigm shift toward comprehensive evaluation of bone strength, bridging the gap between bone quantity and quality for improved prevention and management of fragility fractures.

Key Words: Fragility fractures; Bone mineral density; Dual-energy X-ray absorptiometry; T2 mapping; Vertebral Bone Quality score

Core Tip: Fragility fractures remain a global health challenge, with many occurring in patients without dual-energy X-ray absorptiometry-defined osteoporosis. Advanced imaging biomarkers such as quantitative magnetic resonance imaging (T1ρ, T2 mapping, proton density fat fraction, diffusion-weighted imaging) and Vertebral Bone Quality/modified Vertebral Bone Quality scoring provide deeper insights into bone microarchitecture and marrow composition. These tools enhance fracture risk prediction beyond bone mineral density, enabling radiation-free, opportunistic screening and artificial intelligence-driven models that bridge bone quantity and quality for improved prevention and management.

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INTRODUCTION

Research studies estimate that 13.5 million fragility fractures will occur globally every year[1]. 500 million people would be living with a condition called osteoporosis, a chronic disease that weakens bones, leaving people at significant risk of getting a fragility fracture[2-4]. Around one in five men and one in two women aged above 50 years have experienced a fragility fracture in their life, leading to approximately 8.9 million fragility fractures each year[5,6].

About 80% or every four in five women with risks of developing a hip fracture said that death is better than living with the loss of movement and independence due to the fractures. Nervousness because of the fear of falling, reputation issues and limitations to carry out daily chores are caused by experiences of fractures[7]. Fragility fractures due to osteoporosis cost hospitals 400 billion dollars and account for about 3% of their healthcare expenditure. The expenditure of fragility fractures will increase by two times by 2050. Up to 70% fragility fractures occur every minute for individuals above 55 years of age. The risk is greater than breast cancer in women, while in men, the risk is greater than prostate cancer[8,9].

More than 10 million hip fractures were recorded in 2019 in patients aged above 55 years[10,11]. Hip fractures are associated with mortality rates up to 20%-24% in the first year, and among survivors, 40% cannot walk on their own, and 33% either become totally dependent and require nursing home care[12]. The World Health Organization Osteoporosis Working Group states that the neck of the human femur is the primary region that must be used to evaluate the prevalence of osteoporosis. Diagnosis of osteoporosis is done by using dual-energy X-ray absorptiometry (DEXA), which helps in measuring the bone mineral density (BMD) of the femoral neck of the femur. According to World Health Organization criteria, osteoporosis is diagnosed when BMD has a standard deviation of 2.5, which is below the mean BMD of the female population. The prevalence of osteoporosis increased progressively with age[13-16].

In East Asia, osteoporosis is a rising issue due to the increasing elder population[17-19]. China is said to have the largest older population in the world, and studies show an apparent increase in osteoporosis prevalence with age, which affects more than one-third of people age 50 years and above[7]. In India, studies show that out of the entire Indian population who are over the age of 50 years in 2015, women with osteoporosis accounted for about 46 million. In Brazil, it is reported that the prevalence of postmenopausal women with prevalence of osteoporosis varies from 15% to 33%. In the United States in 2010, there were over 99 million adults aged 50 years and older. It is estimated that 10.2 million older adults have osteoporosis, which accounts for 10.3%[12].

LIMITATIONS OF DEXA-BASED BMD IN FRACTURE RISK PREDICTION

DEXA interpretation has a very big disadvantage in relying only on the DEXA scan's cover report without the review of raw images, along with the available data. DEXA reporting and interpretation may not be that accurate due to the absence of clinical context and data, possibly leading to incorrect decision-making. To monitor treatment or disease progression and compare studies over time, it is critical to perform DEXA scans at the same place, device and patient to compare the values directly.

Position of spine and variations in anatomy influence DEXA accuracy. L1 to L4 vertebrae are used to measure spine BMD, and the spine is straight with the exact amounts of soft tissue on both sides of the vertebrae. The apparent vertebral segment area increases when the spine is rotated, leading to a decreased BMD reading with no effect on the content of bone mineral. One or two vertebrae should be excluded if they are influenced by circumstances such as scoliosis or kyphosis, or even degenerative changes. But the main decision should be based on the neck of the femur BMD if three vertebrae are affected. Correct labelling of L1-L4 is crucial; failure of which leads to inaccurate T-scores. Anatomical/genetic variations, like patients who have four or even six lumbar vertebrae, will also affect identification. Evaluation for osteophytes, surgical clips, gallstones, *etc.*, is necessary from one vertebra to the next, with a sudden change of BMD[20,21].

BMD is not the only primary determining factor of fracture. By the DEXA definition, most of the minimal trauma fractures do not occur in patients with osteoporosis. Garvan and fracture risk assessment tool (FRAX) are known risk calculators; they give us information about absolute risk and not the predicted risk, and are also not accurate enough[22]. DEXA can detect BMD loss before it appears on radiography, allowing for early diagnosis before presenting of fractures. However, mistakes can arise in interpreting results if DEXA is used outside of these given populations. If the clinical picture does not link or match with the T scores reported, then it can affect the determination of therapy need.

Clinical Judgment should play a significant role if the results conflict with the given data, even though DEXA is the benchmark test to measure bone density. In premenopausal women, younger men and children, Z-scores should be used as indicators of fragility fracture risk instead of T-scores[23]. Discordance is sometimes caused between true fracture and DEXA results risk sometimes because the bone strength is highly dependent on factors apart from BMD. The Fracture Risk Assessment Tool helps in guiding the treatment and careful decisions by inculcating these factors.

Bone microarchitecture is a topic with great potential, and newer technologies may one day improve a patient's risk analysis[20]. There are still many new qualities apart from BMD that contribute to bone strength, which means that our knowledge of DEXA is ever-growing. A few qualities are not detectable by DEXA. Therefore, depending too much on DEXA analysis would lead to poor diagnosis and decisions, particularly for patients who don't fall in the test's design criteria[24,25].

RATIONALE FOR EXPLORING ADVANCED IMAGING BIOMARKERS

Significant changes in BMD only occur slowly at a minimal rate; thus, it is not a practical and accurate standalone method for patient care and monitoring. This disadvantage is evident within a year of treatment when serial DEXA scans do not detect relatable DEXA changes[25]. Osteoporosis is often characterized by microarchitectural deterioration of bone tissue, leading to loss of bone mass and a decrease in structure and integrity, causing fragility fractures linked with high rates of mortality[26,27]. Osteoporosis remains behind the curtains and only presents when a fracture takes place. To prevent such fractures, it is necessary to have correct and precise methods to identify patients at high risk of developing one. Bone quality is more crucial to detect the risk of fractures, which current standard methods fail to assess[28].

MicroRNAs and bone turnover markers show promising potential in identifying individuals with accelerated bone turnover, even in the absence of significant changes in bone mass[29-32]. These methods respond very quickly to osteoporotic changes and are very effective in assessing the progression of treatment. These methods allow healthcare workers, especially doctors, to study the efficacy of treatment and management, find out individuals who need therapy adjustments because of suboptimal response, and check adherence to medication regimens to provide the best possible care. These methods, in a few cases, can indicate secondary pathologies and causes by detecting bone turnover rates that seem abnormal[33]. Bone turnover markers and microRNAs have great potential in assessing treatment efficacy, early detection of fractures and finding out the pathophysiology of osteoporosis. But in the elderly population, these methods remain under evaluation. An additional advantage of these methods is their relatively non-invasive nature[34-36].

PATHOPHYSIOLOGY OF FRAGILITY FRACTURES

Resorption is the process in which small amounts of minerals are degraded and removed from bones, but in order to maintain balance and strength, deposition of new minerals, named mineralization, also takes place. This balance, when it leans towards the resorption side, bones become weak, brittle and vulnerable to fractures. Continuous degradation (resorption) and redeposition of minerals, also known as remodelling, is linked to osteoporosis pathophysiology. Learning how remodelling in bones is balanced in our body is necessary to understand osteoporosis and its prevention, and management[33,37,38].

Evolution has made bones stronger yet lighter. The geometry and microarchitecture play a significant role in giving these properties. Long bones are cylindrical in shape, consisting of a strong cortical layer outside, which surrounds the

spongy trabecular part, which acts as a core. The bones constituting the vertebrae are created with a similar architecture [39]. Gradual resorption occurs daily due to remodelling and causes a decline in the trabecular bone, which widens the central cavity inside the cortical bone. Compensation appears to some extent by adding newer layers, but only on the outside. High risks of hip fractures are present in young adults living with wide femur bones. These continuous and gradual cycles of bone remodelling affect the architecture and also impact osteoporosis and its manifestations[40].

This balance that takes place between bone deposition and resorption is influenced by the functioning of two main types of cells, osteoblasts and osteoclasts, respectively. Osteoclasts function by pumping protons outside the intracellular space, therefore reducing pH and dissolving bone mineral, helping in resorption. They also produce proteolytic enzymes like cathepsin K (which dissolve bone matrix). Osteoblasts produce new bone mineral, aiding in bone deposition. The functions of these two cell types and their balance determine whether bone is degraded, maintained or growing[12,39].

In the bone remodelling cycle, usually the first ones to function are osteoclasts, causing resorption. Osteoblasts produce a fresh matrix of bone during bone formation. This takes place after a short reversal phase, when the pit created by resorption is filled by precursor cells of osteoblasts. A net bone mass loss takes place during excessive remodelling as the time taken for mineralization is much more than that of resorption. Communication between these cells through signalling pathways takes place during remodelling. However, extensive research is yet to be done on how these signalling pathways and other intrinsic and extrinsic factors affect bone physiology[41].

BONE QUALITY *VS* BONE QUANTITY

Bone quantity, which was conventionally thought to be the primary detector of fracture risk, referring to low bone mass or BMD, is linked to higher fracture rates with ageing and bone diseases. However, past studies over the past three decades show that bone quantity alone cannot explain or determine all fracture risks or the benefits and effects of drug therapies. This has shifted attention to bone quality, which includes composition, microdamage mechanisms, structure, and the modelling-remodelling processes[42].

Bone is mainly composed of type I collagen, surrounded by hydroxyapatite crystals. Non-collagenous proteins and glycoproteins, which are minor in amount, crucially regulate formation and mineralization. Collagen type 1 is a triple helix of two α1 and one α2 chains of amino acids. The mineral carbonated hydroxyapatite contains impurities like carbonate, magnesium, fluoride and sodium, which affect mechanical properties. Mineral crystals organize within the collagen framework, with apatite crystals aligning in and around collagen fibrils. Enzymatic crosslinking connects these collagen components, thus giving the bone structure elasticity and stability[43,44]. At the tissue level, fibrils assemble into fibres, which eventually arrange into many layers (lamellae). In cortical bone, these lamellae/Layers circle the Haversian canals, forming osteons bordered by hypermineralized bone cement. Both cortices and trabeculae have osteocyte lacunae.

MICROARCHITECTURAL DETERIORATION AND MARROW COMPOSITION

Bone marrow (BM) is a soft tissue present in the cavities of bones and is responsible for haematopoiesis, regulating bone remodelling and also the immune system. The constituents of BM are dynamic and variable, as there is a constant change in the cellular portion and tissues, which vary with age and systemic conditions. Based on the presence of red cells or adipose cells, BM is called red marrow and yellow marrow, respectively. Yellow marrow comprises about 95% of the marrow; on the other hand, red marrow includes only 5% of the marrow[45].

Microarchitectural deterioration in osteoporosis includes the decrease in bone mass and quality by affecting structural integrity at both trabecular and cortical levels[46-48]. The balance mentioned earlier between demineralization and bone formation is disrupted, typically with increased osteoclast activity and insufficient mineralization, resulting in net bone loss and weakened bone microstructure. Age-related decrease in osteoblast number and activity, influenced by hormonal changes such as oestrogen deficiency, nutritional factors, reduced physical activity and exercise and medications like glucocorticoids, further impairs bone formation and repair[49-51]. This results in thinning and loss of connectivity of trabeculae, increased levels of cortical porosity and also accumulation of microdamage.

Marrow composition changes accompany along with these structural changes. Increased BM fat replaces hematopoietic tissue, negatively affecting bone remodelling by altering the local microenvironment and reducing osteoblast differentiation[51-54]. Together, these alterations in bone microarchitecture and marrow composition reduce bone strength and increase fragility independently of BMD, emphasising the importance of assessing both quality and quantity for fracture risk prediction and treatment.

QUANTITATIVE MAGNETIC RESONANCE IMAGING IN BONE ASSESSMENT

Magnetic resonance imaging (MRI) has been a handy, non-invasive tool to help in the crucial clinical diagnosis of many musculoskeletal (MSK) disorders. Problems in the connective tissue, such as rotator cuff tears, meniscal tears and ligament and tendon lesions, are the most common scenarios where MRI is widely used, and most of the protocols are designed to assess these types of cases[55]. Over a period of time, the MRI of the MSK system has been dependent on traditional sequences with the use of qualitative assessment. Quantitative assessment tools like quantitative MRI (QMRI) have been in the spotlight lately. QMRI will help in critical early diagnosis and management by providing additional

deep insights into the anatomical and physiological aspects. Even though this method has gained recognition, it still has its own liabilities that need intense studies and corrections.

MRI is a non-invasive tool, and there is no risk of radiation exposure to the patients, adding to its list of benefits. More detailed analyses, like tissue architecture, microstructure, function and constituents, are provided by QMRI, which would help in diagnosing fractures much quicker and earlier. Very short echo time, which is a disadvantage in signal-to-noise ratio, has made it challenging to apply T1ρ and T2 in tissues of MSK. However, translation of QMRI data from cartilage to tendons is very tedious and slow[55]. The techniques or methods under QMRI, which are used to evaluate physiologic composition of articular cartilage, can be grouped into relaxometry methods without contrast agents (T2, T2* and T1ρ mapping) or with contrast agents (delayed gadolinium-enhanced MRI of cartilage), diffusion imaging, magnetization transfer, chemical exchange saturation transfer imaging and sodium MRI[44].

TECHNIQUES OF BMD ASSESSMENT

T2 mapping

T2-mapping requires gaining many images with different echo times that provide signal intensities following a T2 relaxation curve, by means of sequences such as single echo spin echo, multi-echo spin echo, and dual echo steady state. Acquisition can be lengthy, and patient movement can cause imprecise mapping. A downfall from a technical point of view with multi-echo spin echo T2 mapping is sensitivity to B1 inhomogeneity, which is mainly prominent at high field strengths like 3T. Methods utilising a T2-preparation pulse have been projected to reduce B1 sensitivity and provide faster acquisition, though fewer echoes may compromise precision[56].

Postprocessing can be done on the scanner online or offline with the use of algorithms such as MATrix LABoratory. Automated processing provides pixel-by-pixel maps of T2 relaxation times. Offline processing includes registration, segmentation, and region-of-interest analysis. Interpretation requires carefulness, as absolute T2 values differ by anatomic location and scanner, and are influenced by the magic angle. Abrupt changes or irregularities on T2 maps could be abnormal[57,58]. T2 mapping is authenticated for non-invasive quantitative analysis of tissue structure and composition, and could be used in most of the MRIs without contrast. It is recurrently used for the evaluation of articular cartilage, where changes in density and arrangement of the extracellular matrix appear as changes in the T2 values. T2 mapping could notice early variations in water content and concentration of collagen before structural abnormalities, detect early-stage degeneration, evaluate reparative tissue and monitor therapy. It can also assess muscle composition, including oedema and other inflammatory changes. Fatty degeneration raises T2 values and is a puzzling factor; fat suppression techniques might reduce these effects. Obesity, exercise-related oedema and incomplete fat removal should be considered[56].

T1ρ mapping

T1ρ ("spin-lock" relaxation) assesses biochemical changes in tissues. It reflects magnetic relaxation under a radiofrequency pulse and is sensitive to low-frequency interactions between water and macromolecules. Conventional continuous-wave spin-lock pulses are vulnerable to field inhomogeneities; adiabatic spin-lock pulses decrease these effects and the magic angle artefact[59].

T1ρ is sensitive to proteoglycan (PG) content in cartilage and finds out initial PG loss in osteoarthritis. It has shown consistency in reading cartilage damage in osteoarthritis and rheumatoid arthritis. T1ρ reflects interactions between protons and the macromolecular environment of cartilage, and alterations such as PG loss are reflected in T1ρ values. It provides a non-invasive analysis of PG content without the use of contrast agents or any extra hardware. Disadvantages include variability between pulse sequences, angular and layer dependence, and confounding by multiple tissue components[60].

Proton density fat fraction

Proton density fat fraction (PDFF) derived by chemical-shift encoded MRI gives a quantitative assessment of fat by modelling water and fat signals. It provides the ratio of mobile triglyceride protons to total mobile protons, reflecting triglyceride concentration. PDFF allows quick tissue assessment with region of interest (ROI)-based quantification on fat-fraction maps; R2 maps can evaluate iron content at the same time[61]. MRI-PDFF has established accuracy in quantifying hepatic fat when compared to magnetic resonance spectroscopy and biopsy, and is effective in follow-up of non-alcoholic fatty liver disease and clinical trials. It is practicable for evaluating fat accumulation in multiple tissues, including bone marrow, muscle, testis and adipose tissue[61].

Diffusion-weighted imaging

Diffusion-weighted imaging (DWI) measures variations in the diffusion of water molecules within tissue. It is well-known in neuroradiology but is less commonly used in MSK imaging. DWI images are produced by applying two diffusion gradients - one dephasing and one rephasing. Diffusion leads to incomplete reversal of phase shifts, producing signal attenuation. For muscle MRI, DWI can detect minor lesions and fatigue-related disorders not seen on traditional sequences. DWI can be used with diffusion tensor imaging (DTI) to evaluate anisotropy and muscle fibre orientation. DTI parameters quantify diffusivity and anisotropy, helping in early detection of fibre disorganisation from mechanical injury or exercise-related trauma. DTI has its uses in muscle physiology, anatomy, pathology and also sports-related injury[62].

DWI and DTI are dependent on acquisition parameters and are vulnerable to artefacts from motion, misregistration and susceptibility effects. Muscle DTI parameters are considered to be sensitive to age, gender, body mass index, exercise status and also temperature. Future research and improved postprocessing are necessary for wider clinical use.

Applications in vertebral and proximal femur assessment

Diffusion-weighted (DW)-PSIF imaging, consisting of a delta value of 3 milliseconds, is a valuable tool for distinguishing benign and malignant vertebral fractures. Quantitative chemical-shift imaging and apparent diffusion co-efficient values (DW single-shot turbo spin-echo) also show significant variations between the two things, but these differences are inferior compared to DW-PSIF due to a substantial overlap[63].

In addition to images from standard scanning routines like non-contrast enhanced and contrast enhanced T1-weighted, T2-weighted and short tau inversion recovery images, DIXON turbo spin-echo sequences give more information. In combination with other accessible imaging sequences, these data can support in producing of more effective tools for segmenting MSK structures and facilitate QMRI through automated segmentation and analysis. This is used for studying vertebral bodies, cartilage endplates, and intervertebral discs[64].

Correlation with fracture risk and bone strength

The radiological evaluations of the quality of bones explained by far reflect only the composition of bone minerals. While radiological investigations of the mineral constituents provide estimates of BMD as well as along with other changes in the structure that correlate with stability and rigidity, different parts of bone, like collagen and fat content, could explain resistance to fracture. QMRI measurements are sensitive to the presence of water and fat (including fat present in BM) in the bone. Since the fat content of BM is directly linked to the metabolism of bones, there is a proven correlation between BM adiposity and the risk of fractures. Saturated, monounsaturated and polyunsaturated fat fractions increase with an increase in age. Usually, lower DEXA BMD and increased saturated bone marrow fat fractions are linked with greater chances of fractures[44,65]. The QMRI measures supplement BMD estimates and can outdo DEXA in predicting fracture risk when incorporated into clinical risk models, helping in early identification and better management of osteoporosis and fragility fractures[66].

Vertebral Bone Quality and modified Vertebral Bone Quality scoring

The Vertebral Bone Quality (VBQ) score is a perfect measure of BMD, which uses routine preoperative MRI in spine surgery[67-71]. VBQ score associates with age and is replicated across continuous scanning. But, external factors, which include the MRI machine, regulations and criteria, influence the VBQ scores[59]. The VBQ score is calculated from routine T1-weighted MRI images by measuring the signal intensity (SI) of the medullary portion of the lumbar vertebral bodies (L1-L4) and dividing it by the SI of the cerebrospinal fluid (CSF) at the level of L3, as shown in Figure 1A. The formula is given as: VBQ score = median SI (L1-L4 vertebrae)/SI (L3 CSF)[72]. Higher VBQ scores are related to increased fat infiltration in the vertebral marrow, demonstrating lower BMD and a higher risk of fragility fractures[72-75]. The method is found to be practical for opportunistic bone quality screening without any additional radiation exposure.

Modified VBQ enhancements and standardization

False positive outcomes may happen in the conventional VBQ technique as a result of overestimation, which may occur due to levels of intravertebral fat and vascular structures present, mainly on the posterior part of vertebrae. The newly modified VBQ (mVBQ) scoring gives a simpler, much more efficient and comparatively precise way of studying bone quality in lumbar diseases. This modified VBQ method could be beneficial in quick preoperative screening for patients [76,77].

In a retrospective cohort study, Li *et al*[70] studied the performance of the modified VBQ (defined as the VBQ scoring measured in the anterior half of the vertebrae) and the VBQ-classic in assessing bone quality in patients with lumbar diseases. They found that the modified-VBQ scores were significantly lower than those of the VBQ-classic and showed a stronger linkage with lumbar T-scores. The authors theorized that this might be attributed to the posterior part of the vertebral body containing a higher density of vascular and neural structure, which could present measurement artefacts and lead to overestimation of VBQ scores in that particular region, as shown in Figure 1B[77].

Clinical utility in vertebral fragility fracture prediction

MRI-derived VBQ score is much more helpful than DEXA-based BMD measurements because of its independent nature in predicting and assessing fragility fractures and osteoporosis[78,79]. Since patients who undergo orthopaedic surgery consultation require constant and much more frequent MRIs, it is believed that the MRI-derived VBQ scoring would be a beneficial means for assessing the quality of bones to enhance the care and patient management[80].

This MRI-based VBQ score could be a non-invasive and also a replicable method to assess the quality and risk of osteoporotic fractures. Researchers recently commented that the VBQ score, measured from non-contrast T1-weighted images and d T2-weighted images sequences of lumbar spine MRI, could detect individuals with osteoporosis with an area under curve (AUC) of 0.713-0.846. The VBQ scoring is dependent on the field strengths of magnetic resonance platforms and VBQ scores of 1.5 T magnetic resonance platform attained better differentiation of individuals having or not having osteoporosis than that of 3.0 T.35 VBQ-T1-weighted images score of L1-4 vertebrae has also proven to be significantly linked with trabecular bone microarchitecture derived from microcomputed tomography like bone volume fraction (r = 0.314), trabecular number (r = 0.326) and trabecular separation (r = 0.349)[81,82].

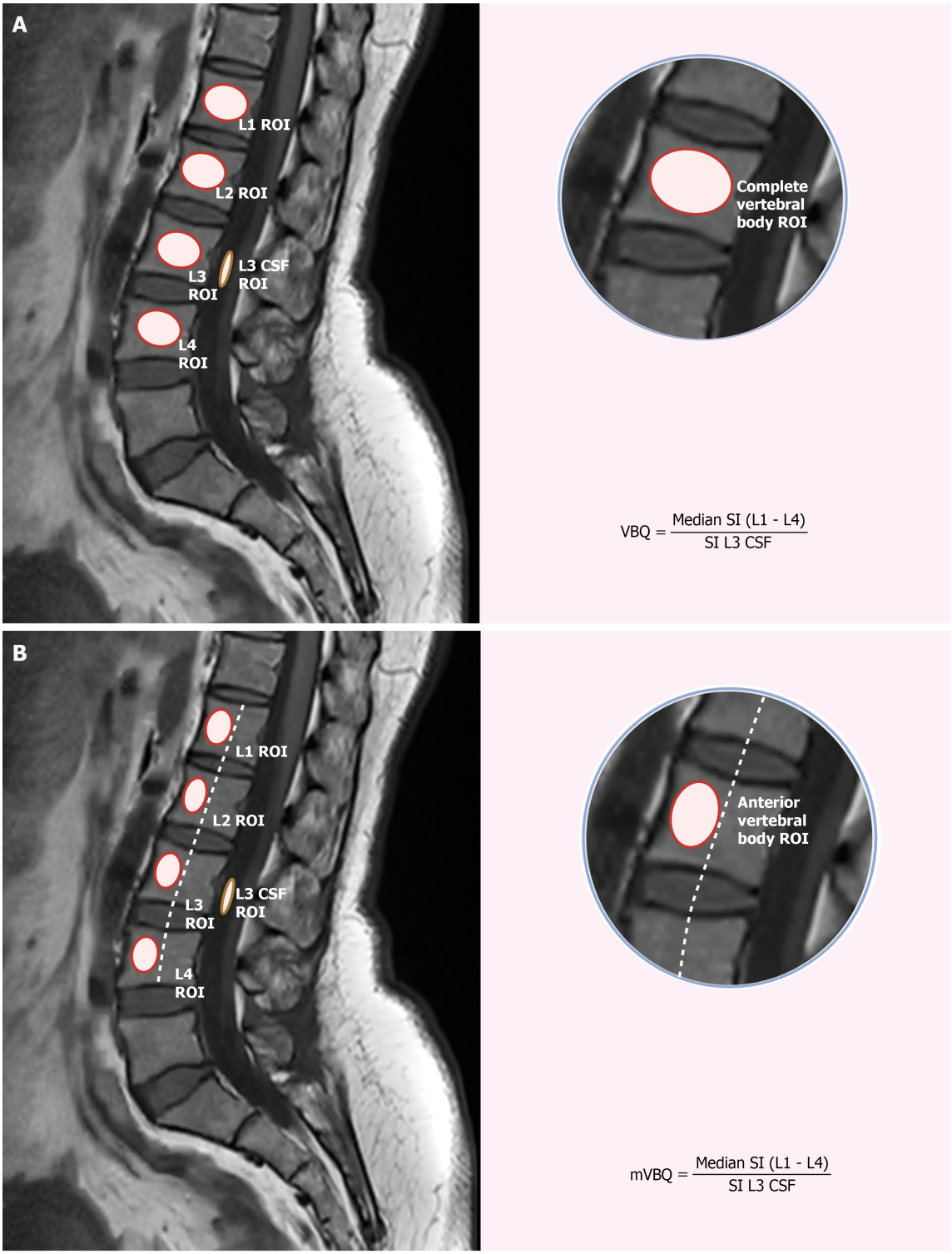


Figure 1 Schematic diagrams for Vertebral Bone Quality score and modified Vertebral Bone Quality score calculation. A: Calculation of Vertebral Bone Quality score; B: Calculation of modified Vertebral Bone Quality score. VBQ: Vertebral Bone Quality; mVBQ: Modified Vertebral Bone Quality; ROI: Region of interest; CSF: Cerebrospinal fluid.

Comparative performance vs BMD and FRAX

VBQ scoring has just a feeble negative linkage with BMD (T-score), which means it reflects bone quality beyond what the BMD captures. Several studies show that VBQ predicts new vertebral fractures independently of BMD, and in some cases, shows greater predictive ability than DEXA, the benchmark for measuring BMD. Prediction models that constitute the VBQ score with clinical risk factors, age, and fracture history have shown high discriminatory ability (AUC ≥ 0.8), comparable to or even exceeding FRAX and TBS in a few long-term studies[81,83]. While BMD accounts for about 70% of bone strength, it also remains the backbone for osteoporosis diagnosis. VBQ adds value by finding cases of poor bone quality at the borderline or non-osteoporotic BMD, particularly in predicting vertebral fracture recurrence[84]. VBQ demonstrates encouraging potential as a clinically feasible tool, serving as a valuable - and at times superior - alternative

or complement to BMD and FRAX, enabling more precise prediction of vertebral fragility fracture risk across diverse patient populations[60,79].

Sensitivity and specificity of QMRI and VBQ/mVBQ

A study reported the VBQ score to have a sensitivity of 93% and specificity of 65.4% for osteoporosis prediction, showing reasonably good diagnostic ability (AUC = 0.818). The higher sensitivity makes it suitable for identifying high-risk populations, although moderate specificity means there are chances of false positives occurring. In a study, the simplified S1 VBQ score, which is used mainly when L1-L4 vertebrae are challenging to assess, showed a sensitivity of 91% and variable specificity (59%-90%) depending on chosen cutoff thresholds. It showed good repeatability and clinical feasibility for opportunistic BMD screening[79].

Integration with DEXA, high-resolution peripheral quantitative computed tomography, and computed tomography - based assessments

Currently, the widely used assessing tool for the quality of bones is done by DEXA. Lumbar DEXA causes increased BMD readings than the real data, because of the inability to differentiate the intrusion of dense calcifications like degenerated vertebral hyperplasia bone, facet joint hyperplasia and abdominal vascular calcifications, which might lead to loosening of the screw, particularly in the older population[83,85].

Quantitative computed tomography (QCT) precisely shows specific bone density in various areas *via* 3D measurement. QCT is a much more effective and valuable tool to assess spinal BMD as it can exclude interference of any abnormal pathologies in the formation of bones on the final data, especially in individuals with degenerative changes[86-88]. Moreover, QCT-based finite element models of the spine show that they are better at evaluating the strength and stability of bones than DEXA-based BMD. Also, loosening of screws is a topic of consideration to be predicted by QCT. The International Society for Clinical Densitometry suggested that the density information in the central region of the cancellous bone of the vertebral body continuously represented QCT. As within the vertebrae changes in BMD from area to area[24,89].

Predictive modelling and artificial intelligence-enhanced interpretation

The predictive nomogram model, which integrates clinical risk determinants with the VBQ-combined index, gave the strongest discriminatory capability for forecasting non-union of fractures. It produced an outstanding AUC of 0.838 (95% confidence interval: 0.773-0.904), compared to models based solely on clinical variables [age: 0.702 (0.614-0.790); prior vertebral fracture: 0.658 (0.578-0.739)] and those relying only on the VBQ-combined metric [0.793 (0.719-0.868)]. Consequently, the nomogram substantially enhances the prognostic accuracy for imminent non-union of fractures compared with either component alone[79].

Nonetheless, determining the VBQ requires manually delineating multiple regions of interest on MRI scans, making its assessment labour-intensive, dependent on specialised imaging software, and prone to inter-rater inconsistency. An artificial intelligence (AI) - driven algorithm could alleviate these drawbacks and improve real-world applicability by facilitating seamless incorporation into electronic health record systems. Similar AI-enabled automation has already been effectively used for extracting other radiologic measurements, such as spinopelvic parameters from spinal radiographs [90,91].

METHODOLOGICAL CONSIDERATIONS

Imaging protocols and reproducibility

Imaging protocols for VBQ/mVBQ assessments usually use routine non-contrast T1-weighted lumbar spine MRI using the following standardized parameters.

Field strength: 1.5T or 3.0T MRI scanners, with recognition of the fact that VBQ values differ slightly between field strengths requiring institution-specific thresholds. Sequence and Parameters: T1-weighted spin-echo or fast spin-echo sequences, with repetition times approximately 400-600 milliseconds and echo times around 10-20 milliseconds. Slice thickness is 3-4 mm with none or small slice gaps[92].

ROI: Circular or elliptical ROIs of standardized size are placed in the anterior medullary areas in vertebral bodies L1-L4, avoiding regions affected by fractures, haemangiomas or even Modic changes. A similar ROI is also placed in the CSF at the L3 vertebral level for normalization[93,94].

Image analysis: SI measurements of the vertebral marrow and CSF are attained on mid-sagittal or parasagittal slices by using picture archiving and communication system or specialized image analysis software. The VBQ score is computed as the ratio of median vertebral SI to CSF SI.

Reproducibility: Studies show good intra- and inter-observer reproducibility with intraclass correlation coefficients (ICCs) usually above 0.85-0.90 for VBQ measurements when protocols and ROI placement guidelines are standardized. Reproducibility across different MRI systems and field strengths is acceptable but affected by scanner parameters. Therefore, institution-specific thresholds are often recommended. Exclusion of vertebrae with fractures or significant degenerative changes enhances measurement consistency[95].

Inter-reader variability and scoring standardization

Reported interobserver ICCs range from about 0.77 to 0.89, showing good agreement between independent readers scoring VBQ from lumbar spine MRIs. Intraobserver ICCs are even higher, around 0.89, showing high reproducibility when standardized ROI placement and measurement protocols are followed. Variability can be influenced by factors such as magnetic field strength (1.5T *vs* 3.0T), MRI sequence parameters and selection of vertebral levels/ROI size. Still, careful standardization decreases these sources of variation. Automated and AI-assisted approaches to VBQ measurement are emerging to improve standardization and reduce human variability, showing promising validation results. Scoring standardization includes defined ROI placement in the anterior vertebral marrow, exclusion of vertebrae with Modic changes or fractures and normalization of vertebral marrow SI to CSF signal[93,96].

Limitations in accessibility and cost

There are many advantages to the usage of the VBQ method in healthcare systems. MRI is now a standard routine preoperative screening method. Yet, machine variability is a significant topic of concern. MRI is very complex and is based on lots of theoretical physics. Different machine manufacturers, magnetic field strengths, imaging protocols and echo times change significantly, which weakens the reliability of VBQ. QCT needs many more research studies, funding and development in software, limiting its clinical usage. Environmental factors such as race, location, bone density reference standards and machine type could lead to changes in VBQ threshold for fragility fractures from one location to another[85]. Valuable data for evaluating BMD can be gained from individuals through the VBQ method without any additional imaging, radiation exposure, extra expenditure, or time.

Challenges in multicenter validation

Challenges in multicenter validation of the VBQ score involve high heterogeneity from differences in reference standards (DEXA or QCT), sex, mean age, region of publication and VBQ methods, variations in MRI systems, which undermine the consistency of VBQ measurements. Differences in patient cohorts like prevalence of osteoporosis, age and sex are found to affect diagnostic performance. Region-specific variation and changes in VBQ scores within the spine-cervical, thoracic and lumbar regions show distinct characteristics which complicate standardization. Exclusion of vertebrae with degenerative changes decreases applicability in many severely affected patients. Lack of standardized MRI acquisition protocols universally, thus requiring further prospective multicenter cohort studies to optimise VBQ thresholds and improve its clinical utility[22,80].

Clinical implications and future directions

The VBQ score has a very important role in early detection and personalized fracture risk stratification. It is an opportunistic and non-invasive screening tool for osteoporosis, particularly in patients undergoing lumbar spine MRI before surgery. VBQ score is found to be a more delicate risk estimating method in front of evaluations of bone quantity, which is measured by BMD. VBQ scoring only differentiated between normal and abnormal bone mass, and the capability to distinguish between osteopenia and osteoporosis has not met clinical needs yet; thus, further research and development are needed[79].

It is proven that the MRI-based VBQ score is both an independent and a major predictor of fracture risk in relation to DEXA-based BMD[56,97-99]. High sensitivity and moderate specificity are provided by MRI-based VBQ scores in detecting osteoporosis. There is possible integration into routine screening, as MRI is commonly used in spinal and other MSK evaluations, and the VBQ score can be assessed without any additional procedures or costs[90]. Standardization and reliability have been established with excellent interrater and intrarater reliability, showing that it can be applied routinely across different centres and operators. The use of CSF SI normalization helps to reduce scanner variability, making it appropriate for multicenter implementation. Clinical integration is practicable because the VBQ method uses routine T1-weighted sequences, eliminating the need for additional imaging protocols. Automated algorithms, including AI, are in the development phase to facilitate faster and accurate assessments, further supporting efficiency. The VBQ score can be incorporated into preoperative evaluation before spine surgery to detect fracture risk and help in surgical planning, mainly as bone quality influences fixation stability. The VBQ approach could be used in broad screening of at-risk populations (elderly, osteoporotic patients) during routine MRI examinations, thus enhancing early diagnosis and personalized management[96]. Individuals with a higher risk of fractures are now being considered for prophylactic fixation to avoid the morbidity of fragility fractures[100].

Research gaps and ongoing trials

Research gaps recognized for the VBQ score include limited diagnostic uses when used as the only tool due to moderate correlations with DEXA BMD (all AUC values < 0.70). There is a need for a systematic assessment of VBQ scores from different vertebral regions, as region-specific variations are present that affect sensitivity and specificity - insufficient potential multicenter trials with large sample sizes to validate optimal VBQ thresholds and improve clinical applicability. Inconsistency due to MRI system differences, patient anatomy, degenerative changes and imaging protocols limits universal and global standardisation. Underexplored predictive ability for specific patient groups, such as patients with obesity or spinal deformities. Need for integration with other imaging biomarkers and clinical risk factors to develop effective predictive models for fracture risk and surgical outcomes[22,79]. Ongoing trials and research studies are focused on perfecting measurement regions (anterior *vs* posterior vertebral marrow), automated AI-based VBQ quantification and expanding VBQ's usage in preoperative spine surgery assessment and osteoporosis screening.

Future of imaging biomarkers in precision bone health

The future of imaging biomarkers in precision bone health is found to be promising, with significant developments including: Advanced quantitative bone imaging combined with AI-based analysis provides enhanced prediction of fragility fractures by assessing bone macro- and microstructure, genetics and biomarkers for personalized assessment. AI algorithms allow for automated and precise evaluation of bone properties from imaging, improving diagnostics, treatment planning and patient care through early fracture detection, bone density assessment and risk prediction. Integration of multimodal data, including imaging, omics technologies (genomics, proteomics, metabolomics), and large-scale clinical datasets using machine learning, is believed to provide personalized risk stratification and optimized treatment strategies. Emerging biosensor and point-of-care technologies for biochemical bone biomarkers will enhance imaging by allowing real-time, accessible monitoring of bone health. Novel imaging modalities like ultrashort echo time MRI and finite element analysis simulate mechanical bone properties, enhancing fracture risk prediction with higher precision and accuracy and less radiation. Imaging biomarkers will increasingly integrate into clinical workflows for early diagnosis, treatment monitoring and preoperative planning, thus supporting precision bone health management[101,102].

CONCLUSION

Fragility fractures remain a pressing global health burden, often occurring despite normal DEXA-defined BMD. Advanced imaging biomarkers such as quantitative MRI and VBQ/mVBQ scoring provide deeper insights into bone quality, microarchitecture, and marrow composition, surpassing traditional BMD assessment. Their integration into predictive models, supported by artificial intelligence, enables opportunistic, radiation-free screening and precise risk stratification. Together, these innovations mark a paradigm shift toward comprehensive evaluation, prevention, and management of osteoporosis-related fractures.

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