Clinical Interventions in Aging

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ORIGINAL RESEARCH

The Association Between Short-Term Bone Loss and Future Osteoporotic Vertebral Fractures

Ludan Chen[1,*], Jinsheng Yi[1,*], Weijia Xi[1,*], Long Liu[1], Feiyu Niu[1], Wei Zhang[1], Jiexiong Xu[2], Jinhui Cai[1], Qingyu Liu[1,3]

[1]Department of Radiology, The Seventh Affiliated Hospital, Sun Yat-Sen University, Shenzhen, People's Republic of China; [2]Department of Radiology, The Fourth Affiliated Hospital, Guangzhou Medical University, Guangzhou, People's Republic of China; [3]Shenzhen Key Laboratory of Bone Tissue Repair and Translational Research, Shenzhen, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jinhui Cai; Qingyu Liu, Department of Radiology, The Seventh Affiliated Hospital, Sun Yat-sen University, 628 Zhenyuan Road, Xinhu Street, Guangming New District, Shenzhen, Guangdong, People's Republic of China, Tel/Fax +86-0755-81206502, Email caijinhui@sysush.com; liuqingyu@sysush.com

Objective: To investigate the relationship between longitudinal change in Hounsfield Units (HU) value and future osteoporotic vertebral fracture (OVF).

Methods: This longitudinal case–control study involved 52 cases with future OVF and 104 age- and sex-matched controls. Each participant underwent two chest computed tomography (CT) scans. The baseline regional (anterior, middle, posterior, superior, inferior) and integral HU value from T4, T7, T10, and L1 vertebrae were measured. The coefficient of variation (CV) indicated heterogeneity in HU. Bone loss was quantified by the annual rate of HU value loss. Conditional logistic regression was employed to evaluate the independent risk factors (baseline CT characteristics and annual HU value loss) for each vertebra in predicting future OVF.

Results: The baseline regional and integral HU value of T4, T7, T10 and L1 significantly decreased in OVF patients compared to the controls ($p \leq 0.001$), with the integral HU value negatively related to future OVF. A decreased superior/inferior HU rate for T7 vertebra (OR=0.397, p=0.003) and an increase in CV for L1 vertebra (OR=1.110, p=0.034) were independently correlated with future OVF. With a follow-up interval of 22.40 ± 12.28 months for the OVF group and 35.15 ± 12.42 months for the control group, a higher annual rate of HU value loss (per 1% increased) was independently positively connected to the risk of future OVF (OR = 1.074, 1.088, and 1.099, for T4, T7, and T10 vertebrae, respectively, all $p \leq 0.006$).

Conclusion: Reduced baseline vertebral HU value and increased annual HU value loss calculated by chest CT may be crucial for predicting OVF, providing valuable guidance for future short-term (approximately 1–3 years) OVF risk evaluation.

Keywords: osteoporotic vertebral fracture, bone loss, computed tomography, Hounsfield units

Introduction

Osteoporosis is characterized by reduced bone mass and deterioration of microarchitecture that leads to elevated susceptibility to fractures.[1] Osteoporotic vertebral fracture (OVF), as the most prevalent type of osteoporotic fracture with high mortality and morbidity, has imposed substantial economic burden on society.[2] Accurate identification of at-risk-populations for OVF is imperative for facilitating early intervention strategies to mitigate the risk of fractures.

Areal bone mineral density (BMD), obtained by dual-energy X-ray absorptiometry (DXA), is regarded as the gold standard for the osteoporosis diagnosis and the risk assessment method of OVF.[3] Despite the highly prevalence, osteoporosis remains highly underdiagnosed worldwide. Approximately half of osteoporotic fractures occur in patients who had never been screened for osteoporosis through DXA.[4] Additionally, the superimposition effects of severe degenerative changes and aortic calcification may induce an overestimation of BMD when measured by DXA.[5] Sixty percent of osteoporotic fractures occur in patients with a T score higher than −2.5.[6]

https://doi.org/10.2147/CIA.S589861
Received: 18 December 2025
Accepted: 11 March 2026
Published: 19 March 2026

Routine chest computed tomography (CT) examinations have gained growing appeal for opportunistic osteoporosis screening without additional cost, time, and radiation exposure.[7] These scans yield comprehensive insights into vertebrae characteristics by conveniently quantifying the CT attenuation in Hounsfield Units (HU) of the vertebral trabecular region. Several longitudinal precedents have indicated that HU or BMD obtained from initial CT of thoracolumbar bodies could be a potentially valuable tool for predicting future fragility fractures.[8–11] These fractures occurred ranging from 1 to over 10 years following the first examination, but studies investigating dynamic changes in vertebral trabecular bone during follow-up and how these changes influence fractures risk are scarce.

Preceding experimental and clinical studies have demonstrated that the intravertebral architecture and density are not uniformly distributed. A recent study has revealed that the HU values varied across the anterior, middle and posterior regions of the lumbar vertebral body, with the lowest HU values in the anterior region.[12] Besides, intravertebral heterogeneity in microstructure and CT attenuation may affect distributions of stress and strain within the vertebra, thereby altering the strength of the vertebrae and correlating with fragility fracture.[13–15] However, most of these studies were cross-sectional, lacking longitudinal evidence to demonstrate the relationship between these vertebral characteristics (spatial distribution and heterogeneity) and subsequent fractures.

Bone loss with aging is a universal biologic phenomenon among the elderly. As indicated in the Framingham Osteoporosis Study, the annual decrease rate of lumbar spine BMD was 1.12% in old women and 0.09% in old men.[16] Extensive studies have demonstrated that rapid bone loss at multiple skeletal sites (comprising hip, distal forearm, ultradistal radius, lumbar spine) was the key factor contributing to higher fracture risk even after adjustment for baseline BMD.[17,18] Load-bearing regions tend to preserve bone longer with advancing age, while regions experiencing minimal mechanical loading lose bone faster.[19] Thus, fracture is more probable when bone is loaded in an unusual direction, as exemplified by a fall. Nevertheless, limited studies have explored the relationship between bone mass dynamic change and subsequent fragility fractures through routine chest CT scans.

This retrospective longitudinal study applied a three-dimensional approach to evaluate CT attenuation across various anatomical regions of T4, T7, T10 and L1 vertebrae from chest CT. These levels may experience distinct biomechanical loads and bone strength, contributing distinct roles in fractures. We aimed to investigate the relationship between baseline vertebral CT characteristics (encompassing CT attenuation, spatial distribution and heterogeneity in HU values), combining with the annual HU value loss and OVF in short-term follow-up. We hypothesized that lower baseline HU values and greater bone loss may serve as predictors of future vertebral fragility fractures.

Methods

The Institutional Review Board of our center granted ethical approval for this study and waived the requirement for written informed consent due to its retrospective design (No. KY-2023-008-02).

Study Population

This case–control study was retrospectively conducted on 7552 consecutive patients aged 50 years or older who underwent repeat chest CT screening for health check-ups at our center from October 2018 to March 2025. The patients were categorized into the case group (OVF group) or the control group (without-OVF group) based on the presence or absence of acute vertebral fractures during the follow-up period. Spinal magnetic resonance imaging (MRI) was performed to assess whether an acute OVF had occurred when patients experienced back pain or disability during the follow-up period. Inclusion criteria for the case group were as follows: (a) patients aged ≥50 years at baseline; (b) two chest CT examinations (baseline CT and follow-up CT); (c) acute vertebral fracture occurred from T1 to L5 vertebrae due to minimal or minor trauma during follow-up period, with bone marrow edema in the fractured vertebrae confirmed by spinal MRI. The exclusion criteria encompassed: (a) a history of previous vertebral fracture at baseline, vertebroplasty or spinal fixation surgery in the spine; (b) presence of severe scoliosis; (c) severe cardiopulmonary comorbidity, chronic diseases affecting bone metabolism (eg., malignant tumor, chronic kidney disease, rheumatoid arthritis, and Cushing's syndrome) and BMD-related medication use (eg., long-term use of glucocorticoid, bisphosphonates, and calcium supplements). The time of fracture onset was considered as the endpoint of follow-up.

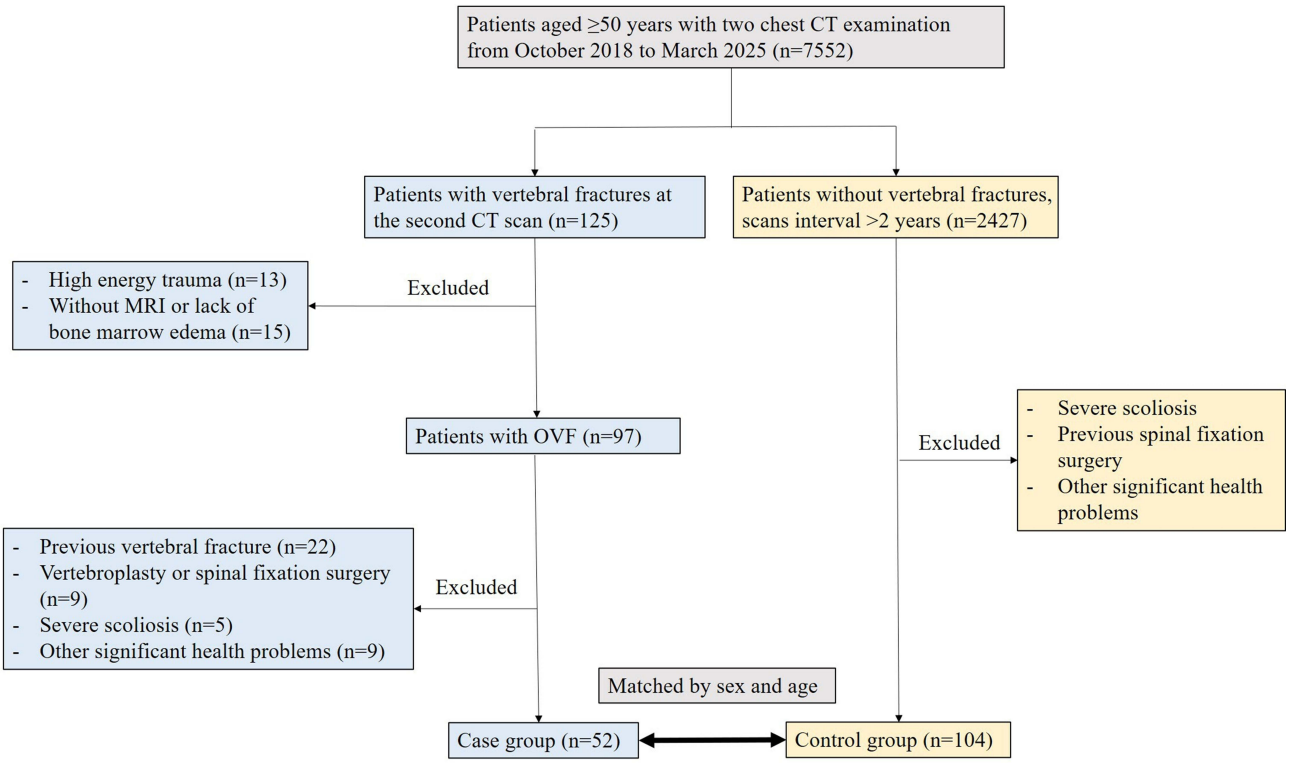

Figure 1 A flowchart of patient selection.
Abbreviations: OVF, osteoporotic vertebral fracture; CT, computed tomography; MRI, magnetic resonance imaging.

A total of 52 patients were ultimately enrolled in the OVF group. Each subject in the OVF group was matched by sex and baseline age (±2 years) in a 1:2 ratio to establish the control group (n=104). The control group had a minimum follow-up of 2-years without vertebral fractures and the exclusion criteria were the same as the OVF group (Figure 1).

Demographic data (including age, sex, weight, height, and body mass index (BMI)), smoking, alcohol, hypertension, and diabetes were collected for all subjects enrolled in this study. Smoking was defined as having smoked 100 cigarettes in their lifetime and currently smoking. Alcohol consumption was identified as alcohol consumption >140g/week for men and >70 g/week for women.[20]

Chest CT Image Acquisition

The CT images were acquired in supine position from three scanners (Aquilion TSX-101A, Toshiba Medical Systems, Japan; Somatom Force, Siemens Healthcare, Germany; uCT 960+, United Imaging, China). The scanning parameters were as follows: tube voltage of 120 kV, automatic milliampere modulation, slice thickness of 1 mm, slice spacing of 0.7 mm. The scanning range covered from the entrance to the thoracic cage to the lower edge of the costophrenic angle. The CT images were reconstructed using a soft standard kernel (Recon FC 03; Body Regular 40; B_SOFT_C) with a pixel matrices size of 512×512. The scanners were calibrated daily to ensure accurate CT attenuation for the vertebrae.

Imaging Measurement Procedure

All HU values of the vertebrae from two CT scans of each subject were evaluated by a training radiologist (J.Y.) with over five years' experience who were blinded to the clinical outcome utilizing an open-source software (3D Slicer, Version 5.7.0). The CT scans of a random sample of 20 participants were assessed by one observer (J.Y.) twice (with 6-month interval) and two observers (J.Y. and L.L.) to evaluate inter- and intra-observer agreement of the measurement.

The vertebral body was segmented into superior and inferior sections, and each section was further subdivided into volumes of interest (VOIs) for HU values measurements: the right-anterior, left-anterior, central, right-posterior, and left-

https://doi.org/10.2147/CIA.S589861

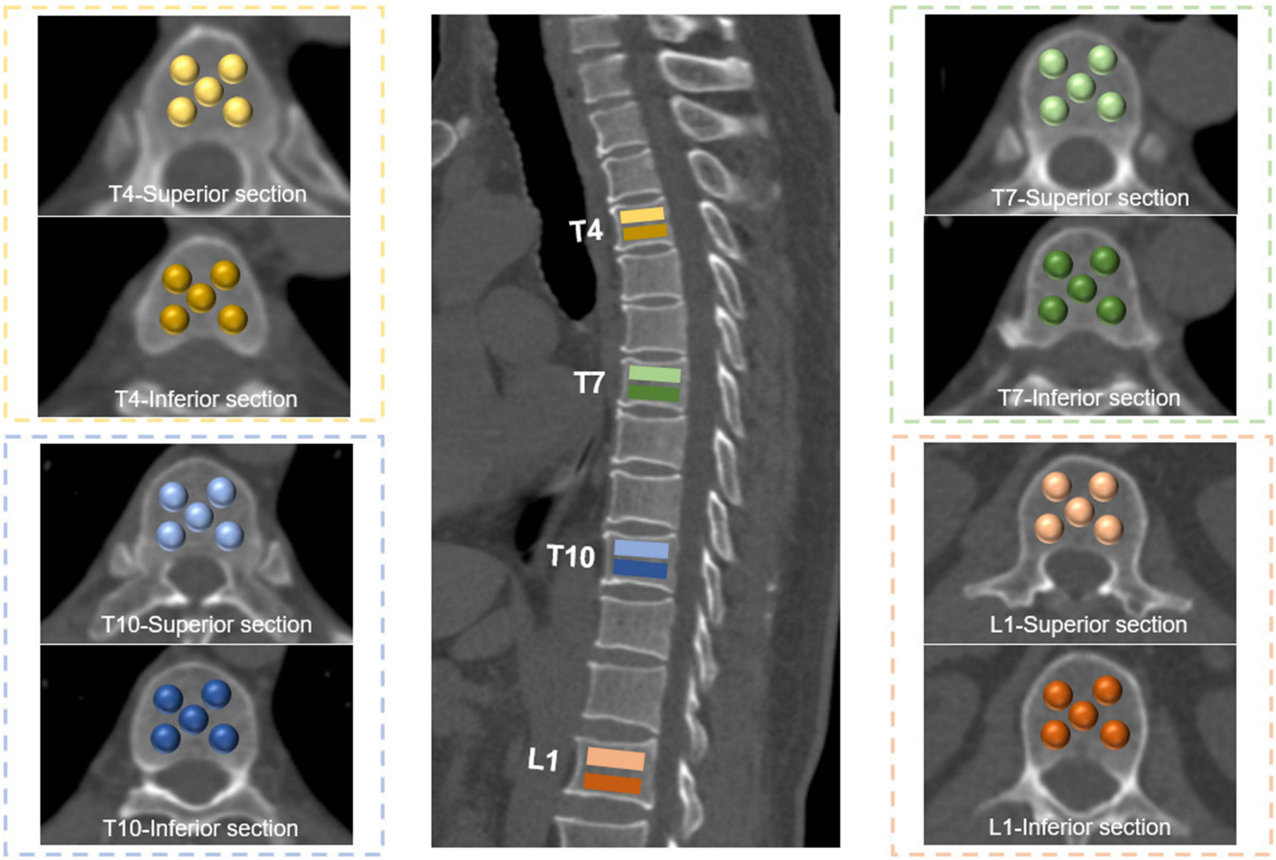

Figure 2 Schematic diagrams of CT attenuation measurements. The T4, T7, T10 and L1 vertebral bodies were divided into superior and inferior sections. Within each section, five distinct locations were identified as spherical VOIs for HU values measurements: the right-anterior, left-anterior, central, right-posterior, and left-posterior sub-regions of the vertebral body.

posterior sub-regions. The VOIs were configured as spheres to facilitate the acquisition of volumetric HU values, avoiding cortical bone, basivertebral veins, and focal lesions like Schmorl's nodes and bone islands. In instances where the vertebral body was insufficient to conduct the measurement (such as fractures in follow-up CT), an adjacent vertebral body was substituted to acquire the attenuation (Figure 2).

Regional Analysis in Vertebral CT Attenuation

For the regional analysis of HU values within the vertebrae, five distinct anatomical regions (the anterior, middle, posterior, superior and inferior regions) were delineated. The anterior, middle and posterior regions were characterized as the mean HU values from the right- to left-anterior sub-regions, the central regions, and from the right- to left-posterior sub-regions of both the superior and inferior sections, respectively. The superior and inferior regions were determined by averaging the HU values of the five sub-regions from the respective section. The integral vertebral was calculated as the average of the HU values obtained from the ten sub-regions within the vertebrae.

Spatial Distribution and Heterogeneity in Vertebral CT Attenuation

The spatial distribution of HU values within the vertebrae were assessed by four regional ratio-based methods: anterior/middle, anterior/posterior, middle/posterior, and superior/inferior HU ratios. The coefficient of variation (CV), calculated as the standard deviation divided by the mean of the HU values across the ten sub-regions, was employed to quantify intravertebral heterogeneity in HU values.

Annual Loss in Vertebral HU Value

The five distinct anatomical regions (the anterior, middle, posterior, superior and inferior regions) and integral annual rate of change in HU was respectively calculated for each individual. Let x_1 and x_2 represent baseline and follow-up HU value, respectively, and *dur* was the time interval (year in unit) between the two examinations; the annual rate of change in HU was calculated as the following formula: *annual rate of HU value loss* = $(x_1 - x_2)/[\text{mean}(x_2, x_1)]/dur$; the absolute annual HU value loss was determined by the following formula: *annual HU value loss* = $(x_1 - x_2)/dur$. In the formula of annual rate, mean CT attenuation was designated as denominator instead of baseline CT attenuation, to mitigate the effect of "regression to the mean" and ensure symmetrical quantification of change.[21,22]

Statistical Analyses

All statistical analyses were performed using R (v4.1.2, R Foundation). Intra- and inter-observer agreement of the HU values measurements were determined by intraclass correlation coefficients (ICCs). The categorical variables were expressed as counts with percentages, and inter-group comparisons utilized chi-square tests. Normality distribution of continuous variables was assessed through Kolmogorov–Smirnov testing. Normally distributed continuous data were presented as mean ± standard deviation (SD), and the *t*-test was employed for comparisons between groups. Continuous data distributed nonnormally were reported as median values with interquartile ranges (IQRs) and inter-group comparisons were performed using Mann–Whitney *U*-test. Univariate and multivariate conditional logistic regression analyses were utilized to examine the baseline CT characteristics (absolute CT attenuation, spatial distribution and heterogeneity) and annual HU loss in predicting future OVF risk. Variables with $p < 0.1$ in the univariate analysis were included in the multivariate analysis. The results of logistic regression were presented as odd ratios and 95% confidence intervals (Cl). Since this was an exploratory analysis, we did not correct for multiple comparisons. Statistical significance was considered at $p < 0.05$.

Results

Patient Characteristics

This study enrolled a total of 52 cases with future OVF and 104 age- and sex-matched without-OVF controls. The demographic and clinical features of the patients are presented in Table 1. No significant differences were observed in height, weight and BMI between the two groups (all $p > 0.05$). The interval from the first chest CT to the OVF onset was 22.40 ± 12.28 months in OVF group, while the follow-up time was 35.15 ± 12.42 months in the control group.

Table 1 Comparison of Baseline Demographic and Clinical Characteristics Between the OVF Group and the Control Group

Characteristics	OVF (n= 52)	Control (n=104)	*P* Value
Sex, n (%)			
Female	34 (65.38)	68 (65.38)	1
Male	18 (34.62)	36 (34.62)	
Age (years)	64 (58–72)	64 (58–72)	0.550
Height (cm)	157.59 ± 7.67	158.59 ± 8.17	0.463
Weight (kg)	58.06 ± 8.91	59.75 ± 9.73	0.294
BMI (kg/m^2)	23.36 ± 3.23	23.72 ± 3.13	0.501
Smoking, n (%)	7 (13.46)	12 (11.53)	0.729
Alcohol, n (%)	8 (15.38)	11 (10.58)	0.387
Diabetes, n (%)	9 (17.31)	13 (12.50)	0.416
Hypertension, n (%)	20 (38.46)	30 (28.84)	0.225
Follow-up time (months)	22.40 ± 12.28	35.15 ± 12.42	< 0.001

Abbreviations: OVF, osteoporotic vertebral fracture; BMI, body mass index.

https://doi.org/10.2147/CIA.S589861

Association Between Baseline CT Attenuation and Future OVF

The intra- and inter-observer agreement for HU value measurements of each ROI in T4, T7, T10 and L1 vertebrae achieved excellent (ICC>0.9).

For T4, T7, T10 and L1 vertebrae, all regional (anterior, middle, posterior, superior, and inferior region) and the integral vertebral HU values at baseline were significantly lower in the OVF group compared with the control group (all $p \leq 0.001$). Specifically, the baseline integral vertebral HU values were 140.40 ± 47.04 versus 172.91 ± 48.24, 125.85 ± 43.59 versus 154.16 ± 46.51, 127.39 ± 41.04 versus 157.33 ± 47.73, 93.18 ± 40.51 versus 124.63 ± 43.16 in two groups for T4, T7, T10 and L1 vertebrae, respectively. The details for each vertebral body were presented in Supplementary Tables 1–4.

Spatial Distribution and Heterogeneity in Vertebral CT Attenuation

Compared to the control group, the baseline anterior/middle HU ratio of T4 and T7 were significantly lower in the OVF group (T4: 0.73 [IQR: 0.66–0.81] versus 0.78 [IQR: 0.71–0.85], $p = 0.003$; T7: 0.73 [IQR: 0.66–0.80] versus 0.79 [IQR: 0.74–0.85], $p = 0.002$). In addition, the baseline superior/inferior HU ratio of T7 in the OVF group was significantly lower (0.95 [IQR: 0.91–0.99] versus 0.99 [IQR: 0.94–1.04], $p = 0.003$) than the control group (Supplementary Tables 1 and 2).

Compared to the control group, patients in the OVF group exhibited higher CV of baseline HU within the T4, T7 and L1 vertebrae (T4: 0.16 versus 0.14, $p = 0.009$; T7: 0.17 versus 0.14, $p = 0.002$; L1: 0.16 versus 0.13, $p < 0.001$). No significant difference in CV of T10 was found between the two groups ($p = 0.984$) (Supplementary Tables 1–4).

Bone Loss in Vertebral CT Attenuation

Compared to the control group, the tendency of annual rate of HU value loss and absolute HU value loss in all regional and integral vertebral HU values for T4, T7, T10 and L1 segments were all higher in the OVF group. For T7 vertebra, the anterior, superior and integral regions exhibited significantly increased annual rates of HU value loss (anterior: 5.54% versus 2.86%, $p = 0.024$; superior: 5.28% versus 3.01%, $p = 0.036$; integral: 5.42% versus 3.02%, p=0.036). For T10 vertebra, all regional and integral vertebral HU showed significantly increased annual rates of HU value loss (all $p \leq 0.034$). For L1 vertebrae, the anterior and inferior regions demonstrated significantly higher annual rates of HU value loss (anterior: 7.11% versus 2.97%, p=0.043; inferior: 5.95% versus 3.10%, $p = 0.025$) (Supplementary Tables 1–4 and Figure 3).

Multivariable Logistic Regression for Future OVF

The risk of OVF was associated with baseline CT attenuation, spatial distribution, intravertebral heterogeneity and bone loss. Baseline CT attenuation for T4, T7, T10 and L1 vertebrae (per 10 HU) were independently inversely related to future OVF (OR = 0.828, 0.780, 0.763, and 0.810 for T4, T7, T10 and L1, respectively; all $p \leq 0.003$). For T7 vertebra, the HU rate of superior/inferior region showed a negative correlation with future OVF (OR = 0.397; 95% CI 0.215–0.734, $p = 0.003$). For L1 vertebra, an increase in CV was positively correlated with future OVF (OR = 1.110, 95% CI 1.008–1.223, $p = 0.034$). The annual rate of HU value loss (per 1%) was independently positively associated with the risk of future OVF (T4: OR = 1.074, 95% CI 1.021–1.129; T7: 1.088, 95% CI 1.031–1.147; T10: 1.099, 95% CI 1.036–1.166; all $p \leq 0.006$) (Tables 2 and 3).

Discussion

This age- and sex-matched case–control longitudinal study evaluated the association between baseline CT characteristics along with the annual HU values loss of the T4, T7, T10 and L1 vertebrae and OVF occurrence. Our results demonstrated that individuals with future OVF exhibit significantly lower baseline HU values in all vertebrae than the controls. Increased heterogeneity in HU values of the T4, T7 and L1 vertebrae, as measured by CV, was detected in the OVF group. Furthermore, annual rate of HU value loss of T4, T7 and T10 in short-term follow-up was positively correlated with future OVF after adjusting for baseline CT attenuation. These findings highlight the significance of short-term bone

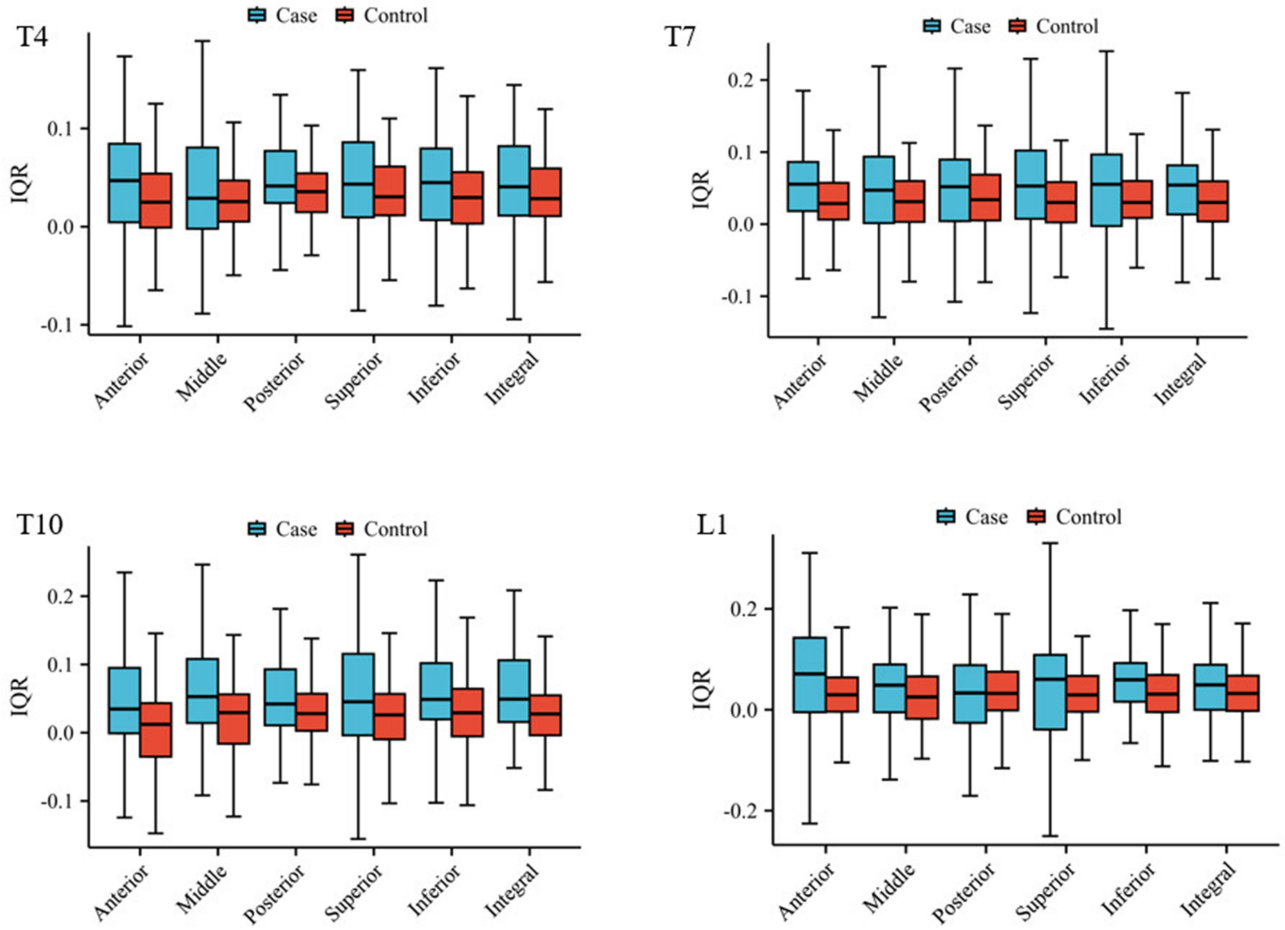

Figure 3 Box plots of the annual rate of HU value loss of T4, T7, T10 and L1 vertebrae between the case (with OVF) and control (without OVF) groups.
Abbreviation: OVF, osteoporotic vertebral fracture.

loss and baseline CT characteristics of the vertebrae as valuable tools for predicting the risk of future spinal fragility fractures.

Recently, opportunistic screening for osteoporosis by routine CT scans has garnered escalating attention. Prior reports have demonstrated that lower HU values in various vertebrae from chest CT images provided a simple and effective method for assessing bone quality and predicting OVF.[7,23] Consistent with these findings, our study observed that individuals who would develop OVF presented with 18%–25% decreased HU at T4, T7, T10 and L1 vertebrae, with the most significant decrease in L1 vertebra (93.2 ± 40.5 versus 124.6 ± 43.2).

Bone loss is an essential phenotype that directly causes osteoporosis. Previous studies have depicted the longitudinal changes in bone mass during aging. In a large-sample retrospective cross-section study among patients aged 18–100 years, the average L1-HU values showed a linear decrease with age at a rate of 2.5 HU per year.[24] A prospective study of 1062 Vietnamese women aged 40–59 observed that bone loss occurred before menopause (aged 45–49 years, 0.56%/year), and then accelerated in the early perimenopausal transition (aged 50–54 years, 1.33%/year).[22] Based on automated BMD from L1–L2 attenuation values, mean annual rates of bone loss in females and males (all aged 50–70 years) were 2.0% and 1.0%, respectively.[25] Utilizing a matched approach to eliminate the impact of sex and age on bone mass change, our study observed the mean annual HU values loss rates were 2.75–3.23% (3.24–4.56 HU per year) in vertebral bodies of subjects without future fractures, and 4.06–5.42% (4.06–6.29 HU per year) in those with future fractures, which was similar to the overall trend demonstrated in previous studies.

Trabecular bone loss at various sites has revealed significant correlations with fractures. A faster decrease in distal radius total volumetric BMD was associated with higher fracture risk (HR=1.54/SD) in old men during 8-year-follow

https://doi.org/10.2147/CIA.S589861

Table 2 Univariate Conditional Logistic Regression Analysis for the Association Between Future OVF and Baseline Characteristics and Annual Rate of HU Value Loss of T4, T7, T10 and L1 Vertebrae

Characteristics	T4		T7		T10		L1	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
CT Attenuation (Increased per 10 HU)	0.844 (0.771–0.923)	**<0.001**	0.841 (0.763–0.927)	**<0.001**	0.827 (0.746–0.916)	**<0.001**	0.760 (0.668–0.864)	**<0.001**
Distribution (Increased per 10%)								
Anterior/Middle	0.524 (0.353–0.779)	**0.002**	0.589 (0.410–0.847)	**0.004**	1.041 (0.791–1.368)	0.776	1.114 (0.944–1.316)	0.202
Anterior/Posterior	0.732 (0.538–0.997)	**0.048**	0.758 (0.563–1.001)	**0.051**	1.123 (0.896–1.406)	0.314	1.018 (0.912–1.136)	0.749
Middle/Posterior	1.186 (0.933–1.508)	0.164	1.191 (0.932–1.520)	0.162	1.115 (0.887–1.402)	0.351	0.838 (0.675–1.039)	0.107
Superior/Inferior	1.374 (0.903–2.093)	0.138	0.480 (0.294–0.782)	**0.003**	1.218 (0.899–1.649)	0.203	0.751 (0.545–1.033)	**0.078**
Heterogeneity								
CV (Increased per 1%)	1.100 (1.034–1.017)	**0.003**	1.072 (1.017–1.131)	**0.010**	1.001 (0.948–1.057)	0.968	1.126 (1.053–1.204)	**<0.001**
Annual rate of HU value loss (Increased per 1%)	1.049 (1.003–1.097)	**0.037**	1.040 (1.005–1.075)	**0.025**	1.056 (1.015–1.099)	**0.007**	1.014 (0.996–1.033)	0.121
BMI	1.037 (0.933–1.154)	0.499	/	/	/	/	/	/
Smoking	0.857 (0.337–2.177)	0.746	/	/	/	/	/	/
Alcohol	0.655 (0.248–1.734)	0.394	/	/	/	/	/	/
Diabetes	0.667 (0.256–1.739)	0.407	/	/	/	/	/	/
Hypertension	0.670 (0.339–1.321)	0.247	/	/	/	/	/	/

Notes: Bold text indicates *P*<0.1.

Abbreviations: OVF, osteoporotic vertebral fracture; CV, coefficient of variation; BMI, body mass index.

https://doi.org/10.2147/CIA.S589861

Table 3 Multivariable Conditional Logistic Regression Analysis for the Association Between Future OVF and Baseline Characteristics and Annual Rate of HU Value Loss of T4, T7, T10 and L1 Vertebrae

Characteristics	T4		T7		T10		L1	
	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
CT Attenuation (Increased per 10 HU)	0.828 (0.742–0.925)	**<0.001**	0.780 (0.662–0.920)	**0.003**	0.763 (0.667–0.874)	**<0.001**	0.810 (0.705–0.932)	**0.003**
Distribution (Increased per 10%)								
Anterior/Middle	0.648 (0.330–1.274)	0.208	0.950 (0.408–2.211)	0.905	//	/	/	/
Anterior/Posterior	1.005 (0.646–1.564)	0.982	1.129 (0.661–1.927)	0.657	/	/	/	/
Middle/Posterior	/	/	/	/	/	/	/	/
Superior/Inferior	/	/	0.397 (0.215–0.734)	**0.003**	/	/	0.872 (0.578–1.316)	0.515
Heterogeneity								
CV (Increased per 1%)	0.997 (0.889–1.119)	0.962	1.044 (0.899–1.212)	0.574	/	/	1.110 (1.008–1.223)	**0.034**
Annual rate of HU value loss (Increased per 1%)	1.074 (1.021–1.129)	**0.006**	1.088 (1.031–1.147)	**0.002**	1.099 (1.036–1.166)	**0.002**	/	/

Notes: Bold text indicates *P*<0.05.

Abbreviations: OVF, osteoporotic vertebral fracture; CV, coefficient of variation.

https://doi.org/10.2147/CIA.S589861

up.[17] BMD loss in total hip in adults aged 50–85 years was an independent risk factor for fragility fractures within seven-year follow-up (with OR of 1.15 in women and 1.34 in men, decrease of 0.01 g/cm^2/y).[26] In older men, low baseline BMD in conjunction with accelerated loss of BMD was associated with hip fracture over a 4–7 years follow-up.[27,28] Greater improvements in BMD were strongly associated with greater reductions in vertebral and hip fractures.[29] While complicating this paradigm, Crandall et al reported that the second BMD assessment 3 years after the initial measurement was not related to improved discrimination in subsequent osteoporotic fracture beyond the baseline BMD.[28] Notably, bone mass changes were majorly estimated by DXA in prior studies. Leslie et al indicated that the limited predictive value of BMD change for fracture risk likely stemmed from the unreliable estimates of DXA in short term (less than 5 years).[30] We employed three-dimensional volumetric measurement approach instead of conventional two-dimensional DXA measurements and highlighted bone loss in the thoracic vertebrae which has rarely been reported previously. As indicated by our findings, both lower baseline HU and higher rate of bone loss (T4, T7 and T10) were independently associated with future fractures, potentially providing novel insights for the stratification of fracture risk over baseline CT alone. Interestingly, although bone loss in the thoracic vertebrae (T4, T7 and T10) exhibited a significant association with future fractures, which were not observed in the L1 vertebra. We speculated that this asynchrony across vertebrae might be attributed to varying loads or earlier detectability among vertebrae. Future studies in biomechanics along with extended follow-up studies might help validate this hypothesis.

Vertebrae exhibit inherent variation among different regions in BMD and trabecular architecture. In the OVF group from our study, the baseline anterior/posterior HU rate in T4 and T7 vertebrae and the superior/inferior HU rate in T7 vertebra were significantly lower, with the superior/inferior HU rate in T7 independently related to future fractures. The trabecular inhomogeneous may explain the dominant role of OVF in the anterior and superior part of the vertebra.[12,31] Furthermore, the decrease of bone loss appeared to be more pronounced in the anterior region compared to other regions at T7 and L1 segments. Our findings aligned with Hugo Giambini et at, who outlined that the anterior BMD of L1–L3 decreased more significantly than the posterior BMD over a 6-year follow-up period (Δ anterior: 18%; Δ posterior: 13%) and this distribution difference over time might increase the risk of wedge fractures.[32] Additionally, we found that patients with OVF demonstrated higher spatial heterogeneity (quantified by CV) in baseline trabecular HU values than the controls within L1, T7 and T4 vertebrae, and this association was independent to baseline integral HU values within L1 vertebra, which was consistent with recent studies.[14,15,33] These findings suggested an inverse relationship between trabecular spatial heterogeneity and vertebral strength. This heterogeneity may be an important determinant of future OVF.

One strength of our study design was the longitudinal routine CT series to assess the relationship between bone loss quantified by annual HU value loss, baseline CT characteristic and future OVF. With the growing popularity of CT equipment, there are increasing patients choosing chest CT examinations for annual health screenings. Opportunistic screening for osteoporosis during routine medical examinations can substantially reduce the cost and complexity of screening programs. This study made secondary use of these CT images to explore the baseline and follow-up CT characteristics to screen out patients with high-risk OVF in short term. Timely anti-osteoporosis intervention is necessary for these patients to prevent fracture occurrence, since certain medications have a rapid anti-fracture effect for those at risk for short-term fracture.[34]

Our study had several limitations. First, it was a single-center investigation with small sample size, potentially limiting the generalizability of the findings. Second, due to the limited information in retrospective nature, it was challenging to obtain complete risk factors for FREX calculation, but we adjusted for sex and age, and excluded the impact of BMI, previous fractures, prior corticosteroid use, and secondary osteoporosis, thereby minimizing the potential confounding effect. Additionally, FREX predominantly focuses on long-term (10-year) fracture risk that is often perceived by patients as an unclear and distant concept, while we prioritized the evaluation of short-term fracture risk aiming to urge patients to initiate intervention measures promptly. Third, the follow-up duration was significantly shorter in the OVF group than the control group due to fracture endpoint, which might influence the estimation of annualized rates. Future efforts in a large cohort employing time-adjusted sensitivity analyses may mitigate such bias. Finally, our analysis utilized a time-consuming manual method for ROIs measuring and focused on HU values at four vertebrae, as these levels roughly represented the segments with various biomechanical loading of the spine, while other vertebrae might provide more patterns of mineral density

alternation. Thus, future researches should employ artificial intelligence for automatic segmentation in larger, multi-center cohorts and validate the relationship between HU values and fracture risk across the entire spine, to develop a more comprehensive understanding of trabecular bone changes and fracture susceptibility.

Conclusion

Our study showed that reduced baseline CT attenuation and elevated annual HU value loss assessed by chest CT were associated with future OVF. These results may provide a novel perspective on opportunistic screening for the risk of osteoporotic vertebral fractures. Future endeavors should validate these findings in multi-center prospective cohorts incorporating artificial intelligence.

Abbreviations

HU, Hounsfield Units; OVF, Osteoporotic vertebral fracture; CV, Coefficient of variation; BMD, Bone mineral density; DXA, Dual-energy X-ray absorptiometry; CT, Computed tomography; BMI, Body mass index; SD, Standard deviation; CI, Confidence interval; IQR, Interquartile range.

Data Sharing Statement

The datasets used in this study are not publicly available because of patient confidentiality but are available from the corresponding author (Qingyu Liu) on reasonable request.

Ethics Approval

Institutional Review Board approval was obtained. This retrospective study was approved by the Ethical Review Board of the Seventh Affiliated Hospital, Sun Yat-sen University, Guangdong, China (No. KY-2023-008-02), which granted permission to access deidentified patient data for this retrospective study, thereby obviating the need for consent to participate. All data were anonymized before the analysis to safeguard patient privacy.

Acknowledgments

The authors thank all their colleagues for their valuable assistance during this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

This study has funded by The Seventh Affiliated Hospital, Sun Yat-sen University Clinical Research 735 Program (No. ZSQY202373516) and Shenzhen Key Laboratory of Bone Tissue Repair and Translational Research (NO. ZDSYS20230626091402006).

Disclosure

All authors declare that they have no conflicts of interest in this work.

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