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Future Osteoporotic Fracture Risk Related to Lumbar Vertebral Trabecular Attenuation Measured at Routine Body CT

Scott J Lee, Peter M Graffy, Ryan D Zea, Timothy J Ziemlewicz, and Perry J Pickhardt

Department of Radiology and Department of Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

ABSTRACT

We sought to determine if vertebral trabecular attenuation values measured on routine body computed tomography (CT) scans obtained for a variety of unrelated indications can predict future osteoporotic fractures at multiple skeletal sites. For this Health Insurance Portability and Accountability Act (HIPAA)-compliant and Institutional Review Board (IRB)-approved retrospective cohort study, trabecular attenuation of the first lumbar vertebra was measured in 1966 consecutive older adults who underwent chest and/or abdominal CT at a single institution over the course of 1 year. New pathologic fragility fractures that occurred after a patient's CT study date were identified through an electronic health record database query using International Classification of Diseases (ICD)-9 codes for vertebral, hip, and extremity fractures. Univariate and multivariate Cox proportional hazards regression were performed to determine the effect of L_1 trabecular attenuation on fracture-free survival. Age at CT, sex, and presence of a prior fragility fracture were included as confounders in multivariate survival analysis. Model discriminative capability was assessed through calculation of an optimism-corrected concordance index. A total of 507 patients (mean age 73.4 ± 6.3 years; 277 women, 230 men) were included in the final analysis. The median post-CT follow-up interval was 5.8 years (interquartile range 2.1–11.0 years). Univariate analysis showed that L_1 attenuation values ≤90 Hounsfield units (HU) are significantly associated with decreased fracture-free survival ($p < 0.001$ by log-rank test). After adjusting for age, sex, prior fracture, glucocorticoid use, bisphosphonate use, chronic kidney disease, tobacco use, ethanol abuse, cancer history, and rheumatoid arthritis history, multivariate analysis demonstrated a persistent modest effect of L_1 attenuation on fracture-free survival (hazard ratio [HR] = 0.63 per 10-unit increase; 95% confidence interval [CI] 0.47–0.85). The model concordance index was 0.700. Ten-year probabilities for major osteoporosis-related fractures straddled the treatment threshold for most subcohorts over the observed L_1 HU range. In conclusion, for patients undergoing body CT scanning for any indication, L_1 vertebral trabecular attenuation is a simple measure that, when ≤90 HU, identifies patients with a significant decrease in fracture-free survival. © 2018 American Society for Bone and Mineral Research.

KEY WORDS: FRACTURE RISK ASSESSMENT; FRACTURE PREVENTION; SCREENING; OSTEOPOROSIS

Introduction

Osteoporosis is an underdiagnosed and undertreated disease that causes significant morbidity and mortality through pathologic fracture rates at various skeletal sites.[1] Identification and treatment of osteoporosis generally reduces future fracture risk,[2] but bone mineral density screening tools are underutilized because of economic and practical factors, such as additional time, radiation concern, and cost.[3] Opportunistic information regarding bone mineral density in eligible unscreened patients could potentially be collected during imaging procedures performed for other indications, maximizing the use of acquired but unused data.

Computed tomography (CT) scans of the chest and/or abdomen are commonly performed imaging procedures in the United States. These scans contain rich bone data, which can be rapidly sampled by measuring vertebral trabecular attenuation values, reported in Hounsfield units (HU). Previous work has shown that lumbar trabecular attenuation values generally correlate *T*-scores from dual-energy X-ray absorptiometry (DXA), the current gold standard for diagnosing low bone mineral density.[4,5] These trabecular attenuation values can be quickly obtained during interpretation of body CT scans performed for other indications and have good inter- and intra-observer reproducibility.[6,7] The standard sagittal reconstructions at body CT also allow for easy identification of vertebral compression fractures.[8] Furthermore, trabecular attenuation values are significantly decreased in patients with prevalent vertebral compression fractures[9] and in those who experience a major hip fracture within 5 years of CT.[10] However, it is currently

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Address correspondence to: Perry J Pickhardt, MD, Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI 53705-6027, USA. E-mail: ppickhardt2@uwhealth.org
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unknown how well trabecular attenuation correlates with future fractures involving the spine or at other sites such as the forearm, lower leg, femur, and humerus.

The purpose of this retrospective cohort study was to determine if trabecular attenuation values of the first lumbar vertebra (L_1) are associated with fracture-free survival for major osteoporotic fracture sites in a cohort of patients undergoing chest and/or abdominal CT for a variety of indications. A secondary endpoint was to build a predictive model for 10-year fracture risk using the initial CT-based trabecular attenuation values stratified by age and sex.

Materials and Methods

Patient cohort

This was a Health Insurance Portability and Accountability Act (HIPAA)-compliant retrospective cohort study; the need for informed consent was waived by our institutional review board. Eligible patients were aged ≥65 years at the time of thoracoabdominal CT scanning performed at our institution between January 1 and December 31, 2003 (Fig. 1). The remote time period was selected to allow for more than a decade of subsequent follow-up for incident fragility fractures. The primary outcome of interest was the occurrence of a fragility fracture after CT, defined as a fracture from standing height or less. Potential fracture cases were identified through an automated search of the electronic health record (EHR) using International Classification of Diseases (ICD)-9 diagnosis codes for fractures. The ICD-9 codes used for this study are included in Supplemental Table S1. The primary outcome date was defined as the ICD-9 diagnostic code entry date into the EHR, occurring at any point after a patient's CT scan until their most recent follow-up date at our institution. Two independent readers (SJL, PMG) reviewed physician notes and procedures in the EHR to confirm the occurrence and mechanism of fracture. For all study participants, accumulation of follow-up time began at the date of their 2003 CT examination. Control patients were right-censored at their last documented appointment with a physician or date of death, whichever came first.

Sample size calculation was performed before screening the full cohort for the presence of ICD-9 fracture-related codes. A statistical significance threshold of 0.05 and a power threshold of 0.80 were used. Based on prior work, we prespecified an expected hazard ratio of 2 for fracture in patients with L_1 attenuation ≤90 HU. We determined that 65 events were needed to achieve a power of 0.80. Of 1412 successfully processed database records, our initial automated search of the EHR yielded 295 (20.1%) independent fracture events during follow-up. To improve study efficiency, we used a random number generator to sample half of the cohort for further inclusion. We used sample size calculations to ensure that the number of events after random sampling was sufficient for statistical power.

The primary exposure of interest was the CT attenuation number (measured in HU) of the trabecular bone space on a single axial section of the first lumbar vertebral body (L_1). Age at CT, sex, and the occurrence of a prior fragility fracture (not resulting from major trauma) before CT, glucocorticoid use (cumulative total >3 months), bisphosphonate use, chronic kidney disease (glomerular filtration rate [GFR] <60 mL/min/1.73m^2), tobacco use (>0.1 ppd for >1 month), ethanol abuse (>3 drinks/day for men, >2 drinks/day for women), cancer history, and rheumatoid arthritis history were collected as

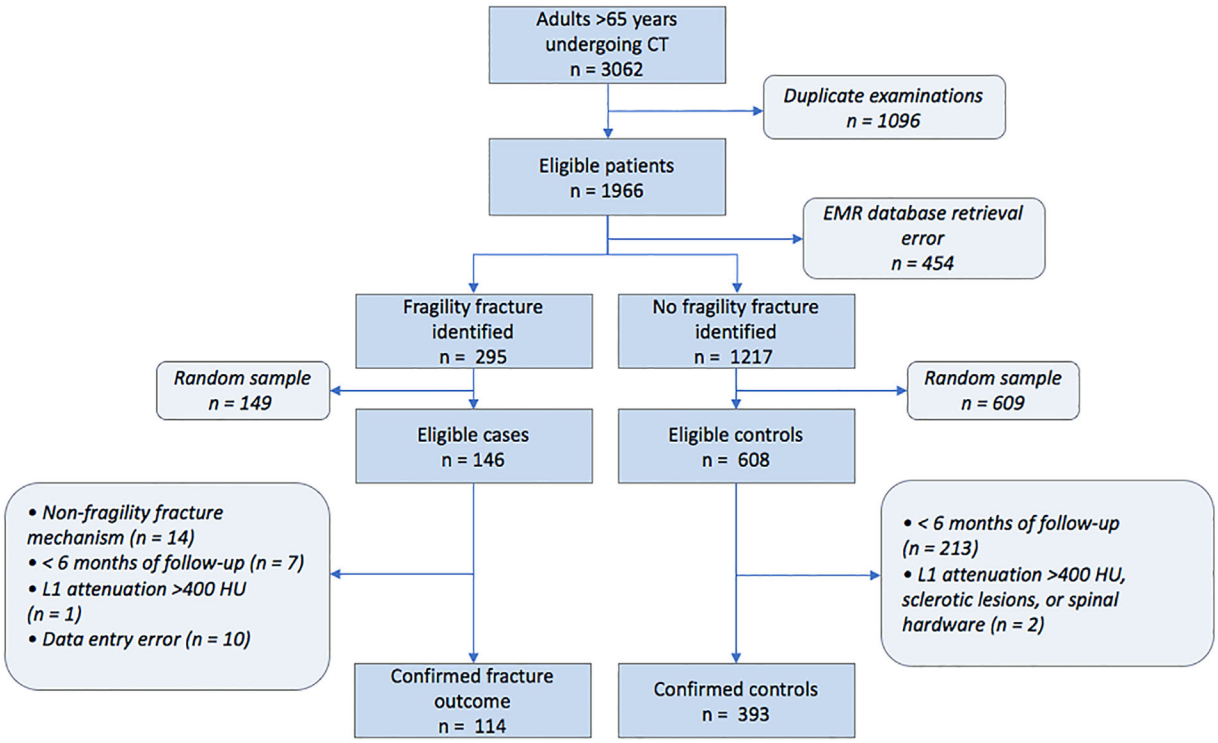

Fig. 1. Flow diagram for patient inclusion and exclusion.

potential confounding variables. Except for prior fragility fracture, the time period searched for confounding factors was any time before CT or during 10-year follow-up. Fractures before CT were identified through manual chart review of all patient EHRs, as well as by review of the sagittal CT images for prevalent vertebral compression fractures. The reviewers (PMG, SJL) were blinded to CT L_1 trabecular attenuation measurements during chart review.

CT image acquisition

CT scans were performed on a variety of GE multi-detector scanners (GE Healthcare, Waukesha, WI, USA) at a constant peak voltage of 120 kV with variable protocol-specific tube current (mA) settings. Of note, kV settings have a strong effect on bony HU values, whereas mA only affects noise levels and not HU values. The number of CT studies utilizing intravenous contrast material was recorded, which has a small but measurable effect on trabecular HU values.[11] An American College of Radiology (ACR)-accredited phantom was used to calibrate all scanners throughout our institution on a daily basis.

Image analysis

A single reviewer (PMG) measured mean L_1 trabecular attenuation, the primary exposure, on a single axial CT image at the appropriate level by manually placing an ovoid region of interest (ROI) within the anterior-superior portion of the trabecular space while avoiding cortical bone and focal sclerotic or lytic lesions (Figs. 2 and 3). In the event of a compression fracture at L_1, either T_{12} or L_2 were utilized for trabecular attenuation measurement. The presence of preexisting moderate (Grade 2) or severe (Grade 3) vertebral compression fractures was noted through review of the sagittal reconstruction according to the Genant visual semiquantitative method.[12] The reviewer was blinded to patient outcomes and prevalent vertebral fractures while measuring L_1 attenuation. Presence and grade of vertebral fractures was confirmed by board-certified radiologists (PJP, TJZ), each with more than 10 years of experience. Image assessment and measurements were all performed on our institutional picture archiving and communication system (PACS).

Statistical analysis

Continuous variables were summarized using means and standard deviations. Follow-up time was measured in years and summarized using median values. Categorical variables were summarized using counts and percentages. Fracture locations were tabulated according to region of occurrence.

Univariate survival analysis was performed by grouping patients according to L_1 attenuation values using a 90-HU threshold, as determined by previous work with prevalent vertebral fractures.[9] Differences in fracture-free survival (excluding preexisting fractures) were compared using a Kaplan-Meier curve and log-rank test. For multivariate analysis, a Cox proportional hazard model was fit to incident fracture-free survival times for all patients. The main exposure of interest was L_1 attenuation, scaled to units of 10 HU, while independently adjusting for all collected confounding variables. A global hypothesis test for all model coefficients was performed using a

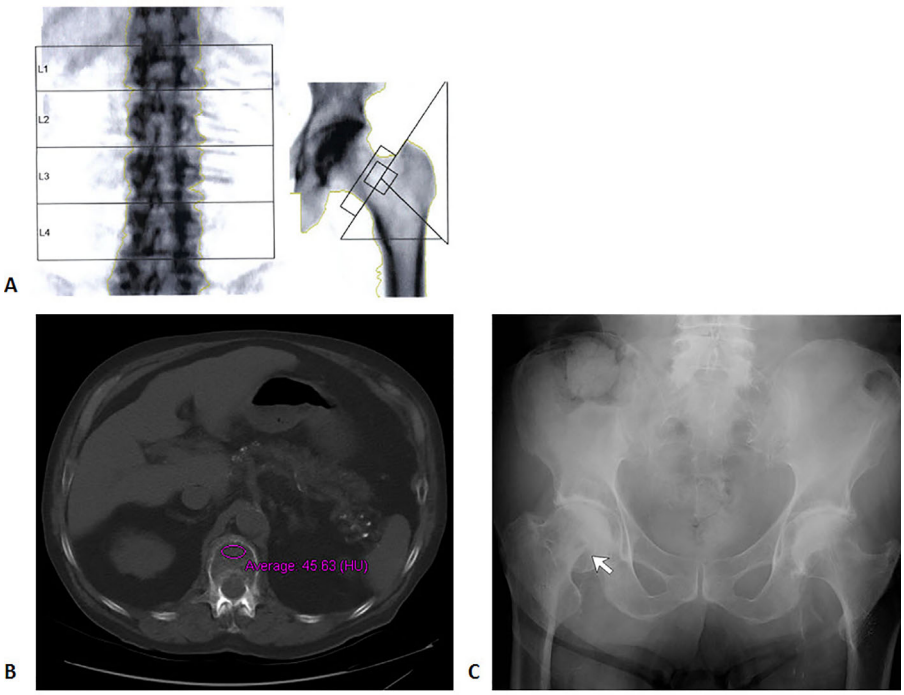

Fig. 2. Right hip fracture in an 88-year-old man. (*A*) DXA study performed 6 years before fracture was interpreted as normal, with L_1 to L_4 *T*-score of 2.3 and left femoral neck *T*-score of 0.2. Substantially increased density of the facet joints is noted, likely explaining the elevated false-negative *T*-score for spinal DXA. (*B*) Abdominal CT scan performed 5 years before hip fracture (1 year after DXA) for unexplained weight loss shows the method for measuring L_1 trabecular attenuation, which was markedly decreased in this case (46 HU). (*C*) Conventional pelvic radiograph after a fall shows an impacted right femoral neck fracture (arrow). The DXA-CT discrepancy in this case suggests that DXA was falsely negative given subsequent fragility fracture.

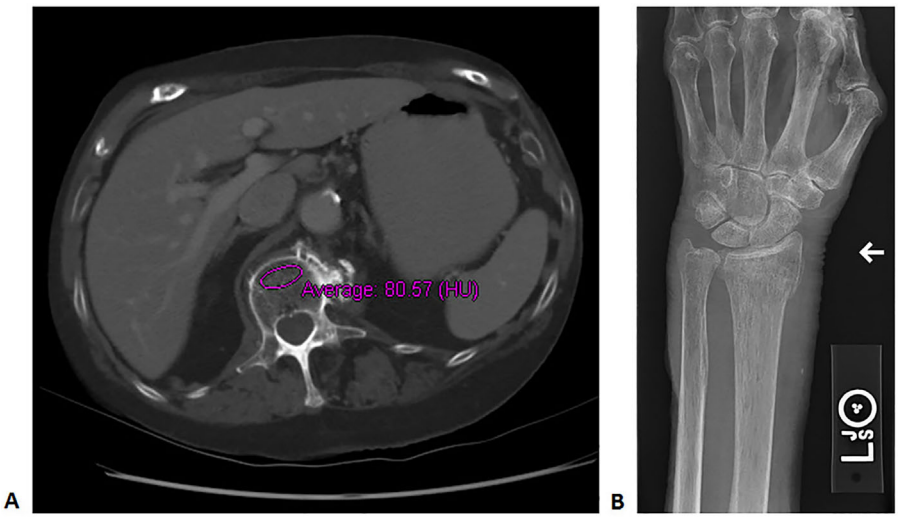

Fig. 3. Distal radial fracture in an 87-year-old woman. (*A*) Abdominal CT scan performed 7 years before fracture for chronic left lower quadrant symptoms shows decreased L_1 trabecular attenuation (81 HU), as well as prominent osteophytes. A DXA study (not shown) 5 years before CT showed an L_1 to L_4 *T*-score of 2.0, which was felt to be falsely elevated because of osteophyte formation visualized at CT (femoral neck *T*-score was osteopenic at −1.8). (*B*) Forearm radiograph shows a distal radial fragility fracture.

likelihood ratio test. Concordance index (c-index) and Nagelkerke's R^2 statistics were calculated to assess model discriminative performance. To address potential model overfitting, optimism-corrected performance statistics were calculated through bootstrapping using 200 resamples. Probabilities for major osteoporosis-related fractures over a 10-year horizon according to L_1 HU values were calculated for various patient subgroups (sex, age, prior fracture). All statistical analyses were performed using *R* (version 3.3.3, R Development Core Team, 2017) and the *rms* package.[13] Study results are reported in accordance with STROBE guidelines.[14]

Results

A patient inclusion and exclusion flowchart is shown in Fig. 1. A total of 507 patients were analyzed. Patient characteristics are provided in Table 1. The mean age for all patients was 73.4 (± 6.3) years. Median follow-up time was 5.8 years (interquartile range 2.1–11.0 years). A total of 114 (22.5%) patients experienced a fracture subsequent to the time of CT. Patients who experienced a fracture during follow-up were significantly older than controls ($p = 0.02$; 95% confidence interval [CI] 0.30–3.08 years). There was no evidence for a significant difference in the

Table 1. Patient Characteristics

	All ($n = 507$)	Incident fracture ($n = 114$)	Control ($n = 393$)
Continuous variables		Mean (SD)	
L_1 attenuation (HU)	128.4 (46.57)	112.5 (44.82)	133.0 (46.1)
Age at CT (years)	73.4 (6.3)	74.73 (6.67)	73.04 (6.12)
		Median	
Follow-up time (years)	5.8	8.3	5.3
Categorical variables		Count (%)	
Female	277 (54.6)	73 (64.0)	204 (51.9)
Male	230 (45.4)	41 (36.0)	189 (48.1)
Prior fracture	97 (19.1)	40 (35.1)	57 (14.5)
Systemic glucocorticoids >3 months	114 (22.5)	25 (21.9)	89 (22.6)
Bisphosphonates	50 (9.9)	6 (5.3)	44 (11.2)
History of cancer	210 (41.4)	34 (29.8)	176 (44.8)
Chronic kidney disease (GFR <60 ml/mi/1.73m^2)	215	52 (45.6)	163 (41.5)
Rheumatoid arthritis	3 (0.6)	0	3 (0.8)
EtOH	57 (11.2)	17 (14.9)	40 (10.2)
Tobacco	165 (32.5)	40 (35.1)	125 (31.8)
Death during follow-up	245 (48.3)	72 (63.2)	173 (44.0)
IV contrast-enhanced CT	324 (63.9)	69 (60.5)	255 (64.9)

GFR = glomerular filtration rate; EtOH = ethanol.

Table 2. Distribution of Fractures by Body Region

Region	No. of fractures
Pelvis/hip	22
Lower leg	10
Spinal compression fractures	52
Radius/ulna	16
Humerus	4
Other	10

proportion of patients with an IV contrast material-enhanced CT in the fracture and control groups ($p = 0.43$). The distribution of incident fractures by body region is presented in Table 2. A more detailed distribution of fractures is given in Supplemental Table S1.

A Kaplan-Meier curve showing the baseline incident fracture-free survival function for the cohort is given in Fig. 4*A*. A Kaplan-Meier curve showing the difference in fracture-free survival according to an L_1 attenuation threshold of 90 HU is given in Fig. 4*B*. There was a significant difference in fracture-free survival in patients with an L_1 attenuation of $\leq$90 HU compared with patients with L_1 attenuation above this threshold ($p < 0.001$ by log-rank test).

Multivariate Cox proportional hazard results adjusted for all collected confounding variables are given in Table 3. The overall likelihood ratio test for the model was highly significant ($p < 0.001$), suggesting that at least one of the included variables are significantly associated with fracture-free survival after CT. The optimism-corrected c-index was 0.700. Adjusted hazard ratios and 95% confidence intervals are also given in Table 3. A 10-unit increase in L_1 attenuation was significantly associated with a decreased risk of fracture after CT (hazard ratio [HR] = 0.63; 95% CI 0.47–0.85).

Example-predicted 10-year probabilities for major osteoporosis-related fractures are presented in Table 4 along with 95% prediction confidence intervals. Predicted probability of osteoporotic fracture for a 65-year-old female patient as a function of L_1 attenuation both with and without prior fracture is presented in Fig. 5. Probability of fracture tended to decrease with increasing L_1 attenuation for both male and female patients, both with and without a prior history of fracture. For most subcohorts, the 10-year probabilities for major osteoporororosis-related fractures according to L_1 HU values straddled the typical osteoporosis treatment threshold.

Discussion

This study shows that decreased L_1 trabecular attenuation in a cohort of adults aged $\geq$65 years undergoing chest or abdominal CT for various indications is associated with an increased risk for future fragility fracture. Based on prior work,[4,9] a prespecified attenuation cut-off of 90 HU was selected and showed significant differentiation of fracture-free survival functions. Multivariate survival analysis showed an effect of L_1 attenuation on fracture-free survival that remained statistically significant when controlling for the presence of a prior fracture, which is well established as one of the most significant risk factors for a future fracture.[15] Additionally, we adjusted for confounding effects of age and sex on fracture risk. However, our model of fracture-free survival showed only modest discriminative capability for individual fracture risk prediction as evidenced by the c-index of 0.700. Overall, these results indicate that L_1 attenuation values from body CT scans could potentially help determine an individual patient's fracture risk when taken in conjunction with other clinical risk factors.

L_1 attenuation values measured at CT have been shown to correlate with different methods of bone mineral density measurement such as DXA and quantitative CT.[6] Additionally, L_1 attenuation is significantly reduced in patients with concurrent vertebral compression fractures throughout the spine and is decreased in rheumatic conditions.[16,17] Despite the number of published studies investigating the ability of L_1 attenuation to detect low bone mineral density in an opportunistic setting, very few have focused on the probability and incidence of new osteoporotic fractures occurring after CT, which is a patient-centered outcome. To our knowledge, this is the first study in a well-defined consecutive cohort with

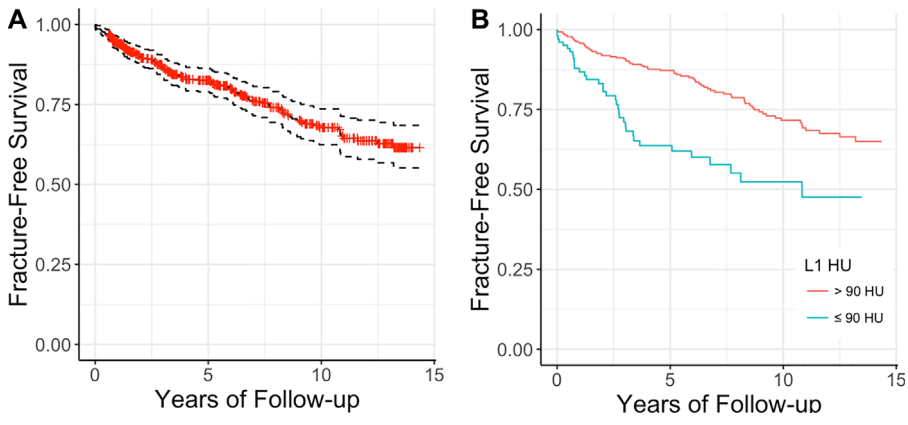

Fig. 4. Kaplan-Meier curves of incident fracture-free survival for all patients (*A*) and for patients divided into L_1 trabecular attenuation categories according to a 90 HU threshold (*B*). (*A*) Kaplan-Meier plot of fracture-free survival in the study cohort (red crosses represent right-censored patients). (*B*) Fracture-free survival for patients, grouped by an L_1 attenuation threshold of 90 HU.

Table 3. Cox Proportional Hazards Model Summary

Model tests		Discrimination indexes (optimism-corrected)	
Likelihood ratio chi-sqare	61.46	C-index	0.700
Degrees of freedom	11	Nagelkerke's R^2	0.09
p value	<0.001		

Variable	Hazard ratio	95% CI	*p* Value
Age at CT	1.19	0.89–1.62	0.23
Sex	0.82	0.55–1.23	0.35
Prior fracture	2.35	1.55–3.54	<0.01
L_1 HU (10-unit change)	0.63	0.47–0.85	<0.01

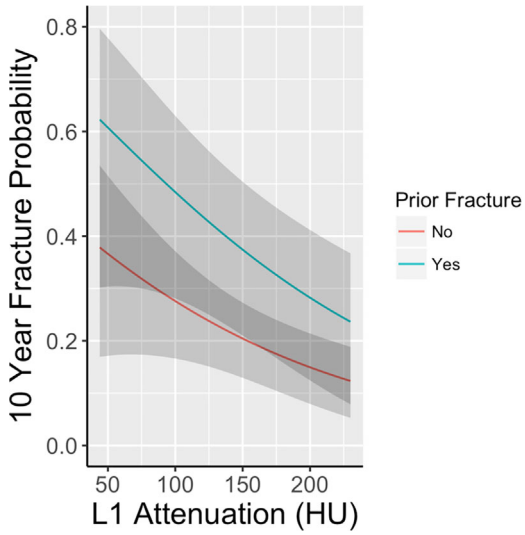

Fig. 5. Estimated probability of fracture-free survival at 10 years of follow-up as a function of varying L_1 attenuation in a 65-year-old female patient with and without a history of prior fracture.

long-term follow-up that has demonstrated the potential value of using L_1 attenuation to predict future fragility fracture risk at multiple sites in a manner similar to DXA. In addition, this study evaluates important confounding clinical variables such as age, sex, and prior fracture history. Conceivably, with further work, this simple measure could be utilized to calculate 10-year major osteoporotic fracture and hip fracture risk and subsequently be included as an input variable into the FRAX tool.

The adoption of opportunistic screening into practice will require quality-control measures to ensure reproducible results. Chief among these is an understanding of the effect scanning protocol has upon these measures. Importantly, the technical acquisition parameter of peak voltage has been shown to significantly alter L_1 attenuation measurements.[18] This work and many prior studies have focused on CT performed at peak 120 kV. There have been conflicting reports of the effect of contrast material on L_1 attenuation, but it appears that it increases L_1 attenuation an average of 10 HU compared with unenhanced images.[11,19,20] Such effects of contrast material on L_1 attenuation may vary with the timing of image acquisition after contrast material administration, an area deserving of further study. Our cohort had a balanced distribution of contrast-enhanced and unenhanced examinations between patients who experienced fracture after CT and controls. Regardless, variation in scanner acquisition parameters may limit the generalizability of our results, and certain cohorts that utilize standardized image acquisition protocols in relatively homogenous populations would likely be optimal for validating the effect of L_1 attenuation on future fracture risk. Examples of such screening programs would include lung cancer and CT colonography cohorts, provided that the included patients have regular long-term follow-up within the same hospital system.

The manual nature of L_1 attenuation measurement also poses a small but potentially significant problem with regard to osteoporosis and osteopenia diagnosis, as well as bone mineral density monitoring in general. Although previous studies have shown that inter- and intra-observer variation infrequently change an osteoporosis or osteopenia diagnosis when using specific cut-offs,[4] an external validation study on an independent population showed slightly reduced diagnostic accuracy when using a DXA reference standard.[21] One promising

Table 4. Estimated 10-Year Fracture Probabilities[a]

Age (years)	Sex	L_1 HU	Estimated 10-year fracture probability	Lower 95% CI	Upper 95% CI
65	Male	50	0.56	0.18	0.76
		70	0.47	0.21	0.65
		90	0.39	0.20	0.54
		110	0.32	0.17	0.44
		130	0.26	0.13	0.37
		150	0.20	0.09	0.31
		200	0.11	0.01	0.21
65	Female	50	0.64	0.23	0.83
		70	0.54	0.25	0.72
		90	0.45	0.25	0.60
		110	0.37	0.21	0.50
		130	0.30	0.17	0.42
		150	0.25	0.11	0.36
		200	0.14	0.02	0.24

[a]These probabilities are for individuals without a prior known fracture.

method to address the issue of variability is to implement automated spinal trabecular attenuation measurement application in a screening CT setting. Spinal segmentation algorithms have been reported, and it is feasible to implement these algorithms in an automated fashion.[22] Having an automated approach to attenuation measurement would likely have greater reproducibility and take less time for both research and clinical purposes, and would also scale well to a larger population level. Furthermore, automation would likely increase the precision of attenuation measurements and reliability of monitoring bone mineral density changes over time.

Although L_1 attenuation measurements can improve detection rates of osteoporosis, we describe an opportunistic approach, utilizing scans obtained for other indications, and are not advocating for a dedicated CT for bone mineral density screening. Other more established dedicated quantitative CT methods for bone mineral density measurement exist. In addition, the utility of deriving DXA-equivalent femoral neck *T*-scores from routine abdominal CT scans performed for other indications has been studied.[19,23] Quantitative CT methods also enable computationally advanced methods of bone structural analysis to be performed, such as finite element analysis.[24] However, given the number of CT scans performed worldwide for various other indications, opportunistic L_1 attenuation measurement could substantially increase rates of low bone mineral density detection in previously unscreened populations. The authors advocate performing a DXA in those identified as having osteoporosis or an elevated fracture risk if treatment is planned because this modality will be more appropriate for treatment monitoring.

Our study has several limitations. The retrospective and consecutive nature of patient inclusion likely introduced significant heterogeneity with respect to clinical fracture risk factors other than those included in our model. Given this limitation, at this point our model results should be cautiously interpreted and externally validated in a larger CT screening cohort with long-term follow-up in which most well-studied clinical risk factors for fracture are collected; a prospective screening CT population would be most suitable for this purpose. Additionally, because this study uses right-censored survival data, we had to assume that censoring of individuals was unrelated to the probability of a fracture after CT. We attempted to control for selection bias by excluding patients who had extremely limited follow-up after CT.

Separate from limitations in study design, there was technical variation in acquisition of the scans and HU measurements used in this study. First, HU measurements were taken from a single image slice, and we did not quantify the variation of HU based on slice thickness within vertebral bodies. Although slice thickness does not appear to significantly affect attenuation measurements in a medullary bone tissue phantom,[25] the effect has not been investigated using human CT data, where trabecular-space heterogeneity could increase attenuation variability because of partial volume effects at larger slice thicknesses. Additionally, craniocaudal zone-dependent changes in trabecular bone density and marrow volume have been described previously by histomorphometry, showing more pronounced trabecular bone loss in the sub-endplate zones relative to the center of vertebrae.[26] Because routine clinical CT scans are not typically reconstructed relative to the spinal vertical axis, axial sections often yield images that traverse vertebrae in the craniocaudal direction; this effect would be accentuated in conditions such as scoliosis and spondylolisthesis, where vertebral bodies can be significantly angulated out of the typical axial plane assessed by radiologists. Further investigation into intravertebral variability of CT attenuation measurements along the cradio-caudal axis would provide insight into which regions have the least variation and be most suitable for repeatable measurements.

Scans were obtained from multiple CT scanner models and manufacturers, and this was not accounted for in the analysis. This issue has been present in opportunistic osteoporosis research thus far and has been discussed in recently published position statements from the International Society for Clinical Densitometry (ISCD).[27] A European Spine Phantom (QRM, Möhrendorf, Germany) with trabecular inserts with bone mineral density values of 50.5, 100.6, and 199.2 mg/cm^3 was scanned at the center of the CT gantry in several different scanner manufacturers and models (GE, Philips, Siemens, and Toshiba), and HU values were recorded. Among GE scanner models, HU measurements of the 50.5, 100.6, and 199.2 mg/cm^3 trabecular inserts had ranges of 63 to 71, 129 to 136, and 244 to 254 HU, respectively. The scanner manufacturer that differed most in CT attenuation values was Philips, whose ranges for the 50.5, 100.6, and 199.2 mg/cm^3 inserts were 43 to 62, 106 to 124, and 214 to 240 HU, respectively. Statistical testing was not performed in these published data, and future studies quantifying the effects of scanner manufacturer and model on water-calibrated CT attenuation values of the trabecular spine may be valuable to guide future opportunistic osteoporosis screening efforts by offering more precise disease thresholds based on several image acquisition variables.

In conclusion, we have shown that decreased L_1 trabecular attenuation is associated with increased risk for future osteoporotic fractures in an adult cohort of patients aged $\geq$65 years undergoing abdominopelvic CT scans for other indications and that this effect holds when adjusting for several common confounding clinical variables.

Disclosures

No authors have relevant financial disclosures. PJP is cofounder of VirtuoCTC, consultant to Bracco and Check-Cap, and shareholder in SHINE, Elucent, and Cellectar Biosciences. TJZ is a consultant for Neuwave Medical, Inc.

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Authors' roles: SJL: literature review, study design, data collection, statistical analysis, manuscript drafting and editing, guarantor of study integrity. PMG: data collection. RDZ: study design and statistical analysis. TJZ: data validation and manuscript editing. PJP: study design, data validation, manuscript revision, guarantor of study integrity.

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