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Highlights

- Osteoporosis testing for spinal fusion patients using a pre-operative CT scan
- Identify osteoporosis on basis of low bone strength and/or bone mineral density
- With osteoporosis, 4.7X higher risk of vertebral fracture (than without osteoporosis)
- If low bone strength and low bone mineral density, 3.7X higher risk of reoperation
- Similar trends for patients with short (≤ 3 fused levels) or long fusion construct

Increased risks of vertebral fracture and reoperation in primary spinal fusion patients who test positive for osteoporosis by Biomechanical Computed Tomography analysis

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Abstract**Background Context**

While osteoporosis is a risk factor for adverse outcomes in spinal fusion patients, diagnosing osteoporosis reliably in this population has been challenging due to degenerative changes and spinal deformities.

Addressing that challenge, biomechanical computed tomography analysis (BCT) is a CT-based diagnostic test for osteoporosis that measures both bone mineral density and bone strength (using finite element analysis) at the spine; CT scans taken for spinal evaluation or previous care can be repurposed for the analysis.

Purpose

Assess the effectiveness of BCT for pre-operatively identifying spinal fusion patients with osteoporosis who are at high risk of reoperation or vertebral fracture.

Study Design

Observational cohort study in a multi-center integrated managed care system using existing data from patient medical records and imaging archives.

Patient Sample

We studied a randomly sampled subset of all adult patients who had any type of primary thoracic (T4 or below) or lumbar fusion between 2005–2018. For inclusion, patients with accessible study data needed a

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pre-op CT scan without intravenous contrast that contained images (before any instrumentation) of the upper instrumented vertebral level.

Outcome Measures

Reoperation for any reason (primary outcome) or a newly documented vertebral fracture (secondary outcome) occurring up to five years after the primary surgery.

Methods

All study data were extracted using available coded information and CT scans from the medical records. BCT was performed at a centralized lab blinded to the clinical outcomes; patients could test positive for osteoporosis based on either low values of bone strength (vertebral strength < 4,500 N women or 6,500 N men) and/or bone mineral density (vertebral trabecular bone mineral density < 80 mg/cm³ both sexes). Cox proportional hazard ratios were adjusted by age, presence of obesity, and whether the fusion was long (4 or more levels fused) or short (3 or fewer levels fused); Kaplan-Meier survival was compared by the log rank test. This project was funded by NIH (R44AR064613) and all physician co-authors and author 1 received salary support from their respective departments. Author 6 is employed by, and author 1 has equity in and consults for, the company that provides the BCT test; the other authors declare no conflicts of interest.

Results

For the 469 patients analyzed (298 women, 171 men), median follow-up time was 44.4 months, 11.1% had a reoperation (median time 14.5 months), and 7.7% had a vertebral fracture (median time 2.0 months). Overall, 25.8% of patients tested positive for osteoporosis and no patients under age 50 tested positive. Compared to patients without osteoporosis, those testing positive were at almost five-fold higher risk for vertebral fracture (adjusted hazard ratio 4.7, 95% confidence interval = 2.2–9.7; $p < 0.0001$ Kaplan-Meier survival). Of those positive-testing patients, those who tested positive concurrently for low values of both bone strength and bone mineral density (12.6% of patients overall) were at almost four-fold higher risk for reoperation (3.7, 1.9–7.2; Kaplan-Meier survival $p < 0.0001$); the remaining positive-testing patients (those who tested positive for low values of either bone strength or bone mineral density but not both) were not at significantly higher risk for reoperation (1.6, 0.7–3.7) but were for vertebral fracture (4.3, 1.9–10.2). For both clinical outcomes, risk remained high for patients who underwent short or long fusion.

Conclusion

In a real-world clinical setting, BCT was effective in identifying primary spinal fusion patients aged 50 or older with osteoporosis who were at elevated risks of reoperation and vertebral fracture.

Keywords

Spinal fusion, osteoporosis, biomechanics, bone quality, finite element analysis, bone strength, bone mineral density

Introduction

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Several studies in spinal fusion patients have shown higher rates of complications to be associated with osteoporosis, including reoperation, nonunion, screw loosening, proximal junction kyphosis, cage subsidence, and vertebral fracture [1-15]. As a result, best practices for spinal fusion care have recently recommended the need for a formal pre-operative evaluation of bone health [16]. Appropriate evaluation can help surgeons identify which patients might benefit the most from treating with an osteoporosis medication or altering the surgical plan, or both, and help establish the medical necessity for any risk-mitigating steps.

Until recently, obtaining a reliable diagnosis of spinal osteoporosis in spinal fusion patients has been challenging. The current clinical standard, measuring bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) imaging, can often show false negatives in the presence of spinal deformities and degenerative changes [14, 17-22] because DXA only provides planar images of the bone. Three-dimensional imaging, such as computed tomography (CT), can overcome this limitation. Some have suggested that quantitative CT should be used instead of DXA to measure BMD diagnostically for spinal fusion patients [23]. However, quantitative CT typically requires the use of an external calibration phantom during imaging and specialized software and is not widely used. Others are investigating obtaining CT-based BMD measurements without a calibration phantom [12, 13], although generalization of some of those investigative techniques remains to be shown. Measurements of Hounsfield Units of attenuation from a CT scan have also been investigated [24]. However, that approach does not constitute a diagnostic test due to various technical limitations [1, 15, 16, 22, 25, 26] and the lack of a consistent diagnostic cut point [27], therefore requiring a confirmation DXA for diagnostic purposes [16].

Another CT-based test for osteoporosis, named biomechanical computed tomography analysis (BCT), identifies spinal osteoporosis on the basis of both BMD and bone strength, the latter obtained from finite element analysis and providing additional diagnostic information over BMD alone [28]. BCT has been validated in the general population for identifying women and men with spinal osteoporosis who are at high risk of vertebral fracture [29-35]. In addition, in part via patient-specific phantomless calibration that utilizes the patient's internal tissues as calibrating references [36], BCT can repurpose most types of spine-containing CT scans, without intravenous contrast, that are taken for any indication. BCT is FDA-cleared in the US as a diagnostic test for osteoporosis, and does not require confirmation by DXA [28, 37].

Previously, we described the use of BCT in a cohort of female spinal fusion patients, age 50–70, in a large academic medical center [38]. In that study, 29% of patients tested positive for spinal osteoporosis by either bone strength or BMD criteria. That study did not include any clinical outcomes. Here, we assessed the effectiveness of BCT for identifying primary spinal fusion patients with osteoporosis who are at high

risk of subsequent reoperation or vertebral fracture. To do so, we conducted an observational study in a real-world clinical setting to assess risks of reoperation and vertebral fracture for patients who tested positive for osteoporosis by BCT.

Materials and Methods

Study Design

This was an observational cohort study in a multi-center integrated managed care system, using existing data available from patient medical records and imaging archives. The study was IRB approved with a waiver of informed consent.

Patient Population

We sampled from all adult patients (age ≥ 18 years, both sexes) in a healthcare system in southern California who underwent any type of spinal fusion surgery at one of eight different hospitals between Jan 1, 2005, and Dec 31, 2018. In generating our analysis cohort from that population of 20,920 patients (Figure 1), patients needed to have: 1) no previous fusion surgery; 2) if no reoperation or vertebral fracture, at least three months of follow-up; 3) a CT scan of the chest, abdomen, abdomen-pelvis or spine without intravenous contrast, taken within one year before surgery or immediately post-operatively. Due to resource constraints on both collecting data and analyzing the CT scans, from these eligible patients (N=4,027) we selected a random subset (N=1,348) for analysis, stratified by sex. From that subset, successful BCT analyses were performed on all those patients who had an archived CT covering vertebrae up to T4 that was suitable for BCT as well as an archived post-operative X-ray displaying the upper instrumented vertebral (UIV) level from T4–L5. The resulting analysis cohort comprised 469 patients with complete study data. The CT scans for these patients were taken on 21 different types of CT scanners, across five different manufacturers; 85% of the CT scans were for the thoracic or lumbar spine, the others comprising either pelvic/abdominal, chest, or whole-body CT scans and all were acquired without intravenous contrast.

Clinical Outcomes

The primary clinical outcome was a second spinal fusion surgery for any reason (“reoperation”), during the observation period of up to five years. A secondary clinical outcome was a vertebral fracture documented during the same observation period. Each patient’s observation period was defined as the time span from their first surgery to death, disenrollment from the managed care program, five years, or the end of the study observation period of March 31, 2019, whichever came first. Any reoperation or vertebral fracture event must have occurred within the patient’s observation period. All procedure, covariate, and outcome data were identified by electronic screening algorithms utilizing billing, procedure, and prescription codes (Figure 1). Covariates that were available in the coded database were

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included in the analysis if deemed relevant to the clinical outcomes or known to affect bone strength. Included covariates were age, sex, race/ethnicity, weight, height, body mass index, diabetes, smoking, other bone conditions (see Table 1 for details), use of steroids or osteoporosis medications during the observation period, and number of fused levels (obtained also from post-op x-rays). Full study data were available for all patients in the analysis cohort and were validated by cross-checking a subset against those in a more detailed spine registry [39, 40].

Biomechanical Computed Tomography analysis

All BCT measurements were performed blinded to the clinical outcomes. As described elsewhere for spinal fusion patients [38], BCT was performed at a centralized facility using the VirtuOst® software system (version 2.3; O.N. Diagnostics, Berkeley, CA, USA) to measure vertebral trabecular BMD (in units of mg/cm^3) and vertebral compressive strength (in units of newtons, N; Figure 2). Because the bone quality at the UIV level is most relevant to surgical planning, measurements were made at the UIV level for all patients (N=469). We also report measurements for one “nominal” vertebral level (T12–L3, L1 being preferable), when available (for N=461 patients); these measurements are cleared by the FDA for identifying osteoporosis and assessing fracture risk [28]. Using cut points previously established for the nominal level, we classified patients as having *BMD-defined osteoporosis*, BDO (BMD $< 80 \text{ mg}/\text{cm}^3$) [41] or *fragile bone strength*, FBS (vertebral strength $< 4,500 \text{ N}$ for women or $6,500 \text{ N}$ for men) [33, 42]. Using BCT, a patient is considered to have osteoporosis if they test positive for FBS and/or BDO (one or both) since both the FBS and BDO classifications independently predict fracture risk and both have established diagnostic cut points for identifying osteoporosis. [28] The absence of osteoporosis is therefore signified by testing negative for FBS and testing negative for BDO. Because of variations in vertebral size along the spinal column, when classifying FBS at the UIV level we adjusted the measured strength at the UIV level by a level-specific scaling ratio (ranging from 1.7 at T4 to 0.8 at L5). Each ratio represented a mean strength for the L1 level to the non-L1 level, as measured separately in an independent cohort of 455 non-fusion subjects. This type of scaling approach has been previously validated for predicting incident vertebral fracture [34, 35]. We did not scale the BMD values, which are directly correlated with the apparent density of the trabecular bone [43] and its volume fraction (1 - porosity) [44]. Thus, values of BMD below the $80 \text{ mg}/\text{cm}^3$ cut point denote clinical osteoporosis when measured at the nominal vertebral level [28, 41] and highly porous trabecular bone when measured at any level.

Statistical Analysis

For each clinical outcome (reoperation and vertebral fracture), we report the crude (unadjusted) and adjusted Cox proportional hazard ratios for the BCT classifications. Adjustments were made for covariates that had significant associations ($p < 0.05$) with the outcomes based on univariate hazard ratio

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analyses for the demographics, patient factors, comorbidities and surgical factors (Table 1). Follow-up time for each patient was the shorter of their observation period and any event time. In these analyses, our main BCT classification for osteoporosis was testing positive for FBS and/or BDO (one or both) at the UIV level. We also performed separate hazard ratio analyses to dissect out the positive-testing patients into two complementary subsets: a) those who tested positive concurrently for both FBS and BDO; and b) those who tested positive for only one of FBS or BDO but not both. For each analysis, the hazard ratio for testing positive was calculated relative to the reference of not having osteoporosis (negative for each of FBS and BDO). Thus, the hazard ratio is interpreted as the relative risk of reoperation (or vertebral fracture) when testing positive versus not having osteoporosis; to indicate a statistically significant level of increased risk compared to the reference, the lower 95% confidence interval needed to have a value 1.0. In addition, we performed Kaplan-Meier survival analyses corresponding to the hazard ratio analyses. The crude 5-year cumulative incidences of reoperation and vertebral fracture (separately) were calculated as 1 minus the Kaplan-Meier estimators (with right-censoring) and the log-rank test was used to compare survival curves.

For basic-science insight and to facilitate comparisons with the literature, hazard ratios are also reported for the individual FBS and BDO classifications if used separately (FBS positive relative to FBS negative; BDO positive relative to BDO negative). For example, a BMD test has no information on bone strength and therefore would only use the BDO classification. In a series of secondary analyses, we also compared the adjusted hazard ratios for the UIV versus nominal levels (for the 461 patients with measurements at both levels) because the nominal level is currently the standard for assessing osteoporosis using BCT. In addition, for the UIV level, to complement the adjusted hazard ratio analyses, stratified analyses were used to measure the crude hazard ratio in sub-groups of patients aged 50 and older, and for “short” (3 three levels fused) versus “long” (4 levels fused) fusion. All analyses were performed for the two sexes pooled. Data analysis was performed using the JMP Pro software (version 16.0.0, SAS Institute, Cary, NC).

After our statistical analysis, one of the physician co-authors performed a *post-hoc* chart read on the subset of patients who correctly tested positive by BCT for reoperation. The objective was to determine if the documented clinical indication for reoperation for these true-positive patients was biomechanical in nature (e.g., hardware loosening, pedicle perforation, adjacent level fracture, non-union, or degenerative adjacent level disease) or due to some other non-biomechanical cause. In addition, although we did not design this study to compare BCT against DXA, we realize that a limited comparison with any available DXA data might provide additional clinical context. Thus, for the 103 patients in our analysis cohort (28%) who also had DXA within one year before the surgery, we report prevalence rates for osteoporosis for DXA (BMD T-score at the hip or spine ≤ -2.5) and BCT (FBS and/or BDO). For each clinical

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outcome, we also directly compared the hazard ratios by including osteoporosis by BCT and by DXA as separate predictors in the same model.

Results

The cohort was 64% female, racially diverse with 25% Hispanic and 12% Black, 89% were aged 50 or older, 38% were obese (BMI ≥ 30 kg/m²), 37% had diabetes, and 52% were smokers (Table 1). Eighty-nine patients (19%) had long fusions (≥ 4 levels fused) and 180 patients (38%) had just one level fused; 391 patients (83%) had a lumbar fusion (UIV at L1 or below) and L4 was the most common UIV level (Figure 3).

Median times for observation and to reoperation and vertebral fracture were 44.4 months, 14.5 months, and 2.0 months, respectively, and the overall rates for reoperation and vertebral fracture were 11.1% and 7.7%, respectively (Table 1). Univariate Cox proportional hazard ratio analysis indicated that none of the covariate characteristics were significantly associated with reoperation: sex ($p=0.86$), age ($p=0.58$), race ($p=0.86$), bodyweight ($p=0.24$), height ($p=0.64$), BMI ($p=0.28$), steroid use ($p=0.32$), smoking ($p=0.22$), diabetes ($p=0.22$), obesity ($p=0.59$), rheumatoid arthritis ($p=0.99$), other bone conditions ($p=0.59$), osteoporosis medication ($p=0.60$); nor was the surgical occurrence of dural tear ($p=0.75$), infection ($p=0.70$), epidural hematoma ($p=0.87$), or any reported surgical complication ($p=0.87$). For vertebral fracture, obesity ($p=0.0036$) and higher body mass index ($p=0.02$) decreased risk, whereas having a long fusion ($p<0.0001$) and a greater number of fused levels ($p<0.0001$) increased risk. Other bone-related risk factors had no effect, including steroid use ($p=0.25$), smoking ($p=0.37$), diabetes ($p=0.41$), rheumatoid arthritis ($p=0.96$), nor did sex ($p=0.15$), age ($p=0.48$), bodyweight ($p=0.21$), or height ($p=0.24$). Osteoporosis medication (during the observation period) was strongly associated with vertebral fracture ($p=0.0001$), presumably because patients with newly identified fractures were placed on osteoporosis treatment. Based on these results, adjustments for hazard ratios were made for both outcomes using age (a standard adjustment factor in bone studies), obesity (a stronger predictor than body mass index), and long fusion (a stronger predictor than number of levels fused).

At the UIV level, patients testing positive for osteoporosis by BCT (FBS and/or BDO) were at statistically significant increased risks of reoperation and vertebral fracture, before and after adjustment for covariates, compared to patients without osteoporosis (Table 2). Hazard ratios for the different classifications had substantially overlapping confidence intervals, with or without adjustment. Overall, 25.8% of patients tested positive for osteoporosis (FBS and/or BDO). Of those, the numerically highest hazard ratios occurred for the 12.6% of patients who tested positive for both FBS and BDO concurrently. For those patients, compared to patients without osteoporosis, the adjusted hazard ratio was 3.7 (95% CI: 1.9–7.2) for reoperation and 5.0 (2.2–11.7) for vertebral fracture. For reoperation, the additional 13.2% of

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patients who tested positive for only one of either FBS or BDO (but not both) were not at significantly higher risk (1.6, 0.7–3.7). By contrast, for vertebral fracture, risk remained significantly higher for these patients (4.3 1.9–10.2) and was similar to the risk for all patients testing positive for osteoporosis (4.7, 2.2–9.7). While the hazard ratios (crude and adjusted) for reoperation did not differ between the FBS and BDO classifications when each was used alone, models containing both classifications together showed a significant hazard ratio for FBS (crude: 2.4, 1.2–4.9; adjusted: 2.4, 1.2–5.0) but not for BDO (crude: 1.3, 0.6–2.7; adjusted: 1.5, 0.7–3.3), demonstrating an advantage of FBS over BDO for identifying high-risk patients; similar trends occurred for vertebral fracture. Taken together, these results indicate that, compared to patients without osteoporosis, the 25.8% of patients who tested positive for osteoporosis were at 4.7-fold higher risk for vertebral fracture and, of those, the 12.6% of patients who tested positive concurrently for both FBS and BDO were at 3.7-fold higher risk for reoperation.

Reflecting those findings, the Kaplan-Meier survival analysis (Figure 4) indicated distinct event rates for patients testing positive by the different classifications. For reoperation, those who tested positive concurrently for both FBS and BDO separated out compared to those testing positive for either FBS or BDO but not both and for those without osteoporosis ($p < 0.0004$), the latter two classifications having similar failure profiles. For vertebral fracture, the response for those without osteoporosis was distinct from the two other classifications ($p < 0.0001$), which in turn had similar failure rates. Overall, compared to patients with no osteoporosis, the failure rates were most statistically distinct for patients who tested positive concurrently for both FBS and BDO when reoperation was the outcome ($p < 0.0001$), and for those tested positive for either FBS and/or BDO when vertebral fracture was the outcome ($p < 0.0001$).

For the $N=461$ patients having BCT measurements at both the UIV and nominal levels, risks of reoperation and vertebral fracture remained significantly higher when the BCT measurements were made instead at the nominal level and trends were all the same as for the UIV level (Table 3). For both clinical outcomes, the hazard ratios consistently trended higher when the BCT measurements were made at the UIV than nominal level.

Risk also remained significantly higher and trends similar for various sub-groups of patients aged 50 and older. Stratified analyses indicated that no patients under age 50 tested positive with BCT. For patients aged 50 and over, the reoperation rate did not differ ($p=0.34$) between patients who underwent a long (14.6%) vs. short (10.8%) fusion. For patients testing positive concurrently for both FBS and BDO, the crude hazard ratio for reoperation remained statistically significant for long (4.6, 1.3–15.8) and short (2.9, 1.3–6.1) fusion (Table 4). For vertebral fracture, the observed rate in patients aged 50 and older was almost six-fold higher ($p < 0.0001$) for those who underwent long (23.2%) versus short (3.9%) fusion, indicating a strong association between long fusion and vertebral fracture; even so, the crude hazard ratio

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for testing positive for osteoporosis (FBS and/or BDO) remained high for both long (4.6, 1.7–12.1) and short (6.4, 2.0–20.7) fusion (Table 4), consistent with the results for the adjusted hazard ratios for all patients (Table 2).

In a *post-hoc* statistical analysis, for the sub-group of 103 patients with both BCT (UIV level) and DXA (hip/spine) data, prevalence of osteoporosis by DXA was over four-fold lower than by BCT. One hundred of those patients were aged 50 or older and 82 were women. Of all 103 patients, only 3/99 (3.0%) patients tested positive for osteoporosis by spinal DXA; 8/100 (8.0%) tested positive by hip DX, and 9/103 (8.7%) tested positive by hip/spine DXA; prevalence of osteoporosis by BCT (FBS and/or BDO) was over four-fold higher at 36.9%. All three of the spine-DXA positives tested positive by BCT, as did 6 of the 8 hip-DXA positives. When osteoporosis by BCT and hip/spine DXA were both entered into the same hazard ratio analysis, despite the small sample size and wide confidence intervals the (crude) hazard ratio for vertebral fracture was statistically significant for BCT (7.3, 1.5–35.5) but not for DXA (1.7, 0.3–8.2), and likewise for reoperation: BCT (4.2, 1.0–17.4), DXA (0.9, 0.1–7.6); adjusted models were not run due to the small sample size.

Post-hoc chart reads were performed on the 15 high-risk patients with concurrent FBS and BDO who correctly tested positive (true positives) for being at significantly higher risk of reoperation (11 women, ages 60–79; 4 men, ages 58–79). Those reads indicated that these patients had reoperation due to hardware pullout (N=1), pedicle perforation (N=1), adjacent level fracture (N=0), non-union (N=5), degenerative adjacent level disease (N=4, one of whom also had non-union), or “other” (N=5, 3 of whom had a prescheduled or unrelated reoperation at the cervical level). Excluding the three patients with prescheduled or unrelated reoperation, these data indicate that 10/12 (83%) of these true-positive patients underwent reoperation because of some biomechanically related issue.

Discussion

These results demonstrate that spinal fusion patients aged 50 or older who had osteoporosis by BCT were at elevated risk for vertebral fracture and reoperation, compared to patients without osteoporosis, regardless of whether the patient underwent long or short fusion or whether measurements were made at the UIV (preferable) or nominal levels. While BMD testing represents the clinical standard for identifying osteoporosis, BCT uses measurements of both BMD and bone strength. This expanded approach is consistent with the Surgeon General of the United States’ definition of osteoporosis as “a skeletal disorder characterized by compromised bone strength, predisposing to an increased risk of fracture” [45, 46]. The BCT test has been validated previously for vertebral fracture risk assessment in the general population [29-35]. The current study extends those results to primary spinal fusion patients. As in those previous studies, high-risk patients for vertebral fracture tested positive for FBS and/or BDO. However, for

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reoperation, only those patients who concurrently tested positive for both FBS and BDO were at significantly higher risk. Those testing positive for only one of FBS or BDO (but not both) were not at significantly increased risk of reoperation but were at increased risk of vertebral fracture. Assessing risk of reoperation pre-operatively is complex and involves many factors [47-53]. To date, such clinical risk assessments have mostly omitted osteoporosis as a risk factor, due in part to the technical limitations [17-21] of using DXA to reliably assess spinal osteoporosis in fusion patients. Our results indicate that pre-operative BCT, utilizing an existing CT scan, can provide a reliable means of incorporating osteoporosis as a clinical risk factor into surgical planning and management of spinal fusion patients.

Together with the literature, our results demonstrate that for spinal fusion patients, more cases of clinically-relevant osteoporosis at the spine can be detected by BCT than by BMD alone, regardless of whether BMD is measured by quantitative CT or DXA. In our limited group of 103 patients with DXA, the prevalence of osteoporosis by DXA (at the hip or spine) was 8.7%, which was over four-fold lower than the 36.9% prevalence of osteoporosis by BCT for that group. Recognizing the small size of that group, this DXA rate for patients encountered from 2005–2018 in our study is consistent with rates for the general US population of adults aged 50 years and older of 9% from 2005–2008 [54] and 10.3% in 2010 [55] and a rate 10.0% for 140 consecutive spinal fusion patients at a single medical center from 2007–2014 [2]. Clinically with CT, the nominal level is usually used for diagnosing osteoporosis whether by BMD [41] or BCT [28] testing. In the present study at the nominal level, the prevalence of osteoporosis by CT-based BMD testing alone (BDO) versus BCT (FBS and/or BDO) was 15.4 % vs. 24.7% (Table 3), consistent with respective rates of 14.3% and 28.6% in our earlier BCT study of 98 female fusion patients aged 50–70 at a major academic center from 2003–2012 [38]. This collective evidence suggests that at least 60% more spinal fusion patients with spinal osteoporosis can be identified by BCT testing (FBS and/or BDO) compared to CT-based BMD testing (BDO), and 2–4 times more compared to DXA testing. As evidenced by the equivalence of the hazard ratios, this greater number of patients identified as having osteoporosis by BCT also appear to be at an equivalent level of elevated risk as the smaller number of patients with osteoporosis by CT-based BMD. Further, in our *ad hoc* hazard ratio models that contained both BCT and DXA for the 103 patients with both DXA and BCT data, we found higher hazard ratios for fracture and reoperation for BCT than DXA. Despite the small sample size and wide confidence intervals for that *ad hoc* analysis, it nevertheless indicates that BCT better identified spinal patients at higher risk of vertebral fracture and reoperation than did DXA.

One noteworthy advance of BCT over CT-based BMD testing alone is that risk of reoperation was significantly elevated only when patients tested positive concurrently by both BMD and bone strength. Related, models that contained both the FBS and BDO as independent classifiers showed a statistical advantage of FBS over BDO. Both these findings demonstrate an added prognostic value of considering

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both bone strength and BMD rather than just BMD alone. Mechanistically, in fusion patients some vertebrae can contain highly porous trabecular bone (test positive by the BDO classification) but can also have thickened cortices or endplates or other features that can strengthen the overall vertebra despite that porosity (test negative by the FBS classification). Our findings suggest that such strengthening can uniquely protect against risk of reoperation, presumably by mitigating certain failure mechanisms not directly depending on high trabecular porosity, such as endplate failure and cage subsidence. By contrast, for vertebral fracture, patients with either weak or porous vertebrae were at high risk of vertebral fracture. That result might reflect the more systemic nature of vertebral fractures, which can occur anywhere along the spinal column, versus the more local nature of reoperation, which is likely more related to problems at the UIV level and thus the specifics of both BMD and bone strength at that or an adjacent level.

As with previous studies on fusion patients that showed a higher risk of reoperation in the presence of osteoporosis [3, 10], our study was not designed to address if osteoporosis was the cause of reoperation. Reoperation has many causes [47-53], and in our study, for example, 58% of the 52 reoperation patients did not have osteoporosis by BCT. However, that osteoporosis is a causative factor is mechanistically feasible since low bone density weakens the bone-screw interface [11] and has been linked clinically with proximal junctional kyphosis, cage subsidence, screw loosening, and pseudoarthrosis [3, 6-9, 12-15]. Beyond the direct effects of osteoporosis in weakening bone, a spinal fusion operation can also accelerate subsequent decreases in BMD over time in adjacent vertebral levels, further increasing risk of vertebral failure [56-58]. And there is emerging evidence that elements of bone fragility and osteoclastic stimulation [59-63] are linked to the etiology of disc degeneration, suggesting that osteoporosis may also contribute to or be coincident with disc degeneration. Consistent with this overall experience, our *post-hoc* chart reads showed that, excluding three patients who had pre-scheduled or unrelated second surgeries, 10/12 (83%) of the true-positive patients underwent reoperation because of biomechanically-related issues. That osteoporosis is causative of reoperation is also consistent with results from a large claims-based analysis, which found an association between therapeutic treatment of osteoporosis and reduced rates of reoperation [4].

Our study has a number of strengths. We used only data from a non-academic clinical setting, including BCT measurements and classifications at the nominal level that are FDA-cleared for clinical diagnostic use and fracture risk assessment [28]. The study included eight large medical centers, involved over 20 different CT scanners, and sampled from a racially diverse patient population, including all adults and both sexes. We included all types of primary fusion procedures regardless of the approach (e.g. ALIF, TLIF, PLIF) or number of fused levels. Our use of a random sample of existing data from all available patients, pending availability of their data, minimized any selection bias associated with surgeon or patient participation and resulted in similar overall reoperation rates for the analysis cohort (11.1%) and

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full eligible population (11.9%). Our primary outcome was reoperation, which is the most important outcome in terms of clinical relevance but is not often addressed due to sample size constraints. Our median observation time of 44 months was much longer than the median 14 months to reoperation and 2 months to vertebral fracture, indicating that our observation time was sufficiently large to capture most reoperation (and vertebral fracture) cases. Our Cox proportional hazard ratio analyses accounted for the variable follow-up and event times across patients. Those analyses also demonstrated increased risk for patients who tested positive by BCT independently of age, obesity, and long vs. short fusion, which was further supported by our stratified analyses.

Despite these strengths, some elements of our study design warrant discussion. The first issue is whether the nature of our study design might have compromised the internal validity of the analysis by introducing some type of bias that would have altered the ability of BCT to identify high-risk patients compared to what would be expected clinically. Our main inclusion criterion required patients to have had a spine-containing CT as part of their medical care before surgery, which in this healthcare system comprised of approximately 20% of all primary fusion patients. For approximately 85% of those included patients, that CT comprised a lumbar or thoracic spine CT. In our clinical practice, there is no link between any indication for ordering such a spine CT pre-operatively and the likelihood of having osteoporosis. Thus, it is unlikely that this inclusion criterion introduced significant bias into the analysis. In addition, to minimize effects of any short-term post-operative mortality (or other loss to follow-up) on our results, we only included patients without reoperation or vertebral fracture if they had at least three months of follow up. However, only 4.4% of all fusion patients did not meet this criterion and again, any links to the presence of osteoporosis are tenuous.

We were also forced to exclude 65% of the 1,348 potentially eligible patients in our random sample due to missing or inappropriate data. Compared to that random sample, the final analysis cohort of 469 patients had significantly more women (64% vs. 52%), older age (63.6 vs. 56.6 years), shorter height (167 vs. 170 cm), higher BMI (29.2 vs. 28.3 kg/m²), and more diabetes (37% vs. 29%); there were also fewer long fusions (19% vs. 34%) and ultimately fewer vertebral fractures (8% vs 13%). A lack of pre-operative CT scans that extended up the spine to the UIV level might explain the observed shorter fusion length in the analysis cohort than the overall random cohort, and thus the lower observed fracture rate. However, our adjusted and stratified hazard ratio analyses demonstrated that osteoporosis by BCT was associated with vertebral fracture for both short and long fusions, indicating that any such differences in the cohort regarding fusion length should not compromise the ability of BCT to assess fracture risk. Reoperation rate did not differ between the random and analysis groups ($p=0.10$), and none of the above factors affected reoperation rate. Thus, while our analysis cohort differed slightly from the collective group of all primary

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fusion patients with CT in our system, any different characteristics were either accounted for in our statistical analysis or did not affect the clinical outcomes.

From a statistical perspective, while a fully prospective study design would have resulted in more control over data collection and more fine-grained detail on surgical approaches and clinical outcomes, our analysis cohort did have a complete set of study data and the sample size was sufficiently large to support the statistical validity of our study conclusions. That said, we made multiple statistical comparisons but did not adjust p-values; some of the reported hazard ratios had 95% confidence intervals that were wide or close to unity; and the overall statistics depended on a relatively small number of events. Further, in retrospect we found that some pre-planned second surgeries were included, which could have diluted statistical power. Thus, replication of our findings in a larger study would further support generality.

One limitation relates to the nature of our clinical outcomes. For our reoperation outcome, we did not distinguish between different causes for reoperation and thus it is not possible to use our current results to predict risk of any particular type of bone-related failure, for example screw loosening, cage subsidence, or proximal junctional kyphosis. That issue remains a topic of ongoing research. Some have shown, for example, that a localized measurement of BMD around the endplate is associated with cage subsidence [58, 64]. Going forward, challenges in conducting clinical studies with granular clinical outcomes include precisely defining such outcomes [2] while ensuring a sufficiently large sample size in order to provide the required statistical power to differentiate between prediction of different modes of clinical failure. For our vertebral fracture outcome, we had no record of the vertebral level of any new fracture, nor could we distinguish between a new fracture after surgery and one that might have existed before surgery but was only noticed and entered into the patient's record after surgical follow-up. The short median time to vertebral fracture of 2.0 months might therefore reflect that many new vertebral fractures occurred shortly after surgery, or, that many fractures existed before surgery but were only noted in the medical record during the first post-surgery visit. Given the consistency across findings from our previous studies in which BCT predicted both existing and new vertebral fractures in the general population [29-35], it is unlikely that our conclusions regarding risk of vertebral fracture would have changed appreciably had our outcome comprised of only radiographically confirmed new fractures.

Regarding generality, one caveat is that our results might apply only to the types of patients included in our cohort, namely only to primary fusion patients who had a UIV level at or below T4. In addition, our patients, being specific to one region of the U.S. and one healthcare system, may have specific characteristics that differ from patients elsewhere. Likewise, surgical practices may vary across different healthcare systems. While the diverse nature of our cohort, the multiple medical centers, the multi-year time span over which patients were sampled, and the strong statistical significance of the Kaplan-Meier

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analyses together support the generality of our main conclusions, specific metrics such as revision rates and prevalence of osteoporosis can vary geographically and thus may not apply broadly. And because we did not account for factors related to the type of surgical approach, beyond our stratification of long and short fusions, our results best apply to primary fusion patients in general and do not address any specific sub-categories. Future studies are therefore needed to integrate the BCT metrics reported here into other pre-operative risk assessments [47-53] for specific patient and surgical categories.

Notwithstanding these limitations and caveats, our results have implications for clinical care. Given the mechanistic nature of BCT, and its prior validation for assessing vertebral fracture risk in multiple cohorts [29-35], our findings suggest that therapeutic treatment [16] should be considered for all spinal fusion patients age 50 and older who test positive by BCT for either fragile bone strength or BMD-defined osteoporosis, whether at the nominal or UIV levels. Such treatment should at least reduce the risk of any future vertebral fracture. Additional mitigating steps might be justified for some of these osteoporotic patients, such as patients undergoing a long fusion, who are at particularly high risk for vertebral fracture, or those testing positive concurrently for both FBS and BDO, who are at almost four-fold higher risk for reoperation compared to patients without osteoporosis. While BCT provides an objective basis to identify such high-risk patients, a determination of what particular mitigating steps might be most appropriate for any particular patient remains an issue of clinical judgement for the surgeon and an important topic of ongoing research.

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Conflicts of Interest:

1. TMK: Consulting; Amgen; Bone Health Technologies; O.N. Diagnostics; UCB Pharma. Equity: O.N. Diagnostics.

O.N. Diagnostics LLC is the developer and provider of the FDA-cleared BCT test that was utilized in this study. Technicians at O.N. Diagnostics performed all BCT analyses for this study, blinded to the clinical outcomes.

2. ALA: None.

3. HF: None.

4. HSB: None.

5. SB: None.

6. KHG: None.

7. DLK: Employee of O.N. Diagnostics, LLC

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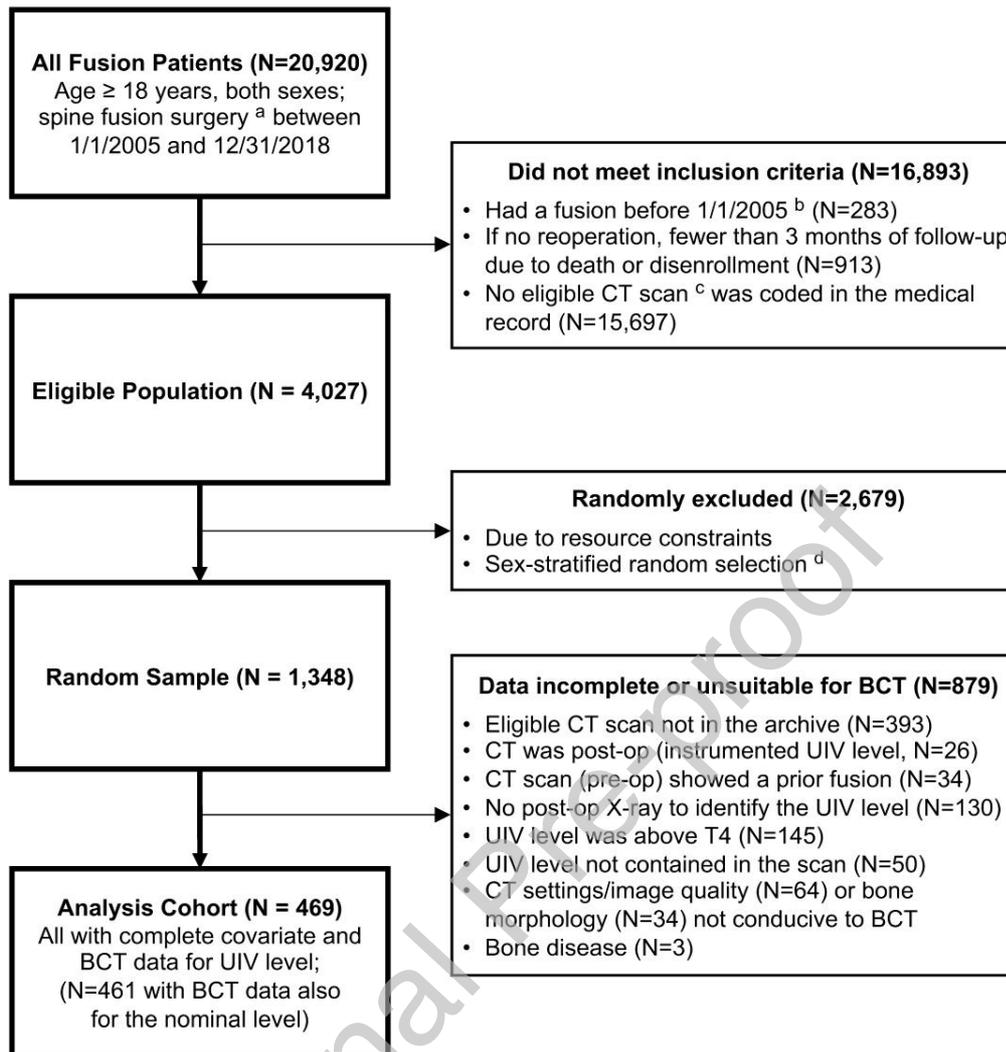


Figure 1: Flow chart for development of the analysis cohort. Starting with a patient population of 20,920 primary fusion patients, a total of 469 patients with complete study data were included in this analysis. **a)** Any fusion was found by EMR search using CPT[®] codes (22533, 22534, 22556, 22558, 22610, 22612, 22630, 22632, 22633, 22634, 22532, 22840, 22841, 22842, 22843, 22844, 22845, 22846, 22847, 22853, 22854); ICD-9 codes (81.0, 81.62, 81.63, 81.64, 84.51); or ICD-10 codes (0RG6, 0RG7, 0RG8, 0RGA, 0SG0, 0SG1). **b)** Revision fusion was found by EMR search using all codes above plus CPT codes (22849, 22850, 22852, 22855); ICD-9 (81.3) or ICD-10 codes (0RW604Z, 0RW60AZ, 0RW634Z, 0RW63AZ, 0RW644Z, 0RW64AZ, 0RW6X4Z, 0RW6XAZ, 0RWA04Z, 0RWA0AZ, 0RWA34Z, 0RWA3AZ, 0RWA44Z, 0RWA4AZ, 0RWAX4Z, 0RWAXAZ, 0SW004Z, 0SW00AZ, 0SW034Z, 0SW03AZ, 0SW044Z, 0SW04AZ, 0SW0X4Z, 0SW0XAZ). **c)** An eligible CT scan was a spine-containing CT scan acquired without intravenous contrast, taken within one year before the fusion surgery, day of surgery, or within two weeks post-operatively. Scans were found by an EMR search using CPT codes (71250, 71270, 72128, 72130, 72131, 72133, 72292, 74150, 74170, 77078, 74176, 74178) or

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ICD-10 codes (BR27ZZZ, BR29ZZZ, BW24ZZZ, BW20ZZZ, BW21ZZZ, BW25ZZZ, BW2000Z, BW2010Z, BW20Y0Z). **d)** Due to resource constraints, a sex-stratified random sample was selected for analysis (56% women), that proportion based on the eligible population with reoperation who were female. CPT is a registered trademark of the American Medical Association.

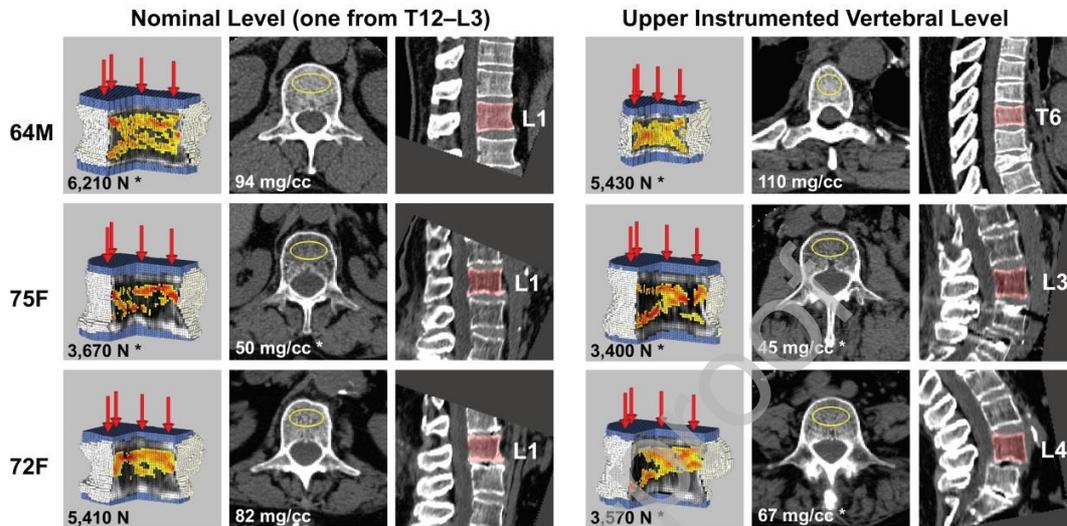


Figure 2: BCT images for three subjects (age/sex), showing the nominal (left) and upper instrumented vertebral (UIV) levels (right). Images depict the finite element model loaded to failure (colored regions showed failed tissue), a mid-transverse section showing the region of interest (yellow ellipse) of the BMD measurement, and a mid-sagittal section showing the analyzed vertebral level highlighted in red. For each subject, the measured values of vertebral strength and vertebral trabecular BMD are shown (strength value is scaled for the UIV level); * denotes a positive test result (FBS or BDO) for that measurement.

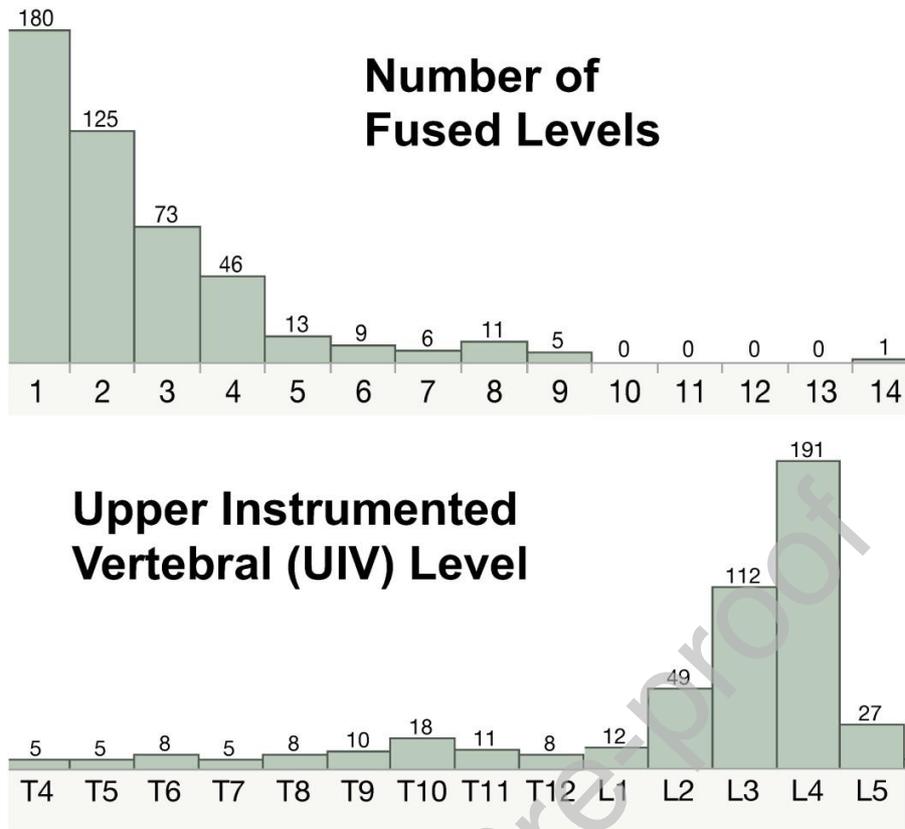
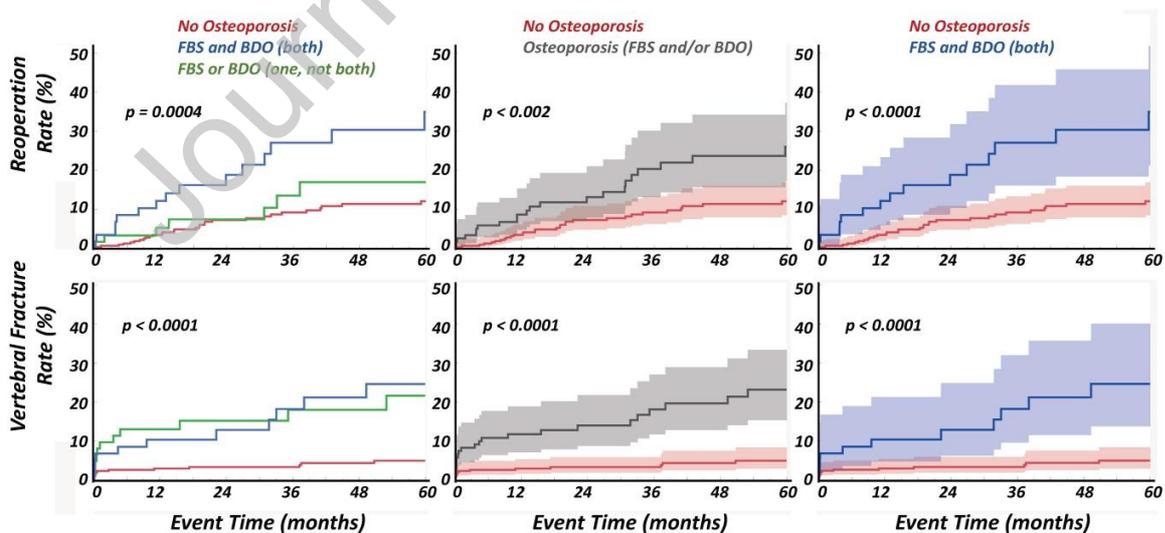


Figure 3: Distribution of the N=469 patients in the analysis cohort by the number of fused levels and the location of the UIV level.



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Figure 4: Kaplan-Meier failure curves (1 – survival) for reoperation (top row) and vertebral fracture (bottom row), comparing the failure rates for different BCT classifications (N=469 patients, BCT at the UIV level). In each column, the reference for comparison is not having osteoporosis (red line, concurrent negative test for each of FBS and BDO, N=348). The left column compares those non-osteoporotic patients to two groups: those testing positive concurrently for both FBS and BDO (blue line, N=59), and those testing positive for only one of FBS or BDO (but not both; green line, N=62); the middle column compares against those testing positive for osteoporosis (test positive for FBS and/or BDO, gray line, N=59+62=121); and the right column compares only against those testing positive concurrently for both FBS and BDO (blue line, N=59). For each panel, the p-values are from the log-rank test, which detects differences in clinical failure rates between any of the classifications in the panel. Shaded regions represent \pm 95% confidence intervals (not shown on the left-most column for clarity).

Table 1: Characteristics of the cohort (N=469 patients).

<i>Characteristic (categorical if %)</i>	<i>Mean (SD) or % of cohort</i>
<i>Demographics</i>	
Age (years)	63.6 (11.6)
Age range (years)	22–93
Age \geq 50 years (%)	88.7
Sex	
Female (%)	63.5
Male (%)	36.5
Race/ethnicity	
Non-Hispanic White (%)	56.7
Hispanic (%)	24.7
Black (%)	11.9
Asian or Pacific Islander (%)	5.8
Other (%)	0.4
<i>Characteristics</i>	
Height (cm)	167 (10)
Mass (kg)	82.1 (19.1)
Body mass index (kg/m ²)	29.2 (5.8)
Vertebral trabecular BMD (mg/cm ³) ¹	118 (38)
Vertebral strength (N) ¹	
Women	6,080 (1,890)
Men	8,610 (2,580)
<i>Comorbidities</i>	

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Obese (BMI ≥ 30 , %)	38.4
Diabetes (%)	36.7
Other bone conditions ² (%)	11.9
Smoker ³ (%)	52.2
Osteoporosis drug use ³ (%)	16.2
Corticosteroid use ³ (%)	26.2
<i>Surgical (any type of primary spinal fusion)</i>	
Number of levels fused	3.4 (1.8)
Short or Long fusion	
Short (≤ 3 levels fused; %)	80.6
Long (≥ 4 levels fused; %)	19.4
<i>Post-Surgical</i>	
Follow-up time (months; median, IQ range) ⁴	
For observation (N=469 patients)	44.4 (16.5–60.0)
To reoperation (N=52 patients)	14.5 (7.5–30.9)
To vertebral fracture (N=36 patients)	2.0 (0.3–29.4)
Reoperation (%)	11.1
Vertebral fracture (%)	7.7

SD = standard deviation; IQ = interquartile (25–75%)

1. Measured at the nominal level (N=461 patients), which is the standard measurement site for assessment of osteoporosis (one vertebral level from T12–L3, preferably L1). Cut point for BMD-defined osteoporosis is 80 mg/cm³ for both sexes; and for fragile bone strength is 4,500 N for women and 6,000 N for men; patients have osteoporosis by BCT if either measurement is less than or equal to the respective cut point.

2. Other bone conditions that could impact bone health were defined as: any history of rheumatoid arthritis, osteopetrosis, Paget's disease, hypophosphatasia, osteogenesis imperfecta; a diagnosis from two years before surgery through the end of follow-up of osteomalacia, multiple myeloma, malignant neoplasms of the spine, or use of tumor necrosis factor (TNF) inhibitor; or a diagnosis during the follow-up period of hypocalcemia or hypercalcemia.

3. During the observation period.

4. All follow-up times started on the date of the patient's surgery. The observation period could not exceed five years but could be shorter if the patient entered the study within five years of the end date of the study or if the patient died or left the health system within the five years. Any reoperation or vertebral fracture had to occur within the patient's observation period.

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Table 2: Cox proportional hazard ratio (HR, crude and adjusted, with 95% confidence intervals) for reoperation and vertebral fracture, and the proportion of patients testing positive for the BCT, for different BCT classifications. The hazard ratio denotes the relative risk of reoperation (or vertebral fracture) when testing positive by each classification compared to not having osteoporosis. All measurements were made at the UIV level. Data for N=469 patients having complete BCT data at the UIV level.

Classification ¹	Proportion Test Positive (%)	Reoperation (52/469 = 11.1%)		Vertebral Fracture (36/469 = 7.7%)	
		Crude HR	Adjusted HR ²	Crude HR	Adjusted HR ²
<i>Test positive for:</i>	(%)				
<i>FBS</i>	21.8	2.8 (1.6–4.9)	3.0 (1.7–5.4)	4.4 (2.3–8.4)	3.7 (1.9–7.5)
<i>BDO</i>	16.6	2.3 (1.3–4.2)	2.7 (1.4–5.0)	3.3 (1.7–6.5)	3.3 (1.6–6.9)
<i>FBS and/or BDO (one or both)</i>	25.8	2.3 (1.3–4.0)	2.6 (1.4–4.7)	4.9 (2.5–9.5)	4.7 (2.2–9.7)
<i>FBS and BDO (both)</i>	12.6	3.3 (1.8–6.1)	3.7 (1.9–7.2)	4.9 (2.2–10.8)	5.0 (2.2–11.7)
<i>FBS or BDO (one, not both)</i>	13.2	1.4 (0.6–3.3)	1.6 (0.7–3.7)	4.8 (2.2–10.6)	4.3 (1.9–10.2)

1 - FBS = fragile bone strength; BDO = BMD-defined osteoporosis. The standard clinical test for osteoporosis by BCT is to test positive for either FBS and/or BDO (one or both can be positive); the last two rows break down these positive testing patients into those testing positive concurrently for both FBS and BDO versus those testing positive for only one (but not both) condition. Testing negative concurrently for both FBS and BDO denotes not having osteoporosis, which was used as the reference for all classifications that considered both bone strength and BMD; for the classifications involving FBS and BDO when considered alone (first two rows), not having osteoporosis was denoted by testing negative for the respective test.

2 – Adjustments were made for age, obesity (BMI ≥ 30 kg/m²), and long fusion (4 or more levels fused); crude = unadjusted.

Table 3: Cox proportional hazard ratio (HR, adjusted, with 95% confidence intervals) for reoperation and vertebral fracture, and the proportion of patients testing positive, for the BCT measurements made at the

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UIV versus nominal levels. Data for N=461 patients having complete BCT data at the UIV and nominal levels. See Table 2 for additional legends.

C Te	Proportion Test Positive (%)		Reoperation HR ¹		Vertebral Fracture HR ¹	
	UIV Level	Nominal Level	UIV Level	Nominal Level	UIV Level	Nominal Level
FE	21.7	21.0	2.9 (1.6–5.2)	2.1 (1.1–3.9)	3.9 (1.9–8.1)	2.6 (1.2–5.4)
BL	16.7	15.4	2.5 (1.3–4.8)	2.3 (1.2–4.5)	3.6 (1.7–7.6)	3.1 (1.4–6.7)
FE BL	25.8	24.7	2.5 (1.4–4.6)	2.0 (1.1–3.7)	5.0 (2.3–10.8)	3.1 (1.5–6.7)
BL	12.6	11.7	3.5 (1.8–6.9)	2.8 (1.4–5.7)	5.4 (2.2–13.2)	3.6 (1.5–8.5)
BL	13.2	13.0	1.6 (0.7–3.8)	1.4 (0.6–3.3)	4.6 (1.9–11.3)	2.7 (1.1–6.9)

1 - Adjustments were made for age, obesity (BMI ≥ 30 kg/m²), and long fusion (4 or more levels fused)

Table 4: Cox proportional hazard ratio (crude, with 95% confidence intervals) for reoperation and vertebral fracture, for stratified analyses of different patient sub-groups from the full analysis cohort (N=469 patients). All measurements were made at the UIV level. See Table 2 for additional legends.

Classification	Patient Sub-Group			
	All Patients (N=469)	Age ≥ 50 (N=416)	Age ≥ 50 & Short Fusion (N=334)	Age ≥ 50 & Long Fusion (N=82)
Reoperation				
FBS	2.8 (1.6–4.9)	2.8 (1.6–5.0)	2.6 (1.3–5.0)	3.4 (1.1–10.7)
BDO	2.3 (1.3–4.2)	2.3 (1.3–4.2)	2.0 (1.0–4.1)	3.3 (1.1–10.5)
FBS and/or BDO ¹	2.3 (1.3–4.0)	2.3 (1.3–4.1)	2.1 (1.1–4.1)	3.0 (0.9–9.4)
FBS and BDO ²	3.3 (1.8–6.1)	3.3 (1.7–6.2)	2.9 (1.3–6.1)	4.6 (1.3–15.8)
FBS or BDO ³	1.4 (0.6–3.3)	1.4 (0.6–3.3)	1.4 (0.5–3.7)	1.6 (0.3–8.3)
Vertebral Fracture				
FBS	4.4 (2.3–8.4)	5.0 (2.5–10.1)	4.3 (1.5–12.9)	4.1 (1.6–10.4)
BDO	3.3 (1.7–6.5)	3.5 (1.8–7.1)	3.9 (1.3–11.6)	3.6 (1.4–8.9)

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<i>FBS and/or BDO</i> ¹		4.9 (2.5–9.5)		5.9 (2.8–12.5)		6.4 (2.0–20.7)		4.6 (1.7–12.1)
<i>FBS and BDO</i> ²		4.9 (2.2–10.8)		5.9 (2.5–14.0)		5.6 (1.4–22.4)		5.5 (1.8–16.5)
<i>FBS or BDO</i> ³		4.8 (2.2–10.6)		5.9 (2.5–13.8)		7.1 (1.9–26.6)		3.8 (1.2–12.0)

1 — test positive for one or both; 2 — test positive for both; 3 — test positive for one but not both.

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