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Evaluation of Bone Mineral Density in Lung Transplant Recipients by Chest Computed Tomography

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Keywords
Lung transplantation · Bone mineral density · Osteoporosis · Computed tomography · Bisphosphonate

Abstract

Introduction: Lung transplantation (LT) recipients are at risk of bone mineral density (BMD) loss. Pre- and post-LT BMD loss has been reported in some cross-sectional studies; however, there are limited studies regarding the serial BMD change in LT recipients. The aim of this study was to investigate the serial BMD changes and the clinical characteristics associated with BMD decline. ***Methods:*** This was a single-center, retrospective observational study. BMD was serially measured in thoracic vertebral bodies (Th4, 7, 10) using computed tomography (CT) before and 3 and 12 months after LT. The frequency of osteoporosis and factors associated with pre-LT osteoporosis and post-LT BMD loss were evaluated. The frequency of post-LT compression fracture and its associated factors were also analyzed. ***Results:*** This study included 128 adult LT recipients. LT recipients had decreased BMD (151.8 ± 42.2 mg/mL) before LT compared with age-, sex-, and smoking index-matched controls (176.2 ± 35.7 mg/mL). The diagnosis of COPD was associated with pre-LT osteoporosis. LT recipients experience further BMD decline after transplantation, and the percentage of recipients classified as exhibiting osteoporosis increased from 20% at baseline to 43% at 12 months. Recipients who had been taking no or small doses of glucocorticoids before LT had rapid BMD loss after LT. Early bisphosphonate use (within 3 months) after LT attenuated BMD loss and decreased new-onset compression fracture. ***Conclusion:*** LT recipients are at high risk for BMD loss and compression fracture after LT. Early bisphosphonate use may decrease BMD loss and compression fracture.

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Introduction

Lung transplantation (LT) is a lifesaving therapeutic option for patients with end-stage lung diseases refractory to medical treatment [1]. Osteoporosis is an important complication for LT recipients because osteoporotic fracture can impair quality of life (QOL) and mortality [2, 3]. The prevalence of osteoporosis in LT recipients has been reported to be 27–61% before LT [4–10] and 40–78% after LT [5, 6, 9].

There have been several cross-sectional studies on pre- and post-LT osteoporosis [4, 5, 8]; however, longitudinal evaluation of serial bone mineral density (BMD) changes is limited to small studies with fewer than 30 cases [6, 7, 9]. Regarding pre-LT osteoporosis, Spira et al. [6] reported an association with glucocorticoid dose before LT, and Trombetti et al. [7] reported associations with chronic obstructive pulmonary disease (COPD) and cystic fibrosis diagnoses and lower body mass index (BMI). Regarding post-LT osteoporosis, Spira et al. [6] reported a correlation between glucocorticoid dose and post-LT BMD decline. Osteoporotic fracture has been reported to occur in 18–27% of post-LT recipients; however, associations with risk factors and preventive therapy have not been fully evaluated [5, 6].

Computed tomography (CT) of the chest is the standard tool for the evaluation of pre- and post-transplant lung parenchymal diseases in LT recipients. Of note, CT of the chest also provides extrapulmonary information, including BMD and vertebral fractures. The utility of CT-derived BMD has been well established [11, 12], although dual-energy X-ray absorptiometry (DEXA) remains the gold standard for the diagnosis of osteoporosis [13].

The aim of the present study was to investigate the serial BMD changes before and after LT using CT in the largest cohort to date. We also evaluated factors that may be associated with pre-LT osteoporosis and post-LT BMD decline. Furthermore, the prevalence of osteoporotic fracture and its associated factors in LT recipients were analyzed.

Materials and Methods

Patient Selection

We screened all LT cases performed at our institution between December 2010 and June 2019. The exclusion criteria were as follows: retransplantation cases; younger than 20 years old at transplantation; chest CT scan unavailable either before LT or 12 months after LT; and CT scan obtained under conditions without phantom data (unavailable to calculate BMD).

To calculate the young adult mean (YAM) and standard deviation (SD), 35 healthy subjects (20–44 years old, young adult group) were recruited from the Kitano Hospital registry, consisting of subjects who underwent CT scans for their medical checkup. Age-, sex-, and smoking index-matched controls without any lung diseases (matched control group) were also recruited from the same registry. Patients who underwent both chest CT and DEXA within 1 month at Kyoto University Hospital between January and December 2022 were also recruited to evaluate the correlation of BMD values from both examinations.

Post-LT Immunosuppressant Protocol and Graft Rejection

Glucocorticoids, tacrolimus, and mycophenolate mofetil were administered to recipients according to the prespecified protocol at our institution. Five hundred milligrams of methylprednisolone were administered intravenously just before reperfusion to the implanted graft lungs. Methylprednisolone was administered to recipients at doses of 125 mg/day from postoperative day (POD) one to three; the dose was then tapered every 3 days down to 0.4 mg/kg/day and maintained until the sixth month; the dose was then decreased to 0.1 mg/kg/day and maintained.

Acute cellular rejection (ACR) was diagnosed based on clinical symptoms, radiological findings, and arterial blood gas. Histological study was not mandatory. Glucocorticoid pulse therapy with 500 or 1,000 mg methylprednisolone for 3 days was performed when ACR was diagnosed.

Antibody-mediated rejection, another form of graft rejection, was diagnosed based on allograft dysfunction, the presence of donor-specific antibodies [14]. The main treatment for AMR was high-dose intravenous immunoglobulin; additionally, depending on the patient, glucocorticoid pulse therapy, plasma exchange, anti-thymocyte globulin, or rituximab might have been administered.

Data Collection

Clinical, physiological, and laboratory data were retrieved from medical records. The pre-LT clinical variables included age, sex, BMI, smoking status, pre-LT glucocorticoid dose, and pre-LT bisphosphonate use. The pre-LT glucocorticoid dose was described as the average dose of prednisolone equivalent (mg/day) used in the last 3 months before LT. The peri-LT variables were types of donors (living donor or brain-dead donor) and transplantation procedure (unilateral LT or bilateral LT), and the post-LT variables included ACR, AMR, length of ICU stay, and post-LT early bisphosphonate use (started within 3 months).

HRCT Scan Acquisition

All individuals in the study cohort (Kyoto University Hospital) and the Kitano Hospital registry underwent thin-section CT examinations without contrast medium in the spine position with full inspiration by either an Aquilion, Aquilion Prime, or Aquilion One CT scanner (all from Canon Medical Systems Corporation, Otawara, Japan). The thickness of the CT scan was 0.5 or 1.0 mm. The obtained images were reconstructed with the FC13 mediastinum algorithm for BMD analysis and the FC51 algorithm for evaluation of the lung.

Measurement of Bone Mineral Density and Diagnosis of Osteoporosis and Osteopenia

BMD was evaluated in the fourth, seventh, and tenth thoracic vertebral bodies (Th4, Th7, and Th10, respectively) before LT and at 3 and 12 months after LT, according to previous studies (online

suppl. Method S1; online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000535269) [11, 12]. The mean BMD of the three vertebrae was used in the following analyses. YAM and SD of BMD were calculated from the young adult group. Osteoporosis was defined as a mean BMD below −2.5 SD of the YAM, and osteopenia was defined as a mean BMD from −2.5 SD to −1 SD of the YAM [15]. A significant BMD loss was defined as a greater-than-1 SD decrease in BMD from baseline, which has been reportedly associated with a 1.4- to 2.6-fold increase in osteoporotic fracture risk [16].

Diagnosis of Compression Fracture

Compression fracture of the vertebral bodies (Th1 to L1) was evaluated in baseline and 12-month CT images by two pulmonologists (RM and TH) and a radiologist (RS) [17]. A compression fracture was diagnosed when a greater than 20% decrease in height was observed in the sagittal image compared to its baseline image or the adjacent vertebrae (online suppl. Fig. S2). Interobserver disagreement was resolved by consensus.

AI-Based Quantitative CT Analysis

To quantitatively evaluate the extent of lung parenchymal lesions in LT recipients, artificial intelligence-based quantitative CT analysis technology (AIQCT) was applied to HRCT images before LT. AIQCT automatically detects and quantifies bronchi, vessels, and eight types of parenchymal patterns (normal lungs, reticulation, ground-glass opacities, honeycombing, consolidation, interlobular septum, hyperlucency, and nodules) and expresses their volume as a percentage of the total lung volume [18].

Statistical Analyses

Continuous variables are presented as the mean and standard deviation (SD) or median with interquartile range (IQR) as appropriate. For correlation analysis between two continuous variables, Pearson's correlation test was used. One-way analysis of variance (ANOVA) with Tukey's multiple comparisons test was used for comparison of continuous variables among three or more groups. Logistic regression models were used to determine predictive factors for pre-transplant osteoporosis, post-transplant BMD loss, and post-transplant compression fracture. Linear mixed models with repeated measurements were used to investigate the effects of baseline BMD values, pre-transplant glucocorticoid usage (3-month average PSL ≥5 mg or <5 mg), time after LT, and early bisphosphonate use on post-LT serial BMD change.

Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC) and EZR version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [19]. For all analyses, $p < 0.05$ was considered statistically significant.

Results

Characteristics of Study Subjects

The consort flow diagram is shown in Figure 1. Of the 206 LT recipients, 128 patients were included in the analyses. The characteristics of the study participants are shown in Table 1. The most common causative disease for LT was interstitial lung disease ($n = 67$), and chronic obstructive pulmonary disease (COPD) comprised seven cases. Glucocorticoids (PSL ≥5 mg/day) were given to 59 recipients (46%) before LT, and bisphosphonate was given to 35 patients (27%) prior to LT.

Bone Density Loss in Recipients prior to LT

The correlation between CT (the first lumbar) and DEXA (the second to fourth lumbar) measurements of BMD was analyzed in 28 patients undergoing both examinations within 1 month. The characteristics of the participants are shown in online supplementary Table S2. A strong correlation was observed between CT and DEXA measurements of BMD (correlation coefficient 0.743, 95% CI: 0.512–0.874, $p < 0.001$) (online suppl. Fig. S3). The calculated BMDs of recipients, controls, and young adults were 151.8 ± 42.2, 176.2 ± 35.7, and 188.5 ± 30.8 mg/mL (mean ± SD), respectively (online suppl. Fig. S4). The BMD of recipients was significantly lower than that of the other two groups ($p < 0.001$ for each, Student's t test).

In univariate analysis, only COPD diagnosis was associated with pre-transplant osteoporosis (odds ratio 6.00, 95% CI: 1.25–28.7, $p = 0.03$) (Table 2). None of the AIQCT indices of the lung were associated with pre-LT osteoporosis in all recipients, while there was an association between the percentage of hyperlucent volume and pre-LT osteoporosis in the LAM-excluded cohort (odds ratio 1.03, 95% CI: 1.00–1.05, $p = 0.02$) (online suppl. Tables S3, S4).

A pre-LT glucocorticoid dose above 5 or 7.5 mg/day of prednisolone was not associated with pre-LT osteoporosis in the entire cohort in the univariate model (odds ratio 1.22, 95% CI: 0.51–2.88, $p = 0.66$ or odds ratio 1.76, 95% CI: 0.74–4.19, $p = 0.20$, respectively) (Table 2). In contrast, a pre-LT 3-month average glucocorticoid dose above 7.5 mg prednisolone was associated with a decreased BMD in the ILD group (odds ratio 6.00, 95% CI: 1.20–30.00, $p = 0.03$), while prednisolone above 5 mg was not (odds ratio 3.59, 95% CI: 0.72–18.00, $p = 0.12$). Recipients who were taking glucocorticoids (PSL ≥5 mg/day) before LT tended to have a lower BMD before LT in the entire cohort (145.1 ± 38.7 vs. 157.6 ± 44.4 mg/mL, $p = 0.10$).

Decrease in Bone Mineral Density over Lung Transplantation

The vertebral BMD of recipients decreased from 151.9 mg/mL (95% CI: 148.9–155.0) before LT to 124.1 mg/mL (95% CI: 121.0–127.2) at 3 months after LT and 118.9 mg/mL (95% CI: 115.9–122.0) at 12 months. The differences from baseline in the least-squares mean were −27.9 mg/mL (linear mixed model, 95% CI: −31.6 to −24.1, $p < 0.001$) at 3 months and −33.0 mg/mL (95% CI: −36.8 to −29.3, $p < 0.001$) at 12 months (Fig. 2a),

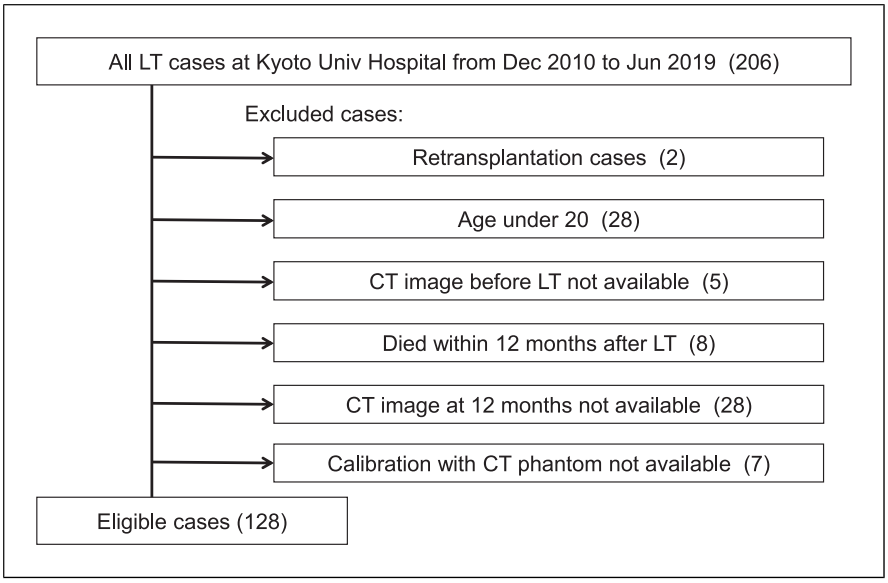

Fig. 1. Consort flow diagram. All lung transplant cases at Kyoto University Hospital from December 2010 to June 2019 were screened.

Table 1. Patient characteristics before lung transplantation

	LT recipients (n = 128)	Matched controls (n = 69)	Young adults (n = 35)
Age, years old	49 (37–56)	52 (45–60)	40 (32–44)
Sex (male), n (%)	66 (52)	43 (62)	25 (71)
BMI, kg/m^2	18.5 (16.6–21.2)	23.2 (21.3–24.8)	23.1 (20.8–26.2)
Ever-smoking, n (%)	48 (38)	47 (68)	6 (17)
Pack-years	0 (0–15)	0 (0–90)	18 (0–50)
Lung diseases indicated for transplantation, n (%)			
ILDs	67 (53)	NA	NA
HSCT-related	21 (16)		
PH	11 (9)		
LAM	8 (6)		
COPD	7 (5)		
Others	14 (11)		
Donor (living/brain-dead), n (%)	51 (40)/77 (60)	NA	NA
Transplantation procedure (unilateral/bilateral), n (%)	44 (34)/84 (66)	NA	NA
3 M average GC (PSL ≥5 mg), n (%)	59 (46)	NA	NA
Pre-LT bisphosphonate, n (%)	35 (27)	NA	NA
Pre-LT vitamin D, n (%)	8 (6)	NA	NA

Continuous variables are described with the median (IQR). LT, lung transplantation; BMI, body mass index; ILDs, interstitial lung diseases; HSCT, hematopoietic stem cell transplantation; COPD, chronic obstructive pulmonary disease; PH, pulmonary hypertension; LAM, lymphangioleiomyomatosis; GC, glucocorticoid. The control group consisted of subjects who underwent computed tomography scans for medical examination. The control group was matched for age, sex, and smoking index (pack-years) with recipients. The young adult group contains healthy subjects who were 20–44 years old and who underwent CT scans for their medical checkup.

corresponding to 18% and 22% reductions at 3 and 12 months, respectively. The BMD decrease in the first 3 months was faster than that in the following 9 months (−9.3 mg/mL/month vs. −0.5 mg/mL/month). To further investigate the timing of BMD loss, BMD was evaluated in 54 recipients who underwent CT 1 month after LT. Compared to the baseline BMD (146.6 mg/mL, 95% CI: 136.2–157.1), the BMD at 1 month after LT (141.5 mg/mL, 95% CI: 131.0–152.0) was not significantly different but was significantly lower at 3 months (120.7 mg/mL,

Table 2. Effect of each factor on pre-transplant osteoporosis (univariate logistic regression)

	Odds ratio	95% CI	*p* value
Age (per 10 years old)	0.99	0.70–1.41	0.97
Sex (male)	1.66	0.69–4.01	0.26
BMI (kg/m^2)	0.93	0.82–1.06	0.30
Pack-years	1.00	0.98–1.02	0.88
COPD	6.00	1.25–28.70	0.03
Living donor	0.93	0.38–2.25	0.87
Unilateral LT	1.25	0.51–3.05	0.62
Pre-LT 3 M average GC (PSL ≥5 mg)	1.22	0.51–2.88	0.66
Pre-LT bisphosphonate	1.93	0.78–4.78	0.16
Pre-LT vitamin D	1.33	0.25–7.02	0.73
Pre-LT cyclosporin A	1.79	0.57–5.62	0.32
Pre-LT tacrolimus	3.10	0.99–9.70	0.052
Pre-LT CKD	8.42	0.73–96.70	0.08

CKD, chronic kidney disease.

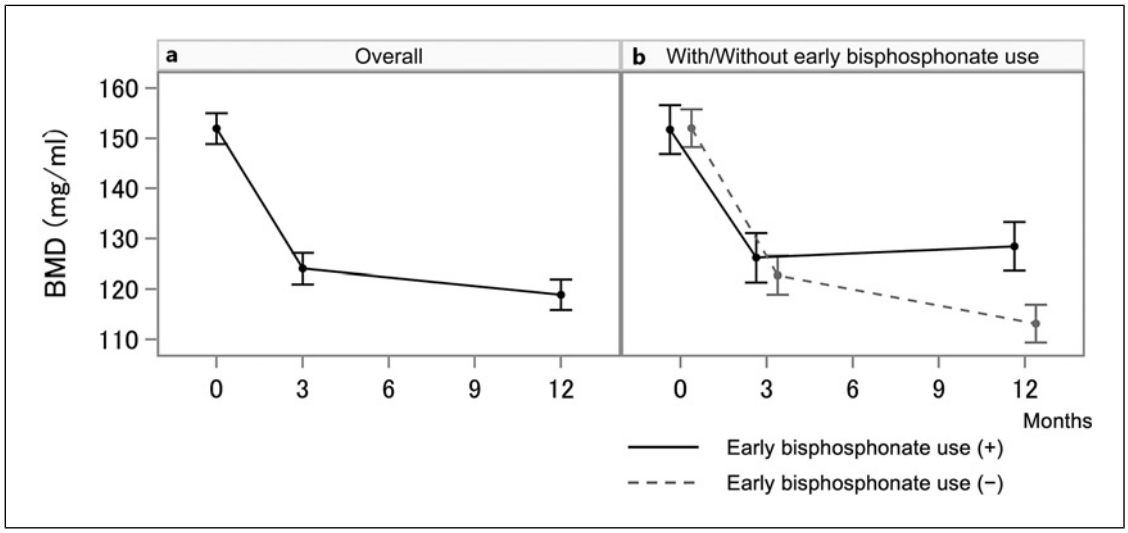

Fig. 2. Change in BMD over time in all the recipients (**a**) and in the recipients with and without early bisphosphonate use (**b**). Error bars indicate the 95% CIs. The differences from baseline in the least-squares mean were −27.9 mg/mL (95% CI: −31.6 to −24.1, $p < 0.001$) at 3 months and −33.0 mg/mL (95% CI: −36.8 to −29.3, $p < 0.001$) at 12 months. The differences in the least-squares mean between groups with and without early bisphosphonate use were 3.5 mg/mL (95% CI: −2.7 to 9.7, $p = 0.27$) at 3 months and 15.3 mg/mL (95% CI: 9.1–21.4, $p < 0.001$) at 12 months. Recipients with early bisphosphonate use had significantly preserved BMD at 12 months ($p < 0.001$).

95% CI: 110.0–131.3, $p = 0.001$) and 12 months (115.7 mg/mL, 95% CI: 105.2–126.1, $p < 0.001$) after LT in these patients. The frequency of osteoporosis increased from 20% before LT to 43% at 12 months after LT (online suppl. Fig. S5).

Greater-than-1 SD BMD Loss after Lung Transplantation

A greater-than-1 SD BMD loss (significant BMD loss) was observed in 70 recipients (55%) at 12 months after LT. Pretransplant glucocorticoids (OR 0.34, 95% CI: 0.17–0.71, $p = 0.004$) and bisphosphonate use (OR 0.32, 95% CI: 0.14–0.71, $p = 0.005$) were associated with a lower frequency of greater-than-1 SD BMD loss (Table 3). As the preventive management of post-LT osteoporosis at our institution was changed during the study period, only 48 of 128 recipients (36%) started bisphosphonate within the first 3 months after transplantation as follows: 8 out of 42 recipients (19%) in the former half period and 40 out of 86 recipients (47%) in the latter half period. Early bisphosphonate use decreased the risk for greater-than-1 SD BMD loss

Table 3. Effect of each factor on ≥1 SD BMD loss after lung transplantation (univariate logistic regression)

	Odds ratio	95% CI	*p* value
Pretransplant factors			
Age (per 10 years old)	0.95	0.72–1.27	0.74
Sex (male)	0.59	0.29–1.20	0.15
BMI (kg/m^2)	0.92	0.83–1.02	0.12
Pack-years	0.99	0.97–1.01	0.30
COPD	0.60	0.13–2.82	0.52
Pre-LT 3 M average GC (PSL ≥5 mg)	0.34	0.17–0.71	0.004
Pre-LT bisphosphonate	0.32	0.14–0.71	0.005
Pre-LT vitamin D	0.82	0.20–3.43	0.78
Perioperative factors			
Living donor	1.51	0.74–3.10	0.26
Unilateral LT	1.14	0.55–2.38	0.73
Post-transplant factors			
Acute cellular rejection	1.16	0.57–2.36	0.69
Antibody-mediated rejection	0.81	0.27–2.46	0.71
ICU stay	0.97	0.91–1.04	0.37
Hospital stay duration	1.00	0.99–1.00	0.40
Post-LT early bisphosphonate use	0.24	0.11–0.52	<0.001
Post-LT cyclosporin	0.71	0.28–1.82	0.48
Post-LT tacrolimus	1.26	0.50–3.15	0.63
Post-LT CKD	1.50	0.42–5.40	0.54

(OR 0.24, 95% CI: 0.11–0.52, $p < 0.001$). The association of early bisphosphonate use with preserved BMD was shown in a linear mixed model as well (Fig. 2b).

ACR occurred in 51 patients (40%), and glucocorticoid pulse therapy was administered to all ACR patients. In contrast, AMR occurred in 14 patients (11%), and glucocorticoid pulse therapy was administered to 8 patients. Neither ACR nor AMR was associated with a greater-than-1 SD BMD loss. Furthermore, none of the LT procedures or other post-transplant management practices were associated with a significant BMD loss (Table 3).

Compression Fracture and Associated Factors

Vertebral compression fracture was observed in 11 recipients (9%) before LT, and new compression fractures were observed in 16 recipients (13%) at 12 months. In univariate analyses, pre-transplant BMD (OR 0.97, 95% CI: 0.95–0.99, $p < 0.001$), BMD at 12 months (OR 0.95, 95% CI: 0.93–0.97, $p < 0.001$), and BMD decrease at 12 months (OR 0.97, 95% CI: 0.95–0.996, $p = 0.02$) were associated with new-onset compression fracture. Early bisphosphonate use was associated with a decreased incidence of new compression fractures (OR 0.21, 95% CI: 0.0–0.95, $p = 0.04$). Neither ACR nor AMR was associated with new-onset compression fracture (Table 4).

Discussion

The present study demonstrated that there was an 18% decrease in BMD at 3 months after LT and a 22% decrease in BMD at 12 months. A significant (greater-than-1 SD) BMD loss was observed in 55% of recipients at 12 months. Pretransplant glucocorticoid use, i.e., not being glucocorticoid naïve, and post-transplant early bisphosphonate use (within 3 months) conferred a lower risk for significant BMD loss. Early bisphosphonate use was also protective against post-transplant fractures of the vertebrae.

The present study showed that BMD declined faster in the initial 3 months after LT and relatively slowly thereafter. This fast-onset and rapid-progressive BMD decline after LT was consistent with glucocorticoid-induced osteoporosis, which is also known to progress in the first several months after initiation [20]. This finding indicated that post-LT glucocorticoids may play a major role in the pathogenesis of post-LT osteoporosis.

Bisphosphonate has been reported to prevent BMD loss in other solid organ transplantations [21–24], and a similar preventive effect was shown in LT recipients in the present study. However, there is no consensus on bisphosphonate use to prevent osteoporosis in solid organ transplantation recipients [25] due to insufficient evidence of fracture prevention in solid organ transplant

Table 4. Univariate logistic regression models for evaluating factors associated with compression fracture

	Odds ratio	95% CI	*p* value
Age (per 10 years old)	1.51	0.92–2.50	0.11
Sex (male)	0.93	0.33–2.65	0.89
Pack-years	1.01	0.98–1.03	0.64
Pre-LT 3 M average GC (PSL ≥5 mg)	0.67	0.23–1.96	0.46
Pre-LT bisphosphonate	0.34	0.07–1.59	0.17
Acute cellular rejection	1.60	0.56–4.59	0.38
Antibody-mediated rejection	3.40	0.92–12.50	0.07
Pre-LT BMD (per 10 mg/mL)	0.73	0.61–0.87	<0.001
BMD at 12 months after LT (per 10 mg/mL)	0.60	0.47–0.76	<0.001
BMD change in 12 months (per 10 mg/mL)	0.77	0.62–0.96	0.02
Post-LT early bisphosphonate use	0.21	0.04–0.95	0.04
Post-LT cyclosporin	1.21	0.31–4.66	0.79
Post-LT tacrolimus	0.89	0.23–3.41	0.86
Post-LT CKD	0.68	0.08–5.70	0.72
ICU stay duration	0.98	0.89–1.08	0.69
Hospital duration	1.00	1.00–1.01	0.22

BMD, bone mineral density.

recipients and a lack of data regarding long-term safety. Bisphosphonates have been reported to be ineffective for fracture in kidney transplantation [21, 22], and there have been conflicting results in liver and heart transplantation recipients [24–26]. Regarding lung transplantation, the only single-arm pilot study has reported a lower incidence of fracture in LT recipients who had received bisphosphonates prior to LT compared to those in historical cohorts (4% vs. 16–50%) [10]. The present study showed an association between early bisphosphonate use and a lower incidence of compression fracture. Further investigation regarding the efficacy and safety of long-term bisphosphonate use after LT is needed.

The present study confirmed the association between COPD diagnosis and osteoporosis in pre-transplant LT recipients, agreeing with previous studies [8, 27, 28]. Of note, the present study provided a quantitative analysis of pre-transplant HRCT images. The extent of hyperlucent areas was associated with osteoporosis in the LAM-excluded cohort, in which most of the hyperlucent areas represented emphysema. Previous studies have reported that the extent of emphysema in COPD and idiopathic pulmonary fibrosis is associated with a decrease in BMD [11, 29]. The present study further supported this impact of emphysema on BMD in pre-transplant recipients, indicating a potential role of quantitative CT analysis in evaluating the risks of pre-transplant osteoporosis.

In contrast, post-transplant BMD loss was not associated with COPD diagnosis, other causative diseases for LT, or quantitative CT indices in the present study. Pre-transplant status, including BMI, was also not predictive of post-transplant BMD decline. Thus, monitoring of BMD and prevention of osteoporosis should be considered in all LT recipients, regardless of pre-transplant status and causative diseases for LT.

The impacts of pre-LT glucocorticoid use on BMD in this study should be carefully interpreted because they varied between pre- and post-LT periods. Pre-LT glucocorticoid use (≥7.5 mg of prednisolone/day) was significantly associated with pre-LT osteoporosis in only ILD patients but not in the entire cohort. These results suggest that a certain amount of glucocorticoids can affect BMD and that not only the doses of the glucocorticoids but also factors other than glucocorticoids might affect BMD depending on the disease. On the other hand, pre-LT glucocorticoid use was associated with a smaller post-LT BMD loss. This seems paradoxical but suggests that newly administered high-dose glucocorticoids can greatly affect BMD loss.

The present study used chest CT images to measure BMD in LT recipients, whereas all previous studies used DEXA. CT-derived BMD has been reported to be superior to DEXA-derived BMD in predicting osteoporotic fractures [30, 31]. In the present study, the CT-derived BMD value was associated with osteoporotic fracture. Chest CT evaluation is needed for all lung transplantation candidates for pulmonary evaluation, and recipients usually undergo CT several times after transplantation. Thus, measuring BMD with the secondary use of chest CT scans may be an easier and less invasive way of detecting osteoporosis and compression fracture without any additional radiation exposure.

The present study has several limitations. The present study was a single-center retrospective study, and information

regarding activities of daily life and QOL was not available. Despite these limitations, this is the largest study that has assessed serial BMD and described the epidemiology of BMD loss, bone fractures, and associated factors in LT recipients.

Conclusions

The present study serially measured the BMD of LT recipients in the largest cohort to date. Significant BMD loss was prevalent, affecting more than half of LT recipients, and the decline was particularly fast in the initial 3 months. Early post-LT bisphosphonate use may reduce BMD loss and osteoporotic fractures. Further prospective studies on the long-term effects and risks of bisphosphonates after LT are needed.

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Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the Institutional Review Board of Kyoto University Hospital – approval: R2389 and R2733, and Kitano Hospital – approval: P14-11-011. All study patients previously provided written informed consent for research use of clinical data and images. Accordingly, the additional informed consent for this study was waived because of the retrospective study design.

Conflict of Interest Statement

Ryobu Mori, Tomohiro Handa, Kohei Ikezoe, Kiminobu Tanizawa, Naoya Tanabe, Tsuyoshi Oguma, Susumu Sato, and Toyohiro Hirai received a research grant from FUJIFILM Corporation; Tomohiro Handa is part of an endowed department sponsored by Teijin Pharma Ltd; Ryuji Uozumi received consulting fees from Daiichi Sankyo, Eisai, Sawai Pharmaceutical, SBI Pharmaceuticals, STATCOM, and EPS Corporation and lecture fees from SAS Institute Japan, outside the submitted work; Naoya Tanabe received research grants from DAIICHI SANKYO COMPANY, Limited; Tsuyoshi Oguma received lecture fees from KYORIN Pharmaceutical, Sanofi, AstraZeneca, GSK, Novartis Pharma, and Boehringer Ingelheim; Susumu Sato received grants from Nippon Boehringer Ingelheim outside the submitted work and is part of an endowed department sponsored by Philips Japan, Fukuda Denshi, Fukuda Lifetec Keiji, and ResMed Japan.

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Author Contributions

T.H. had full responsibility for the integrity of the data and accuracy of data analysis. R.M., T.H., K.I., and K.T. contributed to the study conception. R.M., T.H., K.I., and K.T. collected and analyzed the data. R.U. contributed to the statistical analyses. N.T., T.O., and R.S. contributed to the radiological analyses. A.O., M.H., D.N., Y.Y., S.T., Y.Y., and H.D. are involved in the preoperative, perioperative, and postoperative care of lung transplant patients. Y.O. and S.S. were involved in the rehabilitation of lung transplant recipients. M.F. contributed to the Kitano Hospital Registry. R.M., T.H., K.I., and K.T. contributed to the literature search and wrote and edited the manuscript. A.O., H.D., and T. H. contributed to critical revision of the article for important intellectual content. All authors contributed to the final approval of the article.

Data Availability Statement

The data generated and/or analyzed during the current study are not publicly available due to privacy reason but are available from the corresponding author upon reasonable request.

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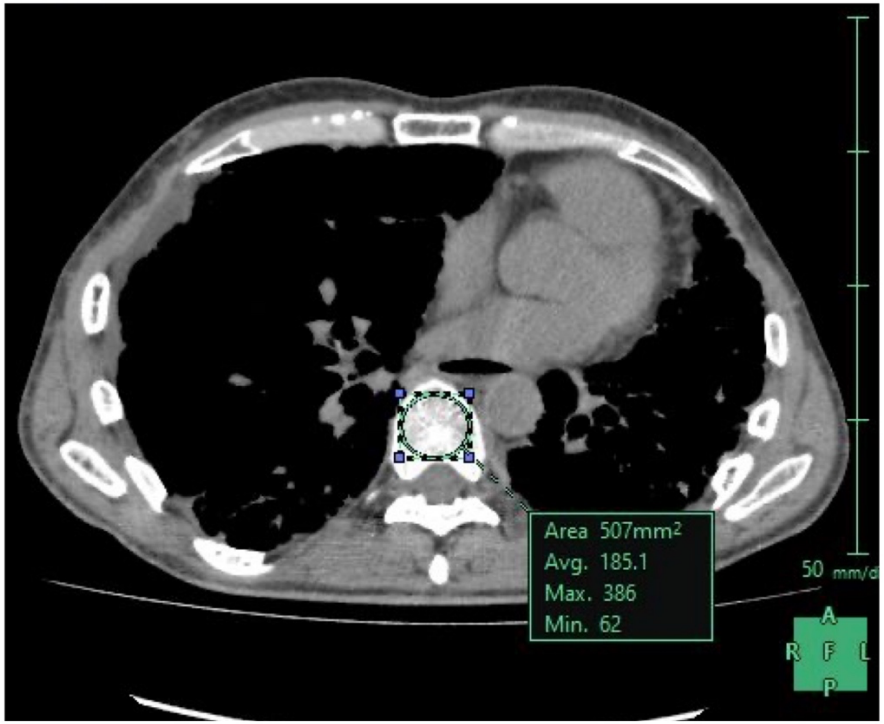
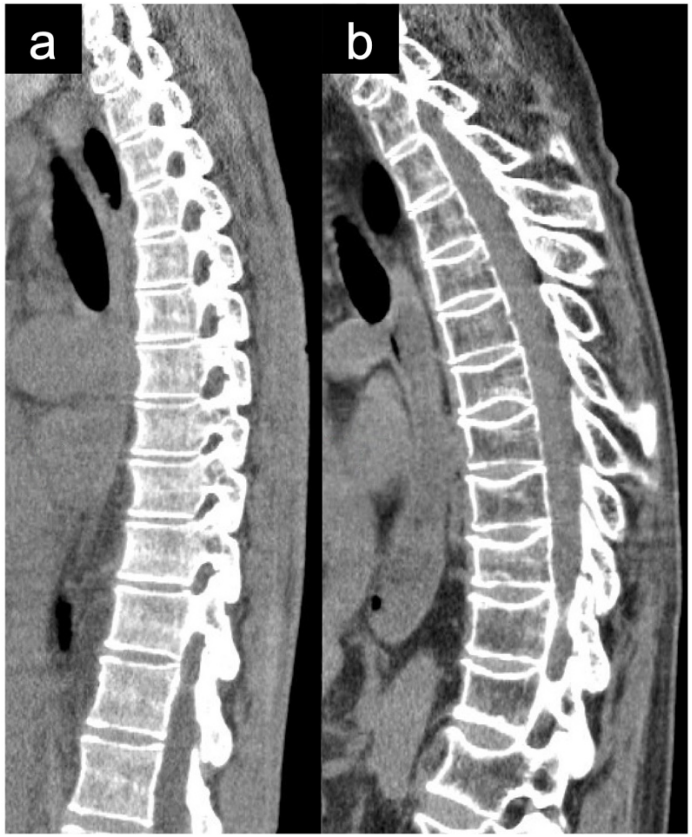
Supplemental Method S1

Measurement of bone mineral density using computed tomography

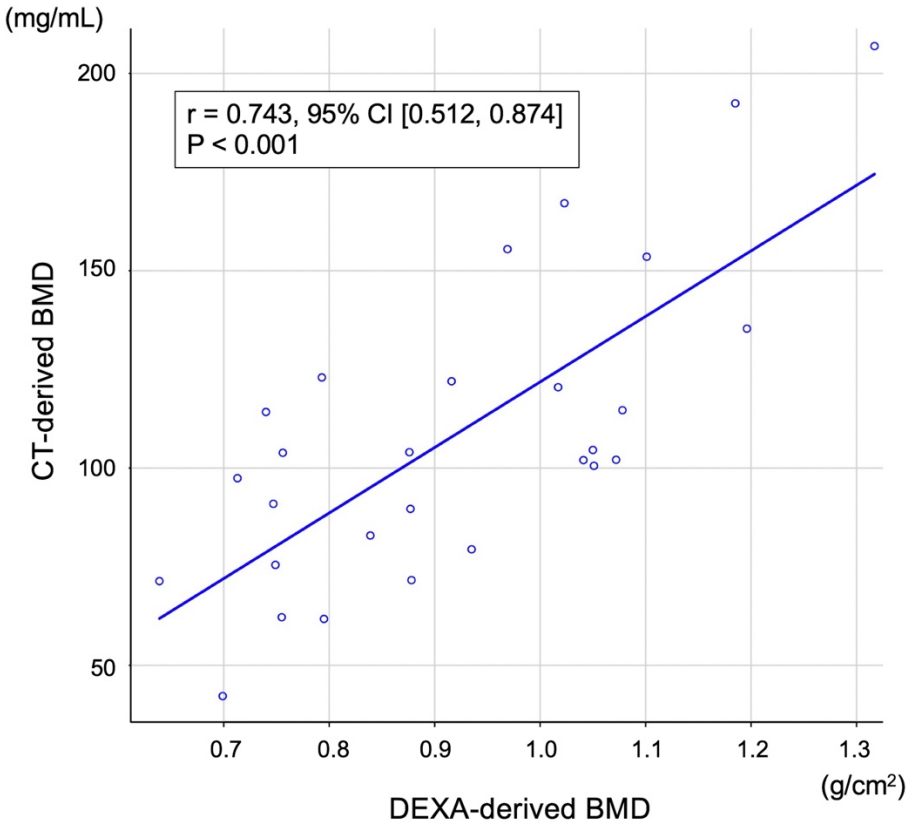
For each vertebral body, a craniocaudal midpoint section was selected, and a rectangular region of interest (ROI) was manually encircled so that the rectangle occupied the largest area of the vertebral body in the slice (Supplementary Figure S1). The BMD of each vertebra was calculated using formulae established for each scanner, a reconstruction function, and thickness of the CT scan (Supplementary Table S1).



Supplementary Figure S1. Measurement of BMD using CT images. The rectangular region of interest was encircled so that the rectangle occupied the largest area of the vertebral body at the craniocaudal midpoint slice of the vertebra. BMD was calculated as the average BMD values of three vertebrae (Th4, Th7, and Th10).

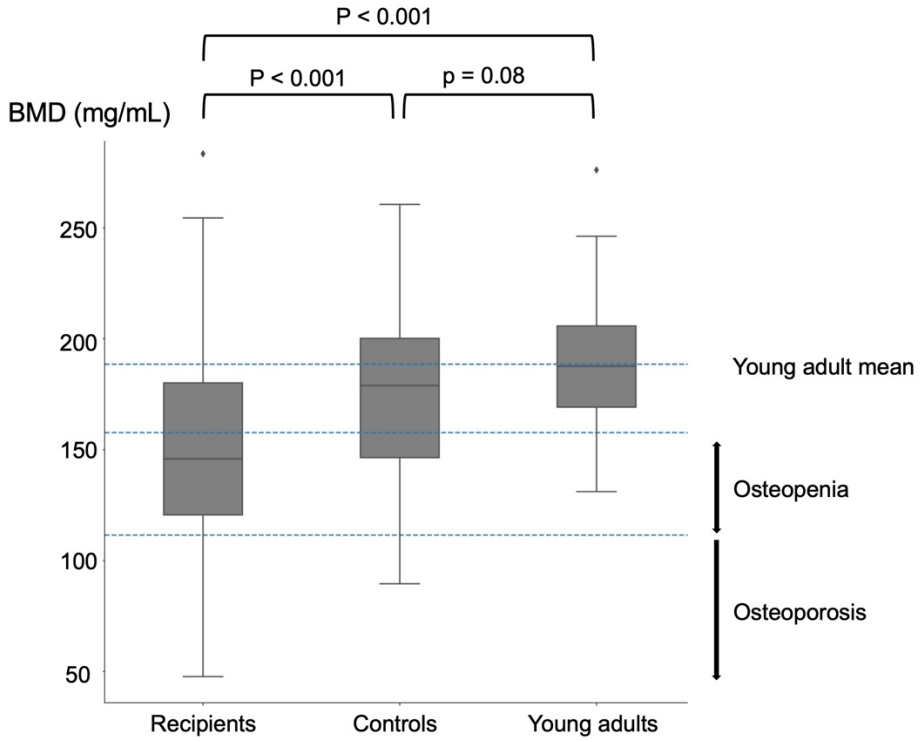


Supplementary Figure S2. The compression fracture of vertebral bodies was evaluated in reconstructed sagittal sections of CT images. The CT image at 12 months (b) was compared to the baseline image (a), and compression fracture was diagnosed when more than a 20% decrease in height at any point compared to a past image or the adjacent vertebra was detected.

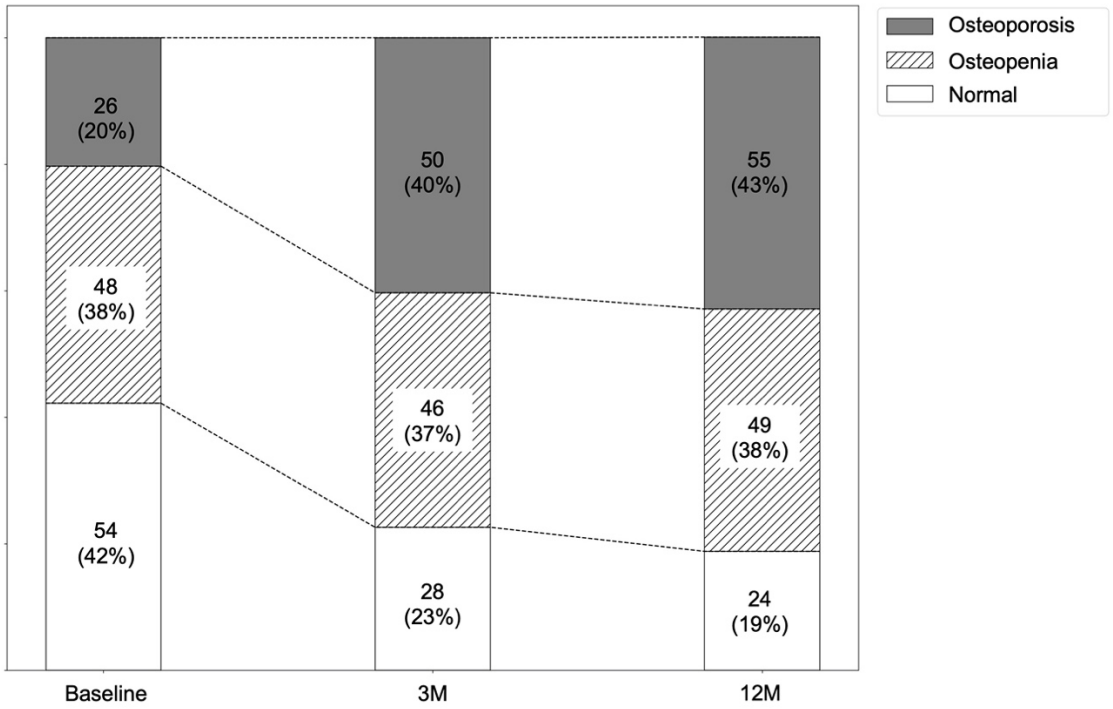


Supplementary Figure S3. The correlation between CT-derived and DEXA-derived BMD was analyzed with Pearson's correlation test.

A strong correlation between CT-derived and DEXA-derived BMD was observed.



Supplementary Figure S4. BMD comparison among pre-LT recipients, controls (age-, sex-, and smoking index-matched), and young adults. The pre-LT BMD of recipients (151.8 ± 42.2 mg/mL) was significantly lower than that of controls (176.2 ± 35.7 mg/mL) and young adults (188.5 ± 30.8 mg/mL).



Supplementary Figure S5. Changes in the proportion of recipients classified as having normal BMD, osteopenia, or osteoporosis over time. The percentage of recipients classified as having osteoporosis increased from 20% at baseline to 43% at 12 months.

Supplementary Table S1. Formulae for calculating BMD from the mean CT density

Scanner	Reconstruction function	Thickness	Formulae
Aquilion 64	FC13	0.5 mm	0.7597 x CT value – 3.5981
	FC13	1.0 mm	0.7578 x CT value – 3.4703
Aquilion prime	FC13	1.0 mm	0.8028 x CT value – 2.1963
Aquilion one	FC13	1.0 mm	0.8051 x CT value – 3.2136

Formulae for calculating BMD from the mean CT density value of the ROI are listed. These formulae were obtained by scanning a CT phantom of known density. Generated BMD values were described with hydroxyapatite equivalent density (mg/mL).

Supplementary Table S2. Characteristics of subjects in whom association between DEXA and CT measurements of BMD was analyzed.

	Subjects undergoing both DEXA and CT (n=28)
Age	67 (52 – 75)
Sex (M / F)	10 / 18
BMI	22.1 (20.1 – 24.2)
Diagnoses, n (%)	Idiopathic interstitial pneumonias 7 (25%) Antisynthetase syndrome 7 (25%) Clinically amyopathic dermatomyositis 4 (14%) Other autoimmune diseases 8 (28%) Primary ciliary dyskinesia 1 (4%) Asthma 1 (4%)
3 months average GC (PSL ≥ 5 mg), n (%)	25 (89%)
Calcineurin inhibitors	
Tacrolimus, n (%)	12 (43%)
Cyclosporin A, n (%)	1 (4%)
Bisphosphonate, n (%)	14 (50%)
CKD, n (%)	7 (25%)

Continuous variables are described with the median (IQR).

Abbreviations: BMI, body mass index; GC, glucocorticoid; LT, lung transplantation; CKD, chronic kidney disease.

Supplementary Table S3. Logistic regression models for the associations of AIQCT indices with osteoporosis prior to lung transplantation (n=124).

AIQCT indices	Odds ratio	95% CI	*P value*
Normal lung	1.08	0.83–1.41	0.58
Ground-glass opacity	1.01	0.97–1.06	0.55
Reticular shadow	0.98	0.91–1.05	0.58
Honeycomb	0.86	0.72–1.02	0.08
Nodules	0.58	0.32–1.02	0.06
Consolidation	1.03	0.94–1.12	0.56
Hyperlucent volume	1.01	0.99–1.03	0.33
Bronchus	0.94	0.84–1.05	0.24
Vessel	0.87	0.71–1.06	0.17
Others	0.59	0.27–1.30	0.19

Supplementary Table S4. Logistic regression models for the associations of AIQCT indices with osteoporosis prior to lung transplantation in the LAM-excluded cohort (n=116).

AIQCT indices	Odds ratio	95% CI	*P value*
Normal lung	1.07	0.88–1.30	0.50
Ground-glass opacity	1.01	0.96–1.06	0.72
Reticular shadow	0.97	0.91–1.04	0.43
Honeycomb	0.86	0.72–1.02	0.08
Nodules	0.53	0.29–0.97	0.04
Consolidation	1.01	0.93–1.11	0.76
Hyperlucent volume	1.03	1.00–1.05	0.02
Bronchus	0.91	0.81–1.02	0.11
Vessel	0.83	0.67–1.02	0.08
Others	0.49	0.21–1.14	0.10