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# Frailty and genetic risk predict fracture after lung transplantation

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## Abstract

Fractures negatively impact quality of life and survival. We hypothesized that recipient frailty score and genetic profile measured before transplant would predict risk of fracture after lung transplant. We conducted a retrospective cohort study of bone mineral density (BMD) and fracture among lung transplant recipients at a single center. The association between predictors and outcomes were assessed by multivariable time-dependent Cox models or regression analysis. Among the 284 participants, osteoporosis and fracture were highly prevalent. Approximately 59% of participants had post-transplant osteopenia, and 35% of participants developed at least one fracture. Low BMD was associated with a polygenic osteoporosis risk score, and the interaction between genetic score and BMD predicted fracture. Pre-transplant frailty was associated with risk for spine and hip fracture, which were not associated with chronic lung allograft dysfunction (CLAD) or death. Chest fractures were the most frequent type of fracture and conferred a 2.2-fold increased risk of CLAD or death (time-dependent $P < 0.001$). Pneumonia, pleural effusions, and acute rejection occurred frequently surrounding chest fracture. Pre-transplant frailty and recipient genotype may aid clinical risk stratification for fracture after transplant. Fracture carries significant morbidity, underscoring the importance of surveillance and osteoporosis prevention.

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Disclosure

The authors declare no competing interests or conflicts of interest.

# 1. INTRODUCTION

Hip and spine fragility fractures are associated with a 20% increased risk of mortality and poor quality of life among patients over the age of 65 (1, 2). Solid organ transplant and advanced lung disease patients have similar burdens of osteoporosis and fracture (3–5). Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) in bone metabolism genes that correlate with osteoporosis (6–10). The stress of lung transplantation has been shown to evoke genomic phenotypes that may otherwise have been silent, so osteoporosis risk alleles might have an amplified effect in lung transplant recipients(11–13).

Compared to the general population, lung transplant recipients are at additional risk of bone disease from a variety of factors (14). These include metabolic risks, such as low body mass index (BMI), frailty, diabetes, and chronic hypoxia, as well as the consequences of lifelong immunosuppressive regimens (15–17). Both glucocorticoids and calcineurin inhibitors interfere with bone homeostasis (18–21). Standard lung transplant protocols therefore include osteoporosis prevention with calcium, vitamin D, and bisphosphonate therapy (22). Despite these interventions, osteoporosis persists after transplantation (17). Among recipients of solid organ transplants, lung allograft recipients suffer from some of the highest rates of low bone mineral density (BMD) (17, 23). Estimates of fracture rates range between 5–37% within the first year (17, 23, 24), or up to 53% within 5 years (25, 26). However, the impact of post-transplant fracture on lung transplant long term outcomes are not well described.

Approximately 50% of lung transplant recipients develop chronic lung allograft dysfunction (CLAD) by 5 years, an important driver of mortality (27, 28). Recently, we described an association between lung transplant recipient frailty and CLAD (29). Similarly, we hypothesized that fracture after lung transplantation would be associated with worse CLAD-free survival. Here, we performed a retrospective cohort study to characterize bone disease among lung transplant recipients and assess the utility of genotype and frailty as predictive tools for bone density loss and fracture occurrence. We also analyzed whether fractures are associated with acute complications, CLAD, and mortality.

# 2. MATERIALS AND METHODS

## 2.1 Study population

The University of California, San Francisco (UCSF) institutional review board approved this study under protocol 13–10738. All participants provided written informed consent. Figure 1 diagrams the inclusion and exclusion criteria for the adult participants who underwent lung transplantation between 2006 and 2016 and had undergone DNA genotyping (30). Participants were excluded if there were insufficient data available in the medical record. Pre-transplant frailty data were available for a subset of participants enrolled in Breathe Again, a single-center prospective cohort study of adults undergoing first-time lung transplant between 2010 and 2017.

### 2.2 Clinical protocols

Standard lung transplant induction therapy included methylprednisolone, mycophenolate mofetil, and basiliximab for lung transplants or anti-thymocyte globulin for heart-lung transplants (30). Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisone. All patients were initiated on 20 mg of prednisone following induction therapy and tapered through the first post-operative year to 0.1 mg/kg. Bilateral lung transplants occurred via clamshell thoracotomy, single lung transplants via lateral thoracotomy, and heart-lung transplants via median sternotomy.

All participants were placed on a bone loss prevention regimen of oral calcium carbonate, cholecalciferol supplementation, and bisphosphonate after 2010. Oral alendronate was first-line therapy. Oral risedronate, zoledronic acid, teriparatide or denosumab were given as second-line therapies. Dual energy X-ray absorption (DEXA) scans were required as part of the transplant evaluation process and serially every 2 years after transplant. For-cause and routine posttransplant surveillance included clinic visits, chest CT scans, bronchoscopies with biopsies and lavage, and pulmonary function testing (30).

### 2.3 Data Abstraction

Clinical data abstracted from electronic medical records included pre- and post-transplant DEXA results, baseline characteristics, laboratory results, and radiology findings. Electronic charts were systematically queried by using the standardized search term, “fracture.” We performed secondary chart review of recipients with fractures to determine type of fracture, date of fracture, mechanism of injury, and any sequelae.

### 2.4 Clinical definitions

Bone mineral disease was graded using a standard definition based on minimum T-score at any site: osteoporosis, T-score $\leq -2.5$; osteopenia, $-2.5 <$ T-score $< -1$; or no disease, T-score $\geq -1$. Infection was defined from clinical microbiology results and clinician assessments as previously described (31). Acute rejection was graded by a pulmonary pathologist using ISHLT guidelines (32). Chronic lung allograft dysfunction (CLAD) was defined using the established criteria of a 20% decline in FEV1 or FVC persisting at least 30 days (31, 33, 34). Baseline lung allograft dysfunction (BLAD) was defined as failure to achieve both FEV1 and FVC $\geq 80\%$ (35, 36).

### 2.5 Genotyping

Single nucleotide polymorphisms (SNPs) were assayed using the Applied Biosystems Axiom Transplant Genotyping Array (# 902865) designed by the iGeneTRAiN consortium (37). A BMD polygenic score (PGS001039) was calculated from the Michigan Imputation server(38). This is a research-derived osteopenia score developed by ultrasound BMD correlation with 9753 genetic variants and validated in 5 independent cohorts across diverse ancestries (10, 39, 40).

### 2.6 Frailty predictor

We quantified frailty using the Short Physical Performance Battery (SPPB), an aggregate score ranging from 0–12 based on tests of chair stands, balance, and gait speed (41). We used SPPB as a binary (score ≥ 10) and a continuous predictor (range 0–12). SPPB ≥ 10 corresponds to frail participants.

### 2.7 Statistical Analysis

Demographics of study participants were analyzed using Wilcoxon rank-sum tests or chi-square tests, as appropriate. Generalized linear models (GLMs) were used to test the association between predictors and outcomes, which were adjusted with adjusted with generalized estimating equations (GEEs) with an exchangeable covariance matrix for longitudinal data to account for repeated observations within participants.

We employed Cox Proportional Hazards (CPH) models for time-to-event analyses. Cumulative incidence or Kaplan-Meier plots were used to visualize these data. Violations of proportional hazards were assessed visually and with the Schoenfeld test. For the small number of patients with multiple first fractures recorded on the same date, these fractures occurred in the same grouped site (e.g. spine), and one was chosen at random to represent the event. Global differences between event rates were assessed by the log-rank test.

Time to first fracture was modeled by competing risk of fracture at different anatomic sites (chest, spine, or hip/leg/arm). CLAD-free survival time was calculated as years after transplant without an event (CLAD or death). Censorship dates were determined based on the last known date of pulmonary function testing. Hazard ratios for type of fracture (chest fracture or hip/leg/arm fracture) and CLAD or death were modeled as time-dependent covariates.

All GLM and CPH models were adjusted for baseline characteristics (age, race/ethnicity, sex, pre-transplant diagnosis, and transplant indication), which have been shown to be associated with adverse transplant outcomes (42, 43). All statistics and plots were performed in R using standard packages (rstatix, geepack, survival, survminer, ggplot2 and ggpubr).

## 3. RESULTS

### 3.1 Study population and bone mineral density

A total of 284 patients were included in this study (Figure 1), with baseline characteristics detailed in Table 1. Our cohort is enriched for double transplant recipients, interstitial lung disease as a transplant indication, and ethnic diversity (27). DEXA data were available for 189 participants. Of these, 138 participants had post-transplant DEXA information available. 87 participants had paired pre- and post- lung transplant DEXA values and 57 participants had paired DEXA values from the immediate 2 years post-transplant. There were no differences in baseline characteristics between participants with DEXA data compared to those without DEXA data available (Supplemental Table 1) or between participants with and without frailty measures (Supplemental Table 2). Notably, only 6.8% of participants were on non-alendronate-based bone loss prevention regimens.

We first assessed how the early post-operative transplant period impacted BMD. We found that pre-transplant BMD was correlated to BMD in the early post-transplant period (Figure 2A; N = 57, Pearson's correlation coefficient 0.88, $P < 0.0001$). Global rates of bone disease posttransplant were estimated by minimum T-score within the first 5 years after transplantation (Figure 2B, N = 138). We found that only 22 (16%) participants had normal bone mineral density within the first 5 years of transplantation, 82 (59%) had osteopenia, and 34 (25%) had osteoporosis. This rate of bone disease exceeds the CDC estimates within the general population, indicating that low bone density is prevalent among lung transplant recipients (44).

### 3.2 Bone mineral density decreases after lung transplantation

Prior studies reported substantial BMD loss within the first 12 months after surgery (45, 46), attributed to high-dose induction corticosteroids and immobility. We also found that T-scores decreased by 0.14 within the first 2 years after transplant (N = 57), representing an average loss of 8% loss (Figure 2C, $P = 0.03$). Although 62% of individuals had a decrease in BMD, minimum BMD for other individuals remained the same or increased. No recipient characteristic discriminated between recipients with decreased or stable BMD (Supplemental Table 3). We also traced the prevalence of osteoporosis relative to transplant by analyzing data from the 87 participants with both pre-transplant and post-transplant DEXA data available. Notably, osteopenia (minimum T-score between −2.5 and −1) and osteoporosis (minimum T-score ≤ −2.5) were highly prevalent in the population prior to transplant, and there was a slight increase in osteopenia after transplant (Figure 2D).

### 3.3 Fracture is common after lung transplantation

We found that 100 individuals, approximately 35% of the cohort, experienced at least one fracture. The mean minimum BMD T-score for participants with fracture was −1.8 ±0.1, compared to −1.7 ±0.1 in those without fracture (mean ± standard error [SE], $P = 0.8$). Only 15% of patients without osteopenia/osteoporosis developed a fracture, versus 33% of those with osteopenia ($P = 0.01$) or 32% of those with osteoporosis ($P = 0.02$). These findings reveal that bone mineral disease was common among lung transplant recipients and associated with increased risk of fracture after transplant.

Although most individuals had one fracture, many had multiple (Figure 3A). One individual had 7 distinct fractures, primarily vertebral. We then quantified anatomic locations of fractures (Figure 3B). The most common site was the chest, a category that included rib fractures (N = 69) but also rare clavicle (N = 3) and scapula fractures (N = 1). Vertebral fractures were second most frequent, followed by fractures of the appendicular skeleton (leg, hip, or arm). Chest fractures occurred earlier in the post-transplant course than other fractures, at a median time of 0.7 years (Figure 3C; 95% Confidence Interval [CI] 0.5–2), $P = 0.04$). Spine fractures occurred at a median of 2.3 years (IQR 1.3–4.9), and extremity fractures occurred at 3 years (IQR 2.2–6.2). Supplemental Table 4 shows baseline characteristics of recipients and fracture mechanism by facture site. Notably, chest fractures were less likely among male recipients (OR 0.82, 95% CI 0.7 – 0.95, P = 0.01). No other baseline characteristics, including pre-transplant Interstitial Lung Disease subtype, were associated with risk for fracture. We note that surgical approach does not fully account

for different mechanisms of chest fractures, as all double lung transplants were performed by clamshell thoracotomy (Table 3).

### 3.4 Polygenic risk score predicts pre-transplant BMD and post-transplant risk of fracture

We hypothesized that genotype might explain which individuals have low pre-transplant BMD. As many SNPs have been associated with BMD and/or fracture risk (6, 7), we assessed this risk with a validated polygenic BMD score that included alleles at 153 different loci (10). We found the strongest association between higher polygenic risk and reduced T-scores at the lumbar spine ($P = 0.0001$, Figure 4A). Higher genetic risk also correlated with lower pre-transplant T-score at the total hip ($P = 0.003$, Figure 4B) and at the femoral neck (P = 0.006, Figure 4C). We further hypothesized that this gene profile would inform risk for fracture after transplant. Indeed, we found a significant interaction between polygenic risk score and T-score in predicting time to any fracture after transplant (Table 2, HR 0.3, 95% CI 0.07 – 0.9, adjusted $P = 0.03$). These data suggest that genetic risk informs which patients are at risk for low pre-transplant BMD and that the effect of BMD on risk of fracture changes depending on genetic profile.

### 3.5 Pre-transplant frailty is associated with risk for spine or pelvic fracture

We next hypothesized that frailty would be associated with risk for fracture. Furthermore, in a nested subset of our cohort, pre-transplant frailty (SPPB ≥ 10) was associated with over 2-fold increased risk for any fracture, controlling for covariates (Figure 5A, adjusted HR 2.02, 95% CI 1.2 – 5.3, P = 0.02). In a model of continuous SPPB score, we found that a one-point worsening in frailty score was associated with a 15% increased risk of post-transplant fracture (adjusted HR 1.15, 95% CI 1.1–13, P = 0.002). As nearly half of the fractures in the frail group occurred within the first year after transplant, we assessed for differences in characteristics between early and late fractures. We found that frail participants with fractures in the first post-operative year were older (60.6 IQR 10 years, P = 0.02) than those with fracture afterwards (58.8 IQR 11 years). These results indicate that pre-transplant frailty is associated with decreased BMD after transplant as well as post-transplant fracture risk.

We further assessed if a frail status going into transplant conferred differential odds for specific types of fracture. We found that frail participants had increased odds of pelvic fractures (Figure 5B, adjusted OR 3.7, 95% CI 2.4 – 5.7, p < 0.0001) as well as fractures in the spine (adjusted OR 2.5, 95% CI 1.6 – 3.8, P < 0.0001). There was no association between frailty and fractures in extremities or in the thorax.

### 3.6 Mechanism of Fracture

We hypothesized that pre-transplant low BMD and frailty would predict mechanisms of fracture (Supplemental Table 4). Most spine fractures were incidental (45.8%), extremity fractures were traumatic (21%), and chest fractures occurred perioperatively (21%) or were incidentally noted (21%). Lower minimum pre-transplant T-scores were associated with pathologic (Supplemental Figure 1A, adjusted P = 0.02) and perioperative fractures (adjusted P = 0.0005). We next assessed if frailty was associated with a particular mechanism of fracture. Indeed, frail participants had increased odds of pathologic

(Supplemental Figure 1B, adjusted OR 1.8, 95% CI 1.2 – 2.7, P = 0.003) and traumatic (adjusted OR 1.5, 95% CI 1.2 – 1.8, P = 0.0002) fractures. These data suggest that pre-transplant BMD and functional status can inform groups at risk of fracture.

### 3.7 Chest fractures predict increased risk of CLAD-related mortality

It is unknown whether fractures are associated with increased risk of CLAD or death among lung transplant recipients. We performed survival analyses comparing CLAD-free survival by first fracture type, with rates of CLAD and death shown in Supplemental Table 5. Adjusted for time-dependent covariates, individuals with chest fractures faced a nearly 2.2-fold increased risk of CLAD or death (Figure 6A, 95% CI 1.6–3.1, $P < 0.001$). In this same model, we observed a trend towards decreased risk of CLAD or death for individuals with hip, leg, or arm fractures (adjusted HR 0.5, 95% CI 0.3 – 1.0, $P = 0.06$) and no difference among participants with spine fractures (Figure 6B; adjusted HR 1.1, 95% CI 0.5 – 2.6, P = 0.7). Multiple fractures conferred a 2.3-fold increased risk of CLAD or death (95% CI 1.5 – 3.3, P < 0.0001). However, this was driven by multiple chest fractures, which accounted for a 3.6-fold increased risk of CLAD or death (95% CI 2.2 – 5.9, P < 0.0001) compared to recipients without chest fractures. In a secondary analysis, we examined CLAD-free survival among the participants with fracture and structured survival time as time from fracture to the event of interest. We found that participants with chest fractures had an increased risk of CLAD or death (Supplemental Figure 2A; HR 2.2, 95% CI 1.3 – 3.9, $P = 0.006$) compared to those with fractures at other sites. We also found a 3-fold increased risk of death among chest fracture participants (Supplemental Figure 2B; HR 3, 95% CI 1.4 – 6.4, $P = 0.005$) compared to those with other fractures. Finally, we identified that recipients with chest fractures had increased odds of death after developing CLAD (1.2 Odds Ratio, 95% CI 1.05 – 1.4, adjusted P = 0.009) compared to participants without fractures. There were no differences in the odds of death after CLAD among recipients with spine fractures (P = 0.9) or extremity fractures (P = 0.1). Taken together, these data indicate that chest fractures place lung transplant recipients at elevated risk of CLAD or death, distinct from other types of fractures.

We sought to determine if chest fractures were associated with clinical sequelae that could explain development of CLAD (Table 3) (47). Within a month of chest fracture, 10% of recipients had acute rejection on lung biopsy, 20% had pleural effusions or pneumonia, and 37% had perioperative surgical complications. Finally, we found that traumatic thoracic fractures carried increased risk of CLAD or death (HR 2.9, 95% CI 1.1 – 7.4, adjusted P = 0.03) compared to other fractures. While chest fractures were not associated with BLAD (P = 0.72), traumatic chest fractures were associated with low peak FEV1 (Supplemental Figure 3A, P = 0.05) and conferred increased odds of BLAD (Supplemental Figure 3C, OR 1.7, 95% CI 1.2 – 2.3, P = 0.001) compared to other chest fracture mechanisms. Together, these data suggest that chest fractures are associated with pulmonary comorbidities that may impair survival.

## 4. DISCUSSION

This single-center, retrospective cohort study assessed the clinical burden, genomic and functional risk for BMD, and outcomes of osteoporosis and fracture among lung transplant recipients. We report that osteoporosis was prevalent before and after lung transplantation and describe a high burden of post-transplant fracture. Genotype and frailty were identified as novel predictors of fractures. Fracture, specifically in the thorax, conferred increased risk for morbidity and mortality after lung transplantation.

While we found that frail participants had twice the risk for fracture after lung transplantation, this risk was mostly confined to fractures in the spine and pelvis. Further, frail participants had lower BMD after transplant and were more likely to suffer from traumatic or pathologic (versus perioperative or incidental) fractures. Interestingly, this frail group of recipients did not have increased risk of poor long-term outcomes compared with non-frail fracture patients. This cohort contrasts sharply to recipients who experienced thoracic fractures, who were not frail but had increased risk of CLAD or death. Multiple thoracic fractures augmented this risk, suggesting that thoracic fracture may be an independent driver of CLAD. These two groups may represent sub-phenotypes of lung transplant recipients. As frailty is a multifaceted construct, more thorough investigation of body composition might reveal additional insights into fracture risk in the chest or spine or reveal the pathobiologies driving these unique recipient groups.

Our study identifies that thoracic fracture is associated with CLAD and death, and a subset is associated with BLAD, adding to the literature documenting that fracture causes substantial morbidity and mortality. Although we did not quantify fracture impact on quality of life, this is an important clinical endpoint to measure in further studies. It is also challenging to establish causality between fracture occurrence and CLAD pathogenesis. One possibility is that chest fractures acutely cause respiratory splinting and limit chest wall excursion and vital capacity. These sequelae may place patients at increased risk for pulmonary complications such as infection, rejection or CLAD. Alternatively, CLAD and thoracic bone fragility could stem from a common thoracic inflammatory milieu. In such a case, the shared mediator would lead to local bone turnover and osteoporosis as well as CLAD.

One unexpected finding was the low rate of hip fractures in this cohort, given that femoral neck and pelvic fractures are strongly associated with osteoporosis in other cohorts (48). We speculate that lung transplant recipients may be spared from appendicular skeleton fractures due to selection bias as part of the transplant evaluation process, likely screening patients with unstable gaits. In support, we found that frail recipients were more likely to develop pelvic fractures. We also report that recipients with extremity fractures had improved CLAD-free survival. As these participants tended to be less frail and experienced more traumatic fractures, one explanation may be that transplant recipients with fractures at these sites capture the subset of patients with greater physiologic reserve, capable of performing activities that put them at risk for extremity fractures; though, there may also be a component of survival bias.

We found that neither BMD nor polygenic score were independently associated with time to fracture. Rather, we determined that the effect of BMD on fracture-risk varied with polygenic score. Favorable genetic profile and BMD conferred a nearly 50% reduction in risk for fracture at any time after lung transplantation. Other studies have shown that genotypes inform bone mineral concentration rather than bone area (49). This suggests that genotyping may be a complementary tool to DEXA scan-based protocols.

Many transplant centers have implemented bone prevention regimens to combat osteoporosis (50, 51). At UCSF, our protocol currently includes routine calcium and vitamin D supplementation with bisphosphonate therapy. Despite strong adherence to this medication regimen, our cohort had a fracture rate of 35% in the first 5 post-transplant years. This number aligns with prior estimates from smaller studies in a different era, which have reported fracture rates as high as 50% following lung transplantation (25, 46). Explanations for the high rate of bone disease include frequent and chronic glucocorticoid use for pulmonary disease, low BMI, relative immobility, kidney disease, and metabolic complications of advanced lung disease (e.g., hypoxia) (52). We speculate that glucocorticoids may add to risk of pathologic and traumatic fractures, which we found to be associated with low BMD and frailty. As low bone density prior to transplant is a strong predictor of post-transplant fracture, increased attention to pre-transplant bone health interventions may be advantageous. Early implementation and additional focus on lifestyle modifications may be necessary to optimize bone health prior to transplantation (53). Further, it is unclear if medical therapy alters bone density within the chest.

These data are from a high-volume transplant center with established protocols for managing bone mineral disease, but this study is not without limitations. These data reflect the largest assessment of BMD after lung transplant to date; however, they represent the protocols of a single center and would be strengthened by validation in additional cohorts. Some participants did not receive DEXA scans or received scans at other medical centers where we do not have the data available to review. Fracture date was assessed as the first documentation of a fracture in the medical record, which does not always track with the day of injury.

These data highlight the high incidence of low BMD and fracture among the lung transplant population and identify two novel predictors of fracture after transplant. Genetic profile and body composition may prove to be useful adjuncts in tailoring optimal bone density management strategies. Future study is needed to identify if patients with thoracic fractures may benefit from targeted interventions.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Availability of data and material

Processed data are provided as supplementary data files and tables. Raw data are available upon request to the corresponding authors. Analysis was performed using standard packages and custom scripts in R. Scripts are available upon request.

## Non-standard abbreviations

| | |
|---|---|
| **BMD** | bone mineral density |
| **BLAD** | baseline lung allograft dysfunction |
| **CLAD** | chronic lung allograft dysfunction |
| **CPH** | Cox Proportional Hazards |
| **CT** | computed tomography |
| **DEXA** | dual energy x-ray absorption |
| **GEE** | generalized estimating equations |
| **GLM** | generalized linear model |
| **FEV1** | forced expiratory volume in the first second |
| **FVC** | forced vital capacity |
| **ISHLT** | International Society for Heart and Lung Transplantation |
| **SNP** | single nucleotide polymorphism |
| **SPPB** | Short Physical Performance Battery |

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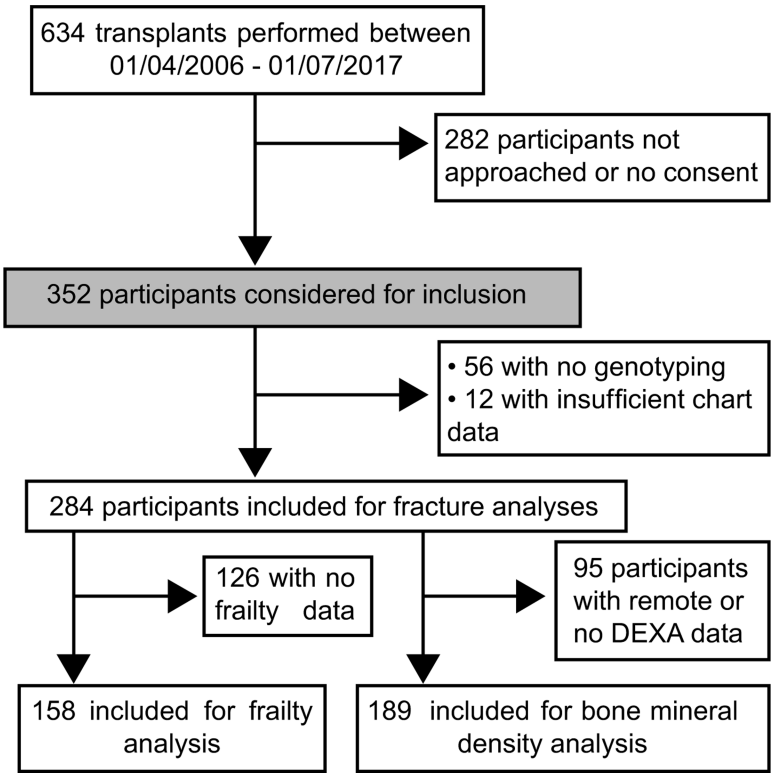


**Figure 1.**
Overview of inclusion and exclusion criteria.

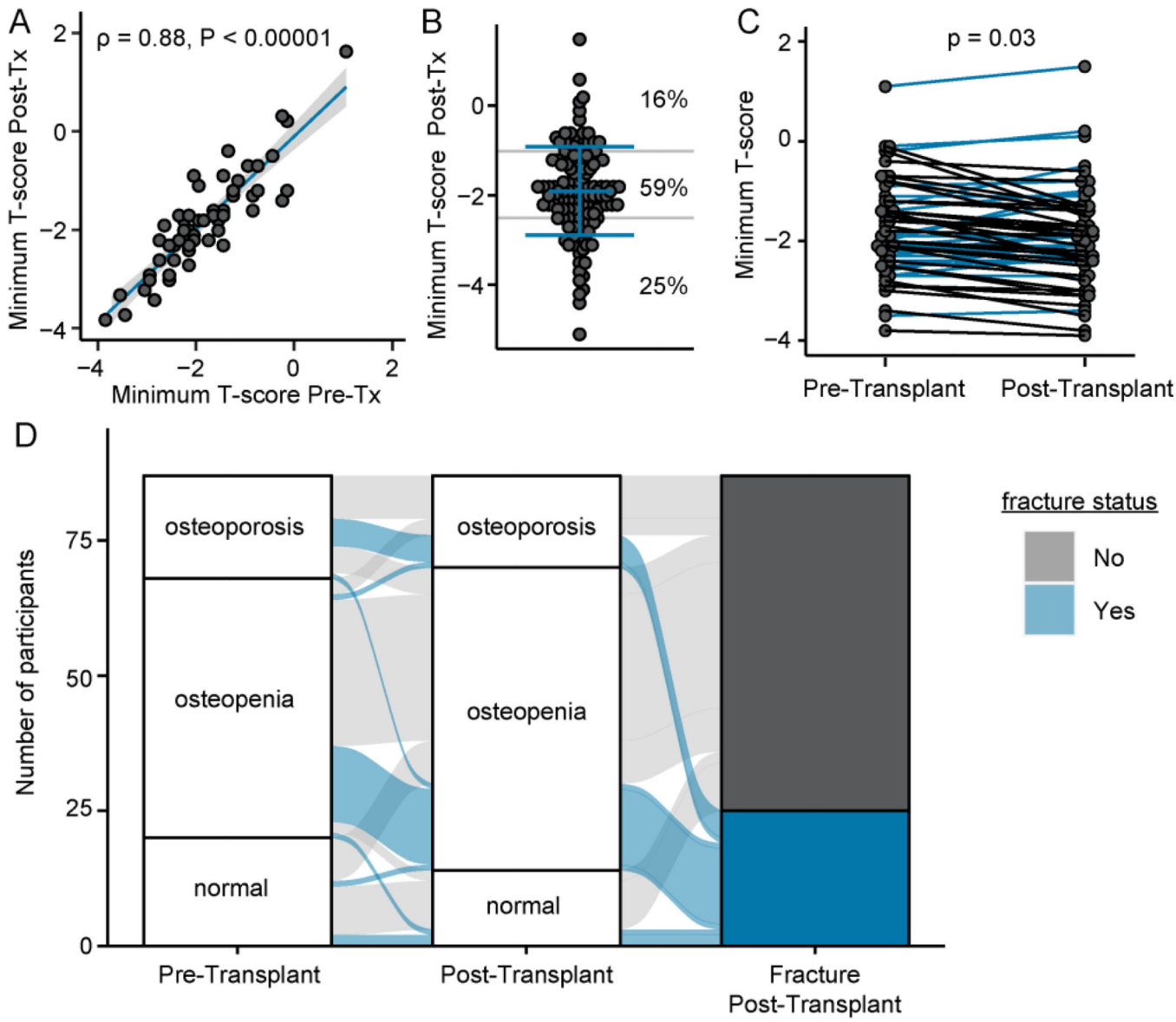


**Figure 2. Lung transplant recipients have a high burden of bone disease.**

**(A)** Correlation between minimum T-scores recorded before transplant (pre-Tx) and within 2 years posttransplant (Post-Tx) for the participants with data available (N = 57). **(B)** Summary plot of the minimum T-scores from all available DEXA scans after transplant during the 5-year period of data collection (N = 138). Dashed lines indicate T-scores of −1 and −2.5, delineating the range of osteopenia. Any T-scores below these lines represent osteoporosis. **(C)** Paired line plot demonstrating the change in minimum T-score after transplant. T-score is the minimum value from either the pre-transplant DEXA scan or a DEXA scan within 2 years of transplant (N = 57, *P*-value by two-tailed paired t-test). **(D)** Alluvial diagram comparing rates of osteopenia and osteoporosis before and after transplant, and which of these cases resulted in fracture. N = 87 individuals with matched pre- and post-transplant DEXA scans.

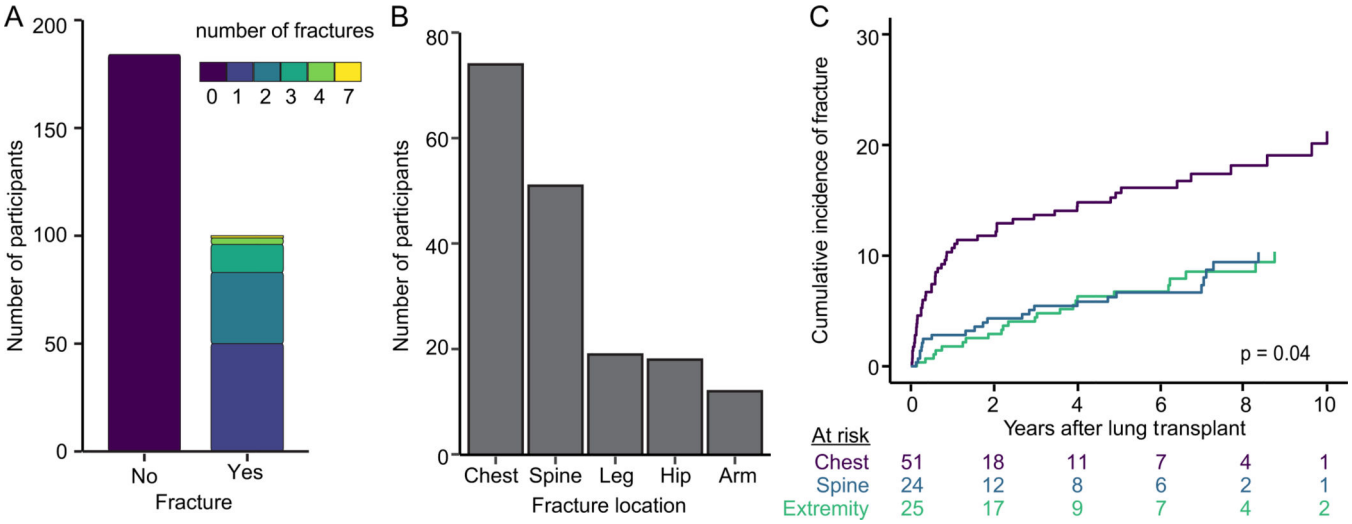


**Figure 3. Fractures are common after lung transplantation.**

**(A)** Number of study participants (N = 284) with and without fractures, stratified by number of fractures per individual. 35% of participants had at least one fracture. **(B)** Study participants with fractures stratified by fracture type. Chest fractures were the most frequent, a category that includes rib, clavicle, and scapula fractures. **(C)** Cumulative incidence of fractures after transplant, separated by anatomic location. Time to fracture was calculated by log-rank test.

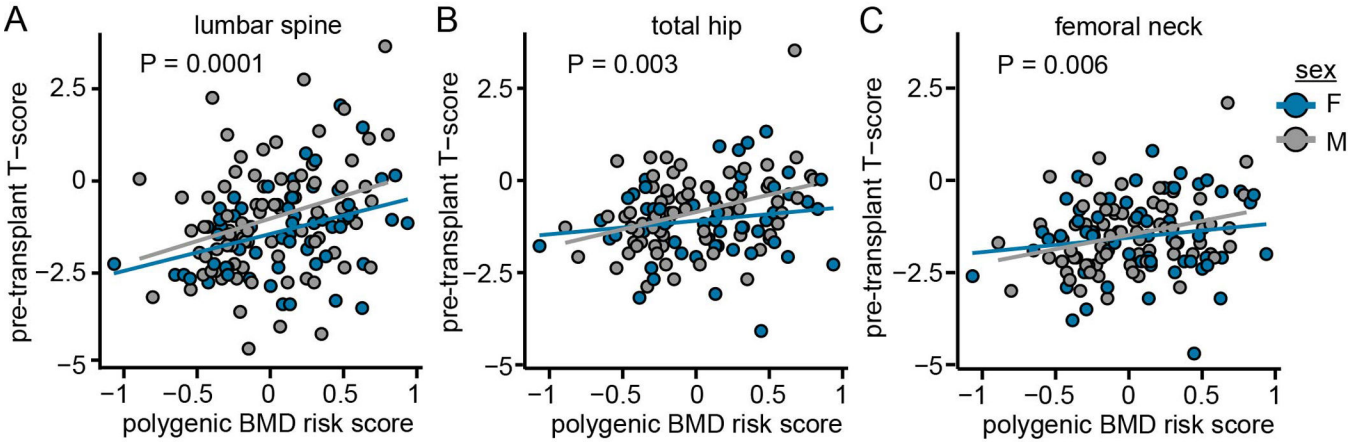


**Figure 4. Genotype risk score predicts pre-transplant BMD.**

A validated 153-loci BMD risk score was calculated across the lung transplant cohort. **(A)** Plot of pre-transplant T-score at the lumbar spine, **(B)** Plot of pre-transplant T-score at the hip, and (**C)** Plot of pre-transplant T-score at the femoral neck. *P*-values were generated with generalized linear models (GLM) adjusted for sex and age. Individual regression lines are shown for male (M) and female (F) recipients.

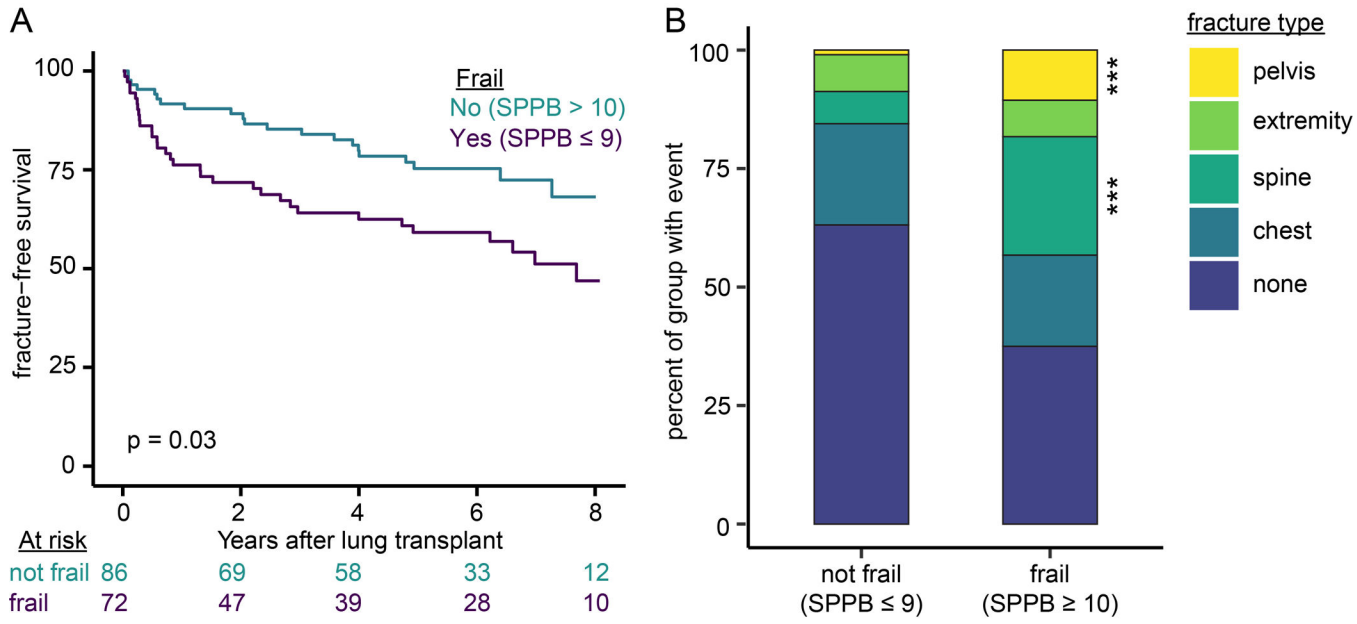


**Figure 5. Pre-transplant frailty is associated with risk of fracture.**

**(A)** Kaplan-Meier plot of fracture-free survival stratified by participant frailty before transplant, measured by SPPB. Frail recipients had increased risk of fracture after lung transplant. **(B)** Fracture occurrence stratified by location, capturing increased rates of pelvic and spine fractures among frail recipients. P-values are from log-rank test (A) and generalized linear models (B). *** P < 0.0001.

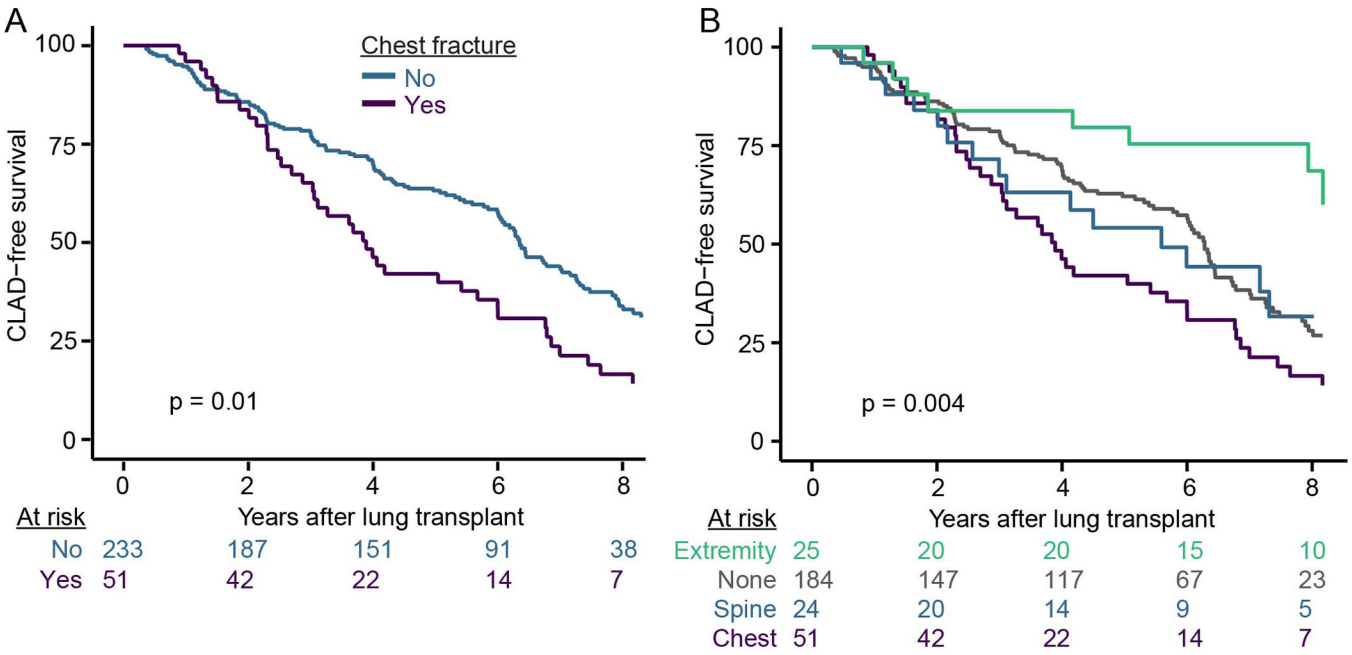


**Figure 6. Patients with thoracic fractures are at increased risk for CLAD and death.**

**(A)** Kaplan-Meier plot comparing CLAD-free survival among participants with chest fractures (N = 51) compared to those without chest fractures (N = 233). **(B)** Kaplan-Meier plot of CLAD-free survival stratified by site of fracture. Events are a diagnosis of CLAD or death. Censoring date was the last pulmonary function test date on file (N = 284). *P*-values shown on plot are by log-rank test comparing all groups.

**Table 1.**
**Baseline characteristics of the study cohort (N = 284).**

Comparison of the indicated characteristics in participants with and without fractures. BMI was collected at the time of transplant. P-values are by Wilcoxon rank-sum test (numerical variables) or chi-square tests (categorical variables).

| | Fracture | | | |
|---|---|---|---|---|
| | **No (N = 184)** | **Yes (N = 100)** | ***P*-value** | **Total (N = 284)** |
| **Age** | | | | |
| Median [IQR] | 57.3 [16.2] | 59.6 [11.3] | 0.12 | 58.1 [15.0] |
| **Sex** | | | | |
| Male | 113 (61.4%) | 46 (46.0%) | 0.018 | 159 (56.0%) |
| Female | 71 (38.6%) | 54 (54.0%) | | 125 (44.0%) |
| **BMI** | | | | |
| Median [IQR] | 24.9 [6.19] | 25.1 [5.87] | 0.18 | 25.0 [6.35] |
| **Transplant Indication** | | | 0.76 | |
| ILD | 129 (70.1%) | 68 (68.0%) | | 197 (69.4%) |
| COPD | 30 (16.3%) | 19 (19.0%) | | 49 (17.3%) |
| CF | 19 (10.3%) | 8 (8.0%) | | 27 (9.5%) |
| pHTN | 6 (3.3%) | 5 (5.0%) | | 11 (3.9%) |
| **Transplant Type** | | | 0.78 | |
| Double Lung | 170 (92.4%) | 90 (90.0%) | | 260 (91.5%) |
| Single Lung | 11 (6.0%) | 8 (8.0%) | | 19 (6.7%) |
| Heart/Lung | 3 (1.6%) | 2 (2.0%) | | 5 (1.8%) |
| **Patient-Reported Race and Ethnicity** | | | 0.13 | |
| White | 129 (70.1%) | 84 (84.0%) | | 213 (75.0%) |
| Hispanic | 27 (14.7%) | 8 (8.0%) | | 35 (12.3%) |
| Black | 14 (7.6%) | 4 (4.0%) | | 18 (6.3%) |
| Asian | 12 (6.5%) | 4 (4.0%) | | 16 (5.6%) |
| Native Hawaiian/Pacific Islander | 2 (1.1%) | 0 (0%) | | 2 (0.7%) |

**Table 2.**

Interaction between BMD and polygenic risk predicts time to fracture

| | HR | 95% CI | P-value |
|---|---|---|---|
| Gene risk score | 0.41 | 0.14 – 1.21 | 0.11 |
| Minimum T-score | 0.93 | 0.73 – 1.19 | 0.58 |
| Male sex | 0.51 | 0.27 – 0.98 | 0.04 |
| Age | 1.03 | 1 – 1.06 | 0.08 |
| Gene risk score: T-score | 0.54 | 0.31 – 0.95 | 0.03 |

## Table 3.
## Mechanism of chest fractures and pulmonary complications.

Clinical characteristics were abstracted within a time frame of 30 days before or after the fracture date noted in the medical record to assess possible associated pulmonary sequelae (surgical complications, biopsy findings, pleural effusion, or pneumonia). Some patients had multiple chest fractures on distinct dates, which are noted as separate data points in this table.

| | Total (N = 73) |
|---|---|
| **Surgical approach** | |
| Clamshell thoracotomy | 64 (88.3%) |
| Lateral thoracotomy | 7 (9.6%) |
| Median sternotomy | 2 (2.7%) |
| **Site** | |
| Rib | 69 (94.5%) |
| Clavicle | 3 (4.1%) |
| Rib/Scapula | 1 (1.4%) |
| **Mechanism** | |
| Incidental | 30 (41.1%) |
| Perioperative | 26 (35.6%) |
| Traumatic | 17 (23.3%) |
| **Surgical complications** | |
| Non-union | 2 (2.7%) |
| Dehiscence | 9 (12.3%) |
| Washout/re-exploration | 15 (20.5%) |
| Chest wall defects | 1 (1.4%) |
| **Biopsy: A grade** | |
| A0/Not indicated | 66 (90.4%) |
| A1 | 6 (8.2%) |
| A2 | 1 (1.4%) |
| **Biopsy: B grade** | |
| B0/Not indicated | 69 (94.5%) |
| B1R | 4 (5.5%) |
| **Pleural effusion** | |
| Yes | 16 (21.9%) |
| **Pneumonia** | |
| Yes | 14 (19.2%) |
| **Cardiopulmonary resuscitation** | |
| Yes | 3 (4.1%) |