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# COVID-19 illness and treatment decrease bone mineral density of surviving hospitalized patients

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**Abstract. – OBJECTIVE: The number patients surviving COVID-19 hospitalization is steadily increasing. Follow-up management for these patients relies on an understanding of the long-term effects of COVID-19. Specifically, there are insufficient data about the lasting effects of COVID-19 on bone health.**

**We aim in this study to evaluate whether COVID-19 illness and treatment adversely affect the bone health of surviving patients.**

**PATIENTS AND METHODS: We assessed the bone mineral density (BMD) of hospitalized COVID-19 patients at diagnosis and at follow-up visits. Using the chest computed tomography (CT) scans of patients that were obtained for clinical management at diagnosis and follow-up visits, BMD was retrospectively measured by quantitative CT. The effect of COVID-19 severity markers and treatment-related factors on BMD were also assessed.**

**RESULTS: BMD decreased by a mean of 8.6% (± 10.5%) from diagnosis to follow-up. The follow-up visits occurred at a mean of 81 (± 48) days after hospital discharge. The BMD decrease was significantly greater than expected for age-related annual BMD loss. The osteoporosis ratio increased two-fold after hospitalization for COVID-19 because of this substantial bone loss. On multivariable linear regression, only severity of COVID-19 pneumonia on initial chest CT and total steroid dose were predictive of change in BMD after COVID-19 hospitalization.**

**CONCLUSIONS: Secondary osteoporosis may occur as a post-acute sequela of COVID-19. Therefore, the bone health status of patients surviving COVID-19 hospitalization should be monitored closely at follow-up visits, to facilitate the prevention and early treatment of osteoporosis complications.**

*Key Words:*
COVID-19, SARS-CoV-2, Osteoporosis, Bone mineral density, Hypocalcemia.

## Introduction

Despite current vaccination efforts, the COVID-19 pandemic remains a global public health emergency. As of February 25, 2022, over 430 million confirmed COVID-19 cases had been reported globally, and the cumulative number of deaths had reached more than 5.9 million[1]. Much is still unknown about how COVID-19 will affect survivors over time. It is important to establish a better understanding of the prevalence and mechanism of post-acute COVID-19 symptoms[2].

There are increasing reports of persistent and prolonged effects for those who survive hospitalization for COVID-19. Long-term effects of COVID-19 are collectively referred to as post-acute sequela of SARS-CoV-2 infection (PASC)[3]. Clinical evidence[4,5] is evolving that PASC can affect multiple organ systems. It is unknown how long these effects might last and whether the effects could lead to chronic health conditions. There is an urgent need to better understand the lasting effects of COVID-19 on survivors[6]. In particular, there is insufficient data about the long-term complications on the musculoskeletal system. Some evidence[7] suggests that COVID-19 survivors may experience deleterious effects on their bone health.

During the previous severe acute respiratory syndrome (SARS) epidemic, osteonecrosis and bone abnormalities with reduced bone density were reported during recovery[8]. This was partly explained by the extent and duration of treatment with corticosteroids, which were a mainstay therapy[9]. However, decreased bone mineral density (BMD) has also been reported following other acute critical illnesses and may occur independently of steroid treatment[10]. The pathological findings seen in SARS-CoV-2 infection are similar to those observed in SARS-CoV-1 infection[11]. Enhancement of osteoclastogenesis by the SARS 3a/X1 protein may also contribute to reduced BMD[12]. This is significant because the risk of fracture increases progressively with decreasing BMD[13].

The aim of this study is to assess whether COVID-19 illness and treatment trigger changes

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in the body that increase the risk of osteoporosis and bone fracture. This knowledge could contribute to a better understanding of the full spectrum of COVID-19 illness and sequela.

## Patients and Methods

### Study Design and Patients

This retrospective study was conducted at the Health Sciences University, Atatürk Sanatorium Training and Research Hospital, a tertiary healthcare hospital in Ankara, Turkey. All consecutive hospitalized COVID-19 patients from August 1, 2020, to September 9, 2021 were evaluated. This study was reviewed and approved by the Institutional Clinical Research Ethics Committee with the number of 2012-KAEK-15/2420.

Adult patients hospitalized with a diagnosis of COVID-19, as confirmed by positive real-time reverse-transcriptase polymerase chain reaction testing of nasal or throat swab, were included. Patients were excluded if they were hospitalized for other diseases or were being treated with steroids for diseases other than COVID-19. Patients were also excluded if they expired prior to completion of follow-up computed tomography (CT) (Figure 1).

Patients were evaluated for inclusion if they underwent non-contrast chest CT within 48 hours of hospital admission and at a post-discharge follow-up visit. The decision to perform chest CT scans was determined clinically and was not influenced by the research study, due to its retrospective design. Patients with radiographic evidence of disease or sequela other than COVID-19, or with significant motion artifact on chest CT

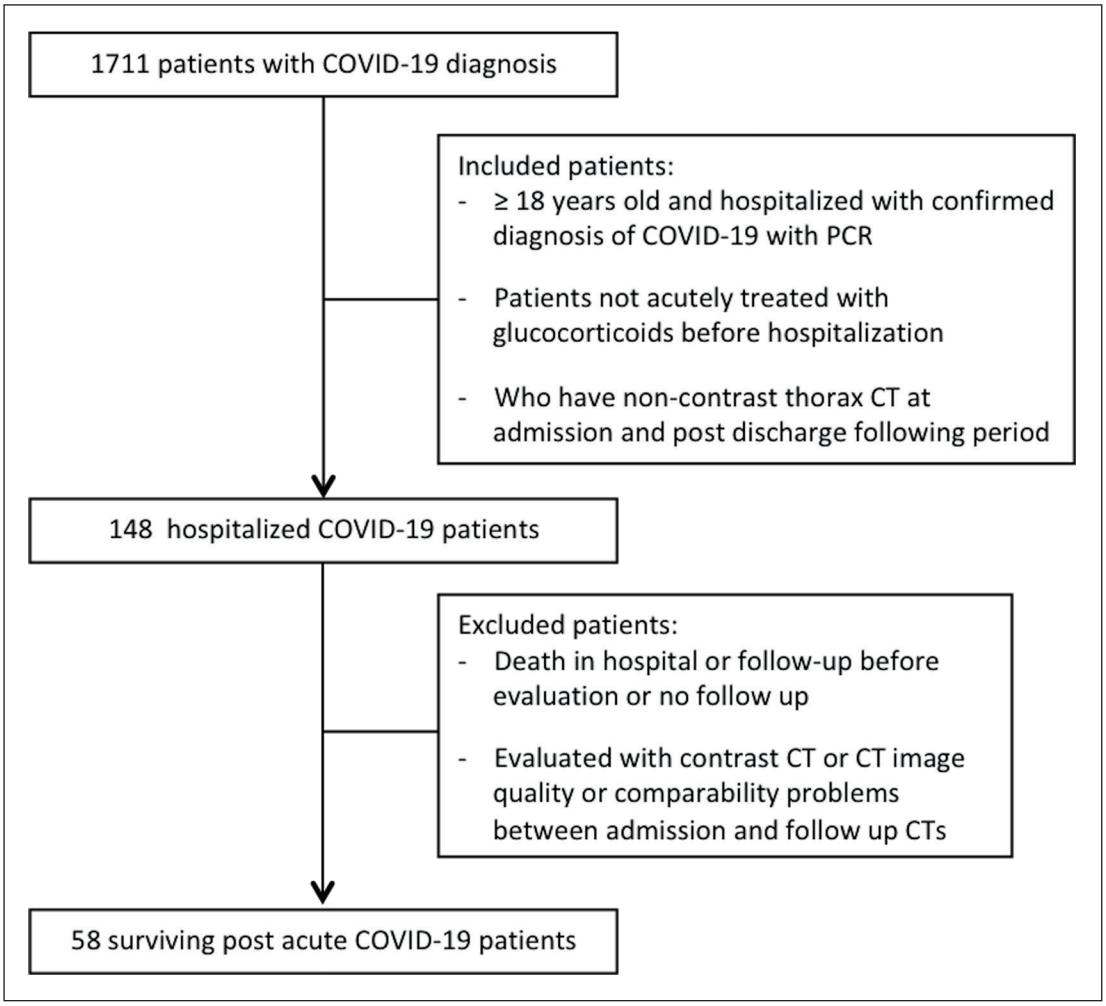


**Figure 1.** Pie chart of total score in the study population (N=410).

were excluded. Patients were also excluded if the chest CT slice thickness differed between baseline and follow-up. After screening, 58 patients were included in the final analysis.

This study was conducted with a repeated measures design, wherein each patient serves as his or her own control. This theoretically eliminates the role of confounders other than COVID-19. An additional advantage of using repeated measures design is that a small sample size does not compromise the power of the study[14]. The written informed consent requirement was waived due to the retrospective nature of the study and the data were analyzed anonymously.

### Data Collection

Data were retrospectively collected from physical and computerized medical records from our hospital. Data were recorded with a standardized form that was evaluated and approved by the Local Clinical Research Ethics Committee with a protocol number of 2012-KAEK-15/2420. Clinical data were collected by the respiratory medicine clinicians who treated the COVID-19 patients. Radiological measurements were made by a radiology specialist experienced with QCT methods, who was blinded to the clinical data.

Variables collected included: age, sex, comorbidities, body mass index (BMI), serum calcium level, and lactate dehydrogenase (LDH) level. Comorbidities included heart disease, lung disease, kidney disease, liver diseases, diabetes mellitus, osteoporosis, rheumatoid arthritis, cancer, immunocompromise, severe neurological conditions, smoking, and alcohol use. The peripheral oxygen saturation ($SpO_2$), C-reactive protein (CRP), and ferritin level values were recorded during the first 24 hours of hospitalization and at the most clinically abnormal measurement. Data on clinical outcomes included use of intensive care unit (ICU), use of high flow oxygen therapy, use of noninvasive mechanical ventilation (NIMV), and length of hospital stay. The cumulative corticosteroid dose was calculated by multiplying the daily dose by the treatment duration.

### BMD Analysis by QCT

All CT scans (initial and follow-up) were performed with the same CT scanner (Philips Ingenuity 128 slice CT scanner). Scans were obtained using the same thin slice volumetric chest CT acquisition protocol: 120 kV voltage, 100 mA current at tube and automatic dose modulation, pitch of 1, and rotation time of 0.4 seconds. From the CT images, only those reconstructed for evaluation of the mediastinum and chest wall with a relatively soft filter (filter B) and with a reconstruction thickness of 1.5 mm were included in QCT analysis.

Phantomless measurement of BMD of the thoracolumbar vertebral bodies was performed according to a standardized method with established software (QCT Pro version 6.1, Mindways Software Inc., Austin, TX, USA)[15,16]. Lower thoracic CT slices that covered T11, T12, and L1 vertebrae were extracted and analyzed with validated technique[17]. COVID-19 pneumonia severity was also analyzed with the QCT method[18]. The healthy lung parenchymal volume (HLV) was considered to be -800 to -850 Hounsfield units. The proportion of HLV relative to total lung volume (TLV) on initial chest CT was calculated (HLV/TLV).

### Statistical Analysis

Conformity of data to normal distribution was evaluated with skewness and kurtosis tests and histogram plots. Skewness and kurtosis values were divided by standard error. If the resulting calculation was within ±3, then skewness and kurtosis of the dataset were considered normal[19]. Descriptive statistics of the data are presented with count and percentage for categorical variables. Normally distributed continuous variables are presented as mean and standard deviation (SD). Non-normalized variables are presented as median with range or interquartile range (IQR). The significance level was set at an alpha of 0.05.

The initial BMD and post-COVID-19 BMD were compared by paired *t*-test. There were no missing data points to account for. The McNemar test was used to compare initial and post-COVID-19 osteoporosis scores. Bivariate correlation between variables was assessed using the Pearson's correlation coefficient (r) for normally distributed variables and Spearman's correlation coefficient ($r_s$) for other variables.

Percent change in BMD after COVID-19 was the dependent variable on linear regression. Univariable linear regression was performed first to identify significant independent variables. The following independent variables were included in multivariable regression: total steroid dose, length of hospital stay, and HLV/TLV on initial chest CT.

While checking the assumptions for linear regression, an influential outlier was identified and excluded from analyses. This patient was hospitalized multiple times for unremitting COVID-19 pneumonia, secondary to rituximab-induced ac-

quired immunodeficiency. The Durbin-Watson statistic was 2.365, so the significant residual autocorrelation assumption was not violated. Collinearity tolerance value was 0.999 and variance inflation factor was 1.001, so multicollinearity was not present in this model. Statistical analysis was performed using SPSS Statistics (SPSS for Windows, Version 26.0, IBM, Armonk, NY, USA).

## Results

### Patient Characteristics

A total of 58 hospitalized COVID-19 patients (40 male, 18 female) were included in the final analysis. The mean age of patients was 63.3 years (± 9.6) (Table I). Twenty-eight (48.3%) patients were older than 65 years at time of COVID-19 diagnosis. The most common pre-existing comorbidity was hypertension (43.1%), followed by diabetes mellitus (39.6%), chronic obstructive pulmonary disease (22.4%), coronary artery disease (20.6%), and asthma (15.5%). A majority of patients had a smoking history (62.5%), but only 12.5% patients were current smokers.

Most patients were overweight. The median BMI was 29.9 kg/m$^2$ (IQR 25.0-34.8). There were no underweight (BMI < 18.5 kg/m$^2$) patients, 19.4% of patients were normal weight (BMI 18.5 - 24.9 kg/m$^2$), 30.6% patients were pre-obesity (BMI 25.0 – 29.9 kg/m$^2$), 25.0% patients were obesity class I (BMI 30.0 – 34.9 kg/m$^2$), 16.7% patients were obesity class II (BMI 35.0 – 39.9 kg/m$^2$), and 8.3% patients were obesity class III (BMI > 40 kg/m$^2$), according to World Health Organization nutritional status categories[20].

Vitamin D levels were measured in only 12 patients due to limited laboratory test availability. Mean serum 25-hydroxyvitamin D level was 17.2 ng/mL (± 9.4). All tested patients had vitamin D deficiency (12/12). The mean serum calcium was 8.9 mg/dL (± 0.5). Twenty-six patients (44.8%) were hypocalcemic and 32 (55.2%) were normocalcemic. Serum calcium level was significantly correlated with inflammatory markers. It was positively correlated with lymphocyte count (r = 0.336, $p$ = 0.010); and negatively correlated with LDH (r = -0.505, $p$ < 0.001), with the most abnormal CRP value ($r_s$ = -0.296, $p$ = 0.024), and with the most abnormal ferritin value ($r_s$ = -0.346, $p$ = 0.008). The median length of hospital stay for hypocalcemic patients was 13 days (IQR 7-19), which was significantly longer than that of normocalcemic patients (median 9 days, IQR 4 - 14) ($p$ = 0.043).

### COVID-19 Management

All patients (58/58) were treated with the antiviral favipiravir for 5-10 days and low molecular weight heparin during hospitalization according to national guidelines[21]. Patients who required supplemental oxygen received corticosteroid treatment (6 mg/day dexamethasone or equivalent dose prednisolone) (50/58, 87.7%). The median total corticosteroid treatment duration was 16 days (IQR 5-27) and the total prednisolone equivalent dose was 572 mg (IQR 181.5 – 962.5). Thirteen (22.8%) patients with rapidly increasing oxygen needs and systemic inflammation were treated with high dose prednisolone (80-250 mg/day) as a pulse steroid treatment for "cytokine storm." The

**Table I.** Baseline and treatment characteristics of patients.

| | Mean (±SD) | n (%) |
|---|---|---|
| **Demographics** | | |
| Age (year) | 63.2 (±9.6) | 58 (100) |
| Gender | | |
| Male | | 40 (69.0) |
| Female | | 18 (31.0) |
| BMI, median (IQR), kg/m$^2$ | 29.9 (25.0-34.8) | |
| **Clinical and laboratory parameters at admission** | | |
| $SpO_2$, % | | 87.6 (±5.3) |
| Lymphocyte count, x10$^3$/µL | | 1.35 (±0.61) |
| LNR | | 0.27 (±0.25) |
| eGFR, mL/min/1.73m$^2$ | | 73.3 (±22.1) |
| LDH, U/L | | 319.9 (±107.7) |
| CRP, median (IQR), mg/L | | 66.1 (33.4 - 98.8) |
| Ferritin, ng/mL | | 467.9 (±458.2) |
| 25-hydroxyvitamin D, ng/mL | | 17.2 (±9.4) |
| Total serum calcium, mg/dL | | 8.9 (±0.5) |
| **Clinical and laboratory parameters in treatment** | | |
| The lowest value of $SpO_2$, % | | 83.9 (±8.5) |
| High flow $O_2$ support or NIMV need | | 8 (14.0) |
| ICU need | | 6 (10.5) |
| Duration of hospitalization, median (IQR), days | | 11 (5-17) |
| Most abnormal value of CRP, median (IQR), mg/L | | 86.9 (44.2-129.6) |
| Most abnormal value of Ferritin, median (IQR), ng/mL | | 521.6 (132.4-910.8) |
| Cumulative corticosteroid dose, median (IQR), mg | | 572 (181.5-962.5) |
| Corticosteroid treatment duration, median (IQR), days | | 16 (5-27) |

IQR: interquartile range; LNR: Lymphocyte/Neutrophil Ratio; BMI: body mass index; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; LDH: lactate dehydrogenase; $SpO_2$: peripheral oxygen saturation; NIMV: Non-invasive mechanical ventilation; ICU: intensive care unit.

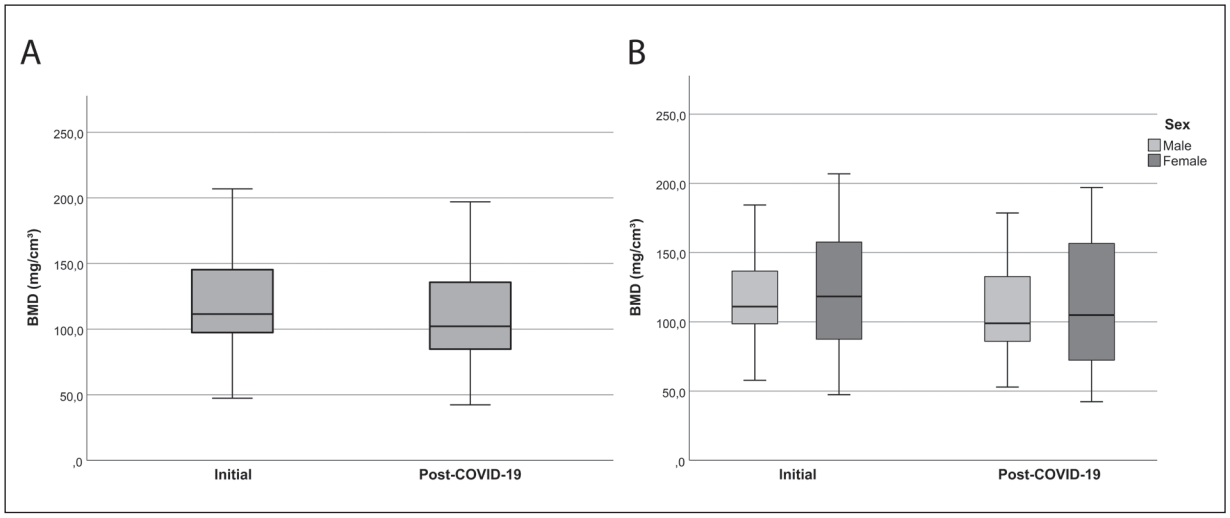


**Figure 2.** BMD calculated by QCT method using follow-up chest CT *vs.* initial chest CT. **A**, The mean BMD calculated from post-discharge follow-up chest CT for all patients (110.1 mg/cm$^3$ ± 38.5) was found to be significantly lower than initial CT (119.2 mg/cm$^3$ ± 36.8) ($p < 0.001$). **B**, The magnitude of BMD decrease among COVID-19 patients after hospitalization was not significantly different between sexes. BMD: bone mineral density.

mean cumulative prednisolone dose used in treatment of these patients was 1,902.2 mg (± 1,346.6), over a median 24 days.

Forty-seven patients (81.0%) had $SpO_2 \leq 93\%$ on admission. Mean $SpO_2$ on admission was 87.6% (± 5.3). $SpO_2$ decreased for most patients during the first week of hospitalization. The mean value for the lowest $SpO_2$ reading was 83.9% (± 8.5). The median serum CRP level at admission was 66.1 mg/L (IQR 33.4 - 98.8) and the mean serum ferritin level at admission was 467.9 ng/mL (± 458.2).

High flow oxygen support or NIMV was indicated in 8 (14.0%) patients, and an additional 6 (10.5%) patients were transferred to ICU for escalating care needs. Oxygen support requirements gradually decreased among surviving patients over the course of their hospitalization. The median length of hospital stay was 11 days (IQR 6-16). Patients with post-treatment $SpO_2 < 88\%$ were discharged home with an oxygen support system.

The BMD at COVID-19 diagnosis was not significantly correlated with disease severity factors such as lymphocyte count, LDH, CRP, ferritin levels, $SpO_2$, or HLV as a percentage of TLV. It was also not significantly correlated with length of hospital stay or use of ICU-level care.

### *Post-COVID-19 BMD*

Follow-up chest CT was obtained at a mean 81 days (± 48) after initial CT. Mean BMD was significantly lower at post-COVID-19 follow-up (110.1 mg/cm$^3$ ± 38.5) than at COVID-19 diagnosis (119.2 mg/cm$^3$ ± 36.8) ($p < 0.001$). BMD decreased by a mean 8.9 mg/cm$^3$ (± 9.8), or 8.6% (± 10.5%), from COVID-19 diagnosis to follow-up. BMD decreased by a mean 9.0 mg/cm$^3$ (± 9.8) in males and 8.5 mg/cm$^3$ (± 10.0) in females. The magnitude of BMD decrease was not significantly different between sexes (Figure 2) and was not significantly correlated with patient age.

On initial chest CT, 23 patients (39.7%) had a normal BMD, 28 (48.3%) were osteopenic, and 7 (12.1%) were osteoporotic, according to diagnostic categories endorsed by the American College of Radiology and International Society for Clinical Densitometry[22,23]. The proportion of osteoporotic patients increased significantly from 12.1% at COVID-19 diagnosis to 24.1% at follow-up ($p = 0.048$) (Figure 3).

The decrease in BMD among patients who were treated with a cumulative steroid dose greater than 600 mg was significantly higher than that of patients treated with a lower steroid dose ($p = 0.011$). The magnitude of BMD decrease was significantly correlated with total steroid dose ($r_s = 0.32$, $p = 0.014$) and duration of steroid treatment ($r_s = 0.27$, $p = 0.045$).

The change in BMD after COVID-19 hospitalization was negatively correlated with length of hospital stay ($r = - 0.35$, $p = 0.010$). The change in BMD after COVID-19 hospitalization was nega-

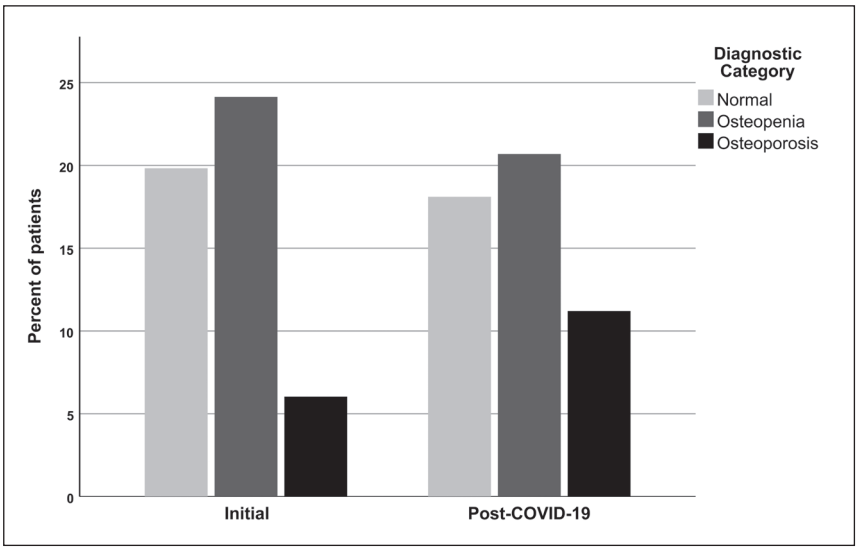


**Figure 3.** Prevalence of osteoporotic COVID-19 patients at initial diagnosis and at follow-up. Osteoporosis prevalence increased two-fold after hospitalization for COVID-19 ($p = 0.048$).

tively correlated with HLV/TLV (reverse of pneumonia severity) on initial chest CT (r = - 0.29, $p$ = 0.029) (Figure 4).

On multivariable linear regression, only HLV/TLV on initial chest CT (beta = - 0.005 $p$ = 0.001) and total steroid dose (beta = 0.00038, $p$ = 0.002) were predictive of change in BMD after COVID-19 hospitalization (Table II).

## Discussion

The most common bone disease is osteoporosis[24], which causes an estimated €37 billion loss per year in the European Union (EU)[25]. The prevalence of osteoporosis varies between 5.7%-6.9% in men and 19.3%-23.4% in women over the age of 50 in EU countries[26]. In Turkey, the prevalence

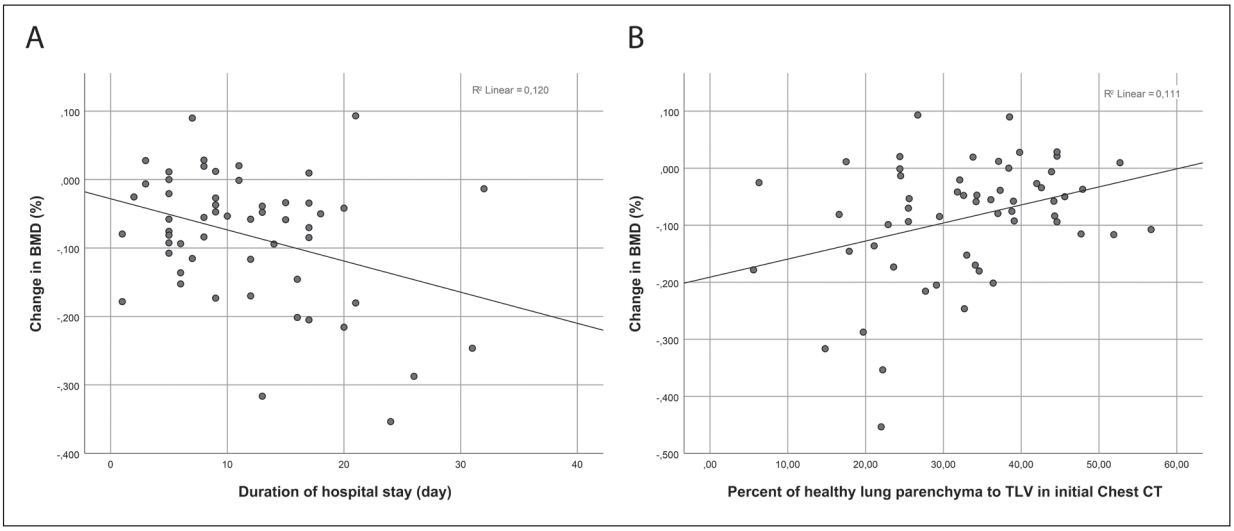


**Figure 4.** ***A***, Correlation between BMD after COVID-19 and length of hospital stay (r= - 0.35, $p$ = .010). **B**, Correlation between BMD after COVID-19 and pneumonia severity on admission chest CT scans of patients. Percent change in BMD after COVID was negatively correlated with HLV/TLV (reverse of pneumonia severity) on admission chest CT of patients (r = - 0.29, $p$= .029). BMD: bone mineral density, HLV: healthy lung volume, TLV: total lung volume, CT: computed tomography.

**Table II.** Independent variables associated with percent change in BMD after COVID-19 in multivariable linear regression.

| Variable | B | SCB | SE | *p*-value |
|---|---|---|---|---|
| Percent of HLV to TLV in initial chest CT | - 0.005 | - 0.390 | 0.001 | 0.001 |
| Total steroid dose used in treatment | 0.00038 | 0.383 | <0.001 | 0.002 |

BMD: bone mineral density; HLV: healthy lung parenchyma volume; TLV: total lung volume;
B: unstandardized B; SCB: standardized coefficient beta; SE: standard error of B.

of osteoporosis is 7.5% in men and 12.9% in women over the age of 50[27]. Risk of hospital admission and death from COVID-19 is higher among people with previous fractures[28]. The present study did not evaluate vertebral fractures, but a higher prevalence of vertebral fractures has been reported among hospitalized COVID-19 patients compared with the general population[29]. Lower vertebral BMD has been reported to be correlated with increased mortality risk in COVID-19 patients[30]. Hospitalized COVID-19 patients were evaluated in the present study, so the higher osteoporosis prevalence reported here may be attributable in part to the aggravating effect of COVID-19 severity.

BMD among COVID-19 patients, as calculated from thoracic and lumbar vertebral bodies using QCT, decreased by a mean of 9.0 mg/cm$^3$ in males and 8.5 mg/cm$^3$ in females in this study. This was significantly greater than expected for the age-related annual rate of BMD loss, which is 0.83 mg/mL$^3$ per year in men and 0.70 mg/mL$^3$ per year in women[31]. As a result, the prevalence of osteoporotic patients in the present study increased two-fold after COVID-19 hospitalization.

These findings support the literature which shows the detrimental effects of COVID-19 on bone health. Patients hospitalized with COVID-19 who have multiple predisposing factors to bone loss should be monitored and preventive treatment may be appropriate. Such predisposing factors include age over 50, decreased mobility, malnutrition, hypocalcemia, increased serum pro-inflammatory cytokines, and use of corticosteroids[32,33].

The first report of a severely hypocalcemic COVID-19 patient was made in April 2020[34]. Since then, several studies have reported that hypocalcemia is correlated with inflammation, biomarkers of thrombosis, disease severity, and mortality in COVID-19 patients[35-37]. Hypocalcemia has also been noted in Ebola and SARS patients, during previous pandemics[38,39]. In this study, 44.8% of patients were hypocalcemic at time of COVID-19 diagnosis, which is lower than that reported in the literature (62.6%-74.7%)[40]. We observed that serum calcium in our COVID-19 patients was positively correlated with lymphocyte count, and negatively correlated with LDH and the most abnormal values of CRP and ferritin. Length of hospital stay was significantly longer among hypocalcemic patients than normocalcemic patients. These findings demonstrate a negative impact of hypocalcemia on COVID-19 disease severity, which is consistent with the published literature[35-40]. Clinicians may be advised to closely monitor calcium levels in their hospitalized COVID-19 patients, and further research efforts should be made to assess the impact of correcting calcium levels on patient outcomes.

Multiple randomized trials have suggested that corticosteroid therapy improves clinical outcomes and decreases mortality in hospitalized COVID-19 patients that require oxygen support[41]. Therefore, high-dose glucocorticoid is now considered to be the standard of care for hospitalized COVID-19 patients[42]. It is well established that corticosteroids increase fracture risk with a dose-dependent effect. This risk is not entirely explained by bone loss[43]. The cumulative dose of corticosteroids, duration of treatment, and age of the patient were major risk factors for osteonecrosis in SARS patients[44]. The mean cumulative dose of methylprednisolone used in SARS patients ranged from 1.5 - 7.2 g, and the mean treatment duration ranged from 11-41 days[45]. Relative to the SARS epidemic, our study demonstrates a shorter corticosteroid regimen (11 ± 11 days) and lower cumulative dosing (572 ± 781 mg). Nevertheless, we found that total steroid dose was independently associated with change in BMD on multivariable analysis. This further suggests that bone loss occurs during the initial periods of corticosteroid use, even with a moderate dose of corticosteroids[46].

Additionally, it is possible that COVID-19 illness may influence bone health. SARS-CoV-1 virus-related osteoclastogenesis has previously been demonstrated *in vitro*[47]. Suppressed osteogenic differentiation and decreased fracture healing secondary to SARS-CoV-2-induced overexpression of miR-4485 have also been reported[48].

Inflammation is a risk factor for osteoporosis, and interleukin (IL)-1 and IL-6 are important regulators of bone resorption[49]. The radiological findings of severity of COVID-19 pneumonia were found to be independently associated with decreased BMD after COVID-19 hospitalization, in the present study. Therefore, the induction of proinflammatory cytokines and lung inflammation by COVID-19 may contribute to bone loss[50].

The number of patients that have survived COVID-19 hospitalization is increasing steadily, so it is important to better characterize the detrimental effects of COVID-19 extend beyond hospitalization. Common problems among surviving patients include continued morbidity, inability to return to previous activities, and physical and emotional symptoms[51]. Our findings highlight that decreasing BMD is an important sequela of COVID-19 illness and treatment.

Osteoporotic fracture is a principal cause of mortality and morbidity among the elderly, and it imposes considerable costs to society[52]. For each standard deviation decrease in BMD, the fracture risk increases 2 or 3-fold[53]. Therefore, it is important to identify and mitigate the risk of BMD loss and osteoporotic fracture among COVID-19 survivors.

Multiple aspects of osteoporosis management have been impacted during the COVID-19 pandemic. Fears of exposure and difficulty scheduling dual-energy X-ray absorptiometry (DEXA) scans for screening, as well as imaging center closures, resulted in fewer DEXA scans being performed during the first year of the pandemic[54,55]. Research has demonstrated that opportunistic screening for osteoporosis with chest CT has comparable sensitivity and specificity for the diagnostic accuracy with DEXA[56]. Bone loss in the thoracic vertebra significantly correlates with lumbar spine mineral density measured with DEXA[57]. In the present study, we utilized the QCT method to assess BMD, using chest CT scans that were obtained for routine clinical management of COVID-19. Clinicians may consider use of this method as an acceptable substitute for DEXA scan screening, during the unprecedented times of the COVID-19 pandemic.

### Study Limitations

We included in this study only the survivors of severe COVID-19 infection requiring hospitalization, which may have enhanced the strength of the association between an exposure and the outcome. Future studies including ambulatory care patients are needed in order to validate our findings in less severe COVID-19 patients. The retrospective study design at a single medical center is also a potential limitation to external validation. We were also not able to study the longitudinal effect of COVID-19 on BMD, due to the relatively short follow-up period of this study.

## Conclusions

Our study demonstrated that both COVID-19 and its treatments adversely affect the bone health of COVID-19 survivors. This effect is more prominent for elderly and frail patients, so these patients should be monitored closely for bone loss and fall risk. Patients who already osteopenic or osteoporotic before COVID-19 illness are expected to be more markedly affected by its detrimental impact on bone health. Therefore, osteoporosis should be treated before or during hospitalization in these patients. The bone health status of all COVID-19 patients should be evaluated during COVID-19 hospitalization, to establish a baseline for monitoring. The QCT method can be used with chest CT scans that are obtained during routine COVID-19 workup and management. Osteoporosis therapies may also be considered for hospitalized COVID-19 patients who require long-term corticosteroid treatment. COVID-19 survivors are at increased risk for secondary osteoporosis; therefore, the bone health status of surviving patients should be monitored closely at follow-up visits.

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### Conflict of Interests

The authors declare that they have no conflict of interests.

### Authors' Contributions

Bahadır M. Berktaş designed the research, analyzed and interpreted the data, drafted the article, Atila Gökçek attained data and performed the research, Nevin Taci Hoca attained data and performed the research, Adem Koyuncu attained data and performed the research. All authors participated the intellectual content of the manuscript.

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