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Vertebral Fractures Increase the Long-Term Mortality of Patients with Coronavirus Disease 2019

ABSTRACT

Objective: To investigate the impact of vertebral fracture (VF) on long-term mortality of patients with COVID-19.

Methods: In this single-center retrospective study, patients with COVID-19 who were admitted during the first wave of the pandemic and who had undergone a thorax computerized tomography scan were consecutively included. Patients with VFs due to trauma or malignancy were excluded. A Multivariate Cox proportional hazard model was used for survival analyses.

Results: Of the 349 patients, 249 (71.3%) had at least one VF. Patients with VF were older (55.3 ± 15 vs. 43.4 ± 13.3, $P < .001$) and had higher rates of diabetes mellitus (19.7% vs. 11%), hypertension (34.1% vs. 17%), dyslipidemia (11.6% vs. 4%), cardiovascular disease (15.3% vs. 6.1%), and acute kidney injury (23.5% vs. 13%) ($P < .05$ for all). The mean survival was lower in patients with VF (1285.6 days, SE: 24.3, 95% CI [1238-1333]) compared to patients without VF (1388.6 days, SE: 16.3, 95% CI [1356-1420]) ($P = .024$). The mean survival was particularly decreased in patients with moderate–severe (1168 days, $P = .001$) or multiple VFs (1276 days, $P = .016$). The association between VF and mortality was adjusted for diabetes mellitus, hypertension, cardiovascular and renal failure. Multivariate Cox proportional hazard model showed that malignancy, renal failure, and VFs were independent predictors of decreased survival.

Conclusion: Vertebral fractures were found to be one of the most common comorbidities in patients with COVID-19. It also represents a potential marker of frailty and an important predictor of decreased survival. Vertebral fractures should be considered in all patients who have had COVID-19. The causal link between VFs and mortality requires large-scale prospective research.

Keywords: Vertebral fracture, osteoporosis, COVID-19, mortality

Introduction

In late 2019, a respiratory infection called coronavirus disease 2019 (COVID-19) was first recognized in China.[1] World Health Organization announced COVID-19 as a pandemic in March 2020, and a drastic lockdown was declared in many countries.[2] During the early pandemic stages, the scientific community initially focused on hard data, such as cardiovascular risk factors, to discern their influence on COVID-19 prognosis. As the lockdown ensued, the surge in mental disorders resulting from the burdensome restrictions became the primary concern. Meanwhile, the impact of bone health on COVID-19 prognosis has been relatively overlooked.

A large body of endeavors have shown that older age, smoking, diabetes mellitus, cardiovascular disease, malignancy, chronic kidney disease, and vitamin D deficiency are highly prevalent among patients with COVID-19.[3-8] These conditions are traditional risk factors for impaired bone health and osteoporosis, suggesting that patients with COVID-19. may be inherently at increased risk of osteoporosis.[9] It is important to note that lockdown measures led to an obligatory sedentary lifestyle, compromising skeletal health. Additionally, fear of contracting the virus and overwhelmed healthcare systems resulted in delayed medical care, with patients often missing necessary treatments for osteoporosis and other bone health conditions, increasing fracture risk. Using glucocorticoids in COVID-19 treatment negatively affects bone health by promoting bone resorption and reducing bone formation. Coronavirus disease 2019-associated inflammation also contributes to bone loss, as chronic inflammation is known to impair bone remodeling. Lastly, the psychological stress associated with the pandemic, including increased anxiety and depression, alters hormone levels, particularly cortisol, leading to bone loss.[10] In summary, the pandemic could increase the prevalence and severity of vertebral fractures (VFs) through reduced physical activity, a sedentary lifestyle,

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delayed medical care, the negative effects of glucocorticoids, inflammation, background comorbidities, and heightened psychological stress, all contributing to weakened bone health.[11]

Vertebral fractures (VFs) represent the most commonly encountered osteoporotic fractures in routine practice.[12,13] The VF has been shown to cause substantial morbidity and mortality in the general population.[14-16] The knowledge on the frequency of VF in patients with COVID-19 is scarce, and its effect on long-term mortality remains to be established. In the present study, we aimed to investigate the impact of VF on the mortality of patients with COVID-19 admitted during the first wave of the pandemic. We surmised that VFs might be more prevalent than anticipated and might significantly affect the long-term survival of patients with COVID-19.

Materials and Methods

Design and Setting

This single-center retrospective cohort study was conducted in a tertiary care university hospital. The study fully adhered to the STROBE guideline. The present study was approved by the Medical Research Ethics Committee (approval date: November 5, 2020, approval number: 145928). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration. Written informed consent was obtained from all participants included in the study.

Study Population

Patients were consecutively included based on the presence of the following criteria: (i) age ≥ 18 years, (ii) confirmed diagnosis of COVID-19, (iii) admission to the emergency department between March 2020 and August 2020, and (iv) thorax computerized tomography (CT) scans for the detection of pulmonary COVID-19. Patients admitted to the emergency department for other conditions and subsequently diagnosed with superimposed COVID-19; patients with negative SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test but diagnosed as "possible" or "probable" COVID-19 based on the Centers for Disease Control and Prevention criteria;[17] patients with a positive SARS-CoV-2 RT-PCR test in the absence of chest computerized tomography (CT) examination; patients with known VF(s) due to malignancy or trauma prior to COVID-19 diagnosis were excluded.

Data Collection

Demographic, clinical, and laboratory data were collected by reviewing digital medical charts. An effort was made to complete the missing information by accessing the "e-Impulse" application [https://enabiz.gov.tr], the trusted personal health record system the Ministry of Health has provided since 2015.[18] The life status in February 2024 of each patient was confirmed through the state-supported death notification system, accessible at [https://obs.saglik.gov.tr] through patients' identification numbers. This online platform provides definitive information on patients' mortality status and dates.

Vertebral Fracture Assessment

Vertebral fractures were evaluated using sagittal image reconstruction from a chest CT scanner with standard acquisition covering the entire thoracic volume from D1 to a plane transverse to D12. A single experienced radiologist (SK), blinded to the underlying diagnosis, performed the radiological assessments. Vertebral fractures were classified according to the semiquantitative score method proposed by Genant et al.[19] The Genant method is a visual semi-quantitative technique used to assess vertebral fractures. Vertebral fractures were categorized as mild, moderate, and severe based on height ratio decreases of 20%-25%, 25%-40%, and over 40%, respectively. This method provides insight into the severity of a fracture by visually estimating the extent of vertebral height reduction and morphological changes. It differentiates vertebral fractures from other non-fracture deformities, ensuring a more accurate assessment. Unlike other approaches, this method does not link the type of deformity (wedge, biconcavity, or compression) to the grading of a fracture. The focus is purely on the overall reduction in height, allowing for a straightforward evaluation of vertebral fractures.

Diagnosis and Management of Coronavirus Disease 2019

The diagnosis of COVID-19 was defined as positive RT-PCR from a nasal and/or throat swab together with signs, symptoms, and radiological findings suggestive of COVID-19 pneumonia. In patients with initial RT-PCR negativity, sequential testing was performed, especially in cases with typical clinical or radiological findings suggestive of COVID-19. The hospitalization decision was based on vital signs (temperature, pulse rate, blood pressure, respiratory rate), oxygen saturation, mental alertness, and pulmonary involvement. Patients with hemodynamic instability, tachypnea, hypoxia, decreased mental alertness, and classical or possible lung involvement according to the criteria determined by the British Society of Thoracic Imaging[20] were hospitalized. Hemodynamically stable patients without lung involvement were managed in the outpatient setting.

Severe Acute Respiratory Syndrome Coronavirus 2 Reverse Transcription Polymerase Chain Reaction Protocol

Ribonucleic acid was extracted with a commercial kit (BioSpeedy Nucleic Acid extraction kit; Bioeksen R & D Technologies Ltd.), and COVID-19 RNA was identified with a commercial RT PCR kit (BioSpeedy COVID-19 RT-qPCR kit; Bioeksen R & D Technologies Ltd.) that targets the RdRP gene of COVID-19 in the swabs. The Rotor-Gene Q 5plex HRM platform was used for amplification and detection.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive data were presented as mean ± standard deviation (SD), median, interquartile range [IQR], and ratio values. The distribution of continuous parameters was determined using the Kolmogorov–Smirnov test. Quantitative independent data were compared using the analysis of variance (ANOVA) test, independent sample *t*-test, Kruskal–Wallis test, or Mann–Whitney *U*-test. The association between categorical variables was analyzed using the chi-square test. The correlations between ordinal data were performed using Kendall's Tau test. The survival curves were plotted using the

MAIN POINTS

- This study focused on the effect of vertebral fractures on long-term mortality in patients with COVID-19.
- The results showed that Vertebral fracture was one of the most common comorbidities in patients with COVID-19.
- It also appears to represent a potential marker of frailty and poor prognosis.
- Our results highlight the importance of vertebral fracture assessment in every individual who underwent a computerized tomography scan due to COVID-19 pneumonia.

Kaplan–Meier method. To determine the candidate variables that confer increased risk of mortality, deceased and alive patients were compared. Significant variables from these univariate analyses were included in the multivariate Cox model using the enter method, where all selected variables are entered into the model simultaneously. The confidence level was set at 95%. *P* value < .05 was considered significant.

Results

General features of the Vertebral Fracture Group Compared to No Vertebral Fracture group at Coronavirus Disease 2019 Presentation

In the present study, 71.3% (n = 249) of patients with COVID-19. had VF. In the VF group, 206 patients (82.7%) had mild, 40 (16.1%) had moderate, and 3 (1.2%) had severe VFs. Two hundred fourteen patients (85.9%) had more than one VF, and the median VF count was 3 [IQR, 2-5].

Demographic and clinical characteristics of the VF (n = 249) and no VF (n = 100) groups were provided in Table 1. Patients with VF were older at the time of COVID-19 diagnosis compared to those without VF. Gender distribution was not different (Table 1). Although the percentage of patients with CT-detectable COVID-19 pneumonia and its severity showed no difference; the duration of hospital stay was longer in patients with VF (Table 1). We found that the severity of CT-detectable COVID-19 pneumonia increased with the increasing severity (Kendall's tau-*b* = 0.144, *P* = .003) and number of VFs (Kendall's tau-*b* = 0.116, *P* = .049). The need for invasive mechanical ventilation was higher in patients

Table 1. Clinical and Laboratory Data of the Patients with Coronavirus Disease 2019 at Initial Admission

Findings	Patients with VF, n = 249	Patients without VF, n = 100	*P*
Age at diagnosis, mean ± SD	55.3 ± 15.7	43.4 ± 13.3	<.001
Gender, male, n (%)	144 (57.8)	54 (54)	.551
Duration of follow-up, months median [IQR]	45 [42-45]	45 [42-46]	.012
Body mass index (kg/m^2), median [IQR]	27.7 [25-31]	27.6 [24.2-30.6]	.597
Current smoker, n (%)	60 (24.4)	27 (27)	.586
CT pneumonia, n (%)	188 (75.5)	67 (67)	.111
Mild	112 (45)	50 (50)	.408
Moderate	47 (18.9)	11 (11)	.081
Severe	29 (11.6)	6 (6)	.120
Hospitalization due to COVID-19, n (%)	196 (78.7)	74 (74)	.396
Duration of hospitalization (days), median [IQR]	9 [6-12]	7 [5-11]	.029
Noninvasive mechanical ventilation, n (%)	10 (4)	4 (4)	1.000
Intensive care unit admission, n (%)	20 (8)	6 (6)	.654
Duration of intensive care unit stay (days), median [IQR]	13.5 [7.3-23.5]	9 [6-12.5]	.157
Invasive mechanical ventilation, n (%)	13 (5.2)	2 (2)	.248
Serum urea (mg/dL), median [IQR]	29 [22-38]	23 [18-30]	<.001
Serum creatinine (mg/dL), median [IQR]	0.9 [0.77-1.1]	0.84 [0.7-1.0]	.152
Serum calcium (mg/dL), median [IQR]	8.9 [8.4-9.2]	9 [8.6-9.3]	.213
25-hydroxyvitamin D* ng/mL, mean ± SD	15.9 ± 7.7	16.2 ± 8.3	.906
Serum C-reactive protein (mg/L), median [IQR]	17 [5-50.3]	12.3 [3.6-33]	.090
Serum procalcitonin (ng/mL), median [IQR]	0.07 [0.04-0.12]	0.05 [0.03-0.1]	.028
Serum ferritin (ng/mL), median [IQR]	191 [87-488]	131 [54-374]	.076
Serum D-dimer (mg/L), median [IQR]	0.5 [0.3-1.1]	0.4 [0.3-0.9]	.081
Serum fibrinogen (mg/L), median [IQR]	416 [326-502]	410 [296-501]	.266
Hemoglobin (g/dL), median [IQR]	13.3 [12-14.3]	13.5 [12.1-14.5]	.377
Leukocyte (mm^3), median [IQR]	5.7 [4.2-7.6]	6 [4.9-74]	.453
Lymphocyte (mm^3), median [IQR]	1.4 [1.0-1.9]	1.5 [1.0-1.9]	.550
Thrombocyte (×10^3/μL), median [IQR]	202 [167-235]	207 [168-257]	.159
Comorbidities at admission, n (%)			
Obesity	76 (31.8)	29 (29)	.896
Chronic kidney disease	18 (7.2)	7 (7)	1.000
Dementia	4 (1.6)	1 (1)	1.000
Malignancy	10 (4)	7 (7)	.273
Chronic obstructive pulmonary disease	32 (12.9)	5 (5)	.034
Asthma	8 (3.2)	3 (3)	1.000
Chronic liver disease	2 (0.8)	1 (1)	1.000

VF, vertebral fracture.
*Available in 70 patients with VF (28.1%) and 21 patients without VF (21%).

with moderate–severe VF compared to patients without VF (11.6% vs. 2%, $P = .026$).

At COVID-19 presentation, patients with VF had higher serum urea and procalcitonin levels (Table 1). There was also a trend for higher serum levels of other inflammatory parameters, including C-reactive protein, ferritin, and D-dimer levels ($P = .090$, $P = .076$, and $P = .081$, respectively). Table 1 compares other laboratory parameters.

Vitamin D levels were available in 91 patients. Thirty-one patients (34.1%) had vitamin D deficiency (<12 ng/mL), 36 patients (39.6%) had vitamin D insufficiency (12-20 ng/mL), and 24 patients (26.4%) had vitamin D sufficiency (>20 ng/mL). The frequency of VF was 80.6%, 69.4%, and 83.3% in vitamin D deficient, insufficient, and replete patients, respectively ($P = .441$).

The VF group had higher rates of type 2 diabetes mellitus (19.7% vs. 11%), hypertension (34.1% vs. 17%, $P = .002$), dyslipidemia (11.6% vs. 4%, $P = .041$), cardiovascular disease (15.3% vs. 6.1%, $P = .020$), and acute kidney injury (23.5% vs. 13%, $P = .039$) at COVID-19 diagnosis in comparison to the no-VF group. Other comorbidities are presented in Table 1.

The median duration of time from COVID-19 diagnosis to death was 2 months [0-10.3] in the VF group and 20 months [0-43] in the no VF group ($P = .315$). In the VF group, the most common cause of death was COVID-19 pneumonia (n = 9, 33%), followed by cardiovascular disease (n = 6, 22.2%), cancer (n = 3, 11.1%), and gram-sepsis (n = 1, 3.7%). In eight patients with VF (29.6%), the reason for death was not identified. In the no VF group, one patient died because of cancer (33.3%), and another patient died due to hemorrhagic shock (n = 33.3%). In one patient with no VF, the cause of death was not identified.

Death Ratio According to Vertebral Fracture and Survival Analyses

The percentage of death was higher in patients with VF as compared to patients without VF (10.8% vs. 3%, $P = .019$). The trends of mortality based on the severity and number of VFs over time are presented in Tables 2 and 3 and Figure 1. The death ratio was higher in patients with multiple and/or severe VFs. The differences between death ratios of VF and no VF groups became more evident after 6 months of COVID-19 diagnosis (Tables 2 and 3, Figure 1).

The difference in survival curves of VF and no-F groups was plotted using the Kaplan–Meier method (Figure 2). The log rank test indicated a lower mean survival in patients with VF (1285.6 days, SE: 24.3, 95% CI [1238-1333]) compared to patients without VF (1388.6 days, SE: 16.3, 95% CI [1356-1420]) ($P = .024$). As shown in Figure 2, the mean survival was particularly decreased in patients with moderate–severe VF (1168 days, SE: 78.4, 95% CI [1014-1321], $P = .001$) and with multiple VFs (1276 days, SE: 27, 95% CI [1223-1329], $P = .016$).

After showing a decreased survival rate in patients with VF compared to patients without VF, we compared deceased and surviving patients to identify other comorbidities that could potentially harbor an increased risk of mortality. It was found that type 2 diabetes mellitus, hypertension, cardiovascular disease, renal disease, and malignancy were more prevalent in the deceased compared to surviving patients (Table 4). Since patients with VF in our sample had higher frequencies of type 2 diabetes mellitus, hypertension, cardiovascular disease, and renal disease, and, for that reason, might have higher mortality, the association between VF and mortality was adjusted for these comorbidities. A multivariate Cox proportional hazard model showed that malignancy, renal disease, and VFs were determinants of decreased survival rate in patients with COVID-19. (Table 5) (Figure 3). The probability of survival decreased with increasing severity and number of VFs (Table 5).

Discussion

In this study, we found that vertebral compression fractures are among the most common comorbidities in patients who underwent computerized tomography scans due to COVID-19 pneumonia. We also showed that vertebral fractures were important predictors of mortality in patients with COVID-19. A compelling trend of decreased survival with an increasing number and severity of vertebral fractures was noteworthy. A higher prevalence of diabetes, hypertension, and cardiovascular disease in patients with vertebral fractures compared to those without fractures implied an association of bone fragility with other comorbidities related to grim prognosis. Overall, these results align with the concept that the presence of vertebral fractures and its severity may serve as a surrogate of frailty and poor survival in patients diagnosed with COVID-19.

The cardinal finding of this study was the increased mortality of COVID-19 patients with incidentally detected VFs. A plethora of evidence has clearly shown that VF is a predictor of increased long-term mortality in non-COVID populations.[21-23] To our knowledge, two studies specifically investigated the association between VFs and mortality in patients with COVID-19.[24,25] These studies focused on short-term mortality per se, yielding equivocal results. The study by Battisti et al showed that VF was not associated with increased mortality in COVID-19 patients, in contrast to non-COVID patients.[24] They proposed that patients with COVID-19 bear an inherent

Table 2. Severity of Vertebral Fractures and Mortality

	No VF, n = 100	Mild VF, n = 206	Moderate–Severe VF, n = 43	*P*
30-day deaths, n (%)	1 (1)	7 (3.4)	3 (7)	.119
3-month deaths, n (%)	1 (1)	9 (4.4)	4 (9.3)	.059[a]
6-month deaths, n (%)	1 (1)	10 (4.9)	7 (16.3)	.001[b,c]
1-year deaths, n (%)	1 (1)	13 (6.3)	8 (18.6)	.001[d,e,f]
2 -year deaths, n (%)	2 (2)	17 (8.3)	8 (18.6)	.004[d,b]
4-year deaths, n (%)	3 (3)	19 (9.2)	8 (18.6)	.010[g,h]

No VF versus Mild VF: [d]$P = .041$, [g]$P = .058$.
No VF versus moderate–severe VF: [a]$P = .029$, [b]$P = .001$, [e]$P < .001$, [h]$P = .003$.
Mild VF versus moderate–severe VF: [c]$P = .05$, [f]$P = .03$.

Table 3. Number of Vertebral Fractures and Mortality

	No VF, n = 100	Single VF, n = 35	Multiple VFs, n = 214	*P*
30-day deaths, n (%)	1 (1)	0 (0)	10 (4.7)	.207
3-month deaths, n (%)	1 (1)	1 (2.9)	12 (5.6)	.118
6-month deaths, n (%)	1 (1)	1 (2.9)	16 (7.5)	.055[a]
1-year deaths, n (%)	1 (1)	2 (5.7)	19 (8.9)	.030[b]
2-year deaths, n (%)	2 (2)	2 (5.7)	23 (10.7)	.025[c]
4-year deaths, n (%)	3 (3)	2 (5.7)	25 (11.7)	.031[d]

No VF vs moderate–severe VF: [a]$P = .028$, [b]$P = .011$, [c]$P = .012$, [d]$P = .018$.

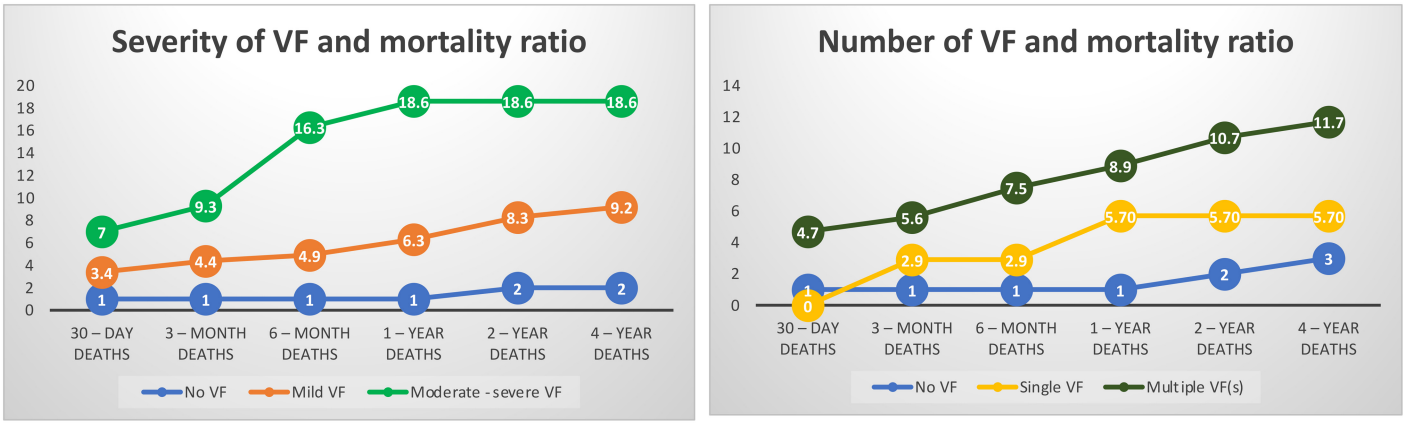

Figure 1. The differences between death ratios of patients with and without VF over the study period. In (A), the death ratios were presented based on the severity of VFs. In (B), the death ratios were presented according to the number of VFs. Numbers in colored circles denote the % of deaths at specific time points on the *X*-axis.

mortality risk that surpasses the risk solely attributed to VFs. While the study by Di Filippo et al indicated a trend towards higher mortality in COVID-19 patients with VFs compared to those without VFs, the difference was not significant.[25] Within the patients with VFs, however, mortality was higher in patients with severe VFs compared to those with moderate and mild VFs, suggesting that VFs might still be a factor worth investigating further. To this end, we explored this impact in a larger cohort and over an extended follow-up period, widening the scope of previous research. We revealed a higher percentage of death in COVID-19 patients with VF compared to those without VF. This study further breaks down the analysis by considering the severity and number of VFs and showed that multiple and/or moderate–severe VFs were associated with higher mortality. This suggested that not only the presence of VFs but also their extent predicted mortality. One can speculate that the close association between skeletal fragility and diabetes mellitus, hypertension, and cardiovascular disease might pose patients with VF at high risk of death.[26-28] Nevertheless, even after adjusting for these comorbidities, the VF still appeared as an independent predictor of increased mortality. This implies that the impact of VFs on mortality is not merely explained by its association with these comorbidities. Our findings highlight the importance of considering VFs as

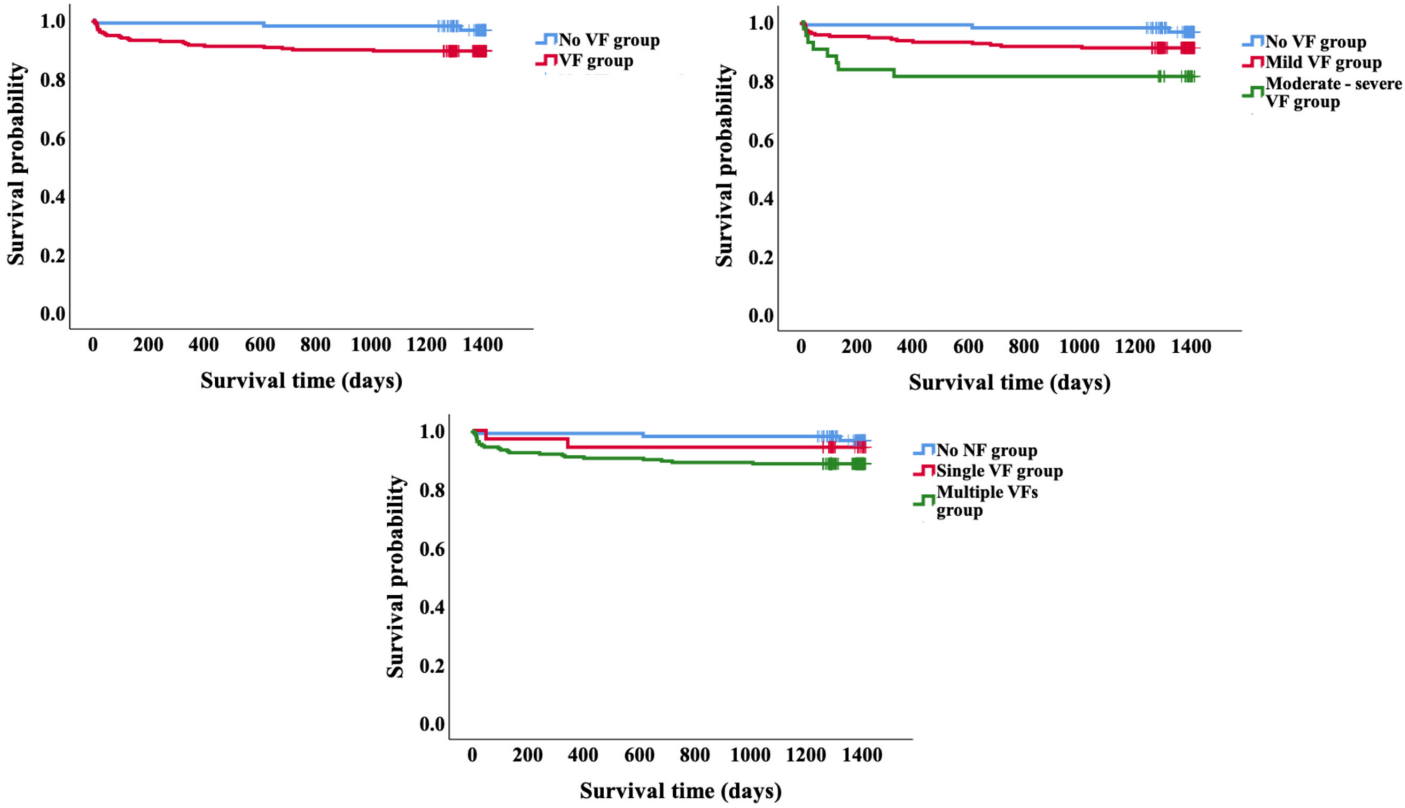

Figure 2. The survival curves were plotted by the Kaplan–Meier method.

Table 4. Comparison of Alive and Deceased Patients with Coronavirus Disease 2019.

Features at Admission, n (%)	Deceased Patients, n = 30	Alive Patients, n = 319	*P*
Gender, male	20 (66.7)	178 (55.8)	.335
Vertebral fracture	27 (90)	222 (69.6)	.019
Mild	19 (63.3)	187 (58.6)	.058
Moderate-severe	8 (26.7)	35 (11)	.003
Single	2 (6.7)	33 (10.3)	.604
Multiple	25 (83.3)	189 (59.2)	.018
Obesity	6 (22.2)	99 (32.2)	.388
Type 2 diabetes mellitus	9 (30)	51 (16)	.073
Hypertension	15 (50)	87 (27.3)	.012
Cardiovascular disease	12 (40)	32 (10.1)	<.001
Renal disease*	22 (75.9)	63 (19.9)	<.001
Malignancy	8 (26.7)	9 (2.8)	<.001
Chronic obstructive pulmonary disease	6 (20)	31 (9.7)	.112
Asthma	1 (3.3)	10 (3.1)	1.000
Chronic liver disease	1 (3.3)	2 (0.6)	.237

*Acute kidney injury and/or chronic renal failure.

a potential marker for increased mortality risk in the prognosis of patients diagnosed with COVID-19.

Another noteworthy point is that the difference in mortality between patients with and without VFs becomes more apparent after the sixth month of COVID-19 diagnosis. This finding favors a previous report suggesting no difference in short-term mortality between COVID-19 patients with and without VF.[24] Based on the results of our study, it can be inferred that VF may affect the prognosis even after COVID-19 recovery, emphasizing the importance of evaluating patients for VF in the long term.

A large body of evidence from Europe has indicated that the prevalence of VF ranges from 8% to 25% in the general population.[29] On the other hand, data on the prevalence of VF in patients with COVID-19 is relatively scarce. In studies assessing thoracic VFs in 50

Table 5. Multivariate Cox Proportional Hazards Model Survival Analysis

Variable*	Adjusted Hazard Ratio (95% CI)	*P*
No vertebral fracture	Reference	
Vertebral fracture (binary)	3.7 (1.02-13.7)	.047
Mild fracture	3.5 (0.9-13)	.065
Moderate–severe fracture	4.9 (1.1-22)	.037
Single fracture	3 (0.5-19.3)	.248
Multiple fractures	3.8 (1-14.2)	.044
Renal disease	9.6 (3.8-24.6)	<.001
Malignancy	10.3 (4-26.6)	<.001
Cardiovascular disease	1.3 (0.6-3.2)	.512
CT detectable pneumonia	1.8 (0.6-5.5)	.338
Type 2 diabetes mellitus	1.5 (0.6-4.1)	.392
Hypertension	0.8 (0.3-2)	.614

CT, computed tomography.

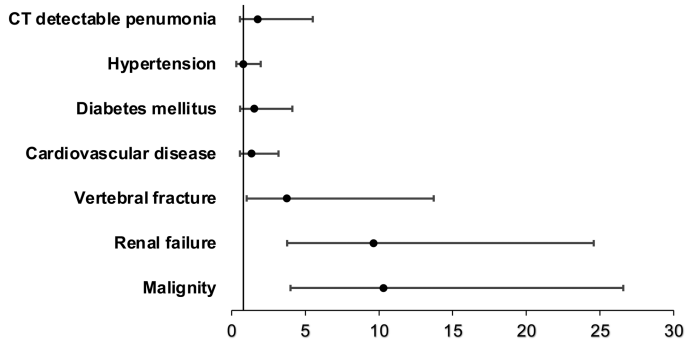

Figure 3. Forest plot of predictors of mortality included in multivariate Cox proportional hazard model.

and 114 patients with COVID-19, the prevalence was 32% and 36%, respectively.[25,30] In another study involving 239 patients with COVID-19 assessed through chest CT, the prevalence of vertebral fractures was found to be 22%.[24] These results suggested that the risk of VFs in patients with COVID-19., at minimum, corresponds to a high risk of VFs in the general population. In the present study, the prevalence of VFs in patients with COVID-19. was 71%, exceedingly higher than previously reported. It is important to emphasize that the previous studies assessed VF frequency using x-ray radiographs or CT scans only on patients with signs and symptoms of pneumonia. As part of our center's policy during the first wave of the pandemic, on the other hand, thorax CT scans were routinely performed on all patients who presented to the emergency department with suspected COVID-19, irrespective of the signs or symptoms of pneumonia. The higher frequency of VFs in COVID-19 patients in this study compared to previous reports might be partly ascribed to a lower threshold for CT scans, resulting in the evaluation of VFs in unselected and larger cohorts using a more sensitive method.

The high prevalence of VFs and their effects on prognosis in subjects diagnosed with COVID-19 raised the question of whether the relationship between COVID-19 and VF is causal or coincidental. The incidental detection of VF during the diagnosis of COVID-19 and the lack of VF information from before the diagnosis of COVID-19 hinders us from making definitive conclusions on this matter. It is known that VF can lead to restrictive pulmonary dysfunction, increasing the risk of pneumonia.[31-34] Therefore, patients with VF might have been more susceptible to COVID-19 due to background restrictive lung disease and impaired pulmonary function, explaining its high prevalence. In this study, the severity of CT-detectable pneumonia increased with the increasing number and severity of VFs. The need for invasive mechanical ventilation and duration of hospitalization due to COVID-19 pneumonia was also increased in the VF group compared to the no-VF group. These findings might lend further support for the negative effects of VFs on pulmonary functions, supporting the notion that the presence of VFs might confer an increased risk of COVID-19.

In this study, COVID-19 patients with VFs were older than patients without VFs, and type 2 diabetes mellitus, hypertension, and cardiovascular disease were more prevalent in patients with VFs. This finding aligns with a large body of literature showing advanced age and cardiovascular comorbidities as predisposing factors for osteoporotic fractures.[26-28] It is well acknowledged that advanced age, type 2 diabetes mellitus, and cardiovascular disease also increase susceptibility to COVID-19. The shared predisposing factors between

VF and COVID-19 might provide another explanation for the high prevalence of VFs in COVID-19 patients. Since VFs are associated with cardiovascular comorbidities and may increase the risk of infection through impairing pulmonary functions, it can be speculated that VFs could be a composite measure of cardiorespiratory risk in affected patients.

The limitations of our study include the retrospective nature, which restricts our ability to evaluate the timing of VFs and does not allow us to draw firm conclusions on the causal link between VFs and mortality. We did not have information on a prior diagnosis of osteoporosis, duration and dose of glucocorticoid use for COVID-19 pneumonia, influence of osteoporosis treatment on studied outcomes, and CT-based bone density. The inclusion of a matched control group in terms of age, gender, and comorbidities would provide clearer insights into how VFs specifically affect mortality rates. Considering the potential effect of VF management on survival, future prospective studies with matched control groups and larger sample sizes will provide more robust evidence regarding the impact of vertebral fractures on mortality. On the other hand, we used CT scans, known for their higher accuracy compared to plain x-ray radiographs, to assess VFs. The VFs were systematically evaluated in a large cohort of unselected COVID-19 patients consecutively admitted to the Emergency Department, thereby minimizing selection biases. Notably, the present study provided the first piece of evidence on the impact of VF on the long-term mortality of patients diagnosed with COVID-19.

Vertebral fractures were one of the most common comorbidities in patients with COVID-19. It also appears to represent a potential marker of frailty and poor prognosis. Our results highlight the importance of VF assessment in every individual who undergoes a CT scan due to COVID-19 pneumonia.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul University-Cerrahpaşa (approval number: 145928; date: November 5, 2020).

Informed Consent: Verbal and written informed consent was obtained from the patients who agreed to take part in the study.

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