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Clinical Research Article

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Radiological Thoracic Vertebral Fractures are Highly Prevalent in COVID-19 and Predict Disease Outcomes

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CAD, coronary artery disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ED, Emergency Department; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; LDH, lactate dehydrogenase; NIMV, noninvasive mechanical ventilation; PaO2/FiO2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; RT-PCR, real-time reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; VF, vertebral fracture.

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Abstract

Context and Objective: COVID-19 has become the most relevant medical issue globally. Despite several studies that have investigated clinical characteristics of COVID-19 patients, no data have been reported on the prevalence of vertebral fractures (VFs). Since VFs may influence cardiorespiratory function and disease outcomes, the aim of this study was to assess VFs prevalence and clinical impact in COVID-19.

Design and Patients: This was a retrospective cohort study performed at San Raffaele Hospital, a tertiary health care hospital in Italy. We included COVID-19 patients for whom lateral chest x-rays at emergency department were available. VFs were detected using a semiquantitative evaluation of vertebral shape on chest x-rays.

Results: A total of 114 patients were included in this study and thoracic VFs were detected in 41 patients (36%). Patients with VFs were older and more frequently affected by hypertension and coronary artery disease ($P < 0.001$, $P = 0.007$, $P = 0.034$; respectively). Thirty-six (88%) patients in VFs+ group compared to 54 (74%) in VFs– group were hospitalized ($P = 0.08$). Patients with VFs more frequently required noninvasive mechanical ventilation compared with those without VFs ($P = 0.02$). Mortality was 22% in VFs+ group and 10% in VFs– group ($P = 0.07$). In particular, mortality was higher in patients with severe VFs compared with those with moderate and mild VFs ($P = 0.04$).

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Conclusions: VFs may integrate the cardiorespiratory risk of COVID-19 patients, being a useful and easy to measure clinical marker of fragility and poor prognosis. We suggest that morphometric thoracic vertebral evaluation should be performed in all suspected COVID-19 patients undergoing chest x-rays.

Key Words: vertebral fractures, COVID-19, osteoporosis, SARS-CoV-2, bone metabolism

Coronavirus disease 2019 (COVID-19) is a pandemic respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was newly recognized first in China and then spread globally (1). The clinical spectrum of COVID-19 manifestations widely ranges from asymptomatic to severe forms. Mild manifestations with favorable prognosis are present in most patients (1, 2). However, particularly in elderly patients with several comorbidities, SARS-CoV-2 infection may be complicated by acute respiratory distress syndrome with a high risk of death (1, 2).

Different studies have so far investigated clinical and laboratory characteristics of COVID-19 patients, including inflammatory and organ injury biomarkers and patient comorbidities (1, 2). Among these, high prevalence of hypertension, diabetes mellitus, and obesity have been reported, with negative impact on prognosis (1, 2).

Osteoporosis is well recognized as one of the major health issues worldwide, being a systemic skeletal disorder characterized by loss in bone strength and altered skeletal microarchitecture leading to an increased risk of vertebral and hip fractures (3). Hospitalized COVID-19 patients are characterized by the presence of multiple predisposing factors to bone fragility with high risk of fractures (3-6), such as high levels of pro-inflammatory cytokines, high rate of hypocalcemia, and advanced age, as well as several comorbidities such as diabetes mellitus, and treatments with high dose of glucocorticoid therapy associated with prolonged immobilization and loss of muscle mass (1, 2, 7-12). Moreover, other authors have hypothesized a possible increase in risk of fragility fractures and related mortality after the COVID-19 pandemic due to the strain on the health system during the emergency, with consequent interruption of adequate care for the patient with chronic diseases (7, 13-15). However, beyond these expert opinions no real data are yet available on the hard clinical endpoint of bone fragility, ie, fracture rates, in hospitalized COVID-19 patients.

Vertebral fractures (VFs) are one of the most relevant clinical manifestations of skeletal fragility and are associated with decreased survival and impaired quality of life in the general population (16, 17). Moreover, VFs negatively influence respiratory function of affected patients, decreasing pulmonary vital capacity and leading to a restrictive pulmonary dysfunction (18, 19).

Since only about one-third of VFs are actually clinically diagnosed using the historical (anamnestic questionnaire-based) approach, radiological and morphometric approaches have emerged as the gold standard to assess the true prevalence and incidence of VFs in the general population and high-risk patients (20, 21). Interestingly, morphometric VFs can be detected also on lateral chest x-rays (21, 22).

To date, no previous data have been reported on VF prevalence in patients affected either by COVID-19 or by other coronavirus diseases, such as SARS, MERS, and Ebola. The aim of this study was to investigate VFs in COVID-19 patients on lateral chest x-rays performed at admission in the Emergency Department (ED), and to evaluate their possible influence on clinical outcomes in these patients.

Patients and Methods

Study design and patients

This retrospective cohort study was part of the COVID-BioB study, which was a large observational investigational study performed at San Raffaele University Hospital, a tertiary health care hospital in Milan, Italy. The study protocol was approved by the Hospital Ethics Committee (protocol no. 34/int/2020).

We included only patients aged ≥18 years with a confirmed diagnosis of COVID-19 who were admitted to our ED. Confirmed COVID-19 was defined as positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasal and/or throat swab together with signs, symptoms, and radiological findings suggestive of COVID-19 pneumonia. Patients admitted for other diseases and subsequently diagnosed with superimposed SARS-CoV-2 infection, as well as patients acutely treated with glucocorticoids before hospitalization for their pulmonary condition, were excluded. We included in our evaluation only patients for whom lateral chest x-rays at ED admission were available. Only lateral chest x-rays that allowed a high-quality assessment were used for the analyses, excluding exams in which pneumonia opacities or low quality-images due to patient intrinsic characteristics (positions and severe scoliosis) prevented a correct evaluation. In particular, we used only x-rays in which all

the thoracic tract of T4 to T12 vertebrae was well viewable and assessable.

Data collection

Data were collected from medical chart review or directly by patient interview and entered in a dedicated electronic case record form (eCRF) specifically developed for the COVID-BioB study, evaluated and approved by Hospital Ethics Committee. Prior to the analysis, data were cross-checked with medical charts and verified by data managers and clinicians for accuracy. The following variables were collected: age; gender; comorbidities (identified in medical history by patient or caregivers or referred to in previous medical documentation, including history of hypertension, diabetes mellitus, coronary artery disease (CAD), chronic kidney disease, osteoporosis, active neoplasms, and severe neurological disabilities); body mass index (BMI, calculated as the ratio of weight in kilograms (kg) divided by height in squared meters); PaO2/FiO2 (calculated as the ratio between the arterial partial pressure of oxygen measured on arterial blood gas test and the fraction of inspired oxygen); ionized serum calcium (measured on arterial blood gas test); estimated glomerular filtration rate (eGFR, as estimated by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation and expressed as mL/min/L·73m^2); lactate dehydrogenase (LDH, U/L); and high-sensitivity C-reactive protein (CRP, mg/L); treatments on ED admission; and clinical outcome (discharge from ED or hospital ward, admission to intensive care unit [ICU] during hospital stay, hospital length of stay, needs for noninvasive mechanical ventilation, and death).

VF assessment

Thoracic VFs were detected on lateral chest x-rays using a qualitative and semiquantitative assessment and evaluation of vertebral shape (21, 22). Using a translucent digitizer and a cursor, 6 points were marked on each vertebral body to describe vertebral shape. Anterior, middle, and posterior vertebral heights were measured, and height ratios (anterior/posterior, middle/posterior) were calculated for each vertebral body from T4 to T12. According to the semiquantitative score method initially proposed by Genant et al (23), fractures were defined as mild, moderate, and severe based on height ratio decreases of 20% to 25%, 25% to 40%, and up to 40%, respectively. Two experienced physicians (M.D., L.D.F.) were blinded to the underlying diagnosis and were then asked to perform the analyses. They also visually assessed VFs (which had to be concordantly assigned by the 2 physicians) and the superior and inferior endplate of the vertebral bodies to exclude artifacts and overestimation of VFs (24, 25).

The Black algorithm was applied to confirm morphometric diagnosis of VFs. To this end, the height ratios in each examined vertebra were used to calculate a fracture threshold (26, 27), and the fracture threshold was calculated as 85% of the arithmetical mean of anterior/posterior height ratio (26, 27).

The interobserver agreement between the 2 physicians for the identification of vertebral fractures was analyzed using the kappa score, ranging from 0 (no agreement) to 1 (complete agreement) where values lower than 0.6 were considered moderate and those greater than 0.8 strong agreement.

Statistical analysis

Descriptive statistics were obtained for all study variables. Continuous variables were expressed as medians [25th to 75th percentile]. Categorical variables were summarized as counts and percentages. Categorical variables were compared by using the Fisher exact test or $\chi 2$ test, and continuous variables were compared using the Mann-Whitney U test. All statistical tests were 2-sided. A P value of < 0.05 was considered statistically significant. Statistical analysis was conducted using IBM SPSS Statistics (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY).

Results

A total of 114 COVID-19 patients with evaluable lateral chest x-rays were included in the study. Approximately three-quarters of patients were male (74.6%), and the median age was 57 (51-71) years. Patient characteristics upon admission at ED are summarized in Table 1.

In our population, the main comorbities were history of arterial hypertension (39.5%), followed by CAD (12.3%), diabetes mellitus (10.5%) and chronic kidney disease (9.6%). Osteoporosis was previously diagnosed in only 3 patients (2.8%). Five patients (4.4%) were on chronic glucocorticoid medication, 4 (3.5%) on vitamin D supplements and 1 (0.9%) on bisphosphonate therapy.

Ninety patients (78.9%) were hospitalized after initial evaluation in ED, and 13 of these (11.6%) were admitted to the ICU during hospitalization, while 16 (14.5%) patients died.

Thoracic VFs on lateral chest x-rays at ED admission were detected in 41 patients (36%) (Fig. 1). A total of 65 VFs were detected; according to Genant classification, 39 of these (60%) were classified as mild, 21 (33.3%) as moderate, and 5 (7.7%) as severe (Figs 1 and 2; Table 2)

Table 1. Baseline Characteristics of Patients With COVID-19: Demographic Information, Comorbidities, and Clinical and Laboratory Parameters at Hospital Admission of COVID-19 Patients Cohort Included in the Study

Baseline Characteristics of Patients With COVID-19	
	No. (%)
Demographic information	
Total No.	141
Age, median (IQR), yrs	57 (51-71)
Gender	
Female	29 (25.4%)
Male	85 (74.6%)
BMI, median (IQR), kg/m^2	26 (23-38)
Comorbidities	
Total No.	114
Hypertension	45 (39.5%)
Coronary artery disease	14 (12.3%)
Diabetes	
Type 1	1 (0.9%)
Type 2	11 (9.6%)
Chronic Kidney Disease	11 (9.6%)
Cancer[a]	7 (6.1%)
Osteoporosis	3 (2.8%)
Severe neurological disabilities	0 (0%)
Clinical and laboratory parameters at admission	
SpO2, %	96 (94-98)
PaO2/FiO2 ratio	324 (284-352)
Tympanic temperature, °C	38 (37.3-38.7)
Ionized calcium, median (IQR), mmol/L	1.1 (1.06-1.15)
eGFR, median (IQR), mL/min/1.73m^2	74.9 (60.3-91.1)
LDH, median (IQR), U/L	302 (238-379)
CRP, median (IQR), mg/L	44.8 (16.1-80.8)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate, calculated using the CKD-EPI equation; IQR, interquartile range; LDH, lactate dehydrogenase; PaO2/FiO2 ratio, ratio between the arterial partial pressure of oxygen measured on arterial blood gas analysis and the fraction of inspired oxygen; SpO2, peripheral oxygen saturation.

[a] Only active neoplasms were included reported

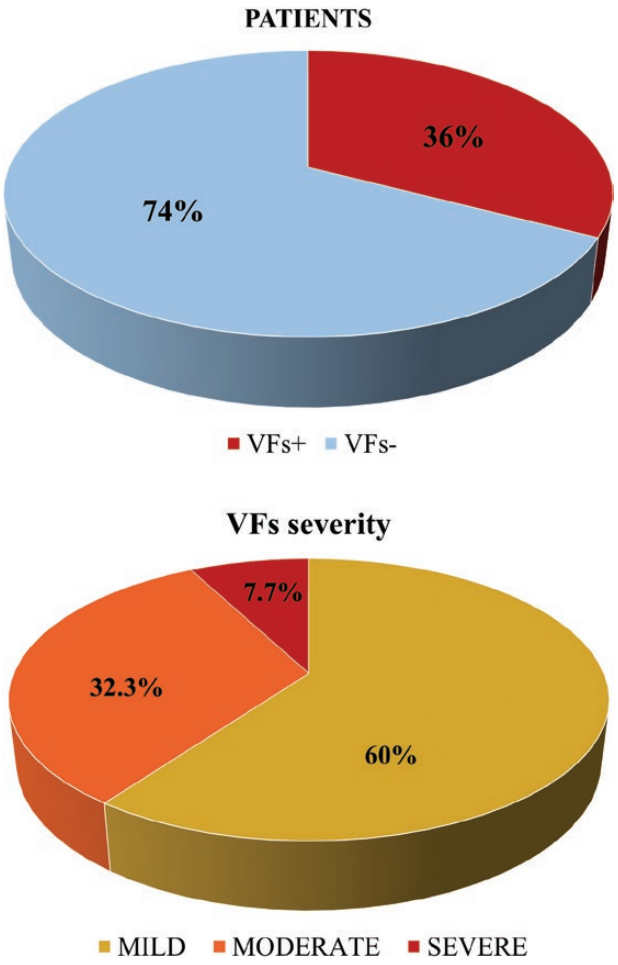

Figure 1. a) Prevalence and b) distribution by severity degree of vertebral fractures in our 114 studied COVID-19 patients.

Average height ratio and average fracture threshold, according to the Black algorithm, were 0.931 and 0.791, respectively (Table 2). Therefore, the number of vertebral fractures detected applying this algorithm was the same detected by the semiquantitative method of Genant.

There were 28/41 (70.7%) patients with at least one mild vertebral fracture, 18/41 (43.9%) with at least one moderate, and 5/41 (12.2%) with at least one severe. In 19 of 41 (46.3%) fractured patients, multiple VFs were detected. Among these 19 patients, we found 6 (31.6%) patients with 2 mild VFs, 1 (5.3%) patient with 3 mild VFs, and 2 (10.5%) patients with 2 moderate VFs. In 7 (36.8%) patients, both mild and moderate VFs and in 3 (15.8%) both moderate and severe VFs were found; thus, in order to evaluate impact of VFs on outcomes, those with both mild and moderate VFs were assigned to the "moderate" group and those with both moderate and severe fractures were assigned to the "severe" group.

The interobserver agreement between the 2 physicians for the identification of mild, moderate, and severe vertebral fractures was k = 0.84, k = 0.87, and k = 1, respectively. No differences were found between VFs+ and VFs– group with respect to sex distribution, BMI, or clinical and biochemical parameters evaluated in the ED (Table 3). Regarding the prevalence of comorbidities, arterial hypertension and CAD were found statistically more frequently in VFs+ group (arterial hypertension: VFs+ 56% vs VFs– 30%, $P = 0.007$; CAD: VFs+ 22% vs VFs– 7%, $P = 0.034$). VFs+ patients were also older compared to VFs– (VFs+: 68 [55.5-76] years vs VF–: 54 [48-64] years, $P < 0.001$) (Fig. 3; Table 3).

Serum ionized calcium analysis from arterial blood gas tests performed in the ED was collected in 78 patients; hypocalcemia, defined as a calcium value below 1.18 mmol/L, was found in 60 patients (87.2%). No

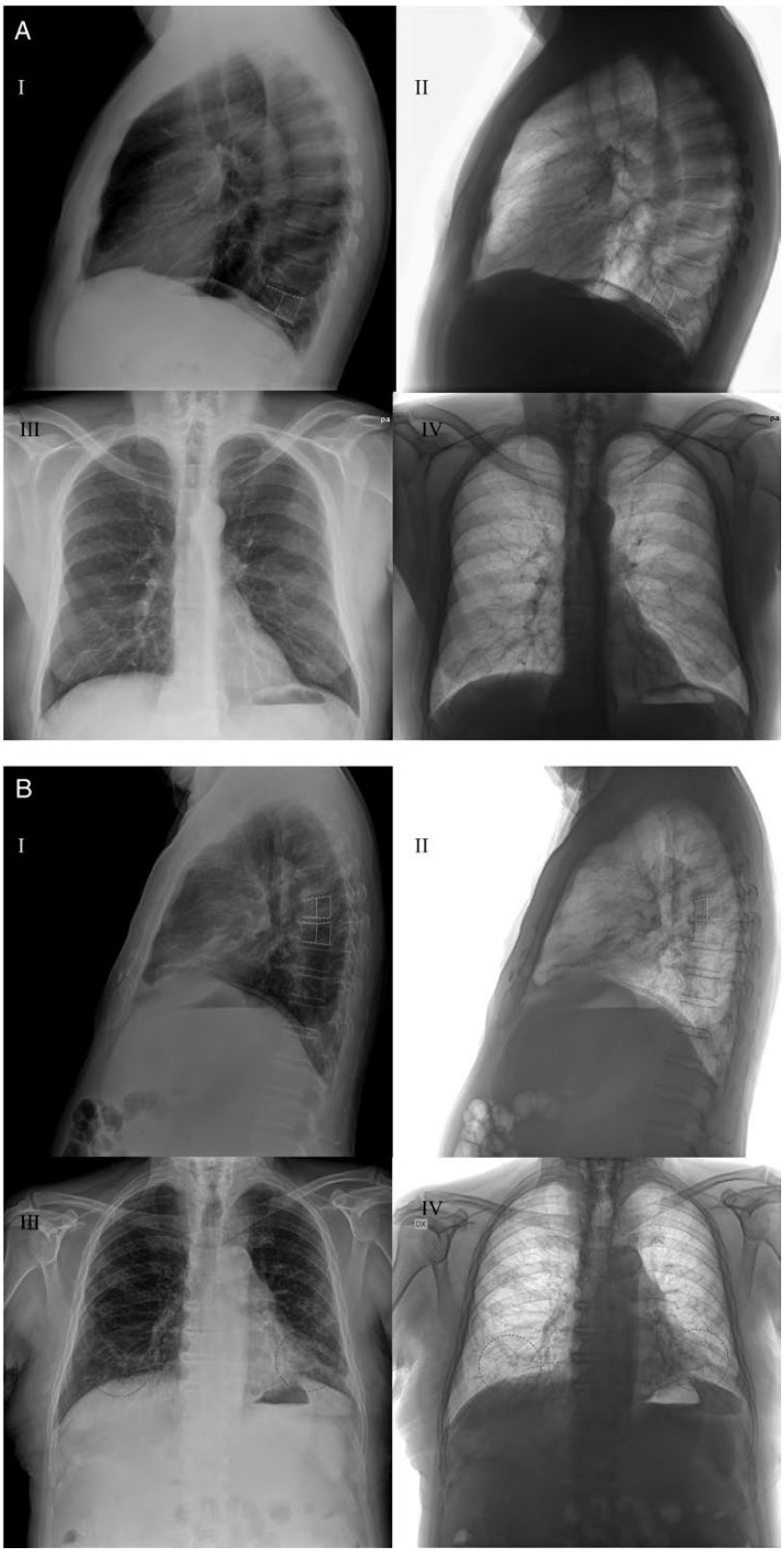

Figure 2. Semiquantitative vertebral evaluation performed in 4 representative patients on lateral chest x-rays. For every patient are reported two lateral view images on which morphometric VFs were assessed, one in typical mode ("bone white") (I) and one in inverted gray-scale mode ("bone black") (II), as well as typical (III) and inverted (IV) frontal view images showing COVID-19 radiologic signs. Frontal views imaging are also included to document COVID-19 radiologic signs. The fractured vertebrae are reported with superimposed measurement markers. a) In lateral chest x-rays it is possible to identify a T11 mild VF with a height ratio decrease of 22% using posterior and anterior vertebral heights. In frontal view no COVID-19 pneumonia signs were present. b) In lateral chest x-rays it is possible to identify a T6 moderate VF with a height ratio decrease of 27% and a T7 mild VF with a height ratio decrease of 21%, using posterior and anterior vertebral heights. In frontal view it is possible to see bilateral

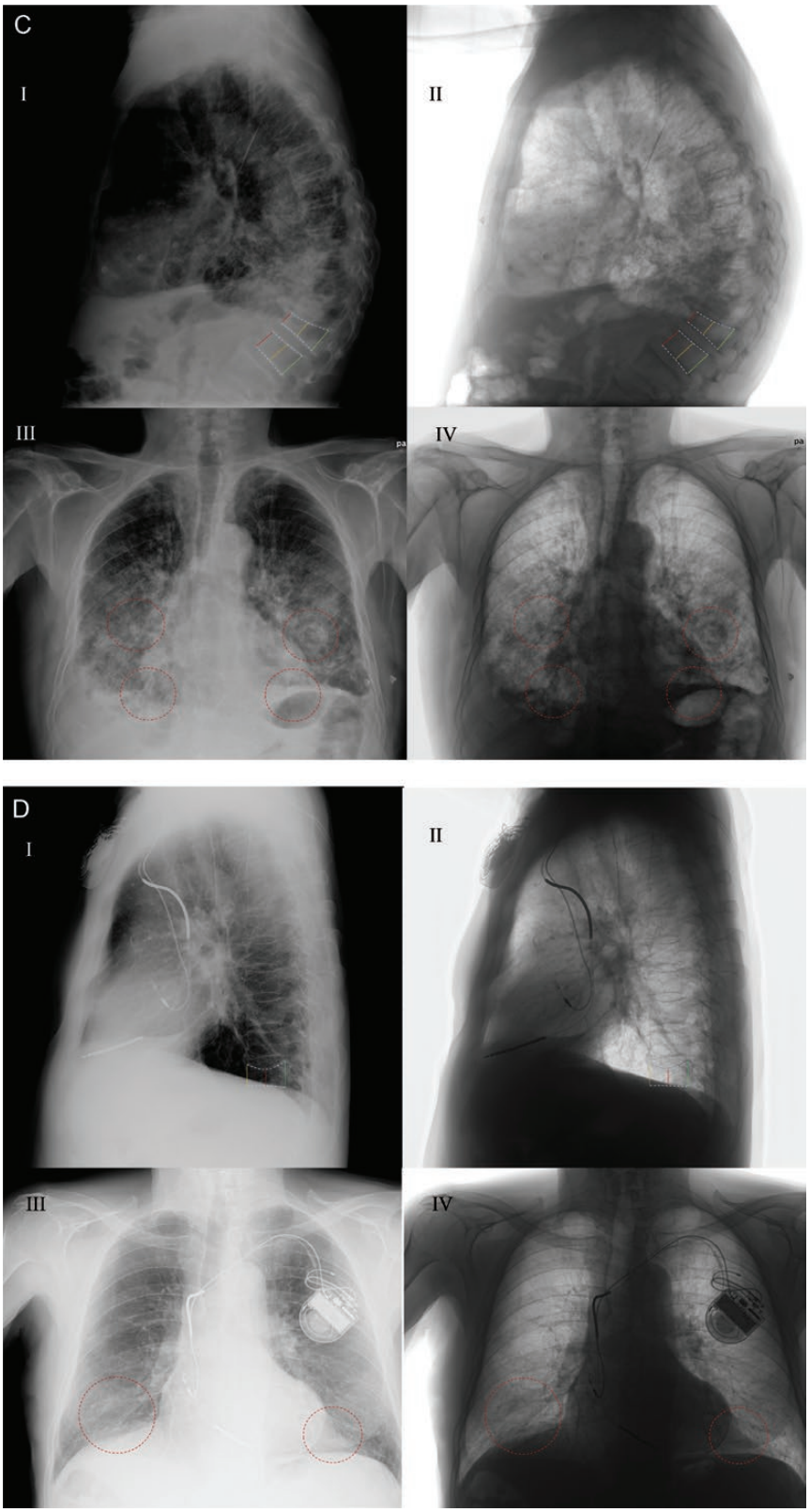

Figure 2. (Continued). ground-glass opacities related to COVID-19 infection. c) In lateral chest x-rays it is possible to identify a T11 severe VF with a height ratio decrease of 55% and a T12 moderate VF with a height ratio decrease of 34%, using posterior and anterior vertebral heights. In frontal view is possible to see bilateral ground-glass opacities and lung consolidations related to COVID-19 infection. d) In lateral chest x-rays it is possible to identify a T12 severe VF with a height ratio decrease of 42% using posterior and middle vertebral heights. In frontal view is possible to see slight bilateral ground-glass opacities related to COVID-19 infection.

Table 2. Site and Severity of Vertebral Fractures Detected

	VFs Localization and Severity					
Level	**Total, n (%)**	**Mild n (%)**	**Moderate, n (%)**	**Severe, n (%)**	**Average A/P ratios**	**Fracture thresholds**
T4	0	0	0	0	0.936	0.795
T5	0	0	0	0	0.934	0.794
T6	3 (4.6)	1 (2.5)	2 (9.5)	0	0.928	0.788
T7	14 (21.5)	9 (23)	5 (23.8)	0	0.931	0.791
T8	10 (15.4)	7 (17.9)	3 (14.3)	0	0.919	0.781
T9	10 (15.4)	8 (20.5)	2 (9.5)	0	0.930	0.79
T10	7 (10.7)	3 (7.8)	3 (14.4)	1 (20)	0.935	0.795
T11	11 (17)	5 (12.9)	4 (19)	1 (20)	0.933	0.793
T12	10 (15.4)	6 (15.4)	2 (9.5)	3 (60)	0.934	0.794
Total	65 (100)	39 (100)	21 (100)	5 (100)	0.931	0.791

Abbreviations: VFs, vertebral fractures; AP, anterior/posterior

Table 3. Demographic Information, Comorbidities, and Clinical and Laboratory Parameters Differences Between COVID-19 Patients With and Without VFs

	VFs+ group (n=41)	**VFs– group (n=73)**	***P* Value**
Age, median (IQR), yrs	64 (55-76)	54 (48-64)	$P < 0.001$
Gender			
Female	11 (27%)	18 (25%)	$P = 0.79$
Male	30 (73%)	55 (75%)	
BMI, median (IQR), kg/m^2	26 (23.5–28)	26 (23–28.5)	$P = 0.57$
Hypertension	23 (56%)	22 (30.1%)	$P = 0.007$
Coronary artery disease	9 (22%)	5 (6.8%)	$P = 0.018$
Diabetes	5 (12.2%)	7 (9.5%)	$P = 0.66$
Chronic Kidney Disease	5 (12.2%)	6 (8.3%)	$P = 0.49$
Cancer[a]	2 (4.9%)	5 (6.8%)	$P = 1$
Osteoporosis	1 (2.4%)	2 (2.7%)	$P = 1$
SpO2, %	96 (94-97.7)	96 (95-98)	$P = 0.29$
PaO2/FiO2 ratio	314 (261-355)	324 (295-352)	$P = 0.33$
Tympanic temperature, °C	38.1 (37-38.5)	38 (37.5-38.8)	$P = 0.9$
Ionized calcium, median (IQR), mmol/L	1.1 (1.08-1.15)	1.09 (1.04-1.14)	$P = 0.16$
Hypocalcemia	27/32 (84%)	41/46 (89%)	$P = 0.54$
eGFR, median (IQR), mL/min/1.73m^2	71.5 (58.6-88.9)	76.9 (60.3-91.6)	$P = 0.43$
LDH, median (IQR), U/L	359 (257-411)	289 (222-357)	$P = 0.05$
CRP, median (IQR), mg/L	36.6 (15.2-84.7)	46 (16.4-73.5)	$P = 0.77$

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate calculated using the CKD-EPI equation; IQR, interquartile range; LDH, lactate dehydrogenase; PaO2/FiO2 ratio, ratio between the arterial partial pressure of oxygen measured on arterial blood gas analysis and the fraction of inspired oxygen; SpO2, peripheral oxygen saturation; VFs, vertebral fractures.
[a] Only active neoplasms were included in this reported.

significant differences were found between VFs+ and VFs– group in ionized calcium levels and rate of hypocalcemia ($P = 0.16$, $P = 0.54$; respectively) (Table 3).

In univariate analysis, the variables statistically significant associated with VFs were age, hypertension, and cardiovascular disease (OR 1.05, 95% confidence interval [CI] [1.02-1.09], $P < 0.001$; OR 2.96, 95% CI [1.34-6.55], $P = 0.007$; OR 3.82, 95% CI [1.19-12.34], $P = 0.025$; respectively) but in multivariate only age resulted statistically significant (OR 1.04, 95% CI [1.003-1.08], $P < 0.001$) (Table 4).

Thirty-six (88%) patients in the VFs+ group compared with 54 (74%) patients in the VFs– group were hospitalized ($P = 0.08$) (Table 5). Four (11%) patients in the VFs+ group and 9 (12.5%) patients in the VFs– group were admitted to the ICU during hospitalization ($P = 0.76$) (Table 5). Patients with VFs more frequently required noninvasive mechanical ventilation (NIMV) compared to those without VFs

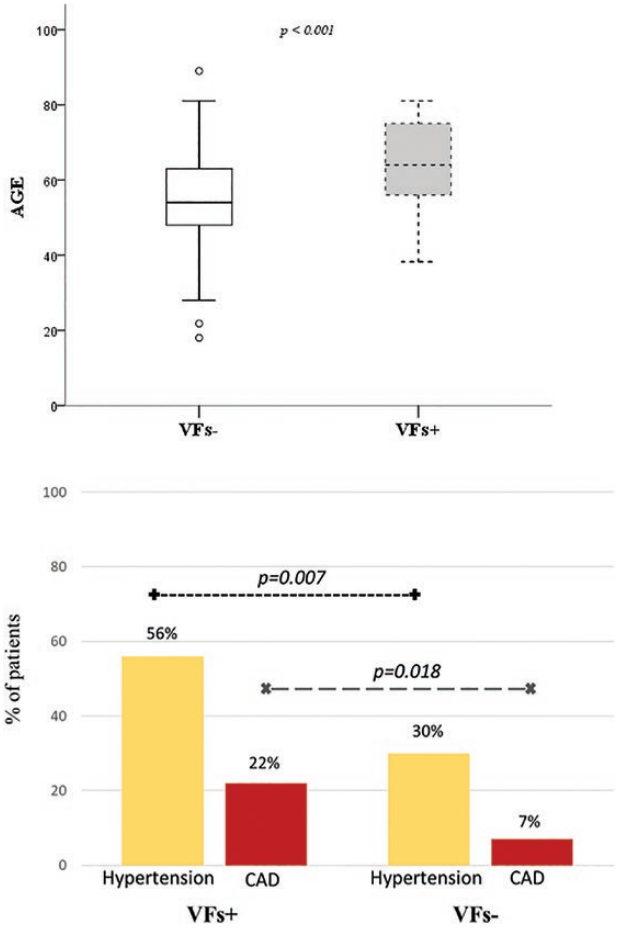

Figure 3. Comparison of A age and B hypertension, and coronary artery disease between patients with and without vertebral fractures. Patients with VFs were older and more frequently affected by hypertension and coronary artery disease compared to those without fractures. Abbreviations: VFs, vertebral fractures; CAD, coronary artery disease.

(48.8% vs 27.4%, $P = 0.02$) (Table 5). No differences were found about hospital length of stay (Table 5). Mortality was 22% in the VFs+ group and 10% in the VFs– group ($P = 0.07$) (Table 5). In particular, mortality was statistically higher in patients with severe VFs compared to those with moderate and mild VFs (60%, 7%, 24% in severe, moderate, and mild VFs group, respectively, $P = 0.04$), despite no statistically significant differences regarding clinical and laboratory characteristics found among these 3 groups (Tables 5 and 6).

Discussion

To the best of our knowledge, this is the first study assessing the presence and the clinical impact of VFs in COVID-19 patients. We found that VFs were highly prevalent in our study population, as up to 36% of patients presented a vertebral deformity, although only 3% had a previous

Table 4. Univariate and Multivariate Analysis of Predictive Factors for Vertebral Fractures in Patients With COVID-19.

Univariate Analysis of Predictive Factors for Vertebral Fractures		
Variables	**Odds Ratio [95% Confidence Interval]**	***P* Value**
Age	1.05 [1.02-1.09]	$P < 0.001$
Male gender	1.12 [0.47-2.68]	$P = 0.79$
BMI	1.03 [0.93-1.14]	$P = 0.53$
Hypertension	2.96 [1.34-6.55]	$P = 0.007$
Coronary artery disease	3.82 [1.19-12.34]	$P = 0.025$
Diabetes	1.31 [0.38-4.42]	$P = 0.66$
Chronic kidney disease	1.55 [0.44-5.43]	$P = 0.49$
Cancer	0.7 [0.13-3.8]	$P = 0.67$
Multivariate analysis of predictive factors for Vertebral Fractures		
Variables[a]	**Odds ratio [95% confidence interval]**	***P* Value**
Age	1.04 [1.003-1.08]	$P < 0.001$
Hypertension	1.39 [0.52-3.76]	$P = 0.51$
Coronary artery disease	1.83 [0.5-6.75]	$P = 0.36$

[a]Only variables statistically significant in univariate analyses were included in multivariate analyses;

diagnosis of osteoporosis reported in their past medical history.

Vertebral fracture prevalence detected in our study population was much higher as compared with epidemiological data reported in previous studies on general populations, despite the fact that only the thoracic tract was evaluated.

In recent studies evaluating European women aged 50 years and over, the incidence of new VFs was reported in 10.7/1000 person-years and prevalence of morphometric VFs ranged from 18% to 26% (28, 29). Although osteoporosis is typically identified as a health issue only in postmenopausal women, we have found a high prevalence of VFs also in male patients. VFs were detected in 35% of COVID-19 male patients and in 37% of female patients, without any significant difference related to gender in prevalence of VFs. To date, underdiagnosis of osteoporosis and VFs in male patients remains a critical medical issue, despite recent evidence with several reports of significant data regarding this topic. The European Vertebral Osteoporosis Study revealed that 8% to 20% of men aged 50 to 79 years had at least one VF, and in the United States the incidence of VFs in osteoporotic men had been estimated to be 15.3 and 33.4 per 100 000 person-years in patients aged 65 to 74 years and >75 years, respectively (30, 31). Nevertheless, the impact of VFs in our COVID-19 population seems to exceed

Table 5. Clinical Outcomes In (a) Patients With vs Without Vertebral Fractures and (b) According to Severity of Fractures

a) Clinical outcomes in patients with or without vertebral fractures			
	VFs+ group (41)	**VFs– group (73)**	***P* Value**
Hospitalization	36 (87.8%)	54 (73.9%)	$P = 0.08$
Length of stay, days	15 [8.7-33.5]	12 [7-22.5]	$P = 0.26$
ICU admission	4 (9.7%)	9 (12.3%)	$P = 0.77$
NIMV requirement	20 (48.8%)	20 (27.4%)	$P = 0.02$
Mortality	9 (22%)	7 (9.6%)	$P = 0.07$
b) Clinical outcomes according to the degree of fracture severity			
Hospitalization			
Mild (21)	20 (95%)		$P = 0.33$
Moderate (15)	12 (80%)		
Severe (5)	4 (80%)		
ICU admission			
Mild (21)	3 (14.3%)		$P = 0.52$
Moderate (15)	1 (6.6%)		
Severe (5)	0 (0%)		
NIMV requirement			$P = 0.6$
Mild (21)	11 (52.4%)		
Moderate (15)	6 (40%)		
Severe (5)	3 (60%)		
Mortality			
Mild (21)	5 (23.8%)		$P = 0.04$
Moderate (15)	1 (6.6%)		
Severe (5)	3 (60%)		

P values reported in bold are statistically significant.
Abbreviations: ICU, intensive care unit; NIMV, noninvasive mechanical ventilation; VFs, vertebral fractures.

that expected in the general population, particularly the male population, beyond this previously reported issue of underdiagnosis. Nevertheless, the complete agreement of VF detection based on the Black algorithm and the Genant method, which was previously reported (27), does not seem to support the hypothesis of a methodological issue potentially leading to overestimation of (mild) VFs due to false positives in our study.

In fact, there is also an increasing number of pathological conditions known to cause secondary osteoporosis and fragility fractures similarly in women and men, including long-term corticosteroid therapy, active acromegaly, and type 1 and type 2 diabetes mellitus (32-37). The high prevalence of thoracic VFs in our severe COVID-19 patients first admitted to the ED and successively hospitalized could be explained by possible VF influence on respiratory function of affected patients (although an objective measure of the degree of kyphosis was not available). It has been previously reported that prevalent VFs with decreased bone mineral density (BMD) are associated with an increased risk of pneumonia and impaired respiratory function including restrictive pulmonary dysfunction, decrease in vital capacity, FEV1 (forced expiratory volume in the first second), and inspiratory time in patients without previous pulmonary diseases (18, 19, 38, 39).

Not surprisingly, in our cohort, hypertension and CAD were found to be more prevalent in patients with VFs. Besides the possible impact of older age on this association, over the recent years, there has been growing evidence to suggest the existence of close correlation between hypertension, cardiac and vascular disease, and skeletal fragility. Recent findings showed an association between cardiovascular disease (CAD, cerebrovascular disease, peripheral atherosclerosis, heart failure) and high Framingham risk score with lower BMD and major osteoporotic fracture incidence in men and women (40-43). Mechanistically, osteoprotegerin, expressed in endothelial cells with a pivotal role in vascular calcification and osteoporosis, may be associated with vascular dysfunction promoting leukocyte adhesion to endothelial cells by inducing expression of VCAM-1, ICAM-1, and E-selectin (44, 45).

In our study, the overall mortality rate was found to be doubled although not statistically different in patients with vs without VFs. However, we found it to be significantly higher in patients with severe VFs as compared to those with mild and moderate VFs without significant differences in age distribution between groups, although fractured patients as a whole were older than not fractured subjects. NIMV requirement was found to be statistically higher in patients with vs without VFs, confirming the possible negative influence of VFs on respiratory function, although no significant differences were found regarding hospitalization or ICU admission in patients with and without VFs.

Our findings are consistent with previous literature that identified an association between VFs and increased mortality, findings not only explained by advanced age, general health, and concurrent chronic diseases (17, 46-48). Therefore, due to the relationship between older age (which was associated with VFs in multivariate analysis although not correlated with fracture severity), presence of cardiovascular disease and osteoporosis, and the negative influence of VFs on respiratory function, our data are consistent with the concept that VFs and their severity can be an objective clinical marker of frailty and negative prognosis in patients with COVID-19. Moreover, since the high prevalence of VFs in our patients may be associated with poor health status and in turn underlie the higher risk and severity of COVID-19,

Table 6. Comparison Between Fractured Patients According to Severity of Fractures. Demographic Information, Comorbidities, and Clinical and Laboratory in Between COVID-19 Patients With Mild, Moderate, and Severe VFs

	Mild (21)	Moderate (15)	Severe (5)	*P* Value
Age, median (IQR), yrs	63 (55-73)	61 (56-77)	77 (59-80)	*P* = 0.38
Gender				
Female	8 (38%)	3 (20%)	0 (0%)	*P* = 0.17
Male	13 (62%)	12 (80%)	5 (100%)	
BMI, median (IQR), kg/m^2	25 (23-27)	27 (24-33)	28 (25-28)	*P* = 0.15
Hypertension	9 (42.8%)	11 (73.3%)	3 (60%)	*P* = 0.19
Coronary artery disease	2 (9.5%)	4 (26.7%)	3 (60%)	*P* = 0.05
Diabetes	4 (19%)	1 (6.7%)	0 (0%)	*P* = 0.36
Chronic kidney disease	2 (9.5%)	2 (13.3%)	1 (20%)	P = 0.8
Cancer[a]	2 (9.5%)	0 (0%)	0 (0%)	*P* = 0.37
Osteoporosis	0 (0%)	1 (6.6%)	0 (0%)	*P* = 0.4
SpO2, %	96 (94-97.7)	97 (94-98)	96 (93-97)	*P* = 0.96
PaO2/FiO2 ratio	303 (273-341)	333 (224-372)	333 (251-352)	*P* = 0.87
Tympanic temperature, °C	38.2 (37.4-38.6)	38 (37-38.3)	37.7 (37-39.5)	*P* = 0.7
Ionized calcium, median (IQR), mmol/L	1.1 (1.05-1.15)	1.12 (1.1-1.16)	1.05 (1.03-1.06)	*P* = 0.12
eGFR, median (IQR), mL/min/1.73m^2	76.5 (58.8-88.9)	67 (50-92.8)	68.6 (62-71.5)	*P* = 0.6
LDH, median (IQR), U/L	359 (281-385)	375 (238-556)	289 (198-350)	*P* = 0.73
CRP, median (IQR), mg/L	84 (32-392)	71 (16.4-187)	67 (17.6-791)	*P* = 0.69

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate calculated using the CKD-EPI equation; IQR, interquartile range; LDH, lactate dehydrogenase; PaO2/FiO2 ratio, ratio between the arterial partial pressure of oxygen measured on arterial blood gas analysis and the fraction of inspired oxygen; SpO2, peripheral oxygen saturation; VFs, vertebral fractures.

[a] Only active neoplasms were reported.

bone centers could be hypothesized to have a possible role in identifying patients with increased susceptibility to the viral pandemic.

No significant differences in the rate of hypocalcemia between fractured vs nonfractured patients were found. This may be due to the widespread presence of hypocalcemia in our study population, which confirms findings from previous reports by our and several other groups (9, 49-52). Because in Italy there is a very high prevalence of hypovitaminosis D and since low circulating levels of vitamin D have also been correlated with disease severity, it cannot be excluded that the very high prevalence of VFs and hypocalcemia observed could be due to this condition (9, 49-57).

Limitations of our study are the retrospective nature, which does not allow us to evaluate the timing of VFs; the limited number of enrolled patients due to the huge pressure on EDs, which did not allow lateral chest x-rays to be performed in many patients; and the lack of a BMD evaluation or vitamin D level assessment to better characterize bone metabolic status. The higher mortality rate in our patients with severe as compared to mild and moderate VFs should be interpreted with caution due to the low number of patients affected by severe VFs and needs to be confirmed in larger studies. Moreover, we could not evaluate possible influence of height reduction on disease outcomes and respiratory function since only height at hospital admission was available. Finally, we have only evaluated the thoracic spine. Therefore, despite thoracic VFs being the type most commonly observed in osteoporosis, our finding is likely to be an underestimate.

These limitations aside, this is the first study that investigated skeletal fragility in COVID-19 patients.

Pathophysiologically, it can be hypothesized that VFs in our population could be linked to increased combined cardiorespiratory risk since they may be associated with cardiovascular comorbidities but also predispose to respiratory failure and infection. Clinically, the results of our study demonstrate that VFs are one of the most frequent comorbidities in severe SARS-CoV-2 infection, almost reaching the level of one of the few clinical features which has been consistently shown to be strongly correlated with COVID-19 risk and prognosis, such as arterial hypertension with which VFs correlate well and with a much higher prevalence than other frequently reported COVID-19 comorbidities such as CAD, diabetes mellitus, and chronic kidney disease (1, 2). Moreover, VFs were clinically meaningful, associating with a doubling in mortality risk, which was significantly higher in patients with severe as compared to mild and moderate VFs. It is interesting to note that our data confirm the hypothesis recently published by

Napoli et al (7) who properly warned the medical community about the high likelihood of an increased risk of skeletal fragility and osteoporotic fracture with potential huge consequences on overall health status and recovery of affected patients. Our data from the field reinforce the need of implementing previously published recommendations concerning the importance of bone fragility care during the COVID-19 pandemic with at least those patients who are already treated with antiosteoporotic drugs maintaining their adherence to treatments including vitamin D (7, 57), which have also been suggested very recently to have no relevant predisposing effect on COVID-19 (58). Moreover, continuity of care should also include bone density monitoring (59), despite very restricted access to clinical facilities during the COVID-19 pandemic (7). Finally, all patients with fractures should start antiresorptive treatment right away, even during hospital stay (60). This recommendation should be also strengthened in COVID patients with fractures (7).

In conclusion, since thoracic VFs are easy to measure, associate with age, and integrate the cardiorespiratory risk of COVID-19 patients, they are a good marker of patient fragility and poor prognosis and we suggest that morphometric vertebral x-rays evaluation should be performed in all patients with suspected COVID-19.

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