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Association of diaphragm thickness and density measured on chest CT with disease severity in COVID-19 patients

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ABSTRACT

Introduction: A decrease in muscle mass of the diaphragm could be a significant risk factor for pneumonia. The aim of our study was to evaluate whether diaphragm thickness (DT) and density measured on chest computed tomography (CT) were associated with clinical course and mortality in adult patients with coronavirus disease 2019 (COVID-19) in emergency department admission.

Methods: We retrospectively analyzed 404 patients with a positive polymerase chain reaction test for COVID-19 and pneumonia findings on chest CT between September 1 and November 1, 2020. Bilateral DT measurements were performed at the level of the celiac artery origin, and the total mean diaphragm thickness (TMDT) was estimated. Hemidiaphragm density was measured at the level of the celiac artery origin. The relationship between demographic characteristics, comorbidities, TMDT, mean hemidiaphragm density (MHD) and clinical outcomes was investigated using the logistic regression analyses. The reliability of the measurement of the two observers was evaluated by intraclass correlation analyses.

Results: Intraclass correlation analyses demonstrated almost perfect inter-observer agreement for TMDT and substantial agreement for MHD. There was a statistically significant relationship between the presence of a thinner diaphragm and mortality ($p < 0.001$). Bilateral diaphragm densities were lower in the patients with severe disease and mortality ($p < 0.001$). The threshold values of TMDT were 3.67 mm and 3.47 mm for the prediction of ICU admission and mortality, respectively. TMDT (odds ratio [OR]: 0.634, 95% confidence interval [CI]: 0.447–0.901), age (OR: 1.053, 95% CI: 1.027–1.081) and MHD (OR: 0.920, 95% CI: 0.883–0.959) were found to be independent predictors for severe disease in the multivariable model. In addition, MHD (OR: 0.883, 95% CI: 0.827–0.942) and age (OR: 1.040, 95% CI: 1.003–1.078) were independent risk factors for mortality.

Conclusion: Our study demonstrated that a low diaphragm thickness and density measured on chest CT were associated with severe disease in patients with COVID-19 and could be evaluated as poor prognostic markers.

1. Introduction

Coronavirus disease (COVID-19) is a viral infection caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1-3]. The World Health Organization declared it a pandemic on March 11, 2020 [4]. The disease may be asymptomatic or may progress from mild respiratory disease to severe pneumonia with acute respiratory distress syndrome, which requires intensive care unit (ICU) admission and can result in death. Chest computed tomography (CT) is a reliable, practical and rapid method that can be used in the diagnosis, severity, and prognosis of COVID-19 [4,5-7].

The diaphragm is the primary muscle of respiration. A decrease in muscle mass and strength of the diaphragm is defined as an important risk factor for pneumonia and other respiratory tract infections [8]. There are studies investigating the relationship between respiratory tract diseases and diaphragm thickness (DT) using ultrasound (US) measurements [9-11]. A low baseline DT measured by US has been associated with an increased rate of ICU admission, prolonged mechanical ventilation (MV), and increased mortality [12]. However, in the literature, there are only a limited number of CT-based studies investigating DT. In one of these studies, the success of the diaphragm pacing system in amyotrophic lateral sclerosis was evaluated [13]. In another CT study,

Abbreviations: DT, diaphragm thickness; CT, computed tomography; COVID-19, coronavirus disease 2019; TMDT, total mean diaphragm thickness; MHD, mean hemidiaphragm density; WHO, World Health Organization; RT-PCR, reverse transcription polymerase chain reaction; ICU, intensive care unit; US, ultrasound; MV, mechanical ventilation; ILD, Interstitial lung disease; DM, diabetes mellitus; HT, hypertension; CAD, coronary artery; ICC, Intraclass correlation coefficient; ROC, receiver operating characteristic.

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it was determined that a lower DT loss during MV was a protective factor for reintubation and mortality [14].

The number of studies investigating the relationship between COVID-19 severity and DT is also low [15,16]. Corradi et al. found that a low DT detected by US was independently associated with the need for invasive MV or increased risk of death [16]. However, to the best of our knowledge, there is no study in the literature investigating the relationship between COVID-19 severity and DT using CT. Therefore, in this retrospective study, we aimed to explore the association between DT and diaphragm density measured on chest CT and the clinical outcomes of COVID-19.

2. Methods

After receiving approval from the institutional review board (approval number: E2–21-522), we retrospectively investigated patients diagnosed with COVID-19 based on a positive RT-PCR test between September 1, 2020 and October 1, 2020 and underwent a non-contrast chest CT examination in emergency department admission. Patients under the age of 18 years, intubated patients, and those with major motion artifacts on CT images were excluded from the study. Interstitial lung disease (ILD) patients were also excluded from the study, as the presence of ILD may have some effect on DT. The chart review was performed by a radiologist with 4 years of experience who was blinded to the clinical outcomes of the patients. The preexisting comorbidities of the patients, such as diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) were noted from their electronic medical records. Data on outcomes, including home isolation, hospitalization, ICU admission, and mortality, were also collected. The patients treated in ICU were evaluated as the severe disease group, while those treated in the inpatient ward or isolated at home were included in the mild disease group.

The initial chest CT scans of the patients were used for the parenchymal involvement evaluations and measurements. The measurements of each patient were independently made by two radiologists with 16 years and 5 years of experience who were blinded to the clinical outcomes of the patients. High-resolution chest CT was performed using two 128-slice multidetector scanners (GE Revolution EVO 128 Slice CT Scanner, GE Medical Systems, Milwaukee, WI, USA) reserved only for COVID-19-suspected cases. All the scans were performed without intravenous contrast media injection with the patients in the supine position at end-inspiration. The following technical parameters were used: tube voltage, 100 kV; tube current, 90–300 mAs; spiral pitch factor, 0.98; collimation width, 0.625; and slice thickness, 1.3 mm with a sharp

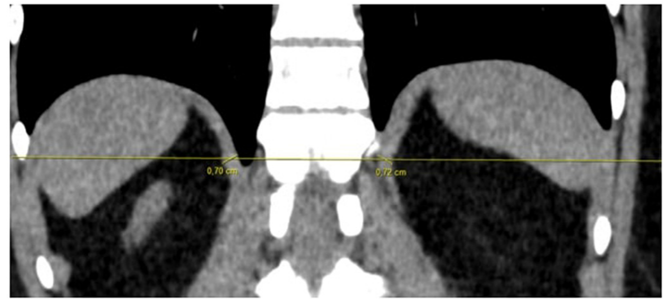

Fig. 2. Measurement of hemidiaphragm thicknesses on coronal CT images corresponding to measurement points on axial CT images.

reconstruction kernel. The reformatted images of all the patients were obtained in the axial and coronal planes at a 1.5-mm slice thickness. A sharp kernel was used to evaluate the lung parenchyma, but measurements were performed at the soft tissue window settings.

On the axial CT images, both the hemidiaphragm thicknesses at the level of the middle and posterior vertebral bodies at the level of the origin of the celiac trunk were measured, and the hemidiaphragm thicknesses corresponding to these levels in the coronal sections were also measured. The methods described by Lee et al. and Ufuk et al. were utilized in the measurement of DT [17,18] (Figs. 1, 2). The axial and coronal measurements made from the same point were averaged. The mean value obtained from these measurements was then defined as the total mean DT (TMDT) for each patient. Hemidiaphragm density, corresponding to the middle part of the vertebral body at the level of the celiac body origin, was also measured (Fig. 3).

2.1. Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). In descriptive statistics, the normality of data distribution was determined using the one-sample Kolmogorov-Smirnov test, and continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as numbers and percentages. The reliability of the measurement of the two observers was evaluated by intraclass correlation coefficient (ICC) scores with a 95% confidence interval (CI). An ICC of 1.0 was considered to represent perfect agreement; 0.81–0.99, almost perfect agreement; 0.61–0.80, substantial agreement; 0.41–0.60, moderate agreement; 0.21–0.40, fair agreement; and 0.20 or less, slight agreement. The mean of the

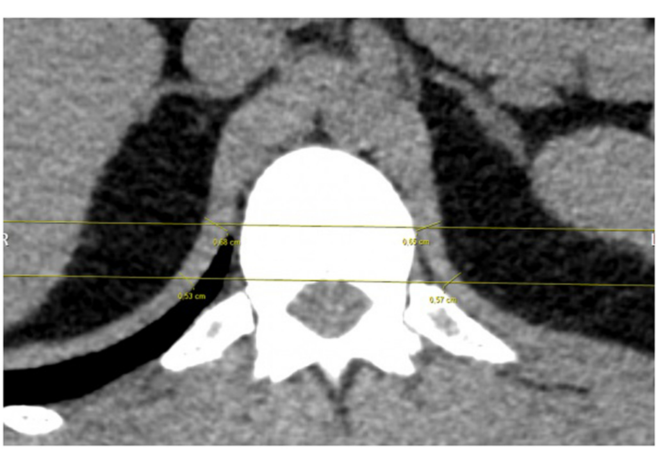

Fig. 1. Measurement of hemidiaphragm thicknesses at the level of the middle and posterior vertebral body at the level of the celiac artery origin on axial CT images.

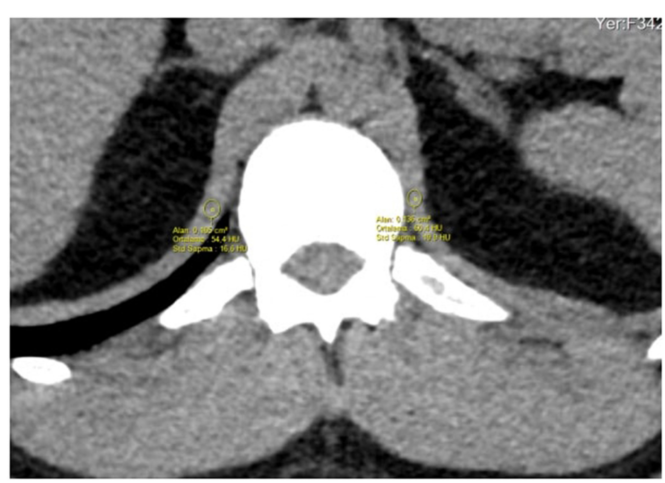

Fig. 3. Measurement of hemidiaphragm densities at the level of the middle part of the vertebral body at the level of the celiac artery origin on axial CT images.

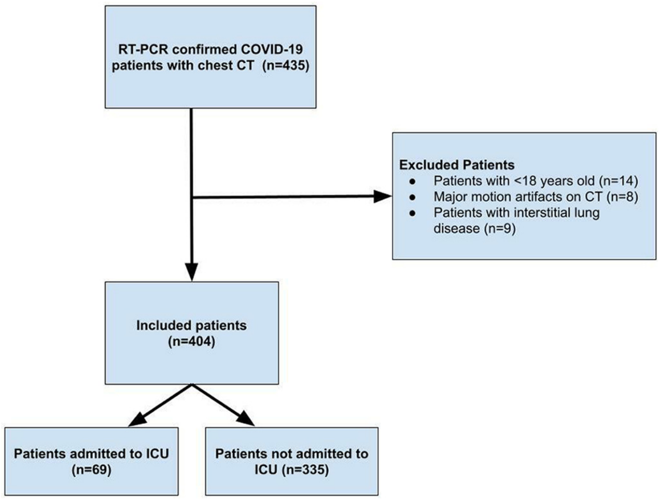

Fig. 4. Flow diagram describing patient selection.

measurements of the two observers was included as the exact measurement to perform further analyses.

The Mann-Whitney *U* test was used to compare continuous variables between the two groups. Differences between categorical variables were calculated with the chi-square test. The effect of continuous variables on ICU admission and mortality was calculated using the binary logistic regression analysis, and significant variables were further analyzed with the receiver operating characteristic (ROC) analysis. The correlation analysis was undertaken with Spearman's rank correlation. Sensitivity and specificity were calculated at the optimal cut-off value. A p value of <0.05 was considered statistically significant.

3. Results

The study group consisted of 404 adult patients (59.9% male and 40.1% female; mean age, 49.2 ± 16.8 years) (Fig. 4). There was no significant difference between the genders in terms of disease severity.

ICC between the observers was found to be almost perfect agreement for TMDT and substantial agreement for mean diaphragm density measurements (Table 1). There was a poor correlation between increasing age and decreasing TMDT ($r = 0.385$, $p < 0.001$). The bilateral mean hemidiaphragm thicknesses at the level of both the middle and

Table 3
ROC analysis of the total mean diaphragm thickness for the prediction of severe disease and mortality

	AUC (95% CI)	Cut-off value (mm)
ICU	0.734 (0.669–0.800)	3.67
Mortality	0.717 (0.607–0.828)	3.47

ROC: Receiver operating characteristics; AUC: Area under the curve; ICU: Intensive care unit.

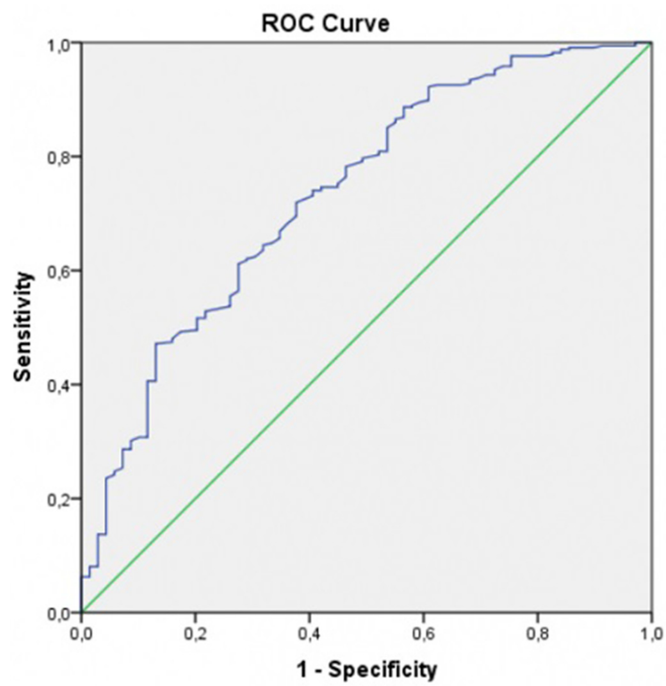

Fig. 5. ROC analysis in ICU and non-ICU patients for total mean diaphragm thickness.

Table 1
Inter-observer agreement for measurements.

	Radiologist 1	Radiologist 2	Intraclass correlation coefficient	Lower bound (95% CI)	Upper bound (95% CI)	p
Total mean diaphragm density (mm)	4.33 ± 1.69	3.83 ± 1.53	0.904	0.759	0.954	<0.001
Mean hemidiaphragm density (HU)	45.14 ± 10.91	47.59 ± 13.59	0.776	0.602	0.874	<0.001

Table 2
Relationship of demographic characteristics and CT measurements with clinical outcomes.

	Total ($n = 404$)	ICU ($n = 69$)	Non-ICU ($n = 335$)	p	Mortality ($n = 25$)	Survival ($n = 379$)	p
Female	162 (40%)	24 (34.7%)	138 (41.1%)	0.323	9 (36%)	153 (40.4%)	0.666
Male	242 (60%)	45 (65.3%)	197 (58.9%)	0.323	16 (64%)	226 (59.6%)	0.666
Age (years)	49.2 ± 16.8	65.8 ± 15	45.7 ± 15.1	<0.001	67.9 ± 12.7	47.9 ± 16.3	<0.001
Mean right hemidiaphragm thickness at the mid-vertebral body level (mm)	4.28 ± 1.5	3.48 ± 1.19	4.45 ± 1.51	<0.001	3.36 ± 1.24	4.34 ± 1.5	<0.001
Mean left hemidiaphragm thickness at the mid-vertebral body level (mm)	4.07 ± 1.5	3.39 ± 1.64	4.21 ± 1.43	<0.001	3.64 ± 2.34	4.1 ± 1.42	0.002
Mean right hemidiaphragm thickness at the posterior vertebral body level (mm)	4.11 ± 1.44	3.28 ± 1.01	4.28 ± 1.46	<0.001	3.24 ± 1.13	4.16 ± 1.44	<0.001
Mean right hemidiaphragm thickness at the posterior vertebral body level (mm)	3.96 ± 2.29	3.09 ± 1.1	4.14 ± 2.43	<0.001	2.90 ± 1.02	4.03 ± 2.34	<0.001
Total mean diaphragm thickness (mm)	4.11 ± 1.3	3.31 ± 0.98	4.27 ± 1.3	<0.001	3.28 ± 0.98	4.16 ± 1.3	<0.001
Right hemidiaphragm density (HU)	49.63 ± 9.35	42.01 ± 9.90	51.2 ± 8.43	<0.001	37.8 ± 9.5	50.4 ± 8.8	<0.001
Left hemidiaphragm density (HU)	47.88 ± 10.18	39.78 ± 10.35	49.5 ± 9.33	<0.001	35.6 ± 10.9	48.7 ± 9.6	<0.001
Mean hemidiaphragm density (HU)	48.75 ± 8.97	40.9 ± 9.48	50.37 ± 7.97	<0.001	36.7 ± 9.52	49.55 ± 8.36	<0.001

CT: Computed tomography; ICU: Intensive care unit; HU: Hounsfield unit.

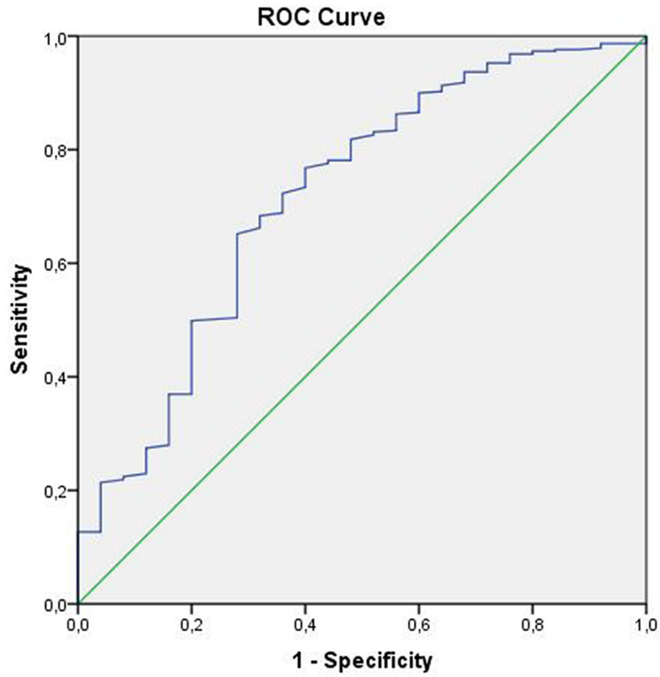

Fig. 6. ROC analysis for total mean diaphragm thickness for mortality status.

posterior vertebral bodies and TMDT were found to be statistically significantly lower in the severe disease group. The disease resulted in mortality in 25 (6.1%) patients who had significantly thinner hemidiaphragms than the survivor group. Bilateral hemidiaphragm densities and mean hemidiaphragm densities (MHD) were also statistically significantly lower among the patients with the severe disease and those that died (Table 2). The optimal cut-off value of the TMDT was calculated as 3.67 mm for the prediction of patients who required ICU treatment and 3.47 mm for the prediction of mortality (Table 3) (Figs. 5, 6).

Gender, age, comorbidities, TMDT and MHD were evaluated with the univariable logistic regression analysis, and parameters with a p value of <0.10 were further analyzed using the multivariable analysis. The univariable logistic regression analysis showed that TMDT, MHD, age, HT, DM, CAD, COPD, and CKD were associated with disease severity. TMDT (odds ratio [OR]: 0.634, 95% confidence interval [CI]: 0.447–0.901), age (OR: 1.053, 95% CI: 1.027–1.081) and MHD (OR: 0.920, 95% CI: 0.883–0.959) were independent risk factors of severe disease in the multivariable model. MHD (OR: 0.883, 95% CI: 0.827–0.942) and age (OR: 1.040, 95% CI: 1.003–1.078) were independent risk factors for mortality (Table 4).

4. Discussion

US is the diagnostic method that is frequently used in the evaluation of diaphragmatic dysfunction. Comprehensive information on muscle thickness and contractility can be obtained by performing measurements at the end of both inspiration and expiration on US [19]. In the literature, there are sonographic studies of the diaphragm evaluating the relationship between COVID-19 and diaphragm dysfunction frequently in ICU patients [20,21]. Farr et al. measured DT at the end-inspiration and end-expiration in severe post-COVID-19 cases and compared these measurements with a non-COVID control group. The authors reported that the mean thickening ratio indicating the contractility of the diaphragm was significantly reduced in the COVID-19 group ($p = 0.02$) [15].

In a US study based on DT measurements, Corradi et al. showed that in 77 patients with COVID-19, a thinner diaphragm was associated with poor outcomes, including ICU admission and death. DT was identified as an independent risk factor of COVID-19 severity. A low diaphragm thickness may limit the strength of the inspiratory pump, facilitating the progression from mild to severe respiratory failure in the case of pneumonia, and the lungs may not be able to sustain ventilation properly in the presence of increased inspiratory load [16]. Despite the different imaging modalities used, we also determined that TMDT (OR: 0.634, 95% CI: 0.447–0.901) was an independent risk factor of severe COVID-19. It should be noted that when compared to US, diaphragmatic anatomy can be better evaluated on CT providing an objective quantitative evaluation, and associated lung and mediastinal pathologies can also be revealed [22,23].

Metabolic deterioration due to respiratory disease causes clinical progression, increasing the need for intensive care and MV, and this may result in loss of diaphragm muscle mass. Lee et al. compared DTs between two chest CTs taken at an average of 18 days apart on mechanically ventilated patients. They observed that DT significantly decreased during MV. They concluded that weakness in the diaphragm had clinical importance in lung diseases, such as infections that increased respiratory load [17]. Since initial CTs were assessed in our study, interval changes in muscle mass could not be evaluated. However, we found that a thinner diaphragm, which we think represents muscle weakness, was associated with poor outcomes in patients with COVID-19. It is worth mentioning again that a thinner diaphragm was also significantly associated with mortality.

Quantitative muscle measurements to evaluate muscle quality can provide information concerning the progression of several diseases [24,25]. Hocaoğlu et al. evaluated the correlation between the volume and density of the pectoralis muscle on chest CT and mortality rate due to COVID-19. They found that a lower pectoralis muscle density was associated with poor outcomes, including higher mortality [26]. Similarly, we found a significant relationship between a low diaphragm density and poor prognosis. The diaphragm density measurement can be simply

Table 4
Univariable and multivariable logistic regression analyses of risk factors associated with COVID-19 severity and mortality.

	COVID-19 disease severity		COVID-19 disease mortality	
	Univariable	Multivariable	Univariable	Multivariable
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender (male)	1.313 (0.765–2.256)		1.204 (0.519–2.794)	
Age (years)	1.087 (1.064–1.110)	1.053 (1.027–1.081)	1.076 (1.046–1.107)	1.040 (1.003–1.078)
Total mean diaphragm thickness (mm)	0.391 (0.282–0.542)	0.634 (0.447–0.901)	0.436 (0.270–0.701)	0.824 (0.489–1.387)
Mean hemidiaphragm density (HU)	0.874 (0.843–0.907)	0.920 (0.883–0.959)	0.838 (0.791–0.888)	0.883 (0.827–0.942)
DM	2.894 (1.507–5.557)	1.215 (0.517–2.859)	3.677 (1.498–9.029)	1.526 (0.449–5.190)
HT	3.664 (2.074–6.475)	1.020 (0.474–2.191)	3.104 (1.337–7.209)	0.771 (0.254–2.339)
CAD	2.884 (0.820–10.135)	0.791 (0.191–3.266)	1.537 (0.189–12.514)	
COPD	3.439 (1.424–8.305)	1.499 (0.493–4.557)	2.448 (0.675–8.871)	
CKD	5.092 (1.242–20.883)	1.260 (0.158–10.036)	17.857 (4.172–76.426)	4.934 (0.514–47.334)

DM: Diabetes mellitus; HT: Hypertension; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease.

performed using the data obtained from the picture archiving and communication systems and it may be helpful in estimating COVID-19 prognosis.

5. Limitations

There are several limitations to this study. First, the study had a retrospective and single-center design. Second, there are only a small number of publications in the literature that performed DT measurements using CT, and to our knowledge, no study investigated the relationship between DT and COVID-19 disease using CT. Third, US is currently the diagnostic tool that is frequently used in DT research in COVID-19 and other respiratory tract diseases, but there is no research comparing CT and US in terms of the DT measurement. Therefore, thicknesses obtained from CT in our study and those reported by US studies could not be compared quantitatively. Future studies comparing US and CT in relation to DT can further contribute to the literature. Our results may be a useful reference for future CT studies that will assess the relationship between DT and COVID-19 or other respiratory tract diseases.

6. Conclusion

This is the first CT study that investigated the relationship between diaphragm thickness and density and the clinical course of COVID-19. DT and diaphragm density measured on the initial chest CT of patients provide important prognostic information about the course of the disease. It should be kept in mind that the disease may have poor prognosis in the clinical follow-up of patients with a thinner diaphragm on the initial chest CT.

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CRediT authorship contribution statement

Selçuk Parlak: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Muhammed Said Beşler:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Muhammet Batuhan Gökhan:** Visualization, Validation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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