Transient diaphragmatic thinning in patients with interstitial pneumonia due to SARS-CoV-2

Dear Editor,

The function of the diaphragm is critical for optimal breathing as it is the primary muscle responsible for inhalation. In a variety of acute and chronic degenerative disorders, diaphragmatic impairment is recognised as a significant contributor to death or major clinical outcomes.[1] It has also been demonstrated that diaphragmatic dysfunction increases intensive care need and prolonged intubation.[2] Although this is likely to also be true for acute SARS-CoV-2 pneumonia, evidence is lacking, but a preliminary report suggests that reduced diaphragmatic thickness could be a potential predictor of CPAP (continuous positive airway pressure) failure and requirement for invasive ventilation in critically ill patients with COVID-19 respiratory failure admitted to the ICU.[3] We therefore investigated diaphragm changes in subjects with SARS-CoV-2 pneumonia during both the acute phase of the disease and recovery.

We prospectively and consecutively screened subjects admitted to the Internal Medicine Department of Bufalini Public Hospital in Cesena (Italy), from February to May 2020, with a clinical suspicion of interstitial pneumonia from SARS-CoV-2. Subjects were enrolled if they satisfied the following inclusion criteria: pneumonia diagnosis and confirmed SARS-CoV-2 infection (positive naso-pharyngeal swab [NPS]; PCR test and computed tomography [CT] images as per the WHO diagnostic criteria); age >18 years; no other known conditions affecting diaphragm thickness (DT) or causing sarcopenia (i.e., chronic neurodegenerative and neuromuscular diseases, diabetes mellitus with associated organ failure, metastatic neoplasm, autoimmune diseases, uncompensated ischaemic diseases, end-stage kidney failure and interstitial lung disease); and provision of informed consent. All participants received a comprehensive clinical evaluation and all noteworthy findings were recorded. The control group comprised 50 subjects with negative NPS, free from focal or interstitial abnormalities, chronic obstructive pulmonary disease (COPD), neoplasm or other known chronic respiratory disorders at chest CT were selected from a pool of 540 chest CT scans, after matching by age, sex and body mass index (BMI). No study participant required admission to critical care facilities.

Clinically recovered COVID-19 patients (with negative NPS) were re-assessed using a follow-up CT scan, and their DT was longitudinally compared. DT was measured on CT scans using a 64-slice scanner (Diamond Select Brillance CT 64-slice; Philips, Amsterdam, The Netherlands) and standard CT images (maximum, voluntary, end-inspiratory apnoea). The following two CT slices were used: 1) median sagittal plane, to assess the anterior pillar at the right intersection between the paramedian and midclavicular lines; 2) coronal plane, right above the splenic border on the middle axillary line to assess the left antero-lateral hemidiaphragm. Each side of the diaphragm was measured by two radiologists, and the results were cross-checked. In case of inter-observer disagreement, a consensus was achieved with a facilitator.

Continuous variables were described as medians and interquartile ranges (IQRs), nominal variables as numbers and percentages. Between-groups comparisons were performed using the χ^2 test, non-parametric Mann-Whitney's U-test for independent samples or Wilcoxon signed-rank test for paired samples, as appropriate. The correlation between continuous variables was determined using the Pearson's coefficient (r). For all tests, an alpha level of $P = 0.05$ was set for statistical significance. Statistical analyses were performed using SPSS Statistics v24.0 (IBM Corp, Armonk, NY, USA). Based on existing reference values available in literature,[4] we considered a minimum sample size of 23 and 27 patients, respectively, estimating a 15% reduction in both DT to be clinically significant for patients diagnosed with COVID-19 pneumonia. This sample size had a type-I probability error of 0.05, and a desired statistical power of 0.8. Expecting a 10% risk of patient dropout at the follow-up CT, we decided to prospectively recruit at least 30 patients. Our study protocol was approved by the Ethical Committee of the Comitato Etico della Romagna (protocol no.5419/2020). All patients provided written informed consent.

Of 210 patients hospitalised with COVID-19 pneumonia, 34 (median age 54 years, IQR 45–75; females:47.0%) satisfied the inclusion criteria and constituted the study population. Five patients (14.7%) suffered from uncomplicated diabetes, 5 from cardiovascular diseases (14.7%), 1 (2.9%) from non-metastatic cancer, 1 (2.9%) from COPD and 2
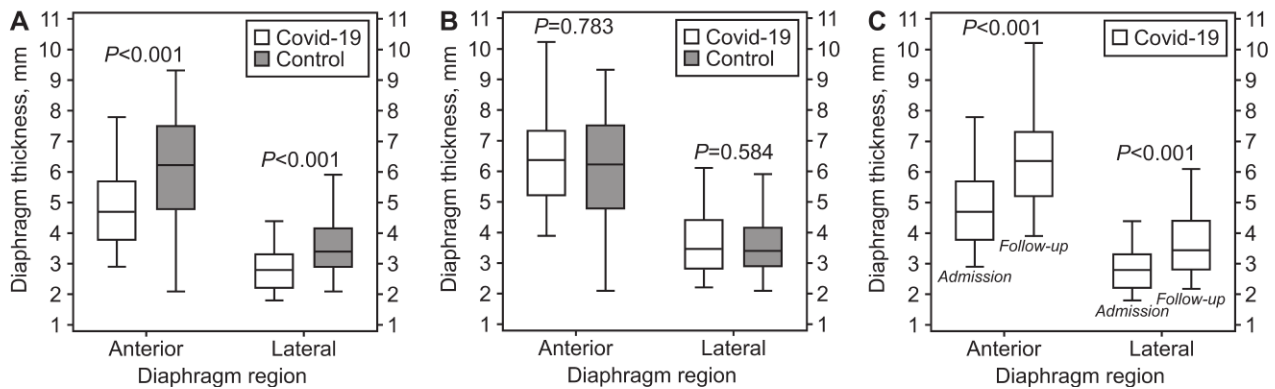
Figure Comparisons between study and control groups in thickness of two different areas of the diaphragm, anterior and lateral, respectively (in mm) at baseline (Panel **A**) and after recovery (Panel **B**) and comparisons of thickness at baseline and after recovery among COVID-19 patients (Panel **C**). Black horizontal lines inside the boxes = median values; box height = IQR values; whiskers: 1.5 × IQR; small circles = outliers. IQR = interquartile range.

from early-stage chronic kidney disease; 4 (11.8%) were active smokers and 12 (35.3%) were ex-smokers, while 9 (26.5%) were obese (BMI ≥30 kg/m²). Overall, patients presented with moderate hypoxemia (ratio of arterial oxygen partial pressure [in mmHg] to fractional inspired oxygen 253; IQR 323–360) and respiratory alkalosis (pH 7.45, IQR 7.43–7.47; partial pressure of carbon dioxide 29.9, IQR 33.2–35.6), no abnormalities in median white blood cell, platelet and lactate dehydrogenase counts were observed, while high mean C-reactive protein values were documented (6.9 mg/L; IQR 19.3–51.3). Fifteen patients (44.1%) received corticosteroid therapy. Chest CTs were obtained after a median time of 6.0 days (IQR 2.8–10.3) from symptom onset. In the study group, the median DT in the anterior and lateral regions at hospital admission was respectively 4.7 mm (IQR 3.8–5.8) and 2.8 mm (IQR 2.2–3.3), whereas the control group results were respectively 6.3 mm (IQR 4.8–7.5) and 3.4 mm (IQR 2.9–4.4). Between-group differences in both anterior and lateral DT were statistically significant (Figure, Panel A). In the study group, no statistically significant association was found between both-regions DT and all demographic, laboratory and clinical variables explored.

The follow-up CT scan was performed after a median of 97.0 days (IQR 88.8–113.0) from the baseline examination. No difference in DT between study and control groups was found (Figure, Panel B). A statistically significant recovery to normal values in DT was documented (Figure Panel C). The anterior/lateral diaphragmatic thickness ratio was documented unchanged ($P = 0.765$) at both hospital admission (median 1.6, IQR 1.4–2.1) and during follow-up (median 1.6, IQR 1.3–2.4), indicating stability in segmental muscle proportions with time.

This study showed that patients with SARS-CoV-2 pneumonia may experience diaphragmatic thinning during the acute disease phase, and that this change appears to reverse after clinical recovery. To our knowledge, a similar finding has not previously been observed in any study on COVID-19 pneumonia. The reduction in DT during acute SARS-CoV-2 interstitial pneumonia could be explained by acute phase reactions.[5] Apart from atrophy, resulting from systemic inflammation, increased pro-inflammatory cytokine production and autophagy, a worsening of oxidative stress and an increase of nitric oxide levels may be the causes of thickness loss.[6]

We observed a 25% reduction in DT during COVID-19 pneumonia, which may be considered a proxy for reduction in diaphragmatic strength.[7] Because the diaphragm is the main muscle in the respiratory system, this observation is of clinical relevance, and muscle wasting during periods of increased respiratory workload are more likely to lead to respiratory pump failure.[8–10] It would be interesting to investigate whether diaphragmatic thickness can be used as a predictor of disease progression and severity in SARS-CoV-2 pneumonia, but this would require further research and specifically designed studies.

S. Battisti,[1,2,3] G. Sanson,[4] E. Paolucci,[5] E. Giampalma,[1] E. Russo,[6] C. Bergamini,[6] V. Agnoletti,[6] S. Di Bella,[7] A. Palermo,[8] S. Scarlata[9]

[1]Radiology Department, Bufalini Hospital, Azienda Unità Sanitaria Locale (AUSL) Romagna, Cesena, [2]Istituto Romagnolo per lo Studio dei Tumori, Meldola, [3]Dipartimento di Medicina Specialistica Diagnostica e Sperimentale, Alma Mater Studiorum, University of Bologna, [4]Clinical Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, [5]Internal Medicine Department, and [6]Anesthesia and Intensive Care Unit, Bufalini Hospital, AUSL Romagna, Cesena, [7]Infectious Diseases Department, University Hospital of Trieste, Trieste, [8]Unit of Endocrinology and Diabetes, and

⁹Unit of Respiratory Pathophysiology and Thoracic Endoscopy, Campus Bio Medico University and Teaching Hospital, Rome, Italy
Correspondence to: Professor Simone Scarlata, Unit of Respiratory Pathophysiology and Thoracic Endoscopy, Campus Bio Medico University and Teaching Hospital, Via Alvaro del Portillo, 200, 00128 Rome, Italy. e-mail: s.scarlata@unicampus.it

References

1 McCool FD, Tzelepis GE. Dysfunction of the diaphragm. N Engl J Med 2012; 366: 932–942.
2 Dres M, et al. Critical illness-associated diaphragm weakness. Intensive Care Med 2017; 43: 1441–1452.
3 Corradi F, et al. Low diaphragm muscle mass predicts adverse outcome in patients hospitalized for COVID-19 pneumonia: an exploratory pilot study. Minerva Anestesiol 2021; 87: 432–438.
4 Scarlata S, et al. Reproducibility of diaphragmatic thickness measured by M-mode ultrasonography in healthy volunteers. Respir Physiol Neurobiol 2019; 260: 58–62.
5 Pascarella G, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med 2020; 288: 192–206.
6 Hadda V, et al. Decline in DT and clinical outcomes among patients with sepsis. Heart Lung 2020; 50: 284–291.
7 Cardenas LZ, et al. Diaphragmatic ultrasound correlates with inspiratory muscle strength and pulmonary function in healthy subjects. Ultrasound Med Biol 2018; 44: 786–793.
8 Vassilakopoulos T. Respiratory muscle wasting in the ICU: is it time to protect the diaphragm? Thorax 2016; 71: 397–398.
9 Schepens T, et al. Diaphragm-protective mechanical ventilation. Curr Opin Crit Care 2019; 25: 77–85.
10 Brown PI, et al. Ventilatory muscle strength, DT and pulmonary function in world-class powerlifters. Eur J Appl Physiol 2013; 113: 2849–2855.