



## BRIEF COMMUNICATION

# Diaphragm dysfunction in severe COVID-19 as determined by neuromuscular ultrasound

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## Introduction

The substantial burden of chronic disability post-hospitalization for coronavirus disease 2019 (COVID-19) has become increasingly clear.<sup>1</sup> In a recent study, nearly half of post-COVID-19 patients were not able to return to work 60 days after hospital discharge.<sup>1</sup> Survivors of severe COVID-19 frequently report persistent shortness of breath, cough, and fatigue post-hospitalization.<sup>1,2</sup> While these symptoms may stem from direct involvement of the lung parenchyma itself, the possibility of underlying neuromuscular respiratory weakness should be considered. Neurological manifestations of COVID-19 are increasingly recognized with prominent involvement of the neuromuscular system ranging from mild creatine kinase (CK) elevation to flaccid tetraplegia requiring tracheostomy.<sup>3</sup> Here we report neuromuscular ultrasound findings that define

## Abstract

Many survivors from severe coronavirus disease 2019 (COVID-19) suffer from persistent dyspnea and fatigue long after resolution of the active infection. In a cohort of 21 consecutive severe post-COVID-19 survivors admitted to an inpatient rehabilitation hospital, 16 (76%) of them had at least one sonographic abnormality of diaphragm muscle structure or function. This corresponded to a significant reduction in diaphragm muscle contractility as represented by thickening ratio (muscle thickness at maximal inspiration/end-expiration) for the post-COVID-19 compared to non-COVID-19 cohorts. These findings may shed new light on neuromuscular respiratory dysfunction as a contributor to prolonged functional impairments after hospitalization for post-COVID-19.

the prevalence of structural and functional alterations to the diaphragm muscle after hospitalization for COVID-19.

## Methods

Consecutive patients ( $n = 21$ ) who were hospitalized for severe COVID-19 on admission to a dedicated unit at a single rehabilitation hospital (Shirley Ryan AbilityLab) were scanned as a part of their routine care. They were admitted to inpatient rehabilitation from 14 separate acute care hospitals between July 21, 2020 and September 24, 2020. Non-COVID-19 comparison patients ( $n = 11$ ) whose acute hospital course included requirement for ventilator support were identified on admission to the same rehabilitation hospital from September 18, 2020 until January 2, 2021. Acute care data were

obtained as available through chart review of medical records as summarized in Table 1. The diaphragm muscle was assessed on a portable ultrasound system (Xario 200, Canon Medical Systems USA Inc.) with either a 5.0- to 18.0-MHz linear array (18L7) or 1.8- to 6.0-MHz convex array (6C1) selected to optimize image clarity on the basis of individual characteristics including body habitus. Briefly, each hemi-diaphragm was identified in the zone of apposition, and thickness was measured at end-expiration and maximal inspiration (Figure 1). Normal values have been established for diaphragm end-expiratory muscle thickness ( $>0.14$  cm) and thickening ratio ( $>1.2$ ), calculated as thickness at maximal inspiration/thickness at end-expiration.<sup>4</sup> As the test was performed as a part of routine patient care, the sonographer was not blinded to the patient's diagnosis and the data from the scan were obtained via chart review. Approval was obtained from Northwestern University IRB (STU23625789). For statistical analysis, the Student's *t*-test was utilized for parametric nominal data and a chi-square test was utilized for all ordinal data. For nominal data that did not have a normal distribution, as determined by the Shapiro–Wilk test, the non-parametric Mann–Whitney *U*-test was performed

instead. Unless otherwise noted, the data are expressed as mean  $\pm$  standard deviation.

## Results

The baseline characteristics of 21 consecutive patients who survived severe COVID-19 and 11 non-COVID-19 comparisons who were admitted to an inpatient rehabilitation hospital are reported in Table 1. Statistically significant differences were noted between the COVID-19 group and comparisons in the prevalence of hypertension (COVID  $n = 16/21$ , non-COVID  $4/11$ ,  $p = 0.027$ ), prediabetes and diabetes mellitus (COVID  $n = 12/21$ , non-COVID  $1/11$ ,  $p = 0.008$ ), and cancer (COVID  $n = 3/21$ , non-COVID  $6/11$ ,  $p = 0.016$ ). The average time spent on a ventilator was  $48 \pm 35.2$  days (range 0–153 days) for post-COVID-19 patients and  $38 \pm 43.3$  days (range 0–136 days) for non-COVID-19 comparisons ( $p = 0.197$ ) and the median peak CK level was 190 U/L (range 39–3090 U/L) in post-COVID-19 patients and 512 U/L (range 10–9299 U/L) in non-COVID-19 comparisons ( $p = 0.976$ ). Six of the post-COVID patients had electromyography (EMG) and nerve conduction studies performed at some point during their acute or post-acute

**TABLE 1.** Baseline characteristics, laboratory values, and lengths of stay of patients in inpatient rehabilitation

Subject Characteristics	COVID-19	Non-COVID	<i>p</i> -values (sig<0.05)
Age	60.3 $\pm$ 13.7 (32-89)	65.4 $\pm$ 10.3 (47-81)	$p = 0.267$
Sex M:F	17:4 ( $n = 21$ )	8:3 ( $n = 11$ )	$p = 0.593$
BMI	30.4 $\pm$ 6.4 (21-48)	33.2 $\pm$ 6 (24-43)	$p = 0.273$
Comorbidities	Hypertension 76.2% (16/21)	Hypertension 36.4% (4/11)	Hypertension: <b><math>p = 0.027</math></b>
	Diabetes mellitus and pre-diabetes mellitus 57.1% (12/21)	Diabetes mellitus and pre-diabetes mellitus 9.1% (1/11)	Diabetes mellitus and pre-diabetes mellitus: <b><math>p = 0.008</math></b>
	Hyperlipidemia 23.8% (5/21)	Hyperlipidemia 0% (0/11)	Hyperlipidemia: $p = 0.078$
	Asthma and/or COPD 14.2% (3/21)	Asthma and/or COPD 27.3% (3/11)	Asthma and/or COPD: $p = 0.371$
	Cancer 14.2% (3/21)	Cancer 54.5% (6/11)	Cancer: <b><math>p = 0.016</math></b>
	Acquired immunodeficiency 14.2% (3/21)	Acquired immunodeficiency 18.2% (2/11)	Acquired immunodeficiency: 0.773
	Cerebrovascular accident 4.7% (1/21)	Cerebrovascular accident 9.1% (1/11)	Cerebrovascular accident: $p = 0.631$
Days in ICU	39.8 $\pm$ 20.7 (0-83)	24.8 $\pm$ 23.3 (0-78)	$p = 0.157$
Days Hospitalized	44.9 $\pm$ 22.3 (12-80)	38.3 $\pm$ 20.6 (10-78)	$p = 0.471$
Days of Mechanical Ventilation	48 $\pm$ 35.2 (0-153)	38.7 $\pm$ 43.3 (0-136)	$p = 0.197$
Days Since ICU <sup>†</sup>	30.9 $\pm$ 22.4 (9-80)	64.6 $\pm$ 53.4 (14-174)	$p = 0.201$
LTACH Disposition	33.3% (7/21)	54.4% (6/11)	$p = 0.245$
CRP (mg/L)	210 $\pm$ 129.4 (14-423) ( $n = 15$ )	136.3 $\pm$ 101.6 (23.4-296) ( $n = 9$ )	$p = 0.155$
Troponin (ng/mL)	0.8 $\pm$ 2.1 (0.009-8.09) ( $n = 13$ )	0.31 $\pm$ 0.43 (0.005-1.55) ( $n = 11$ )	$p = 0.070$
CK (U/L) <sup>‡</sup>	190 (39-3090) ( $n = 12$ )	389.5 (10-9299) ( $n = 8$ )	$p = 0.976$

Significant *p*-values have been bolded.

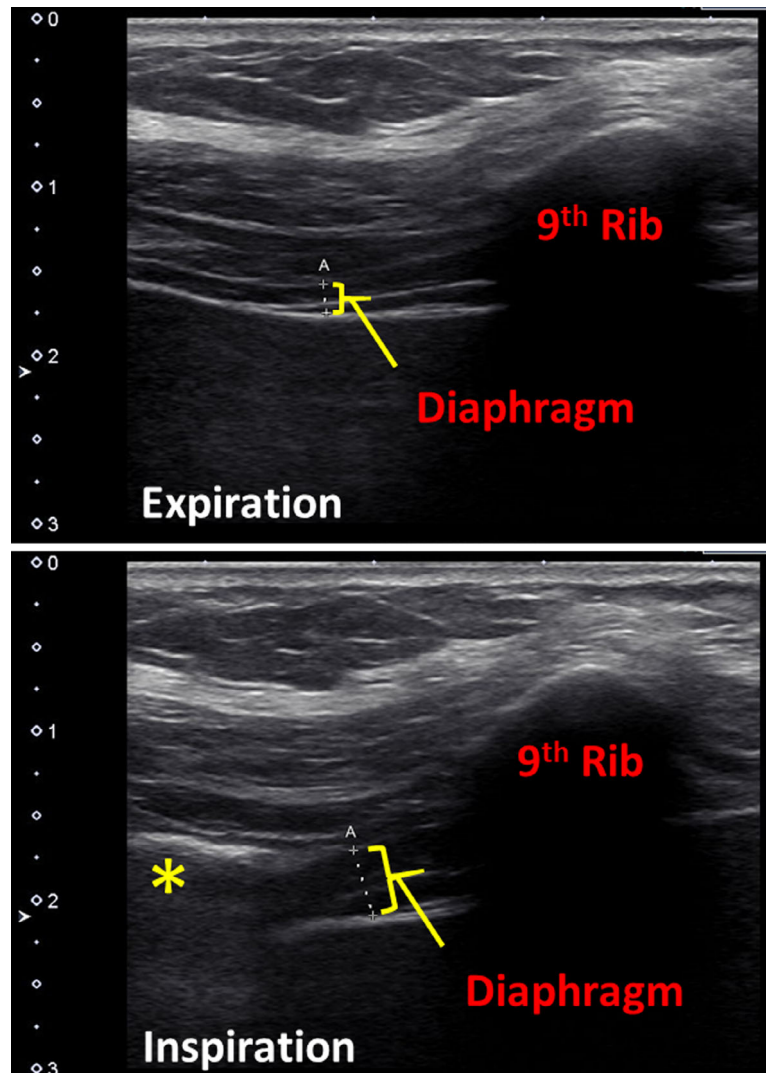
Mean  $\pm$  SD (Range) or % as appropriate.

Lab values reported as peak noted during acute hospitalization.

<sup>†</sup>As measured as days between ICU discharge and diaphragm scan.

<sup>‡</sup>Median reported given non-parametric dataset.

**FIGURE 1.** Technique for neuromuscular ultrasound examination of hemidiaphragm. Top panel, thickness of diaphragm at end inspiration or total lung capacity (0.40 cm). Bottom panel, thickness of diaphragm at maximal expiration, or functional residual capacity (0.19 cm) with descending lung denoted by yellow asterisks. The diaphragm thickening ratio was calculated as 2.11 (0.40 cm/0.19 cm)

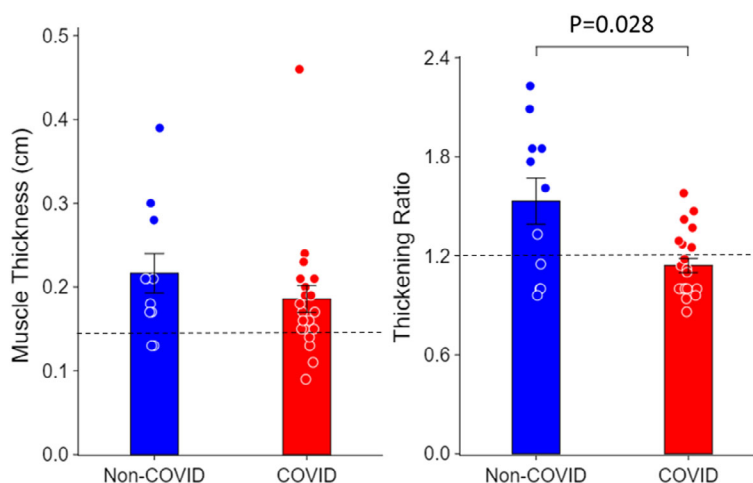


care stays and only two of these six had phrenic studies performed. Only one of the six studies supported a diagnosis of critical illness myopathy (16.7%). Chest x-ray or CT chest/abdomen data were available for 20/21 post-COVID patients and 9/10 non-COVID patients. Evidence of an elevated hemidiaphragm was only reported in one of the post-COVID patients. In the post-COVID-19 cohort, there were four patients (18.2%) who had an end-expiration thickness value below the normal cut off compared with two (18%) of the non-COVID-19 patients. A total of 14 (66.7%) post-COVID-19 patients had a reduced thickening ratio on at least one side, as compared to four (36%) of the non-COVID-19 patients. The mean diaphragm muscle thickness at end-expiration for the post-COVID-19 patients was  $0.18 \pm 0.07$  cm, in comparison the non-COVID-19 patients was  $0.22 \pm 0.08$  ( $p = 0.23$ ). The mean thickening ratio (diaphragm

thickness at end-inspiration/end-expiration) for the post-COVID-19 patients was  $1.14 \pm 0.19$ , in comparison the non-COVID-19 patients was  $1.53 \pm 0.46$  ( $p = 0.0278$ ). Overall, 16 of 21 (76%) post-COVID-19 patients and 5 of 11 (45%) of non-COVID patients had at least one structural or functional abnormality on diaphragm ultrasound (Figure 2).

## Discussion

This study utilizes ultrasound to evaluate the diaphragm in COVID-19 survivors and looks specifically at post-critical illness diaphragm sonographic findings outside of the intensive care unit setting. Our findings demonstrate that hospitalized COVID-19 survivors who require inpatient rehabilitation have a high prevalence of diaphragm dysfunction. These findings are similar to a previous



**FIGURE 2.** Sonographic diaphragm muscle comparisons in survivors of COVID-19 that require inpatient rehabilitation as compared to controls. The more affected side of the two hemidiaphragms was plotted and compared between non-COVID patients (blue) and COVID-19 patients (red). Left panel, the diaphragm muscle thickness at end expiration was not statistically significant,  $p = 0.15$ . Right panel, the diaphragm muscle thickening ratio (i.e., contractility) was significantly reduced in the COVID-19 cohort compared to non-COVID cohort,  $p = 0.0004$ . The dotted horizontal lines indicate lower limit of normal for each parameter

report of sonographically identified diaphragm dysfunction in patients with confirmed myopathy of various subtypes, which speaks to the extent of muscle involvement in the subset of patients who require inpatient rehabilitation post-COVID-19.<sup>5</sup> Given the large number of post-COVID-19 patients who suffer from persistent dyspnea months after onset of disease,<sup>6</sup> this study raises the possibility that diaphragm muscle dysfunction is a major contributing factor.

We propose that the mechanism of diaphragm involvement for the majority of post-COVID-19 patients is likely related to a combination of factors including post-ventilator diaphragm dysfunction, post-intensive care syndrome, and in a subset, critical illness myopathy. The pathophysiology of CIM is considered a multifactorial condition associated with exposure to high-dose corticosteroids, muscle membrane dysfunction, microcirculatory changes associated with inflammation, and impaired glucose transporter type 4 translocation to the muscle membranes.<sup>7</sup> In severe COVID-19, this process may be amplified by the exaggerated systemic inflammatory response that contributes to endothelial dysfunction, impaired circulation, as well as aggressive use of corticosteroid treatment. This combination of factors results primarily in atrophy of type 2 muscle fibers. The human diaphragm is susceptible to type 2 muscle fiber compromise from severe COVID-19 as it is comprised of a nearly even mix of type 1 and type 2 myofibers.<sup>8</sup>

Our study provides insight into neuromuscular respiratory weakness as an important contributor to prolonged functional impairments in patients with post-acute

sequelae of COVID-19. It remains unclear to what extent diaphragm involvement may exist in milder cases of COVID-19 not requiring hospitalization as subjective dyspnea and fatigue are among the most frequently reported symptoms in these “long haulers.”<sup>9</sup> Clinicians should consider pulmonary function tests (PFTs) and/or neuromuscular diaphragm ultrasound study if there is persistent shortness of breath in non-hospitalized patients post-COVID-19. New onset of restrictive pattern seen on PFTs, a substantial drop in forced vital capacity from sitting to supine, or an abnormal diaphragm muscle ultrasound should trigger referral for pulmonary and neuromuscular medicine evaluations. Currently, persistent dyspnea post-COVID-19 is primarily attributed to lung parenchymal damage, overlooking diaphragm dysfunction as a possible contributor.<sup>10</sup> More research is needed into diaphragm muscle status in non-hospitalized post-COVID-19.

This study is limited in its unblinded evaluation of only patients admitted to inpatient rehabilitation post-COVID-19, which presumably represents many of the worst-case scenarios. Comparative non-COVID-19 patients for this population are difficult to find given the length of mechanical ventilation and hospital stay in post-COVID-19 patients. For example, the average days on a ventilator in this subset of post-COVID-19 patients was 43 days compared to a prior Seneff et al. study of over 5,000 patients in 42 ICUs which reported averages across different facilities ranged from 2.6 to 7.9 days of mechanical ventilation.<sup>11</sup> Additionally, due to the observational nature of the study, other comparative studies such as electromyography and nerve conductions of the phrenic

nerve and diaphragm, pulmonary function tests, and chest x-rays were not routinely ordered and thus not available for most patients studied.

The high prevalence of diaphragm dysfunction in survivors of severe COVID-19 highlights that multifactorial diaphragm dysfunction may be an overlooked factor in COVID-19 infections and may be contributing to the prolonged symptoms and slow recovery in many of these patients. Further study of diaphragm dysfunction, the effects of pulmonary rehabilitation, and the role of impaired diaphragm function in terms of COVID comorbidity will be informative in the care and understanding of acute and chronic complications of infection.

## Author Contributions

EF, SD, AJB, and CKF established the diaphragm ultrasound protocol. EF, ARW, LFW, and CKF performed data analysis. EF, RS, and LR identified the patients in this study. EF and ARW developed the first draft of the manuscript. All authors contributed intellectual content to the manuscript and approved the final version for submission.

## Conflict of Interest

None declared.

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