COVID-19 associated phrenic nerve mononeuritis: a case series

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ABSTRACT
This study characterised the hemidiaphragm elevation on 3-month interval chest X-rays (CXRs) of patients post COVID-19 pneumonia. 467 CXRs were screened; 19 (4.1%) had an elevated hemidiaphragm. There were 15 (3.2%) patients of interest with new hemidiaphragm elevation, persisting on average 7 months post COVID-19 diagnosis. Symptomatic patients underwent diaphragm ultrasound (n=12), pulmonary function test (n=10), muscle function test (n=6) and neurophysiology (n=5), investigating phrenic nerve function. Ultrasound demonstrated reduced/paradoxical diaphragmatic movements in eight; four of eight had reduced thickening fraction. Neurophysiology peripheral limb studies did not support the differential diagnoses of critical illness neuropathy/myopathy. We propose that, in selected patients, COVID-19 may cause phrenic nerve mononeuritis.

INTRODUCTION
COVID-19 is caused by the SARS-CoV-2 virus, which binds to ACE2 receptors to infect human cells. ACE2 receptors have widespread expression within the body, including in airway epithelial cells and in the nervous and skeletal muscle tissues. As such, there are several clinical manifestations of infection, including diaphragmatic dysfunction, perhaps contributing to respiratory failure. Case reports exist which are suggestive of diaphragm weakness in acute COVID-19 infection, but these performed few investigations, limiting the inferences drawn.

A COVID-19 pneumonia follow-up cohort showed evidence of new hemidiaphragm elevation on chest X-ray (CXR). We hypothesised SARS-CoV-2 directly causes phrenic nerve mononeuritis, leading to hemidiaphragmatic palsy, which may contribute to long-term respiratory symptoms. We aimed to set up an outpatient management pathway for these patients.

METHODS
Four hundred and sixty-seven 3-month interval erect CXRs were reviewed from patients with COVID-19 pneumonia in the North Sector of NHS Greater Glasgow and Clyde, Scotland, from March 2020 to January 2021 (see online supplemental appendix 1 for the methods and figure 1).

RESULTS
The mean age of the patients was 60±9 years. Of the 12 clinic patients, only 2 were free from dyspnoea and orthopnoea (see table 1). We did not contact patients without CXR hemidiaphragm elevation to enquire about their symptoms to compare with our cohort, which is a limitation of our study.

CXR and CT thorax
Of 467 patients, 19 (4.1%) had an elevated hemidiaphragm on 3-month interval CXRs; this was a new finding in 15 of 19 patients (3.2% total). Of the 15 patients, 3 were excluded due to functional status or death and so 12 patients attended the clinic.

Of the 12 patients, 5 had no previous imaging available. Of the 12 patients, 2 had elevated left hemidiaphragms, 12 mm and 33 mm above the right hemidiaphragm, respectively. Ten patients had elevated right hemidiaphragms, elevated 59±22 mm above the left hemidiaphragm (mean±SD; range 40–115 mm). Of the 12 patients, 4 had fibrotic changes on CT thorax (see footnote † in table 1) with associated reduction in their FVC percentage predicted and/or gas transfer (for CXRs, see online supplemental figures 1–23). Patient 10 had an MRI of her cervical spine showing osteoarthritis and cervical myelopathy.

Diaphragm ultrasound results
All 12 patients attending the clinic had diaphragm ultrasound: 8 had poor (<10 mm) or paradoxical movements (see footnote * in table 1). Measuring the diaphragm thickening fraction (DTF) was only possible in four patients (see the Discussion section). The diaphragm thickness at end inspiration on the normal side was 5.3±0.7 mm vs 1.7±0.6 mm on the abnormal side. DTF on the normal side measured 89±26% vs 28%±20% on the affected side (mean±SD) (figure 2).

Neurophysiology
Five patients underwent neurophysiology (see footnote ‡ in table 1) because they were symptomatic with abnormal ultrasound. Patients 3 and 10 had phrenic nerve conduction studies (NCS) showing an absent compound muscle action potential (CMAP) on the side of the raised hemidiaphragm, with a normal response on the other side. This could indicate unilateral phrenic nerve axonal pathology or less likely unilateral diaphragm myopathy. Patient 2 had normal NCS, electromyography (EMG) and phrenic studies. Patient 5 had normal NCS and EMG but did not tolerate phrenic nerve studies. In patient 12, phrenic CMAPs were absent bilaterally, perhaps due to technical issues or bilateral phrenic nerve/diaphragmatic muscle pathology.
DISCUSSION

This study revealed at least 3.2% of our cohort had a new elevated hemidiaphragm on CXR after COVID-19 pneumonia, persisting for an average of 7 months following COVID-19 diagnosis. Diaphragmatic weakness may contribute to ‘Long COVID-19’. However, checking for hemidiaphragm elevation on CXR lacks sensitivity and specificity in the diagnosis of unilateral phrenic nerve paralysis (diaphragmatic paralysis) —differential diagnoses relevant here include atelectasis and pulmonary fibrosis. Of the 12 patients, 4 had CT and pulmonary function test in keeping with a diagnosis of pulmonary fibrosis, which could cause elevated hemidiaphragm loss through infraction of intrathoracic volume. Phrenic nerve pathology and critical illness neuropathy/myopathy remained potential differential/contributory diagnoses; hence, muscle function tests (MFTs) and neurophysiology studies are being performed.

Our cohort had normal or restrictive spirometry (except for patient 1, who had COPD). Only two patients met the criteria for unilateral diaphragm dysfunction taken from the European Respiratory Society (ERS) statement on respiratory muscle testing,8 that is, vital capacity <80% and fall in vital capacity >15% when supine; both patients had fibrotic changes on CT thorax. However, seven patients underwent MFTs and five of these had maximal inspiratory pressure (PImax) or sniff nasal inspiratory pressure (SNIP) <60%, predicted, which is another criterion indicating unilateral diaphragmatic dysfunction.8 Moreover, 88% of the patients with ultrasound abnormalities had abnormal MFTs, suggesting potential correlation; a larger sample size is needed to study this hypothesis. Given PImax/SNIP can be affected by underlying lung disease, nasal congestion or artefact from generating a negative mouth pressure with oral muscles (ie, sucking) when tested, the results need clinical context interpretation.

Ultrasound has been used to measure diaphragm dysfunction during acute COVID-19 infection.3–5 Farr et al3 studied 25 inpatients undergoing rehabilitation, having been ventilated for COVID-19 pneumonia. They found 80% had at least one structural or functional diaphragmatic abnormality. Inferences drawn from their study are limited because it was unblinded and they only used ultrasound to assess diaphragm dysfunction, which has disadvantages (see end of paragraph). Our study adds to emerging evidence by demonstrating the chronicity of elevated hemidiaphragm post COVID-19 and its presence in non-ventilated patients. We used ultrasound as an outpatient bedside test of diaphragm function and found it useful because it is readily available, non-invasive and portable. However, ultrasound has limitations, including interobserver and intraobserver variability2 and the diaphragmatic excursion being effort-dependent. Furthermore, agreeing with Maurier et al,4 ultrasound was technically challenging in obese patients, whose zones of apposition were obscured by subcutaneous fat. Diaphragmatic MRI could be used in such patients.9

Importantly, our neurophysiology findings opposed the differential diagnoses of critical illness neuropathy/myopathy, and 8 of 12 patients did not receive invasive mechanical ventilation. We therefore hypothesise that, in certain patients, SARS-CoV-2 directly infects the phrenic nerve or the diaphragm muscle (the former most likely given the hemidiaphragm elevation), agreeing with others.2–5 Recovery from such nerve injury takes time; Summerhill et al10 found return of diaphragm function could take up to 3 years, with a mean recovery time of 14.9 months.

![Figure 1](https://example.com/figure1.png)

**Figure 1** Proposed standard operating procedure to investigate patients found to have new elevated hemidiaphragm on COVID-19 pneumonia three-month interval CXR. Patients were reviewed at the respiratory outpatient clinic by a respiratory physician for history-taking, specifically asking about symptoms suggesting diaphragmatic weakness, for example, dyspnoea and orthopnoea, and those suggesting nocturnal hypoventilation. This was followed by clinical examination and then diaphragm ultrasound. Symptomatic patients also had PFTs, erect and supine VC, and muscle function tests, including PImax and SNIP. The criteria for unilateral diaphragm dysfunction are taken from the European Respiratory Society (ERS) statement on respiratory muscle testing.9 Bloods were taken to screen for causes of neuropathy (unremarkable, aside from mildly elevated glucose and HbA1c in a patient with type two diabetes mellitus and low folate in two patients). Symptomatic patients with lung function and/or ultrasound appearance suggestive of respiratory muscle weakness were referred for neurophysiology. Patients symptomatic of respiratory muscle weakness should be followed up for at least 2 years within the respiratory outpatient clinic. Such patients may require onward referral to thoracic surgery if weakness persists. CXR, chest X-ray; ESR, erythrocyte sedimentation rate; FBC, full blood count; HbA1c, haemoglobin A1c; LFT, liver function tests; PImax, maximal inspiratory pressure; SNIP, sniff nasal inspiratory pressure; TFTs, thyroid function tests; U&E, urea and electrolytes.

### Table 1 Patient characteristics, treatments, imaging findings, and pulmonary function and muscle function test results of those undergoing diaphragm ultrasound examination to investigate new hemidiaphragm elevation post COVID-19 pneumonia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>BMI</th>
<th>MRC Dyspnoea Scale and orthopnoea (Y/N)</th>
<th>Smoking status (current/never/ever)</th>
<th>Significant comorbidities</th>
<th>Level of care</th>
<th>Dex (Y/N %)</th>
<th>Length of hospital stay (days)</th>
<th>Number of days between COVID-19 PCR detection and US</th>
<th>Number of days between COVID-19 PCR detection and latest CXR</th>
<th>Degree of hemidiaphragm elevation on CXR (mm)</th>
<th>US findings and DIFT (%)</th>
<th>FEV₁pp, FVCpp, ratio, DLCOpp and KCOpp</th>
<th>Fall in VC from erect to supine</th>
<th>PImax cmH₂O (%)</th>
<th>SNIP cmH₂O (%)</th>
<th>Summary data</th>
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<td>M</td>
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<td>4, Y</td>
<td>Current</td>
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<td>HDU, CPAP</td>
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<td>9</td>
<td>18±24</td>
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<td>24±101</td>
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<td>-</td>
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<td>HTN</td>
<td>HDU, CPAP</td>
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<td>45</td>
<td>-</td>
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Continued
Brief communication

Hence, we propose symptomatic patients undergo surveillance for 2 years before considering onward referral to thoracic surgery for consideration of plication.11

Future prospective research should ascertain whether diaphragmatic dysfunction aids prognostication in COVID-19, regarding both ventilator weaning and the likelihood of developing long-term respiratory symptoms. Correlation between

**Table 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>BMI</th>
<th>MRC Dyspnoea Scale</th>
<th>Orthopnoea (Y/N)</th>
<th>Smoking status (current/ex/never)</th>
<th>Significant comorbidities</th>
<th>Level of care</th>
<th>Dex (Y/N %)</th>
<th>Length of hospital stay (days)</th>
<th>Number of days between COVID-19 PCR detection and latest CXR</th>
<th>Number of days between COVID-19 PCR detection and US</th>
<th>Degree of hemidiaphragm elevation (mm)</th>
<th>US findings and DTf (%)</th>
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<td>Intensive Care Unit</td>
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<td>12</td>
<td>199</td>
<td>175</td>
<td>33</td>
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**Figure 2** (Top) Chest X-ray progression of patient 3 throughout the COVID-19 illness (days since positive COVID-19 PCR detection), from top left, clockwise: (A) day 3; (B) day 19, in medical high dependency; (C) day 47 in Intensive Treatment Unit (ITU); and (D) day 88, post-COVID-19 pneumonia outpatient follow-up. Note the new elevation of the right hemidiaphragm, most marked on images C and D, which persists after resolution of the consolidative changes. The position of the hemidiaphragms is highlighted by the arrows (red arrows: right; white arrows: left). (Bottom) Ultrasound images of the same patient’s hemidiaphragms, performed 7 months following COVID-19 pneumonia diagnosis. Diaphragm ultrasound was performed using intercostal and subcostal approaches, as described elsewhere.8 9 We used a Sonosite Edge II ultrasound machine (Fujifilm Sonosite, Europe). Diaphragmatic excursion was measured with two-dimensional and motion (M) mode imaging using a 5-2 MHz curved probe via a subcostal view (A and C). Excursion of the hemidiaphragm is almost absent on the right (A) compared with the left hemidiaphragm (4.73 cm, normal) (C). Diaphragmatic thickness was measured using a 13-6 MHz linear probe via an intercostal view at the zone of apposition (B and D). Diaphragm thickness at end inspiration/expiration was measured to calculate diaphragm thickening fraction (DTf) for both hemidiaphragms, where DTf=(end-inspiration thickness−end-expiration thickness)/end-expiration thickness×100. DTf <20% is highly suggestive of diaphragm dysfunction.8 9 Right DTf=((0.13−0.11)/0.11)×100=18%; left DTf=((0.43−0.19)/0.19)×100=126%.

Hence, we propose symptomatic patients undergo surveillance for 2 years before considering onward referral to thoracic surgery for consideration of plication.11

Future prospective research should ascertain whether diaphragmatic dysfunction aids prognostication in COVID-19, regarding both ventilator weaning and the likelihood of developing long-term respiratory symptoms. Correlation between
ultrasound and diaphragm MRI would be of interest. Finally, we should describe the natural progression of this pathophysiological process to determine whether therapeutic intervention for diaphragmatic paralysis is indicated.

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REFERENCES