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COPD and COVID-19 Pneumonia: A Retrospective Single Center Analysis of Respiratory Status and Outcome

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Abstract: Acute respiratory syndrome caused by SARS-CoV-2 is associated with severe mortality in the general population. COPD patients are at risk for severe pneumonia and poor prognosis associated with COVID-19 infection. This may be due to insufficient lung reserve or the expression of the ACE-2 receptor in the small airways. We wanted to find out if COPD patients had more severe COVID-19 pneumonia and worse clinical outcomes. We did a retrospective analysis of 101 patients with COVID-19 admitted to the Pulmonology Department of Monaldi Hospital (Naples) from November 2020 to May 2021. The calculated criteria were obtained only by patients with positive real-time reverse-transcriptase-polymerase chain reaction (RT-PCR). The study included computed tomography (CT) scans with specific COVID-19 results. We used fractional inhaled oxygen (PaO_2/FiO_2) to assess respiratory status and Chung score on chest TC to assess the severity of COVID-19 pneumonia. We investigated comorbidities, need of ventilation (NIV/CPAP), hospitalization and patients' outcome. We used descriptive statistics, Chi square test and independent sample test to analyze our population. Out of 101 patients, 10,89% of them had COPD in anamnesis or had enphysema on chest TC. In the patients without COPD the mean P/F ratio was 167,9 (SD: 93.854). Their mean Chung score was 12,178 (SD: 3,505). They had an average of 20.111 (SD: 11.037) hospitalization days. 40% of them needed non-invasive ventilation (including CPAP) and 28,9% of them died. In patients with COPD the mean P/F ratio was 124,273 (SD: 61,254). Their mean Chung score was 11,727 (SD: 4,149). They had a mean hospitalization days of 22,273 (SD: 11,714). 63,636% of them needed non-invasive ventilation (including CPAP) and 72,727% of them died. In COPD patients we observed a higher prevalence of obesity, a higher number of deaths and a higher LDH value. In particular in obese patients that needed noninvasive ventilation we found a longer hospitalization and a higher LDH value. Although the two groups studied had the same severity of respiratory status and pneumonia, we found a worse outcome in patients with COPD.

Keywords: COVID-19, COPD, Obesity, Lactate Dehydrogenase

1. Introduction

In December 2019 multiple cases of unexplained respiratory diseases with similar clinical manifestations emerged in the Wuhan City Hubei Province of China. The emergence of a new type of pneumonia of unknown origin was the beginning of an outbreak that became a pandemic declared by the World Health Organization [1]. The acronym COVID-19 means "coronavirus disease 2019" and began to be used on February 11, 2020. [2] Sars-CoV2 (severe acute respiratory syndrome coronavirus 2) is a novel coronavirus that belongs to a family of isolated RNA viruses, some of which have been previously described to cause Severe Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [3]. The symptoms and clinical manifestations of COVID-19 are similar to SARS and MERS

but its prevalence is higher [4]. Up to May 2022 there were 516476402 confirmed cases of COVID-19 worldwide, including 6258023 confirmed deaths. [5] Pneumonia and acute respiratory distress syndrome are major complications of COVID-19.

SARS-CoV-2 infection can activate innate and adaptive immune responses and lead to severe inflammatory responses later in the disease. These uncontrolled inflammatory responses can lead to local and systemic tissue damage and the severity of disease depends on serum levels of proinflammatory cytokines. [6].

Most patients with COVID-19 experience mild to moderate symptoms. Some infected individuals may develop excessive inflammation caused by the production of large amounts of cytokines. The virus initially invades the respiratory mucosa and then infects other cells, triggering an immune response producing a systemic cytokine release syndrome (CRS). [7]. CRS often leads to systemic inflammation and failure of many organs such as lungs and may result in severe pneumonia. [8]. CRS can be caused directly by viral damage or indirectly by over-activation of the immune system that stimulates immune cells such as neutrophils and macrophages to invade tissues. Theoretically, this is a protective response to limit the spread of the virus. Several studies have shown that levels of various cytokines such as TNF-α IL-6 IL-17 IL-17 and IL-1β are significantly increased in COVID-19. High levels of IL-6 appear to be associated with critical illness.

The angiotensin converting enzyme 2 (ACE2) regulates the renin-angiotensin system. ACE2 converts angiotensin (Ang) II to Ang 1-7 to regulate blood pressure homeostasis and acts to prevent lung damage too. We can find it in different parts of the human body, but its main expression is in the kidneys, intestine and on the epithelial cell membrane of the respiratory tract [9]. SARS-CoV-2 binds to ACE-2 cell receptors [10] and activates the pro-inflammatory cascade. [11].

The Ang II hormone stimulates cytokines release such as IL-6 IL-8 and TNF-α. Ang1-7 is a vasodilator hormone involved in the anti-inflammatory response to prevent lung damage. When SARS-CoV-2 enters the host cell, ACE2 expression reduces.

ACE2 down-regulation is associated with RAS imbalance, growth of inflammatory response and organ damage [12] with the development of fever, muscle aches and dyspnea. In an experimental hamster model the virus caused temporary damage to olfactory epithelial cells, causing a sensory dysfunction that explains the temporary loss of taste and smell. [13] ACE 2 receptors are found not only in the small respiratory tract but also in other parts of the epithelium or endothelium. [14] It is not known if pathological changes or endothelial dysfunction of the respiratory system are the direct result of viral infection disorders or they are the result of the association of several factors such as the increase in cytokines and the coagulation disorders.

Several reports showed that high levels of CRP, PCT, D-dimer, LDH and ferritin are associated with more severe clinical course and are able to predict poor prognosis [15].

C-reactive protein (CRP) is an acute phase protein commonly used as an indicator of systemic inflammation, clearly suggesting the possibility of using this easy marker to predict disease progression risk in patients with COVID-19.

High CRP levels are strongly associated with excessive production of inflammatory cytokines and tissue destruction found in patients with severe COVID-19. [16].

D-Dimer is a product of fibrinolytic degradation and it is another important inflammatory index. It is usually increased in hypercoagulation conditions such as deep vein thrombosis, pulmonary embolism or disseminated intravascular coagulation. Elevated D-Dimer levels have also been found in patients with severe COVID-19 that is closely associated with increased mortality. [17] Procalcitonin (PCT) is calcitonin precursor synthesized by parafollicular C cells of the thyroid gland. Its synthesis increases during infections thanks to the action of TNF-α and interleukin 6. PCT blood level seems to be associated with COVID-19 severity too. [17] High lactate dehydrogenase (LDH) level is usually considered an indicator of tissue and cell damage. [18] LDH could be related to the severity of COVID-19 pneumonia and could also guide doctors in choosing therapeutic strategy such as the kind of oxygen-therapy or non-invasive ventilation. [19].

2. COPD and COVID-19

COPD is the third cause of death in the world. It had a prevalence of 251 million cases in 2016. Smoking, gases and particulate exposure can damage the respiratory tract leading to the development of airway obstruction. [20-22].

In recent years there has been an increase in COPD in developing countries due to increased exposure to tobacco, an aging population and a lack of access to diagnosis. [23].

COPD exacerbations are often associated with hospitalization and poor prognosis. [24].

Flare-ups can be caused by bacteria, but above all viral infections such as coronavirus and they often lead to worsening of symptoms and respiratory failure. [25].

COVID-19 can have a bad impact on lung function and caution is needed, especially in patients with COPD. So we would like to know if Sars-CoV2 cause more COPD exacerbations, more hospitalizations or more deaths.

In scientific literature the reporting on cases of COPD has concentrated always on hospitalised and intensive care unit (ICU) patients. [26].

Even before the pandemic there was an underestimation of the prevalence of COPD. From the pandemic due to the reduced availability of performing spirometry, the disease in many cases has not been diagnosed. [27].

The method for determining COPD diagnosis in previous research has not been precisely defined, which could lead to variations in prevalence around the world.

COPD prevalence has ranged from 0% to 10% in Chinese studies reporting on hospitalized patients. [28].

As data from other countries has become available, COPD rates among hospitalized COVID-19 patients appear to be similar, with estimates ranging from 5.6 to 9.2 percent in Italy. [29, 30].

COPD may be a risk factor for more severe COVID-19, according to recent available data. [31].

COPD patients appear to have a greater risk of severe COVID-19 pneumonia and poor outcomes.

This could be due to the loss of respiratory reserves or higher ACE-2 receptor expression in airways. [26].

SARS-CoV-2 enters the cells thanks to his envelope spike protein, which is triggered by the cellular serine protease TMPRSS2 to facilitate fusion of the virus with the cell's angiotensin converting enzyme 2 (ACE-2) receptor. [32, 33].

Janice M. Leung et colleagues recently shown that ACE-2 expression was considerably higher in COPD patients compared to control people in three separate cohorts with accessible gene expression profiles from bronchial epithelial cells. [34] Other researchers confirmed that current smoking was also linked to greater ACE-2 expression in airway epithelial samples when compared to former and never smokers. [35, 36].

COPD patients have more comorbidities and consequently an increased risk of hospitalization. [37].

According to the most recent reviews, the severity of COVID-19 appears to be related to a higher prevalence of comorbidities in patients. [38].

3. Aim

We want to verify if patients with COPD have more severe COVID-19 pneumonia, based on respiratory status and radiological involvement and if they have a worse clinical course based on the hospitalization end need of non-invasive ventilation (CPAP/NIV) and if they have worse outcomes. We also want to verify if other comorbidities can affect COPD patients' outcome.

4. Methods

We did a retrospective analysis of 101 COVID-19 patients (56 males and 45 females) admitted to the Pulmonology Department of Monaldi Hospital (Naples) from November 2020 to May 2021. In addition to age and sex, clinical information collected included severity of symptoms and comorbidities.

Only patients with positive real-time reverse-transcriptase-polymerase chain reaction (RT-PCR) and highly suggestive symptoms with computed tomography (CT) imaging results with typical findings of COVID-19 were enrolled in the study.

Typical CT findings included bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, sometimes with a rounded morphology and a peripheral lung distribution.

We evaluated the level of some inflammatory indices (CRP, procalcitonin, LDH, D-dimer) and we used fractional inspired oxygen ratio (PaO_2/FiO_2) to evaluate respiratory status and Chung score on chest TC to evaluate the severity of COVID-19 pneumonia. We analyzed the comorbidities of all patients, the need for non-invasive ventilation, the days of hospitalization and patients' outcome.

The comorbidities that we investigated are arterial hypertension, obesity (patients with BMI>30 kg/m^2), diabetes, ischemic heart disease, atrial fibrillation, COPD, cancer in the last five years, chronic renal failure, dementia, chronic liver disease and stroke.

Imaging findings of viral pneumonias are varied, overlapping with other infectious and inflammatory lung diseases. Viruses in the same viral family share a similar pathogenesis; therefore, CT may help identify distinguishing patterns and features in immunocompetent patients. [39] We analyzed the Chung TC score of our patients.

Chung score evaluate for the following radiologic characteristics in patients with Sars-CoV2: *(a)* presence of ground-glass opacities, *(b)* presence of consolidation, *(c)* number of lobes affected by ground-glass or consolidative opacities, *(d)* degree of lobe involvement, in addition to overall lung "total severity score," *(e)* presence of nodules, *(f)* presence of a pleural effusion, *(g)* presence of thoracic lymphadenopathy (defined as lymph node size of ≥10 mm in short-axis dimension), and *(h)* presence of underlying lung disease such as emphysema or fibrosis.

Each of the five lung lobes is assessed for the degree of involvement and classified as none (0%), minimal (1%–25%), mild (26%–50%), moderate (51%–75%), or severe (76%–100%). No involvement correspondes to a lobe score of 0, minimal involvement to a lobe score of 1, mild involvement to a lobe score of 2, moderate involvement to a lobe score of 3, and severe involvement to a lobe score of 4. An overall lung "total severity score" is reached by summing the five lobe scores (range of possible scores, 0–20). [40].

We used fractional inspired oxygen ratio (PaO_2/FiO_2) to evaluate respiratory status of patients.

According to the Berlin criteria of 2012, PaO_2/FIO_2 ratio must be evaluated with PEEP or CPAP greater than or equal to 5 cm H_2O. If it is between 200 and 300 mmHg it is defined as a mild ARDS, if it is between 100 and 200 mmHg a moderate ARDS and if it is less than 100 mmHg a severe ARDS.

5. Data Analysis

We used descriptive statistics to describe the sample and the recorded clinical features. Continuous variables were expressed as the mean and standard deviation (SD), whereas categorical variables are given as numbers and percentages for the total sample (N = 101) and distribution in demographic groups, i.e. males and females and according to patients with or without a diagnosis of COPD. Some registrations were missed, resulting in lower numbers of participants in some different investigated variables. The Chi-square test was used for testing statistically significant differences between categorical variables, whereas the independent sample test was used for testing statistical significant difference of continuous variables according to the two groups in the study. Differences were considered statistically significant when the p value was less than 0.05. Statistical analysis was performed using JASP 0.16.2 (Jeffreys's Amazing Statistics Program).

6. Results

In table 1 there are demographic and clinical features of the 101 patients we studied. There were 56 males and 45 females. The mean age was about 68 years. 78% of patients (n: 79) were non smokers, about 15% were current smokers and about 7% of them were former smokers.

We analyzed the prevalence of comorbidities (Tables 1-2) at first in all the population of the study and after in patients with or without a diagnosis of COPD. 10,8% (n: 11) of patients had COPD anamnesis or emphysema on chest TC.

In the total sample the most frequent comorbidity was arterial hypertension (66.3%). Arterial hypertension and obesity have been shown to be more frequent in COPD than in non-COPD group, but only for obesity it has been possible to hypothesize a relationship with COPD because we reached statistical significance in the analysis. (p value 0.008).

In the Table 3 we reported the prevalence of the main clinical features on admission both for the whole population and for the two groups (COPD vs non-COPD).

In the total sample the most frequent symptom was dyspnea (89%) followed by fever and cough; in only 10-15% of patients were present anosmia/ageusia and diarrhoea/vomit. For the blood gas arterial analysis the mean value of PaO_2/FiO_2 ratio was 163.149 (SD: 91.659), the mean Chung score was 12.129 (SD: 3.560), the mean D-dimer was 860.545 (SD: 2711.925), the mean CRP was 8.397 (SD: 6.560), the mean procalcitonin was 0.186 (SD: 0.341). There were no statistically significant differences between the two groups studied.

Among the inflammatory indices only the LDH value was more elevated in COPD group: 532.000 (SD: 370.900) with p value 0.008.

We analyzed respiratory support, hospitalization and outcome in all the population and in patients with or without a diagnosis of COPD (Table 4). About 39.6% (n: 40) of all patients needed CPAP and 2.97% (n: 3) needed NIV; the other patients were treated with high flow oxygen terapy (HFNC) (38.6%) and low flow oxygen therapy (18.8%), without statistical significance between the two cohorts. The mean hospitalization was 20.347 (SD: 11.072) days, without significant difference between COPD e non-COPD groups. 71% of patients without a diagnosis of COPD discharged (n: 64) and 72.7% of COPD patients (n: 8) died (p value 0.004).

At the end, we selected all the patients who needed non-invasive ventilation: 7 (42.574%) of them had a diagnosis of COPD and 36 (40%) of them were non-COPD. We evaluated also the severity of ARDS (Table 5) and we found not significative statistical differences in the two groups studied. In patients ventilated, we observed that obese patients needed more hospitalization days (p value 0.032) and had a higher serological LDH index (p value 0.019) (Figure 1).

Table 1. *Demographic and clinical characteristics of the total sample and divided by gender.*

	Total sample n (%)	**Gender**	
		Males n=56 (55.446%)	**Females n=45 (44.554%)**
Age, mean (SD)	**68.327 (12.945)**	**65.375 (12.650)**	**72.000 (12.488)**
Smoking:	**n (%)**	**n (%)**	**n (%)**
Non smoker	79 (78.218)	39 (69.643)	40 (88.889)
Current smoking	15 (14.851)	11 (19.643)	4 (8.889)
Former smoker	7 (6.931)	6 (10.714)	1 (2.222)
Comorbidities:	**n (%)**	**n (%)**	**n (%)**
Arterial hypertension	67 (66.337)	36 (64.286)	31 (68.889)
Obesity	23 (22.772)	15 (26.786)	8 (17.778)
Diabetes	17 (16.832)	8 (14.286)	9 (20.000)
Ischemic heart disease	13 (12.871)	10 (17.857)	3 (6.667)
Atrial fibrillation	13 (12.871)	6 (10.714)	7 (15.556)
COPD	11 (10.891)	6 (10.714)	5 (11.111)
Cancer	8 (7.921)	5 (8.929)	3 (6.667)
Chronic renal failure	5 (4.950)	1 (1.786)	4 (8.889)
Dementia	3 (2.970)	0 (0.000)	3 (6.667)
Chronic Liver disease	2 (1.980)	1 (1.786)	1 (2.222)
Stroke	1 (0.990)	0 (0.000)	1 (2.222)

Table 2. *Comorbidities divided by COPD.*

	COPD n (%)	**Non-COPD n (%)**	**p value**
Arterial hypertension	9 (81.818)	58 (64.444)	0.250
Obesity	6 (54.545)	17 (18.889)	0.008
Diabetes	2 (18.182)	15 (16.667)	0.899
Ischemic heart disease	2 (18.182)	11 (12.222)	0.577
Atrial fibrillation	2 (18.182)	11 (12.222)	0.577
Cancer	2 (18.182)	6 (6.667)	0.182
Chronic renal failure	0 (0.000)	5 (5.556)	0.423
Dementia	1 (9.091)	2 (2.222)	0.205
Chronic Liver disease	0 (0.000)	2 (2.222)	0.618
Stroke	0 (0.000)	1 (1.111)	0.725

Table 3. *Clinical variables at admission.*

Symptoms:	Total sample	COPD	Non-COPD	p value
	n%	n%	n%	
Dyspnea	90 (89.109)	10 (90.909)	80 (88.889)	0.839
Fever	77 (76.238)	6 (54.545)	71 (78.889)	0.073
Cough	67 (66.337)	6 (54.545)	61 (67.778)	0.381
Ageusia/Anosmia	10 (9.901)	0 (0.000)	10 (11.111)	0.244
Diarrhea/Vomit	14 (13.861)	2 (18.182)	12 (13.333)	0.660
ABG:	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p value**
Ph	7.476 (0.043)	7.486 (0.044)	7.475 (0.026)	0.399
pO_2	69.089 (18.142)	67.636 (17.212)	69.267 (18.337)	0.780
pCO_2	35.257 (5.466)	36.364 (5.988)	35.122 (5.419)	0.480
HCO_3^-	26.081 (3.669)	27.436 (4.208)	25.916 (3.589)	0.196
Lac	1.526 (0.633)	1.364 (0.434)	1.546 (0.652)	0.371
PaO_2/FiO_2	163.149 (91.659)	124.273 (61.254)	167.900 (93.854)	0.137
Chung score	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p value**
	12.129 (3.560)	11.727 (4.149)	12.178 (3.505)	0.694
Inflammatory indices:	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p value**
CRP	8.397 (6.560)	6.364 (5.714)	8.646 (6.641)	0.278
Procalcitonin	0.186 (0.341)	0.145 (0.295)	0.191 (0.348)	0.681
LDH	389.416 (190.302)	532.000 (370.900)	371.989 (149.714)	0.008
D-dimer	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p value**
	860.545 (2711.925)	409.273 (272.878)	915.700 (2868.260)	0.561

Table 4. *Results.*

Respiratory support:	Total sample	COPD	Non-COPD	p value
	n (%)	n (%)	n (%)	
CPAP	40 (39.604)	6 (54.545)	34 (37.778)	0.309
HFNC	39 (38.614)	2 (18.182)	37 (41.111)	
O_2	19 (18.812)	2 (18.182)	2 (2.222)	
NIV	3 (2.970)	1 (9.091)	17 (18.889)	
Hospitalization	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p value**
	20.347 (11.072)	22.273 (11.714)	20.111 (11.037)	0.544
Outcome:	**n (%)**	**n (%)**	**n (%)**	**p value**
Discharged	67 (66.337)	3 (27.273)	64 (71.111)	0.004
Dead	34 (33.663)	8 (72.727)	26 (28.889)	

Table 5. *Ventilated patients divided by ARDS severity and by presence of COPD.*

ARDS	Total ventilated patients	COPD	Non-COPD	p value
	n (%)	n (%)	n (%)	
Mild	3 (6.977%)	0 (0.000%)	3 (100.000%)	0.720
Moderate	16 (37.209)	3 (18.750%)	13 (81.250%)	
Severe	24 (58.814)	4 (16.667%)	20 (83.333%)	

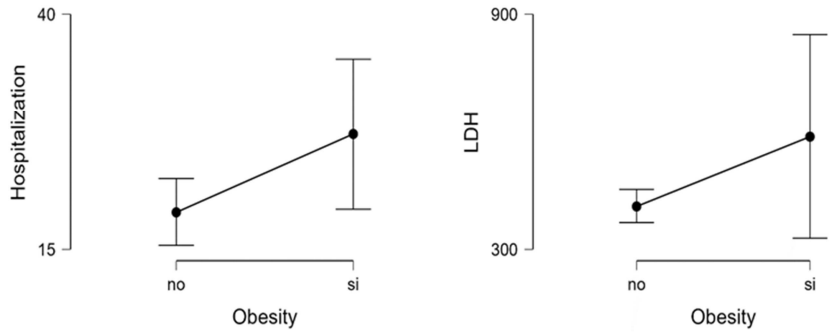

Figure 1. *Hospitalization and LDH values in obese ventilated patients.*

7. Discussion

According to recent reviews, the severity of COVID-19 appears to be related to a higher prevalence of comorbidities in hospitalized patients. [41, 42]

We analyzed in particular patients with COPD. They did not have a statistical significant difference from the rest of the study population in respiratory status assessed by PaO_2/FiO_2 and pneumonia severity based on Chung TC score. The same applies to the days of hospitalization and the need for ventilation. However, we noted that COPD patients have a worse outcome than non-COPD patients. Why?

In our study, patients with COPD have a higher prevalence of obesity. COPD has severe systemic effects [43] including weight loss and skeletal muscle atrophy, in addition to the progressive airflow limitation, lung hyperinflation, and progressive dyspnea.

However, the present world obesity is altering the traditional nutritional irregularities seen in COPD patients.

In addition to cachexia with loss of muscle mass we have that many people with COPD are overweight or obese. [44].

According to studies, adipose tissues are high in ACE2 receptors, which act as gateways for SARS-CoV-2 to enter human cells. Obesity can also affect immune function and increase vulnerability to infections. Several recent meta-analyses showed that obesity was associated with poor prognosis of COVID-19. [45].

Among the inflammatory indices only the LDH value was more elevated in the COPD group with statistical significance. In literature high lactate dehydrogenase level was significantly associated with severe COVID-19 pneumonia on admission. [19] The increased LDH level was considered an indicator of tissue and cell destruction, as well as the damage usually induced by SARS-CoV-2. [18] Lactate dehydrogenase enzyme (LDH) is a sensitive indicator of the cellular metabolic state, aerobic or anaerobic direction of glycolysis and cell injury.

We know that COPD patients have a worse metabolic state with muscle fatigue due to their pathology. They have airflow restriction and geometrical alterations in the thorax caused by pulmonary hyperinflation and their muscles must work against high mechanical loads.

In most situations, the damage and adaptation of the respiratory muscles achieve a balance that allows for enough breathing for the patient's survival.

Diaphragm and other respiratory muscles can respond to the disease's persistent mechanical load by expressing adaptive alterations.

This equilibrium, however, can be altered by mechanical or metabolic stress on the muscles such as pneumonia or pulmonary embolism. [46].

When compared to healthy smoking and non-smoking groups, patients with COPD have higher resting serum LDH activity. [47].

At this point we assume that the combination of COPD and SarsCoV2 infection can lead to a relevant metabolic dysregulation.

8. Conclusions

Sars-CoV-2 infection is associated with high mortality in COPD hospitalized patients, despite the low prevalence of COPD reported COVID-19 cases. We can conclude that patients with COPD, with the same respiratory status and severity of pneumonia compared to the remaining population under examination, have a worse outcome. This could be related to the higher prevalence of obesity and a worse underlying metabolic state probably due to respiratory muscle fatigue in association with cytokine dysregulation and increased inflammation due to viral infection.

Further studies would be needed on larger population samples.

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