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Review article

Acute neuromuscular syndromes with respiratory failure during COVID-19 pandemic: Where we stand and challenges ahead

Giuliana Galassi a,⁎, Alessandro Marchioni b

a Department of Biomedical, Metabolic, and Neural Sciences, University Hospitals of Modena, Italy
b Respiratory Diseases Unit, Department of Medical and Surgical Sciences, University Hospitals of Modena, Italy

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ABSTRACT

Coronavirus disease 2019 (COVID-19), a disease caused by the novel betacoronavirus SARS-COV-2, has become a global pandemic threat. SARS-COV-2 is structurally similar to SARS-COV, and both bind to the angiotensin-converting enzyme 2 (ACE2) receptor to enter human cells. While patients typically present with fever, shortness of breath, sore throat, and cough, in some cases neurologic manifestations occur due to both direct and indirect involvement of the nervous system. Case reports include anosmia, ageusia, central respiratory failure, stroke, acute necrotizing hemorrhagic encephalopathy, toxic-metabolic encephalopathy, headache, myalgia, myelitis, ataxia, and various neuropsychiatric manifestations. Some patients with COVID-19 may present with concurrent acute neuromuscular syndromes such as myasthenic crisis (MC), Guillain–Barré syndrome (GBS) and idiopathic inflammatory myopathies (IIM); these conditions coupled with respiratory failure could trigger a life-threatening condition. Here, we review the current state of knowledge on acute neuromuscular syndromes with respiratory failure related to COVID-19 infection in an attempt to clarify and to manage the muscle dysfunction overlapping SARS-COV-2 infection.

1. Introduction

Corona Virus Disease 2019 (COVID-19) is a new illness caused by a novel coronavirus (SARS-COV-2) [1-3]. Although the large majority of patients infected with SARS-COV-2 have mild symptoms, a proportion of cases develop acute respiratory distress syndrome (ARDS) and multi-organ failure [1-3].

Previous works [1-12] highlighted neurologic manifestations in patients infected with the coronavirus. The infection potentially arises from hematogenous spread and/or neuronal retrograde dissemination. Similar to other coronaviruses, SARS-COV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor to access human cells [1-6]. Since intranasal infection of mice with either SARS or MERS results in virus access to the brain, it is likely that SARS-COV-2 can also penetrate the nervous system [1-6]. Entry to the central nervous system (CNS) would be facilitated by the expression of the SARS-COV-2 receptor ACE2 in the brain, where it acts as a cell surface peptidase present on the surface of endothelial cells, arterial smooth muscle cells and neurons [6,9-11]. Management of neuromuscular diseases (NMD) becomes a challenge since most of them are chronic, disabling, progressive and may require immunosuppressive drugs. The respiratory failure related to COVID-19 in patients with acute NMD can arise from distinct conditions: 1) the immune-mediated viral damage of the lung, 2) the dysfunction of the respiratory muscles [1-6,9,10]. From a pathogenetic point of view, the cytokine storm (CSS) and the immunological dysregulation constitute the underlying mechanism common to these two conditions. The aim of this review is to summarize the current knowledge on the pathogenesis and management of acute NMD with respiratory failure during COVID-19 pandemic.

2.1. Cytokine storm syndrome (CSS) and immunological dysregulation: The common route leading to respiratory failure in COVID-19

The CSS associated with a dysregulated immune response represents a main pathogenetic mechanism of severe COVID-19 disease, which
encompasses fever, coughing, dyspnea and pneumonia [9,11,13,14]. In most severe cases, cytokine release shows clinical and laboratory features similar to hemophagocytic lymphohistiocytosis or macrophage activation syndrome (HLH/MAS), a hyperinflammatory disease characterized by hyper-cytokinaemia and multiorgan failure [13,14]. HLH/MAS typically exhibits high fever, elevated ferritin levels and hypertriglyceridemia associated with massive release of different cytokines. Interleukin 6 release (IL-6) and the activation of endothelial cells are both hallmarks of HLH/MAS, but also of severe SARS-COV-2 infection, and play an important role in vascular leakage, activation of the complement and coagulation cascade [14]. The hyperinflammatory status related to severe COVID-19 is characterized by upregulation of proinflammatory cytokines such as IL-1β, IL-6, IL-7, IL-17, TNF-α, granulocyte-colony stimulating factor (g-CSF), interferon-γ inducible protein 10, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1-α, thus resembling the cytokine profile described in HLH/MAS [13]. Moreover, a subset of patients who died from severe SARS-CoV-2 infection showed hemophagocytosis in the pulmonary lymphnodes, a typical marker of HLH/MAS [15,16]. However, while in HLH/MAS, the immunological derangement is accompanied by systemic disseminated intravascular coagulation and hepatosplenomegaly, in severe COVID-19, the pathological manifestations are observed mainly in the lung, with development of ARDS and pulmonary thrombotic microangiopathy [1,13,14]. Furthermore, ferritin, a marker of disease activity and macrophage activation typically hyper-expressed in HLH/MAS, is upregulated in response to IL-1β and IL-6 during severe SARS-COV-2 infection and showed a correlation with poor outcome, suggesting a further amplification of the inflammatory process [15,16]. The magnitude of CSS in SARS-COV-2 infection may be enhanced by the immunological dysregulation described in patients with severe COVID-19 [1,13,14]. Regulatory T cells (Tregs) are a subset of CD4 T cells which have a role in inducing immune tolerance, preventing autoimmune diseases and limiting aggressive immune responses to viral infections [17]. Decrease of Treg levels in peripheral blood could play a role in the inability to limit cytokine storm and in delaying the resolution of acute lung injury [17,18]. Treg depletion has been described in severe COVID-19, but also in other viral infections such as respiratory syncytial virus (RSV) [18]. Imbalance between regulatory (i.e. Tregs) and effector arms (i.e. neutrophils, Th17 cells, macrophages, dendritic cells) of immune response, ultimately results in virus-induced inflammatory tissue damage inducing ARDS development but also affecting other organs, including the nervous system [19]. Indeed, in a murine-model of acute encephalitis induced by coronavirus, Treg depletion is associated with amplification of tissue damage and poor outcome [20]. Moreover, Treg depletion in animal model of RSV infection increased inflammatory cytokine and chemokine release in the airway and enhanced cellular influx into the lungs promoting tissue injury [21].

2.2. Acute respiratory failure due to immune-mediated pulmonary injury in severe SARS-COV-2 infection

Patients affected by COVID-19 exhibit flu-like symptoms (i.e. fever, fatigue, myalgias, cough) in 81% of cases, while in about 14% of cases severe disease usually occur 1 week after the onset of symptoms with
hypoxemia and progressive development of acute respiratory failure [1-3,5-9,12]. Among the hospitalized patients, up to 30% require ICU care, with mortality rates ranging between 20% and 26% in the critically ill, but this rate can reach 89% in patients undergoing mechanical ventilation (MV) [5]. The time course of SARS-COV-2 manifestations in patients with more severe disease appears to be related to low innate antiviral defenses and high pro-inflammatory cues of cytokine storm development [1,3,5,9,13-16,22]. SARS-COV-2 elicits an initial weak IFN response followed by IFN peak levels resulting in a delayed neutrophil recruitment in the lungs, a prolonged immune stimulation and an increased peak of cytokine, with development of lung injury 7–10 days after the onset of symptoms [23-25].

From a pathogenesis standpoint, SARS-COV-2 infects alveolar cells replicating in lung tissue and inducing recruitment of leukocytes related to the upregulation of chemokine profile. Transcriptional analysis of bronchiolar-lavage fluid obtained from patients affected by COVID-19 showed overexpression of CXCL-2 and CXCL-8 chemokines, that play a critical role in the recruitment of polymorphonuclear cells into the lung [26]. Activated neutrophils accumulation in the alveolar spaces induces reactive oxygen species (ROS) release, such as superoxide radicals and H2O2 and proteolytic enzyme secretion (i.e. neutrophil elastase), leading to damage in the alveolar-capillary barrier, inflammatory edema formation and activation of coagulation [26,27]. Furthermore, the release of neutrophils extracellular traps (NETs) in an attempt to contain the viral infection may play a role in enhancing lung injury and microvascular thrombosis in COVID-19 [27,28]. NETs consist of extracellular DNA fibers comprised of histone and cytoplasmic granule proteins, that provide a scaffold for the binding of platelets, red blood cells and plasma proteins. NETs could act with the immobilization of viruses and bacteria and with the reduction of inflammation through cytokines and chemokines degradation [29]. On the other hand, NETs are also implicated in enhanced tissue injury via endothelial damage and microvascular thrombosis [30].

In COVID-19 pneumonia, the impaired lung perfusion due to pulmonary angiopathy and thrombosis plays a major role in the pathogenesis of respiratory failure, especially in patients with non-ARDS radiological findings [31]. Furthermore, the pathological perfusion in COVID-19 lungs includes disruption of the renin-angiotensin system (RAS) and severe endothelial injury with loss of hypoxic pulmonary vasoconstriction function [31]. SARS-COV-2 binding to receptors results in downregulation and loss of ACE2 function in lung, producing dysregulation of the RAS system. Indeed, ACE2 acts through negative regulation of the RAS system by converting angiotensin II to angiotensin 1-7, which stimulates the vasodilatation of lung vasculature via nitric oxide release, and exerts anti-inflammatory activity [31]. Thus, the download of ACE receptors caused by the virus leads to an increased synthesis of angiotensin II in the lung that may result in an alteration of hypoxic pulmonary vasoconstriction with worsening of ventilation-perfusion mismatch (Fig. 1). Finally, the respiratory failure is the result of severe viral alveolitis and concomitant pulmonary perfusion dysfunction, which justifies the heterogeneity of the clinical presentations with different radiological patterns (Fig. 1). The marker of respiratory failure due to lung and perfusion injury is hypoxemia without hypercapnia.

2.3. Pathways of neurological involvement

Peripheral (PNS) and CNS diseases related to SARS-COV-2 infection may arise from different pathways of virus-mediated tissue injury: 1) hematogenous or trans-neuronal route, 2) CNS and blood brain barrier (BBB) damage, 3) autoimmune response [1-6,9,10]. The first mechanism seems related to the most common neurological symptoms of SARS-COV-2 infection such as hypogeusia, hyposmia, headache, vertigo, and dizziness. It has been speculated that SARS-COV-2 infected damaged endothelial cells of the BBB allow direct passage into the CNS.
Table 1
Summary of the demographic characteristics of adult patients with myasthenia gravis (MG) requiring respiratory support during SARS-COV-2.

| Authors | Age/sex | MGFA classification prior COVID-19 | MGFA classification during COVID-19 | Abs | MG symptom worsen | Lung – CT scan | Therapy | Outcome |
|---------|---------|----------------------------------|-----------------------------------|-----|-----------------|---------------|---------|---------|
| Anand et al [37] | 57/M | I | V | AChR | Hypoosmia, respiratory failure | NR | HCQ,AZM, MV, IVIG | Recover |
| Anand et al [37] | 64/M | Pharmacological remission | V | AChR | Hypoosmia, respiratory failure | NR | HCQ,AZM,CTX,MV | Recover |
| Camelo-Filho [38] | ≥ 60/M I | V | AChR | Exacerbation leading to MV | NR | CTX,AZM,OTV | Death |
| Camelo-Filho [38] | ≥ 60/M I | V | AChR | Exacerbation leading to MV | Pulmonary involvement | CTX, AZM, steroid | Death |
| Camelo-Filho [38] | 20-39/ 0 | IIa | V | NR | Exacerbation leading to MV | No involvement | CTX, OTZ, AZD, steroid, MTX | Poor |
| Camelo-Filho [38] | 40-59/ M | IIa | V | NR | Exacerbation leading to MV | Pulmonary involvement | CTR,CTX,AZM, OVT,steroid | Death |
| Camelo-Filho [38] | 40-59/ M | NIV | V | AChR | Exacerbation leading to MV | No involvement | CTX, AZM,CR, OVT | Stability |
| Camelo-Filho [38] | 20-39/ 0 | I | V | AChR | Exacerbation leading to MV | Pulmonary involvement | CTX, AZM, steroid, PE | Recover |
| Camelo-Filho [38] | ≥ 60/M I | V | AChR | Exacerbation leading to MV | No involvement | CTX, AZM, steroid, PE, Aza | Stability |
| Saied et al [44] | 57/M IIb | V | AChR | Fever, delirium, shortness breath | ARDS | MV,levofloxacin | Death |
| Delly et al [45] | 56/F | IIb | V | AChR | Bulbar,respiratory, limb weakness | Bilateral pneumonia | IVIG, MVC, HCQ, AZM, steroid | Stability |
| Restivo et al [46] | 71/F 0 | V | AChR | Bulbar, respiratory weakness | Bilateral pneumonia | PE, steroid, HOQ, MV | Improvement |
| Octaviana et al [47] | 25/F I | IIIb | None | Ptois, dysarthria, dysphagia, limb weakness | Ground glass pneumonia | NIV, AZM,CTX | Improvement |
| Wanschitz et al [48] | 71/F IIb | V | AChR | Pulmonary failure, head drop, bulbar, limb weakness | Bilateral pneumonia | MV, IVIG, antibiotics, steroids, CP | Improvement |
| Rein et al [49] | 38/F | IIIb | IVb | AChR | Ptois, respiratory, limb weakness | Bilateral pneumonia | IVIG, steroid, HCQ, antiviral | NIV |
| Businano et al [50] | 93/M I | NR | AChR | NR | O2 therapy,CTX | Death |
| Businano et al [50] | 54/M IIb | IIIb(?) | AChR | Ptois, facial weakness | NR | O2 therapy,CTX, HCQ, antiviral | NR |
| Businano et al [50] | 86/F IIb | IIIb(?) | AChR | Bulbar, respiratory weakness | Interstitial pneumonia | O2 therapy, antibiotics, IVIG, MV | Death |
| Zupanic et al [51] | 63/M IIb | V | AChR | Bulbar, respiratory weakness | NR | IVIG, MV | Recover |
| Zupanic et al [51] | 58/M I | V (?) | None | Respiratory weakness | NR | IVIG, antiviral, MV | Recover |
| Zupanic et al [51] | 51/M I | Iib | AChR | Respiratory weakness | NR | IVIG, steroid, NIV | Recover |
| Zupanic et al [51] | 66/M NR | V (?) | NR | Respiratory weakness | NR | IVIG, antiviral, MV | Death |
| Singh et al [52] | 36/F Ila | V | None | Bulbar, respiratory weakness | Bilateral pneumonia | PE, steroid, MMF, MV | Improvement |
| Salik et al [53] | 80/M NR | V | NR | Limb, bulbar, respiratory weakness | Bilateral pneumonia | IVIG, HCQ, AZM, MV | Poor |
| Scopelliti et al [54] | 46/M NR | IV | None | Dyspnea, hypopnoea, ptosis, fatigue | Bilateral pneumonia | Steroids, HCQ, AZM | Recover |
| Moschella et al [55] | 70/M NR | V | AChR | Respiratory weakness | No abnormalities | PE, steroids | Recover |

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As a second major route of entry to the CNS, the olfactory transport machinery represents a potential route of entry to the CNS via the cranial nerves. Indeed, the olfactory nerve serves as a shortcut for many viruses through olfactory receptor neurons projecting dendrites into the nasal cavity and extending axons across the cribiform plate into the olfactory bulb [4,11]. Furthermore, CNS could result from the breakdown of the BBB without direct viral invasion, causing the development of acute coagulopathy which could render patients prone to cerebrovascular events, both thrombotic and hemorrhagic [1,9,13-16]. Although there is no evidence that patients with NMD exhibit a higher risk of COVID-19, NMD and its associated therapies may affect the patient’s ability to cope with infection or its systemic effects. Indeed the onset and / or the exacerbation of PNS disorders during SARS-COV-2 infection could be related to a variety of mechanisms, which might include the activation of autoimmune response with molecular mimicry mechanism, bystander activation and epitope spreading [32,33]. Previous reports has shown that different tissue antigens share sequence homology with the virus suggesting antibody cross-reactivity as an underlying mechanism of autoimmunity neurological diseases [32]. Lucchese and Flöel [32] recently reported three human proteins (namely DAB1, AIFM, and SURF1, as catalogued at https://www.uniprot.org) that are present in neurons of the respiratory pacemaker in the brainstem, potentially sharing antigenic epitopes with SARS-COV-2. Particularly, these authors [32] postulated that damage to the brainstem pacemaker may contribute to respiratory muscle weakness or disease exacerbation after SARS-CoV-2 infection as a consequence of molecular mimicry between neuronal and viral proteins, in turn causing the clinical dissociation between well-preserved lung mechanics and severity of hypoxemia. Sequence analysis of the 41 human proteins associated with acute and chronic immune-mediated neuromyopathies pointed out that SARS-COV-2 shares two hexapeptides (KDKKKK and EIPKEE) with the human heat shock proteins 90 and 60, which however are not specific for NMD, but can be found in other autoimmune disorders [32]. These studies however may support the view of a potential immune-mediated mechanism in the onset of PNS diseases during SARS-COV-2 infection, although it cannot be excluded that the massive release of cytokines and Tregs/Th-17 imbalance could contribute to the pathogenesis of these diseases (Fig. 2). Indeed, Tregs depletion in severe COVID-19 plaies a role in promoting autoimmune disorder through a defect in self-tolerance and abnormal immune-response to self-antigens [33-35].

### 3.1. Acute respiratory failure in NMD during COVID-19 infection

Several reports show that SARS-CoV2 infection can promote the onset of acute hypercapnic respiratory failure (“pump failure”) due to respiratory muscles weakness, both by triggering the onset of acute NMD through an autoimmune mechanism or eventually by an acute exacerbation of a preexisting condition, such as myasthenia gravis (MG) or myotonic dystrophy(DM1) [33,36-41]. Acute respiratory failure in NMD is the result of weakness of different muscle groups, which have distinct effects on respiratory function. The weakness of muscles of the upper airway (facial, oropharyngeal and laryngeal muscles) induces dysphagia, risk of aspiration and upper airway occlusion [42], whereas the inspiratory muscle dysfunction causes hypoventilation and CO2 retention, mainly involving the diaphragm, although intercostals and accessory muscles may be affected. When the weakness of inspiratory muscles is excessive, the ventilatory pump is unable to sustain the load necessary for ventilation and the appearance of microatelectasis leads to hypoventilation and reduction of lung compliance, resulting in further increase of elastic load [43]. Clinically, the patient exhibits “rapid shallow breathing”, characterized by high respiratory rate and low tidal volumes (VT), preceding the onset of hypercapnic respiratory failure. Finally, expiratory muscle weakness causes ineffective cough and the inability to clear bronchial secretions, predisposing the patient to pneumonia and airways obstruction. Fig. 2 summarizes the pathophysiology of respiratory failure in NMD during the course of COVID-19.

### 3.2. Acute neuromuscular syndromes with respiratory failure during COVID –19 pandemic

#### 3.2.1. Myasthenia gravis (MG)

Clinical features of patients with MG and respiratory failure described in the English literature are listed in Table 1 [37-39,41,44-57]. MG may be a risk factor for severe COVID-19 disease for many reasons, including an immunocompromised state related to baseline therapies, respiratory muscle weakness or disease exacerbation after immunotherapy cessation [37,38]. We previously discussed the imbalance between inflammatory T-helper 17 (Th-17) cells and Treg cells in severe

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**Table 1 (continued)**

| Authors | Age/sex | MGFA classification prior COVID-19 | MGFA classification during COVID-19 | Abs | MG symptom worsen | Lung – CT scan | Therapy | Outcome |
|---------|---------|----------------------------------|-----------------------------------|-----|-------------------|---------------|---------|---------|
| Rodrigues et al [57] | 49/F | IIa | V | AChR | Respiratory involvement | Lung abnormalities | HCQ, AZM, OXY, CTX, IVIG, MV | Improvement |
| Rodrigues et al [57] | 90/7 | IIIb | V | AChR | Respiratory involvement | Lung abnormalities | HCQ, AZM, OXY, CTX, IVIG, MV | No improvement |
| Rodrigues et al [57] | 34/7 | IIIb | V | AChR | Respiratory involvement | No abnormalities | Steroid, IVIG MV, antibiotics, PE | Death |
| Rodrigues et al [57] | 28/7 | IIb | V | AChR | Respiratory involvement | No abnormalities | PE, RTX, steroids | Improvement |
| Rodrigues et al [57] | 51/7 | II | V? | None | Respiratory involvement | No abnormalities | PE, steroids | Death |

Abs: antibody; AChR, acetylcholine receptor; AZA, azathioprine; AZM, azithromycin; CT-scan: computed tomography; CLR: clarithromycin; CP: convalescent plasma; CTX, ceftriaxone; F, female; HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulin, LZD, linezolid; M, male; MGFA, Myasthenia Gravis Foundation of America; MMF, mycophenolate mofetil; MTX, methotrexate; Musk, muscle-specific tyrosine kinase; MV, mechanical ventilation; NIV, non-invasive ventilation; NR, not reported; OTV, oseltamivir; PE, plasma exchange; RTX: rituximab.
| Authors            | Age/ gender | Time to GBS (days) | Weakness distribution          | Cranial Nerves | CSF                  | Electrophyiology       | CT-scan / x-ray       | Therapy                  | Outcome   |
|--------------------|-------------|-------------------|--------------------------------|---------------|----------------------|------------------------|------------------------|-------------------------|-----------|
| Toscano et al [58] | 77F         | 7                 | Flaccid areflexic tetraplegia  | IX, XII, VII  | Increased protein    | AMSAN                  | Interstitial           | Bilateral pneumonia     | MV, IVIG   | Poor       |
| Toscano et al [58] | 55 M        | 10                | Flaccid tetraparesis, facial weakness | VII bilateral | Increased protein    | AMAN                   | Interstitial           | Bilateral pneumonia     | MV, IVIG, AZM | Poor       |
| Toscano et al [58] | 61 M        | 7                 | Flaccid paraplegia             | I, VII, IX    | Normal               | AIDP                   |                       |                         | MV, IVG, PE, IVIG | Recover   |
| Virani et al [59]  | 54 M        | 2–3               | Areflexic tetraparesis         | NR            | NR                   | NR                     | Normal                 | Bilateral pneumonia     | MV, IVIG, HCQ | Recover   |
| Webb et al [65]    | 57 M        | 1                 | Areflexic tetraparesis         | NR            | Increased protein    | AIDP                   |                       | Bilateral pneumonia     | MV, IVIG   | Recover   |
| Rajdev et al [66]  | 36 M        | 18                | Ascending motor quadriaparesis | NR            | Increased protein    | AIDP                   | Ground glass           | pneumonia              | MV, IVIG, PE | Recover   |
| Pfefferkorn et al  | 51 M        | 14                | Areflexic tetraparesis         | VII, XII      | Normal               | AIDP                   | Interstitial           | pneumonia              | MV, PE, IVIG | Recover   |
| Padrioni et al [68] | 70F         | 28                | Areflexic tetraparesis         | NR            | Increased protein    | AIDP                   | Ground glass           | pneumonia              | MV, IVIG   | Recover   |
| Lascano et al [69] | 52F         | 15                | Areflexic tetraplegia          | NR            | Increased protein    | AIDP                   |                       | NR                      | MV, IVIG   | Recover   |
| Alberi et al [70]  | 71 M        | 3                 | Areflexic tetraparesis         | None          | Increased protein    | AIDP                   | Bilateral pneumonia    | MV, lopinavir, ritonavir, HCQ | Death     |           |
| Assini et al [71]  | 55 M        | 20                | Bilateral ptosis, dysphagia, dysphonia, areflexia | I, III, VII, IX, X, XII | Normal | AIDP                   |                       |                         | NR                      | MV, IVIG, HCQ | Recover   |
| Assisi et al [71]  | 60 M        | 20                | Limb weakness                  | NR            | Normal               | AIDP                   | Interstitial           | pneumonia              | MV, IVIG   | Recover   |
| Manganotti et al [73] | 72 M    | 18                | Flaccid tetraparesis           | Right-sided VII | Increased protein    | AMSDN                   | Bilateral pneumonia    | MV, IVIG, HCQ, OTV, MP, TZB, MV | Recover    |           |
| Manganotti et al [73] | 72 M    | 30                | Flaccid tetraparesis           | None          | Normal               | AMSAN                   | Bilateral pneumonia    | MV, IVIG, HCQ, lopinavir, ritonavir, MP, MV | Recover    |           |
| Manganotti et al [73] | 76 M    | 22                | Proximal weakness              | None          | Increased protein    | AMSAN                   | Bilateral pneumonia    | MV, IVIG, HCQ, OTV, LZD, CLR, MP, TZB, MV | Recover    |           |
| Helbok et al [74]  | 68 M        | 13                | Areflexic tetraparesis, paraesthesias | NR            | Increased protein, 2 cells | AIDP                   | Ground glass           | pneumonia              | MV, IVG, NIV, MV, PE | Recover   |
| Su et al [75]      | 72F         | 7                 | Ascending sensorimotor quadriaparesis, dysautonomia | NR            | Increased protein    | AIDP                   | Bilateral pneumonia    | MV, IVIG               | Poor       |
| Ottaviani et al [76] | 66F       | 10                | Acute areflexic paraparesis    | VII           | Increased protein    | AIDP                   | Ground glass           | pneumonia              | MV, IVIG, lopinavir, ritonavir, MV | Poor       |
| Bueso et al [77]   | 60F         | 22                | Ascending symmetric weakness   | NR            | Increased protein    | NR                     | Ground-glass           | pneumonia              | MV, IVIG   | Recover   |
| Marta -Enguita et al [78] | 76F | 8                 | Areflexic quadriparesis, paraesthesia | NR            | NR                   | NR                     | Pneumonia              | MV                      | Death      |
| Gagarkin et al [79] | 70F         | 21                | Areflexic tetraparesis, distal sensory loss | NR            | NR                   | AIDP                   | Normal                 | MV, IVIG, HCQ, doxycyclin | Recover    |           |
| Garcia –Manzanedo et al [80] | 77F | 21                | Cervical flexor weakness      | VII bilateral, IX, XII | Increased protein    | ASMDN                   | Bilateral              | interstitial pneumonia | pneumonia MV, IVIG, IVIG | Recover    |           |
| Abrams et al [81]  | 67F         | 20                | Progressive quadriparesis, bulbar involvement | VII, IX      | Increased protein    | NR                     |                         | MV, PE                  | Recover   |
| Tatu et al [82]    | 79F         | NR                | Paraparesis, ataxia, paraesthesia | NR            | Increased protein    | AIDP                   | NR                     | MV, IVIG               | Death      |

(continued on next page)
COVID-19 disease, which could also play a role in MG expression [33]. Restivo et al [46] reported 3 patients without a pre-existing diagnosis of MG who developed acute ocular and bulbar signs overlapping a concurrent SARS-COV-2 infection; in these cases, however, a pre-existing disorder of the neuromuscular junction exacerbated by the SARS-COV-2 pneumonia could not be excluded as the neurological symptoms started within 5 to 7 days after the fever onset with a parainfectious more than a post-infectious profile. Camelo-Filho et al [38] published the largest series of cases, noting that most patients had severe course as 87% were admitted in ICU, 73% needed MV and 30% died. On the contrary in a series of 93 Czech patients, only 34 were hospitalized and none exhibited a myasthenic crisis (MC) [56]. Businaro et al [50] recently published a report on 162 Italian patients interviewed during the first wave of the pandemic: only 11 had probable/confirmed infection. Although some of the need for ventilator support might be related to lung dysfunction, receiving non-invasive nocturnal home ventilatory support.

Table 2 (continued)

| Authors          | Age/Gender | Time to GBS (days) | Weakness distribution | Cranial Nerves | CSF | Electrophysiology | CT-scan/x-ray | Therapy | Outcome |
|------------------|------------|--------------------|-----------------------|---------------|-----|-------------------|---------------|---------|---------|
| Tatu et al [82]  | 75 M       | 21                 | Paraparesis, paraesthesia | VII           | Increased protein | AMSAN | NR | MV, IVIG | Recover |
| Pelea et al [83] | 56 F       | 15                 | Flaccid tetraparesis, dysautonomia | VII bilateral | Increased protein, 9 cells | AMADN | Bilateral pneumonia | MV, PE, IVIG | Recover |
| Rana et al [84]  | 54 M       | 15                 | Areflexic quadriparesis | VII bilateral, ophthalmoparesis | NR | AIDP | Pneumonia | MV, IVIG | Recover |
| Diaz-Porras L et al [85] | 54 M | 1 | Asymmetric tetraparesis | Bilateral VII | Increased protein | AMSDN | Normal | NIV, MV, PE, IVIG | Recover |
| Camdessanche et al [86] | 64 M | 14 | Areflexic tetraparesis | IX, X | Increased protein | AIDP | Ground glass pneumonia | PE, MV | Improvement |
| Khedr et al [87] | 34 M       | 10                 | Areflexic tetraplegia | Bulbar signs | NR | AIDP | Ground glass pneumonia | Normal | PE, MV | Improvement |
| Mackenzie N et al [88] | 39F | 20 | Areflexic tetraplegia, diaphragmatic weakness | NR | Increased protein | AIDP | Normal | PE, MV | Improvement |
| Abolmaali et al [89] | 88F | 2 | Areflexic tetraplegia | Left ptosis | Increased protein | AMSAN | Bilateral pneumonia | HCQ, steroids, ritonavir | Improvement |
| Nanda et al [90]  | 72 M       | 6                  | Progressive tetraparesis | None | Increased protein | AIDP | Bilateral pneumonia | IVIG, MV | Death |

GBS: Guillain Barre’ syndrome; C-T scan: computed tomography; AIDP, Acute inflammatory demyelinating neuropathy; AMAN, acute motor axonal neuropathy; AMAN, acute motor and sensory axonal neuropathy; AMAN, acute motor axonal demyelinating neuropathy; CLIR: clarithromycin; CSF: cerebro spinal fluid; D: day; MRI: magnetic resonance imaging; M: male; F: female; HCQ, hydroxychloroquine; IVIG: intravenous immunoglobulins; LZD: linezolid; MV, mechanical ventilation; MP: methyl prednisolone; NIV, non-invasive ventilation; NR: not reported; OTV: oseltamivir; PE: plasma exchanges.

3.2.3. Acute and inflammatory myopathies

Myopathy with elevated blood-creatine kinase (CK) levels are described in patients with SARS-COV-2 infection and myalgias are common manifestations, while serum CK elevation might depend on clinical severity, ranging from mild to frank rhabdomyolysis [1,2,9,92-112]. Gupta et al [93] stated that the dermatomyositis is the most frequent subtype (40%) of inflammatory myopathies, attributable to COVID-19 pandemic; Mehani et al [94] described 7 patients with paraspinal myositis and 4 were intubated over their hospital stay. Rosato et al [95] reviewed 16 case reports from existing literature and discussed the COVID-19-related rhabdomyolysis in one patient who developed acute muscle weakness, renal failure, hypoxia. Table 3 shows adult cases of acute myopathies with respiratory failure with or without rhabdomyolysis during COVID-19 pandemic.

3.2.4. Other neuromuscular conditions

Dhont et al [40] described 3 patients with DM1 and SARS-COV-2 infection. Receiving non-invasive nocturnal home ventilatory support. Despite maximal supportive care, all 3 died. Dhont et al [40] observed that the mutant RNA-transcript with expanded CUG repeats could act as a trigger for critical elevation of TNF-α, IL-6, and IL-1ß cytokines already described in DM1. Quinlivan et al [113] described a small cohort of Duchenne Muscular dystrophy patients: non developed moderate or severe disease, despite three of these were treated with corticosteroids.
Table 3
Summary of the demographic characteristics of adult patients with acute myopathy with or without rhabdomyolysis requiring ventilation during SARS-CoV-2.

| Authors               | Age/Gender | Time to onset (Day/weeks) | Weakness distribution | CT-scan/x ray | Laboratory/Muscle MRI | EMG | Treatment | Outcome   |
|-----------------------|------------|---------------------------|-----------------------|--------------|----------------------|-----|------------|-----------|
| Mehan et al [94]      | 63 M       | NR                        | Back pain             | NR           | Elevated CRP, ESR, paraspinal myositis | NR | MV         | Improvement|
| Mehan et al [94]      | 54 F       | NR                        | Back pain, leg weakness | NR          | Elevated D-dimer ESR, CRP paraspinal myositis | NR | MV         | Improvement|
| Mehan et al [94]      | 62 M       | NR                        | Back pain, leg weakness | NR          | Elevated CRP, paraspinal myositis     | NR | MV         | Improvement|
| Mehan et al [94]      | 56 M       | NR                        | Back pain             | NR           | Elevated CRP, paraspinal myositis     | NR | MV         | Improvement|
| Rosato et al [95]     | 58 M       | 14 days                   | Severe limb, diaphragm weakness, hypoxia | Pneumonia   | Elevated CK, kidney injury | Myopathic EMG & biopsy | MV, lopinavir/ritonavir, HCQ | Recover |
| Zhang H et al [96]    | 58 F       | 3 weeks                   | Bulbar, facial, limb weakness | NR          | Elevated D-dimer ESR, CRP, ANA, LAC, anti SSA, anti SAE 1 | NR | NIV, AZM, HCQ, DOXY, corticosteroids | Improvement|
| Zhang Q et al [97]    | 38 M       | Few days                  | Myalgia, back pain, dyspnea Myalgia, limb weakness | Bilateral pneumonia | Elevated CK, CRP | NR | NIV, AZM, HCQ, DOXY, corticosteroids | Improvement|
| Jin et al [99]        | 60 M       | 6 days                    | Myalgia, proximal leg weakness | Bilateral pneumonia | Elevated CK, CRP | NR | MV, AZM, TZB | Improvement|
| Suwangwongse et al [100] | 88 M   | 1–2 days                  | Myalgia, proximal leg weakness | Bilateral pneumonia | Elevated CK, CRP | NR | MV         | Improvement|
| Valente-Acosta et al [101] | 71 M   | 1 week                    | Severe leg myalgia, arthralgia | Bilateral pneumonia | Elevated CK, CRP | NR | MV, AZM, TZB | Improvement|
| Beydon et al [102]    | NR         | 1 day                     | Myalgia, bilateral limb weakness | Bilateral pneumonia | Elevated CK, CRP, muscle oedema | NR | MV         | Improvement|
| Borku U et al [103]   | 60 M       | 2 days                    | Myalgia, fever, respiratory distress, fatigue | Bilateral pneumonia | Elevated CK, CRP, muscle oedema | NR | HCQ, AZM OTV | Recover |
| Islam et al [104]     | 42 M       | 5 days                    | Severe weakness, breathing difficulty | Bilateral pneumonia | Elevated CK, CRP, respiratory distress | Fibs, small MUPS, muscle hyperintensity | Rendesivir, MV steroids, TZB | Recover |
| Singh et al [105]     | 67 M       | 4 days                    | Respiratory distress | Bilateral pneumonia | Elevated CRP, ESR, CRP, CK | NR | AZM, HCQ | Death |
| Singh et al [105]     | 39 M       | 1 day                     | Respiratory distress | Bilateral pneumonia | Elevated CRP, ESR, CK | NR | MV         | Death |
| Singh et al [105]     | 70 M       | 8 days                    | Respiratory distress | Bilateral pneumonia | Elevated CRP, ESR, CK | NR | MV         | Death |
| Taxbro et al [106]    | 38 M       | 7 days                    | Myalgia, fever, breathlessness | ARDS         | Elevated CK, hypoxemia | NR | MV, metronidazole, cefotaxime, lopinavir/ritonavir, HCQ | Recover |
| Sacchi et al [107]    | 77 F       | 7 days                    | Respiratory, limb weakness | Pneumonia | Elevated PCR | Anti-Ku, anti Mi 21, anti Mi 21 | Rendesivir, MV steroids, TZB | Recover |
| Madia et al [108]     | 51 M       | 11 days                   | Acute quadriplegia, ARDS | Bilateral pneumonia | Elevated D-dimer CRP | Myopathic changes | AZM, HCQ, TZB, MV | Improvement |
| Madia et al [108]     | 70 M       | 6 days                    | Acute quadriplegia, ARDS | Bilateral pneumonia | Elevated CRP, D-dimer | Myopathic changes | AZM, HCQ, TZB, MV | Death |
| Madia et al [108]     | 53 M       | 12 days                   | Acute quadriplegia, ARDS | Bilateral pneumonia | Elevated CRP, D-dimer | Myopathic changes | AZM, HCQ, TZB, steroids, MV | Improvement |
| Madia et al [108]     | 72 M       | 14 days                   | Acute quadriplegia, ARDS | Bilateral pneumonia | Elevated D-dimer CRP | Myopathic changes | AZM, HCQ, TZB, steroids, MV | Improvement |
| Madia et al [108]     | 52 M       | 14 days                   | Acute quadriplegia, ARDS | Bilateral pneumonia | Elevated D-dimer CRP | Myopathic changes | AZM, HCQ, TZB, steroids, MV | Improvement |
| Madia et al [108]     | 68 F       | 7 days                    | Acute quadriplegia, ARDS | Bilateral pneumonia | Elevated D-dimer CRP | Myopathic changes | AZM, HCQ, TZB, steroids, MV | Improvement |
| Husain et al [109]    | 38 M       | 5–7 days                  | Fever, cough, myalgia, short breath, delirium | Bilateral pneumonia | Elevated D-dimer CRP | Myopathic changes | AZM, HCQ, TZB, steroids, MV | Improvement |
| Hao et al [110]       | 45 F       | 15 days                   | Weakness, myalgia, cough, erythema | Bilateral pneumonia | Elevated D-dimer CRP, K, CK | Myopathic changes | AZM, HCQ, TZB, steroids, MV | Improvement |
| Uslu S [111]          | 38 M       | NR                       | Myalgia, dyspnea | Bilateral pneumonia | Elevated CPR, CK | NR | Levofoxacin, IV, IVIG, cyclophosphamide, Fluids, steroids, NIV | Improvement |
for many years. Recent studies on amyotrophic lateral sclerosis (ALS) documented that SARS-CoV-2 infection can lead to more rapid progression of the disease, emphasizing the need for prompt testing and close monitoring of these patients [114].

4.1. Respiratory muscles assessment in neuromuscular patients with SARS-COV-2 infection

SARS-COV-2 infection in patients with pre-existing NMD could cause an unpredictable deterioration of the respiratory conditions, leading to acute respiratory “pump failure” due to respiratory muscle weakness with CO2 retention (Fig. 2). The respiratory muscle monitoring has a key role in the decision-making process of the respiratory management in spontaneous breathing of patients with NMD. A reliable non-invasive respiratory muscle assessment, either in a regular ward or in ICU is challenging. The non-invasive surrogate markers for diaphragm weakness include maximum static inspiratory mouth pressure (Plmax), maximal sniff nasal inspiratory pressure (SNIP), and vital capacity (VC), which are the most useful measures of respiratory muscle functions used bedside in the hospital setting. Plmax is obtained with a maximal inflation against a closed valve, and reflects the strength of diaphragm, but also the external intercostal and accessory muscles. While normal values form Plmax vary by age and gender, there is agreement in considering a Plmax value < 30 cmH2O suggestive of severe respiratory muscles weakness. SNIP is recorded by pressure transducer connected to a catheter placed in the nostril during a quickly and deeply sniffing maneuver, which determines nasal valve collapses [115,116]. The sniff maneuver is easier to perform than the Plmax in patients with bulbar involvement with weak lips, and provides a reliable estimation of sniff esophageal and transdiaphragmatic pressure in patients with NMD. A SNIP < 40 cmH2O, associated to symptoms or signs related to respiratory weakness, was proposed by EFNS Task force to initiate NIV in patients with ALS [117]. However, validated data about SNIP in acute NMD requiring ICU care are not available.

VC is the volume obtained with a full exhalation after maximum inspiration up to total lung capacity (TLC). VC less than 50% of predicted is associated with several bilateral diaphragm weaknesses, but this value can further decrease to 30% or more when patient is supine [116]. In the last few years, diaphragmatic assessment with ultrasound (US) has proven to be a quick and easy technique for evaluating of respiratory muscles which are the following: VC less than 20 ml/Kg, Plmax less than 30 cmH2O and maximal expiratory pressure (MEP) less than 40 cmH2O or a reduction of more than 30% in any of these measures which are the suggested thresholds as a guide for elective endotracheal intubation in patients with NMD [123].

Nowadays, there is no evidence from randomized trials to support the routine use of NIV instead of MV in patients with acute respiratory failure during SARS-COV-2 infection. However, data obtained from observational studies suggests that a trial of NIV can be attempted, except for cases exhibiting bulbar dysfunction and excessive bronchial secretions [124]. Indeed in GBS, the use of NIV is debated and might be ineffective in presence of bulbar dysfunction and because of the length of time necessary for respiratory muscles to recover [62]. Indeed, in patients with MC demanding ventilation, NIV reduced the need for invasive ventilation up to 38% of cases [125] and it was associated with shorter duration of ventilation, ICU stay and reduction of pulmonary complications, such as atelectasis and pneumonia. In our experience, an early NIV treatment in patient outside ICU setting showed a further reduction of the need for MV in MC patients [126]. NIV could be the first approach in selected patients, but this choice depends on the severity of the respiratory muscle involvement and on the underlying disorders. The outcomes of MG and GBS requiring MV were studied by Velliparam et al [127], who found that GBS patients had higher in-hospital complications and disability at discharge compared with MG subjects.

5. Conclusion and strategies

Respiratory failure during SARS-COV-2 infection is a complex phenomenon. In the most severe form of COVID-19, the variable association
between viral alveolitis and impaired pulmonary perfusion constitutes the main mechanism underlying the onset of hypoxemia. However, the immunological response triggered by virus-host interactions may promote the acute development of muscular weakness, or it can exacerbate the main mechanism underlying the onset of hypoxemia. However, the kinetics or personal relationships that could have appeared to influence the work reported in this paper.

Credit attribution statement
G. Galassi: Conceptualization, Methodology, Writing – review & editing. A. Marchioni: Conceptualization, Methodology, Writing – review & editing.

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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