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Review article

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

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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 coronaviruses.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

Abbreviations: ARDS, Acute respiratory distress syndrome; GBS, Guillain Barre' syndrome; NIV, Non -invasive ventilation; MV, Mechanical ventilation; MC, Myasthenic crisis; COVID-19, Coronavirus disease.

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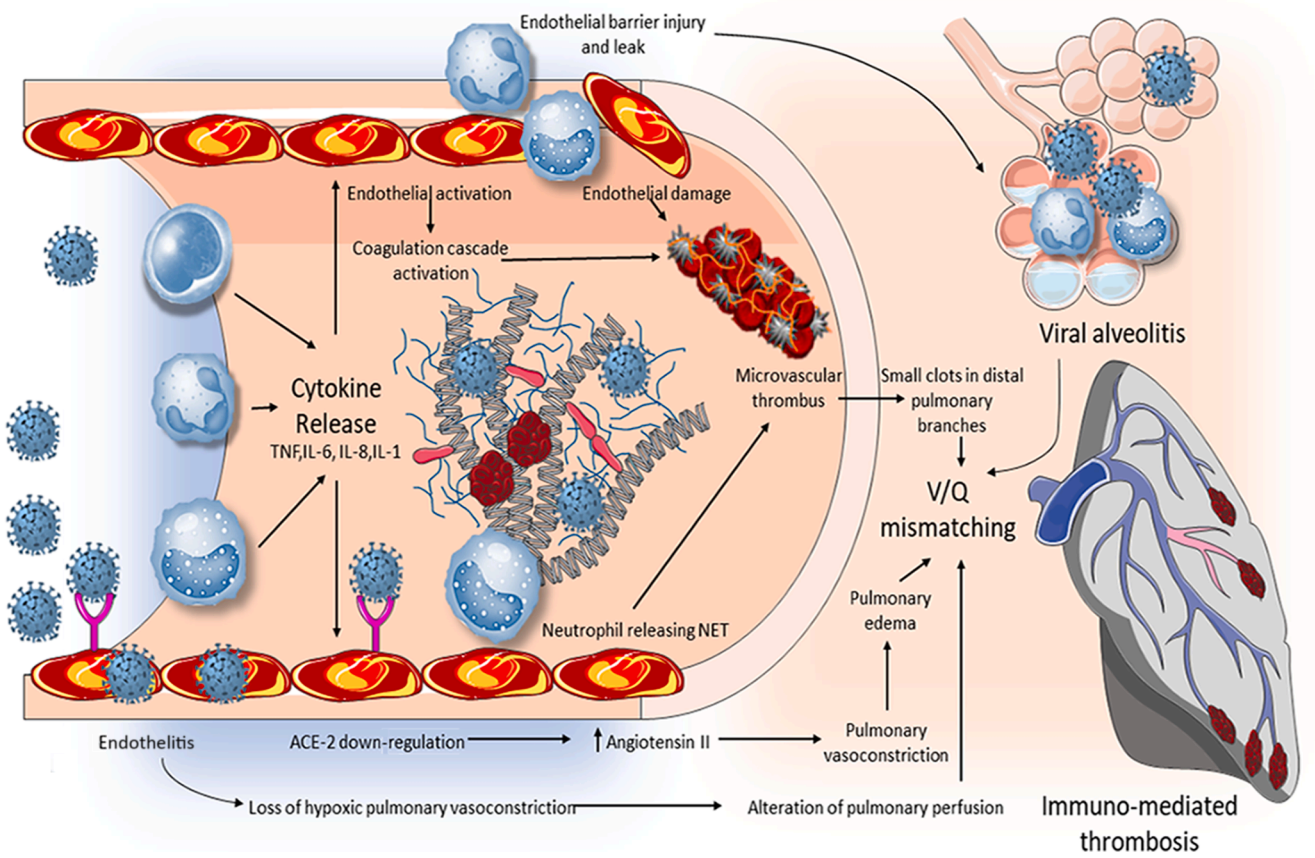

Fig. 1. Pathophysiology of lung and vascular injury in the course of severe SARS-COV-2. Respiratory failure is the result of the combination of inflammatory alveolar damage and pulmonary perfusion dysfunction. After viral infection, activated neutrophils recruitment and accumulation into the lung induce superoxide radicals and proteolytic enzyme secretion leading to damage in the alveolar-capillary barrier, inflammatory edema formation and activation of coagulation. Endothelial cells infection and endothelitis associated with ACE-2 downregulation cause a dysfunction of pulmonary perfusion regulation, which results in a worsening of the ventilation/perfusion ratio. Endothelial damage and cytokine release in the lung promote pulmonary angiopathy and thrombosis in distal pulmonary branches.

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

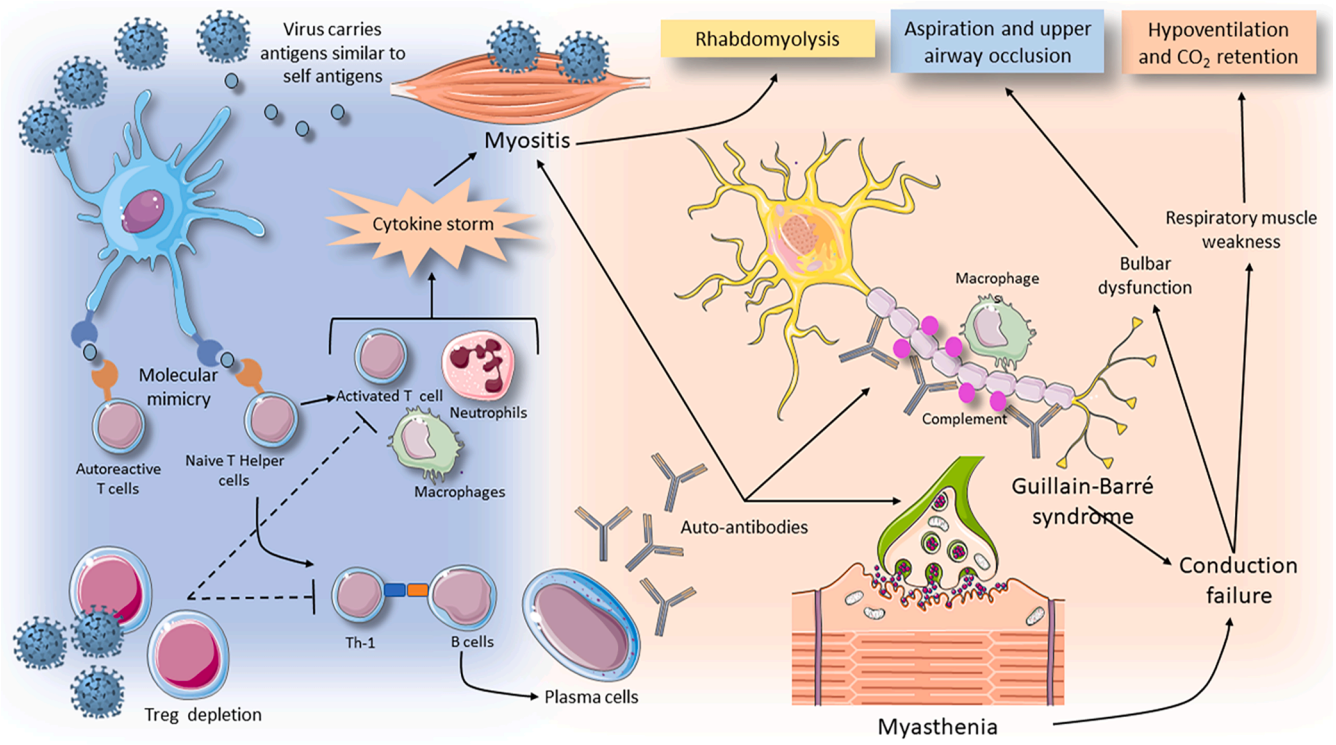

Fig. 2. Pathophysiology of respiratory failure due to acute neuromuscular weakness in the course of SARS-COV-2 infection. During SARS-COV-2 infection, host-virus interaction may trigger an autoimmune process possibly through the mechanism of molecular mimicry, which could promote the onset or worsening of acute neuromuscular diseases. Furthermore, Tregs depletion after viral infection results in a loss of the immune-regulation, leading to development of the cytokine storm and release of autoantibodies. Onset of Guillain-Barré Syndrome or Myasthenia Gravis may precipitate weakness of respiratory muscles. that can ultimately leads to acute hypoventilation and Co2 retention.

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 88% 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) CSS 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	Hypossiemic respiratory failure	NR	HCQ,AZM, MV, IVIG	Recover
Anand et al [37]	64/M	Pharmacological remission	V	AChR	Hypossiemic 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/ NR	IIa	V	NR	Exacerbation leading to MV	No involvement	CTX, OTV, LZD, steroid, MTX	Poor
Camelo-Filho [38]	40–59/ NR	IIa	V	NR	Exacerbation leading to MV	Pulmonary involvement	CLR,CTX,AZM, OTV,steroid	Death
Camelo-Filho [38]	40–59/ M	IIa	V	AChR	Exacerbation leading to MV	No involvement	CTX, AZM,CLR, OTV	Stability
Camelo-Filho [38]	40–59/ NR	IIa	V	AChR	Exacerbation leading to MV	No involvement	CTX, AZM,steroid, PE	Recover
Camelo-Filho [38]	20–39/ NR	I	V	AChR	Exacerbation leading to MV	Pulmonary involvement	CTX, AZM,steroid, PE, AZA	Stability
Camelo-Filho [38]	20–39/ NR	IIb	V	MuSK	Exacerbation leading to MV	No involvement	CTX, AZM,steroid, LZD	Stability
Camelo-Filho [38]	≥ 60/M	I	V	NR	Exacerbation leading to MV	Pulmonary involvement	CTX, AZM,steroid, LZD	Death
Camelo-Filho [38]	≥ 60/ NR	III	V	AChR	Exacerbation leading to MV	Pulmonary involvement	CTX, steroid	Stability
Camelo-Filho [38]	20–39/ NR	IIa	V	AChR	Exacerbation leading to MV	No	CTX, steroid,	Recover
Camelo-Filho [38]	20–39/ NR	IIa	V	AChR	Exacerbation leading to MV	No	CTX, steroid, IVIG, AZA	Stability
Camelo-Filho [38]	20–39/ NR	IIb	V	AChR	Exacerbation leading to MV	No	CTX, AZM,steroid	Stability
Aksoy et al [39]	49/M	II	V	AChR	Hypoxia, fatigue	Ground glass pneumonia	HCQ, CP, steroid, LZD,NIV	Recover
Hübers et al [41]	25/M	I	V	AChR	Respiratory weakness	Bilateral pneumonia	AZM, MV	Stability
Saied et al [44]	57/M	IIIb	V	AChR	Fever, delirium, shortness breath	ARDS	MV,levofloxacine	Death
Delly et al [45]	56/F	IIb	V	AChR	Bulbar,respiratory, limb weakness	Bilateral pneumonia	IVIG,MV, HCQ, AZM,steroid	Stability
Restivo et al [46]	71/F	0	V	AChR	Bulbar, respiratory weakness	Bilateral pneumonia	PE, steroid, HCQ, MV	Improvement
Octaviana et al [47]	25/F	I	IIIb	None	Ptosis, dysarthria, dysphagia,limb weakness	Ground glass pneumonia	NIV, AZM,CTX	Improvement
Wanschitz et al[48]	71/F	IIB	V	AChR	Ptosis, head drop, bulbar, limb weakness	Bilateral pneumonia	MV, IVIG, antibiotics, steroids, CP	Improvement
Rein et al [49]	38/F	IIa	IVb	AChR	Ptosis,respiratory, limb weakness	Bilateral pneumonia	IVIG, steroid, HCQ, antiviral	NIV
Businaro et al [50]	93/M	I	NR	AChR	NR	NR	O2 therapy,CTX	Death
Businaro et al [50]	54/M	IIb	IIb(?)	AChR	Ptosis, facial weakness	NR	O2 therapy,CTX; HCQ, antiviral	NR
Businaro et al [51]	86/F	IIIb	IIIb(?)	AChR	Bulbar, respiratory weakness	Interstitial pneumonia	O2 therapy, antibiotis,	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, steroids,NIV	Recover
Zupanic et al [52]	66/M	NR	V(?)	NR	Respiratory weakness	NR	IVIG, antiviral, MV	Death
Singh et al [52]	36/F	IIa	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,hypophonia, ptosis, fatigue	Bilateral pneumonia	Steroids, HCQ,AZM	Recover
Moschella et al [55]	70/M	NR	V	AChR	Respiratory weakness	No abnormalities	PE, steroids	Recover

(*continued on next page*)

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,OTV. CTX IVIG, MV	Improvement
Rodrigues et al [57]	90/?	IIIb	V	AChR	Respiratory involvement	Lung abnormalities	HCQ,AZM,OTV. CTX, IVIG, MV	No improvement
Rodrigues et al [57]	34/?	IIb	V	AChR	Respiratory involvement	Lung abnormalities	AZM, antibiotics,PE	Death
Rodrigues et al [57]	28/?	IIb	V	AChR	Respiratory involvement	No abnormalities	Steroid, IVIG MV, antibiotics	Improvement
Rodrigues et al [57]	27/?	IIb	V?	None	Respiratory involvement	No abnormalities	PE, RTX,steroids antibiotics	Improvement
Rodrigues et al [57]	51/?	II	V?	MuSK	Respiratory involvement	No abnormalities	MV,steroids, antibiotics	Death

Abs: antibody; AChR, acetylcholine receptor; AZA, azathioprine; AZM, azithromycin; CT-scan: computed tomography; CLR: clarithromicyn; 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.

[1-6,9,10]. As a second major route of entry to the CNS, the axonal 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 cribriform 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 infection 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 autoimmune 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 failure in COVID-19 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-mediate neuropathies 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 CO_2 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 hypoxemia 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 (V_T), 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

Table 2
Summary of the demographic characteristics of adult patients with Guillain Barre' syndrome (GBS) undergoing ventilation during SARS-COV-2.

Authors	Age/ gender	Time to GBS (days)	Weakness distribution	Cranial Nerves	CSF	Electrophysiology	CT-scan /x ray	Therapy	Outcome
Toscano et al [58]	77F	7	Flaccid areflectic tetraplegia	IX, XII, VII bilateral	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 pnrumonia	MV, IVIG, AZM	Poor
Toscano et al [58]	61 M	7	Flaccid paraplegia	I, VII, IX	Normal	AIDP	Interstitial bilateral pneumonia	MV,IVIG,PE	Poor
Virani et al [59]	54 M	2–3	Areflectic tetraparesis	NR	NR	NR	Bilateral pneumonia	MV, IVIG, HCQ	Recover
Webb et al [65]	57 M	1	Areflectic tetraparesis	NR	Increased protein	AIDP	Bilateral pneumonia	MV, IVIG	Recover
Rajdev et al [66]	36 M	18	Ascending motor quadriparesis	NR	Increased protein	AIDP	Ground glass pneumonia	MV, IVIG, PE	Recover
Pfefferkorn et al [67]	51 M	14	Areflectic tetraplegia	VII, XII	Normal protein,9 cells,	AIDP	Interstitial pneumonia	MV,PE, IVIG	Recover
Padroni et al [68]	70F	28	Areflectic tetraparesis	NR	Increased protein	AIDP	Ground glass pneumonia	MV, IVIG	Recover
Lascano et al [69]	52F	15	Areflectic tetraplegia	NR	Increased protein	AIDP	NR	MV, IVIG	Recover
Alberti et al [70]	71 M	3	Areflectic tetraparesis	None	Increased protein, 9 cells	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, ritonavir, lopinavir	Recover
Assisi et an [71]	60 M	20	Limb weakness gastroplegia, paralyitic ileous	NR	Normal	AIDP	Interstitial pneumonia	IVIG, MV	Recover
Manganotti et al [73]	72 M	18	Flaccid tetraparesis	Right-sided VII	Increased protein	AMSDN	Bilateral pneumonia	IVIG,HCQ, OTV, MP, TZB, MV	Recover
Manganotti et al [73]	72 M	30	Flaccid tetraparesis	None	Normal	AMSAN	Bilateral pneumonia	IVIG, HCQ, lopinavir/ ritonavir,MP, MV	Recover
Manganotti et al [73]	76 M	22	Proximal weakness	None	Increased protein	AMSAN	Bilateral pneumonia	IVIG, HCQ, OTV, LZD, CLR,,MP, TZB, MV	Recover
Helbok et al [74]	68 M	13	Areflectic tetraparesis, parasthesias	NR	Increased protein, 2 cells	AIDP	Ground glass pneumonia	IVIG, NIV, MV, PE	Recover
Su et al [75]	72F	7	Ascending sensorimotor quadriparesis, dysautonomia	NR	Increased protein	AIDP	Bibasal pneumonia	MV,IVIG	Poor
Ottaviani et al [76]	66F	10	Acute areflectic paraparesis	VII	Increased protein	AIDP	Ground glass pneumonia	MV,IVIG, lopinavir ritonavir	Poor
Bueso et al [77]	60F	22	Ascending symmetric weakness, hyporeflexia, dysautonomia	NR	Increassed protein	NR	Ground-glass pneumonia	MV,IVIG	Recover
Marta –Enguita et al [78]	76F	8	Areflectic quadriparesis, paraesthesia	NR	NR	NR	Pneumonia	MV	Death
Gagarkin et al [79]	70F	21	Areflectic tetraparesis, distal sensory loss	NR	NR	AIDP	Normal	MV, IVIG, HCQ, doxyciclin	Recover
Garcia –Manzanedo et al [80]	77F	21	Cervical flexor weakness	VII bilateral, IX, XII	Increased protein	ASMDN	Bilateral interstitial pneumonia	Anti-viral, HCQ, IVIG, MV	Recover
Abrams et al [81]	67F	20	Progressive quadriparesis, bulbar involvement	VII, IX	Increased protein	NR	Pneumonia	MV, PE	Recover
Tatu et al [82]	79F	NR	Paraparesis, ataxia, paraesthesia	NR	Increased protein	AIDP	NR	MV, IVIG	Death

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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]	56F	15	Flaccid tetraparesis, dysautonomia	VII bilateral	Increased protein, 9 cells	AMADN	Bilateral pneumonia	MV,PE, IVIG	Recover
Rana et al[84]	54 M	15	Areflectic quadriparesis	VII bilateral, ophtalmopareis	NR	AIDP	Pneumonia	MV, IVIG HCQ,AZM	Recover
Diez-Porras L et al [85]	54 M	1	Asymmetric tetraparesis	Bilateral VII,	Increased protein	AMSDN	Normal	IVIG	Recover
Camdessanche et al [86]	64 M	14	Areflectic tetraparesis	IX, X?	Increased protein	AIDP	Ground glass pneumonia	NIV,MV, lopinavir, ritonavir	Recover
Khedr et al [87]	34 M	10	Areflectic tetraplegia	Bulbar signs	NR	AIDP	Ground glass pneumonia	PE, MV	Improvement
Mackenzie N et al [88]	39F	20	Areflectic tetraplegia, diaphragmatic weakness	NR	Increased protein	AIDP	Normal	PE, MV	Improvement
Abolmaali et al [89]	88F	2	Areflectic tetraplegia	Left ptosis	Increased protein	AMSAN	Bilateral pneumonia	HCQ, steroids, lopinavir/ ritonavir,PE	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; AMSAN, acute motor and sensory axonal neuropathy; AMSDN, acute motor and sensory demyelinating neuropathy; AMADN, acute motor axonal demyelinating neuropathy; CLR: clarithromicyn; 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.

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 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 and of those, only 3 required ventilator support: 2 elderly died of respiratory insufficiency whereas only 1 experienced worsening MG symptoms.These authors [50]concluded that risk of COVID-19 in MG patients seems to be no higher than that of the general population, regardless of immunosuppressive therapies. Rodrigues et al [57] reported a case series of patients with MG exacerbation or crisis associated with COVID-19 and described an in-hospital mortality rate of 25% and a higher rate (37.5%) at 2-month follow-up, concluding that mortality of MC due to COVID-19 is higher than those due to other etiologies.Table 2.

3.2.2. *Guillain-Barré syndrome (GBS)*

Several GBS cases with respiratory failure during COVID-19 pandemic are described in the English literature [58-91] at the time of this writing. Toscano et al first [58] reported 5 patients, 4 with clinical diagnosis of GBS and 1 of facial diplegia and paraesthesia variant: 3 needed MV in absence of dysautonomia. Toscano et al [58] rose an important point as whether the reduced vital capacity in these cases was proportional to muscular weakness and to the extent of the chest abnormalities. Abu-Rumeileh et al [36] reviewed data from 73 cases of GBS and found that in analogy to the classic GBS approximately one-fifth of COVID-19-associated GBS required MV during hospitalization. Uncini et al [60] described respiratory failure in about one-third of patients and ICU admission in at least 40% of patients. Filosto et al [61] during the outbreak in northern Italy, reported a statistically significant high rate of ICU admission, as compared to GBS without SARS-COV-2 infection, whereas Keddi et al [62] in a cohort study in the UK did not support significant causal link between COVID-19 infection and GBS. In the series published by Sriwastava et al [63] who reviewed 50 cases obtained from 37 studies, 30% of patients presented poor outcomes secondary to respiratory failure and 60% required MV. Sriwastava et al [63] suggested that COVID-19 is a trigger for a rapidly progressing neuropathy although some of the need for ventilator support might be related to lung damage from the infection itself.

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; Mehan 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-1β cytokines already described in DM1. Quinlivan et al [113] described a small cohort of Duchenne Muscular dystrophy patients: none 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. * Patients with Rhabdomyolysis.

Authors	Age /Gender	Time to onset (Day/ weeks)	Weaknness 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]	54F	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	NR	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	Myopatic EMG & biopsy	MV, lopinavir/ ritonavir, HCQ	Recover
Zhang H et al [96]	58F	3 weeks	Bulbar,facial, limb weakness	NR	Elevated D-dimer ESR, CK,CRP, ANA, LAC, anti SSA, anti SAE 1	Fibs, no motor unit activation	Steroids, IV fluids,AZM. HCQ, NIV doxycycline	Improvement
Zhang Q et al [97]*	38 M	Few days	Myalgia, back pain, dyspnea	Bilateral pneumonia	Elevated CK, CRP	NR	NIV,AZM, HCQ, doxycycline, IV fluid	Improvement
Jin et al [99]*	60 M	6 days	Myalgia, limb weakness	Bilateral ground glass pneumonia	Elevated CK, myoglobin CRP	NR	NIV, steroids, meropenem, IV fluids, CP, IVIG,	Improvement
Suwangwongse et al [100]*	88 M	1–2 days	Myalgia, proximal leg weakness	Bilateral ground glass pneumonia	Elevated CK, CRP	NR	HCQ, IV fluids NIV	Improvement
Valente –Acosta et al[101] *	71 M	1 week	Severe leg myalgia, arthralgia	Bilateral ground glass pneumonia	Elevated CK, CRP	NR	MV, HCQ, AZM, TZB	Improvement
Beydon et al [102]*	NR	1 day	Myalgia, bilateral limb weakness	Bilateral ground glass pneumonia	Elevated CK, CRP, muscle oedema	NR	MV	Improvement
Borku U et al [103] *	60 M	2 days	Myalgia, fever, respiratory distress, fatigue	Small ground glass nodules, ARDS	Elevated CK, CRP,	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 hyperintesity	Rendesivir, MV steroids,TZB	Recover
Singh et al[105] *	67 M	4 days	Respiratory distress	Bilateral pneumonia	Elevated CRP, ESR, CK	NR	AZM, HCQ,MV	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	Recover
Sacchi et al[107]	77F	7 days	Respiratory, limb weakness	Pneumonia	Elevated PCR	Anti-Ku.anti Mi-2β myositis	MV, lopinavir, ritonavir, HCQ, antibiotics	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 CK, D-dimer,CRP	Myopathic changes	AZM, HCQ,TZB,MV	Death
Madia et al [108]	53 M	12 days	Acute quadriplegia, ARDS	Bilateral pneumonia	Elevated CK, D-dimer, CRP	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]	68F	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, K, CK, anemia, muscle calcification	NR	TZB,AZM,MV, plaquenil	Improvement
Cao et al [110]	45F	15 days	Weakness, myalgia, cough,erythema	Bilateral pneumonia	Anti –Ro52 positive, increased ferritin, CK	NR	Levofloxacin, NIV, IVIG, cyclophospamide	Death
Uslu S [111] *	38 M	NR	Myalgia, dyspnea	Bilateral pneumonia	Elevated CPR, CK	NR	Fluids,steroids, NIV	Improvement

ANA: anti-nuclear antibody; ARDS: acute respiratory distress syndrome; AZM, azithromycin; AKI: acute kidney insufficiency; anti-SSA and anti SAE; antibodies searched in systemic sclerosis; ESR: erythrocyrte sedimentation rate; CPR: C-reactive protein; CK: creatinKinase; CP: convalescent plasma; CTX: ceftriaxone; CT-scan: computed tomography; F, female; Fibs: fibrillation activity; HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulin; IV: intravenous; LAC: lupus anticoagulant; M, male; MV, mechanical ventilation; MUPs: motor unit potentials; NIV, non-invasive ventilation; NR, not reported; OTV: oseltamivir; PE: plasma exchange; TZB: tocilizumab.

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 word or in ICU is challenging.The non-invasive surrogate markers for diaphragm weakness include maximum static inspiratory mouth pressure (PI_{max}), 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. PI_{max} is obtained with a maximal inhalation against a closed valve, and reflects the strength of diaphragm, but also the external intercostal and accessory muscles. While normal values form PI_{max} vary by age and gender, there is agreement in considering a PI_{max} 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 PI_{max} 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 diaphragm function, because it requires minimal cooperation from the patient. In this scenario, variations in diaphragm thickness in the apposition zone (ZOA) may suggest paralysis or severe dysfunction. Findings consistent with severe muscle dysfunction or paralysis are: absence of diaphragm excursion, presence of paradoxical motion (diaphragm move cephalad during inspiration) thickening fraction (TF) $<$ 20% [118]. Bedside diaphragm US is useful to rule out or to confirm severe diaphragm dysfunction particularly in NMD that can present acute respiratory failure due to rapid inability of diaphragm pump, such as MG and GBS.

4.2. Respiratory support:challenges and advices

Most studies conducted during the COVID-19 outbreak reported that 10–20% of the hospitalized patients undergo some form of ventilatory support, either in the ward or in ICU [119]. The decision whether or not to intubate patients with severe disease is an essential component of the patient care. Excessive work of breathing, severe refractory hypoxemia, alteration of consciousness or coma, all are factors that must be considered for the indication for tracheal intubation and MV [22]. However, in most cases, a trial with a non-invasive respiratory support (NIV) is indicated before deciding on the need for intubation. The most commonly respiratory supports used include high-flow nasal oxygen (HFNO) and NIV through face mask interfaces or helmet, although it is not yet known which respiratory support is preferable in COVID-19 respiratory failure. Grieco et al [120] reported the results of a multicenter randomized clinical trial comparing helmet NIV vs HFNO in moderate to severe respiratory failure related to COVID-19.Although no difference was noted regarding the primary outcome (days free of respiratory support within 28 days), treatment with helmet NIV was associated with improved oxygenation and reduced rate of endotracheal intubation [120]. Furthermore, in severe COVID-19 patients with hypoxic lung damage requiring any type of respiratory support (oxygen, HFNO, NIV), immunomodulatory treatment either steroids or others, might enhance improvements in the clinical outcomes. The RECOVERY trial, a large randomized controlled trial, has shown that the use of dexamethasone in hospitalized COVID-19 patients who received either invasive MV or oxygen alone, resulted in lower 28-day mortality, while no benefit was found among patients who did not require oxygen [121]. Furthermore, Tocilizumab, a recombinant humanized anti-IL-6 receptor monoclonal antibody, in a large randomized trial showed additional survival benefit in patients already treated with corticosteroids, and the improvement of other clinical outcomes such as reduced chances of requiring invasive MV and increased chances of successful hospital discharge [122].

In patients with NMD during SARS-COV-2 infection, the timing of elective intubation is crucial; it can be decided on the previously mentioned criteria, but also on functional assessment of the respiratory muscles which are the following: VC less than 20 ml/Kg, PI_{max} less than 30 cmH_2O and maximal expiratory pressure (MEP) less than 40 cmH_2O 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 in NMD. 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 Vellipuram 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 an already existing condition. Non-invasive monitoring of respiratory muscles is challenging and indeed it could be essential to diagnose the onset of respiratory dysfunction in patients with suspected or pre-existing NMD overlapping SARS-COV-2 infection. Successful management of NMD with respiratory failure during COVID-19 pandemic is dependent upon a high clinical index of suspicion and early diagnosis.

Credit authorship contribution statement

Giuliana Galassi: Conceptualization, Methodology, Writing – review & editing. **Alessandro 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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