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Electrodiagnostic findings in patients with non-COVID-19- and COVID-19-related acute respiratory distress syndrome

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Abstract

Background: Critical illness polyneuropathy and myopathy (CIPNM) is a frequent neurological manifestation in patients with acute respiratory distress syndrome (ARDS) from coronavirus disease 2019 (COVID-19) infection. CIPNM diagnosis is usually limited to clinical evaluation. We compared patients with ARDS from COVID-19 and other aetiologies, in whom a neurophysiological evaluation for the detection of CIPNM was performed. The aim was to determine if there were any differences between these two groups in frequency of CINPM and outcome at discharge from the intensive care unit (ICU).

Materials and Methods: This was a single-centre retrospective study performed on mechanically ventilated patients consecutively admitted (January 2016-June 2020) to the ICU of Careggi Hospital, Florence, Italy, with ARDS of different aetiologies. Neurophysiological evaluation was performed on patients with stable ventilation parameters, but marked widespread hyposthenia (Medical Research Council score <48). Creatine phosphokinase (CPK), lactic dehydrogenase (LDH) and mean morning glycaemic values were collected.

Results: From a total of 148 patients, 23 with COVID-19 infection and 21 with ARDS due to other aetiologies, underwent electroneurography/electromyography (ENG/EMG) recording. Incidence of CIPNM was similar in the two groups, 65% (15 of 23) in COVID-19 patients and 71% (15 of 21) in patients affected by ARDS of other aetiologies. At ICU discharge, subjects with CIPNM more frequently required ventilatory support, regardless the aetiology of ARDS.

Conclusion: ENG/EMG represents a useful tool in the identification of the neuromuscular causes underlying ventilator wean failure and patient stratification. A high incidence of CIPNM, with a similar percentage, has been observed in ARDS patients of all aetiologies.

[†]See NeuCOV Study Group in Appendix section.

KEYWORDS
ARDS, CIPNM, COVID-19, ENG/EMG, neurological manifestations

1 | INTRODUCTION

At the end of 2019, many pneumonia cases occurred in Wuhan, China, which later spread to all over the world. This outbreak was caused by a new virus of Corona (CoV) called COVID-19.[1,2] Most of the studies, focusing on symptoms, reported several typical clinical pulmonary manifestations associated with COVID-19 infection. However, besides fever, cough and fatigue, COVID-19 may also lead to hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS) associated with characteristic lung computed tomography (CT) findings.[3] Recent evidence also reported several differences in clinical presentations in patients with ARDS secondary to COVID-19 infection, compared to ARDS from other aetiologies; for example, ARDS from COVID-19 had lower severity of illness scores at presentation and lower Sequential Organ Failure Assessment (SOFA) score-adjusted mortality, compared to ARDS from influenza A (H1N1).[4]

Increasing amounts of scientific literature have reported that approximately 35–40% of patients with COVID-19 developed several neurological symptoms[5,6] including affections of muscles and the neuromuscular system, such as critical illness polyneuropathy and myopathy (CIPNM).[5,7–11] CIPNM is usually one of the leading causes of intensive care unit-acquired weakness (ICUAW) in critically ill patients and represents a common neurological disease frequently observed in critically ill patients treated in intensive care units (ICUs) for different reasons.[12] In particular, this neurological disease has already been described in patients with ARDS of different aetiologies, including influenza A (H1N1) or bacterial infections,[13,14] despite confounding factors mainly concerning mechanisms underlying CIPNM onset.[14–16] Recent evidence[5,9] suggested that critically ill patients affected by COVID-19 may differ from typical ARDS patients in ICU exposures associated with ICUAW and CIPNM.[17] However, data on this topic are scarce and heterogenous, as most of the studies concerning association between COVID-19 infection and onset of ICUAW and CIPNM are limited to clinical evaluation of muscle weakness and the diagnosis of CIPNM has been exclusively based on clinical assessment of strength in all limbs, using the Medical Research Council (MRC) scale. There are only few studies[8,9,18–20] in which CIPNM presence was investigated with instrumental (electroneurography – ENG and electromyographic – EMG) tests which allowed a quantitative approach and, at the same time, were not subject to confounding factors, often present in critically ill patients. In addition, to the best of our knowledge, there is still no evidence of literature regarding an instrumental comparison of the detection of CIPNM in ARDS patients of different aetiologies, including COVID-19.

Given these limitations, we compared patients admitted to the ICU for ARDS of different aetiologies on whom an ENG/EMG evaluation for the detection of the CIPNM was performed, to patients with ARDS from COVID-19 infection. The aim was to evaluate if there were any differences between these two groups of ARDS patients, in terms of frequency of CINPM and outcome at discharge from the ICU.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a monocentric study based on a retrospective analysis performed after the screening of our database on mechanically ventilated patients consecutively admitted to the ICU of Intensive Care of Trauma and Extracorporeal Supports (which is an extra-corporeal membrane oxygenation – ECMO referral centre) of Careggi Teaching Hospital, Florence, Italy, with ARDS of different aetiologies from January 2016 to June 2020.

Limited to the subgroup of patients with COVID-19 infection included in the present paper, there was a small sample overlap with patients already reported in the previous study of Estraneo et al.[7]

Demographic variables (age, gender, dates of admission and discharge from the ICU) of all enrolled patients were recorded. In particular, patients ≥18 years of age were enrolled in the study.

Data about pre-existing comorbidities, such as diabetes or hypertension, were also collected.

Patients with previous neurological disorders were excluded. Patients with central nervous system (CNS) disorders developed during ICU stay were also excluded from the analysis, representing confounding factors both for clinical assessment (MRC score) and short-term neurological outcome.

Neurophysiological evaluation was usually performed in patients who showed marked, widespread hyposthenia (MRC <48), but, who the attending physician considered ready to be weaned off from the ventilator. Patient outcome was evaluated at ICU discharge. The study protocol was approved by the Ethical Committee of Careggi Teaching Hospital, Florence (n.17024, 31 March 2020).

2.2 | Patient management

Patients were managed according to local clinical practice; in particular, the standard therapeutical approach to ARDS, including lung protective ventilation, was applied.[21,22]

All ARDS patients were treated with neuromuscular blockade, for at least 48 h after starting mechanical ventilation, and with light sedation (propofol 1–2 mg/Kg/h). Low doses of systemic steroids were also used, especially in patients with ARDS due to COVID-19

infection.[23] Antibiotics and/or antiretrovirals were administered according to ARDS aetiology.

ECMO treatment was started on the basis of the Italian Ministry of Health criteria.[24] Conditions of severe hypoxia or hypercapnia, exceeding the limit values for protective ventilation (tidal volume less than 6 ml/kg and plateau pressure of 30 cm H2O), represented the criteria for proceeding with the treatment.[25,26]

Early physiotherapy was performed in all patients according to local protocol.[27]

2.3 | Clinical and biochemical evaluation

ARDS was defined according to the Berlin definition.[28] Neurological evaluation, based on the detection of segmental muscle strength at all the four-limb levels, was performed using the MRC scale. In the case of cooperative patients, we considered a MRC score <48 for the clinical suspicion of ICUAW.[29] In non-cooperative patients, such as those treated with CNS acting drugs or those with septic encephalopathy, motor responses to nociceptive stimuli were arbitrarily evaluated as follows: (a) no motor response: MRC = 0, (b) extension: MRC = 1: (c) flexion: MRC = 2 and (d) withdrawal from or localization: MRC = 3. In order to compare the assessment of muscle strength in cooperating and non-cooperating patients, in this latter subgroup of patients the MRC score obtained for each limb was applied to all functional movement of that limb. For example, in the case of a non-cooperating patient showing withdrawal to pain in all limbs, the MRC score reached a maximum value of 36.

The evaluation of osteotendinous reflexes in bilateral upper and lower limbs was also considered.

We collected the following biochemical parameters: creatine phosphokinase (CPK) and lactic dehydrogenase (LDH), using colorimetric method, as muscle damage indices and the mean morning glycaemia.

2.4 | Neurophysiological recording and evaluation

For neurophysiological recording, a Synergy electromyograph (Oxford Instruments, Old Woking) was used. Compound muscle action potentials (CMAP), motor and sensory nerve conduction velocities (MCV and SCV) and sensory nerve action potentials (SNAP) of six motor and four sensitive nerves in bilateral upper and lower limbs were collected. The peroneal, tibial and ulnar nerves were considered for the investigation of the motor component in addition to the evaluation of the tibialis anterior and soleus CMAP bilaterally. Concerning the sensory component, the ulnar and sural nerves were antidromically studied. Spontaneous muscle activity in bilateral tibialis anterior and biceps was detected by needle EMG. Finally, if patients could activate some muscles, the degree of the voluntary recruitment pattern and the degree of polyphasic and amplitude of the motor unit potential (MUP) were qualitatively evaluated, if good effort was obtained.

Neurography values were referenced to upper and lower limits of normality, which were calculated from 80 normal subjects in our laboratories.[30] The presence of CIPNM was defined by a low or very low amplitude of CMAP and, in some cases, of SNAP on ENG exam with normal or mildly reduced nerve conduction velocities, associated with myopathic features on needle electromyography.[31]

Neurophysiological evaluation was performed at least 24 h after the last administration of neuromuscular blockers.

2.5 | Statistical analysis

Qualitative variables were presented as frequency (percentage), and quantitative variables are provided as mean (standard deviation, SD) or median (interquartile range, IQR). We used the Chi-square test or Fisher's exact test (for qualitative variables) and Student's *t* test or Mann-Whitney *U* test (for quantitative variables) to study the different variables in the patient cohorts. For all the tests, we considered *p*-values <.05 as statistically significant.

As no guidelines have indicated a unique severity EMG criterion of CMAP and/or SNAP amplitude reduction in the instrumental diagnosis of CIPNM, we employed a cluster analysis (k-means algorithm in SPSS, ver. 26) to dichotomize our patients, using the whole ENG results. They were segmented as normal/good results in one cluster and as CIPNM in another cluster.

3 | RESULTS

Of a total of 148 patients admitted to the ICU for ARDS, 63 had COVID-19 infection, while 85 were affected by ARDS that resulted from other aetiologies. Among patients with COVID-19 infection, 23 underwent ENG/EMG recording, whereas two were excluded from the study because of new onset stroke during ICU stay. Among patients with ARDS from other aetiologies (influenza A H1N1, bacterial infections, ab ingestis pneumonia, post-traumatic ARDS), a neurophysiological evaluation was performed in 21 subjects, without the exclusion of any patient, resulting in a total of 44 patients available for the analysis.

Patient demographic characteristics are reported in Table 1. Patients with non-COVID-19 ARDS were significantly younger than COVID-19 ARDS subjects (Table 1). The most frequent comorbidities included type 2 diabetes, hypertension and obesity (Table 1).

All patients received multiple pharmacological therapies (sedation with anaesthetic drugs, such as propofol, benzodiazepines, neuromuscular blockers and corticosteroids), regardless of ARDS aetiology. In the case of COVID-19 or H1N1 infection, remdesivir and oseltamivir antiretrovirals were administered, respectively, whereas antibiotics were used for bacterial infections.

Of the 14 patients requiring ECMO, six had ARDS from COVID-19 and eight had ARDS from other aetiologies.

Concerning laboratory findings, all ARDS patients, regardless of the aetiology, showed elevated CPK and LDH levels. Patients with

TABLE 1 Demographic, anamnestic and clinical findings of patients analysed

	ARDS	*COVID−19*	
N.	**21**	**23**	***p***
Mean age years (range)	57 (36–83)	66 (45–84)	.008
Sex F/M (n)	5/16	3/20	.44
Previous history of comorbidities			.12
Diabetes *n* (%)	4 (17)	7 (30)	
COPD *N* (%)	1 (4)	2 (8)	
Hypertension *n* (%)	5 (23)	8 (34)	
CK (U/l) max value mean (SD)	262 (170)	309 (343)	.28
LDH (U/l) mean (SD)	455 (197)	398 (199)	.16
Glycaemia (mg/dl)*mean(SD)	160 (62)	201 (33)	.06
Length of ICU stay days median (IQR)	38 (26–86)	36 (18–42)	.13
Outcome at ICU discharge			
Dead *n* (%)	6 (26.1)	6 (29.1)	.14
Discharged Ventilated *n* (%)	11 (73.3)	10 (58.8)	.20

Note: Descriptive data are reported as mean and standard deviation (SD) or median and interquartile range (IQR), and percentages referred to the whole number of patients with or without intensive care unit-acquired weakness.

Abbreviations: *, mean morning glycaemia; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

ARDS from COVID-19 infection showed higher mean morning glycaemic levels compared to non-COVID-19 ARDS patients, even if the difference was not significant.

The length of ICU stay was similar in all patients with ARDS, irrelevant of the aetiology, with a median stay of 38 days for non-COVID-19 ARDS patients and 36 days for COVID-19 ARDS patients (Table 1).

Clinical evolution was variable, with 17 COVID-19 patients being discharged alive from the ICU (10 discharged with ventilatory support), while six patients were deceased. Concerning ARDS from other aetiologies, 15 patients were discharged alive from the ICU (11 discharged with ventilation support) and six were deceased.

The length of the stay in the ICU prior to the performance of the neurophysiological evaluation varied from 14 to 38 days, with a median of 18 days. According to the cluster analysis, patients with CMAP amplitudes that decreased by more than 50% of the normal value[32] at least in 8/10 muscles investigated were diagnosed to have CIPNM.

The ENG/EMG was normal in 14 patients (eight with COVID-19 infection and six with ARDS from other aetiologies) (Table 2), whereas the neurophysiological test was pathological in the 30 remaining patients (15 with COVID-19 infection, 15 with ARDS from other aetiologies) (Table 2). The percentage of ARDS patients with CIPNM was similar in the two groups (COVID-19 compared to non-COVID-19 subjects) (Table 2).

In Table 3, we reported the mean values of neurophysiological data according to ARDS aetiology and presence of CIPNM. All patients with CIPNM regardless the aetiology showed significantly reduced CMAP amplitude in all explored muscles with the exception of the extensor digitorum brevis muscle without differences in the amount of reduction between the two groups of ARDS patients. No significant differences were observed in either SNAP amplitude or MCV or SCV values in COVID-19 and non-COVID-19 patients. In particular, MCV and SCV were normal or only slightly reduced in all the patients and, importantly, none of them showed MCV/SCV values of <36 m/s and <40 m/s, for lower and upper limbs, respectively[30] (Table 3).

Concerning needle EMG, 32 over 44 (73%) patients were not cooperative and therefore could not perform voluntary recruitment. Only 3 over 12 cooperative patients were able to perform voluntary recruitment, exhibiting an interference pattern associated with an amplitude reduction. Spontaneous activity (fibrillation potentials and positive sharp waves) was recorded in 20 subjects (eight with COVID-19 infection and 12 with ARDS from other aetiologies).

Although 32 of the 44 (73%) patients were uncooperative, with possible skewed distribution of MRC score, patients with CIPNM of any aetiology showed a significantly lower median MRC score compared to patients without CIPNM (p = .001) (Table 2). Patients with CIPNM also showed severely reduced or absent osteotendinous reflexes in bilateral upper and lower limbs.

No differences in LDH values were detected between patients with or without CIPNM, whereas both the CPK levels and mean morning glycaemic values were increased in patients with CIPNM developed after COVID-19-induced ARDS even if differences were not significant (Table 2).

The median length of ICU stay was longer in patients with CIPNM (38 days for COVID-19 patients and 48 days for ARDS non-COVID-19 patients) but was not significantly different compared to patients without CIPNM (35 days for COVID-19 and 36 days for ARDS non-COVID-19 patients) (Table 2).

Mortality was higher in patients with CIPNM (33%), regardless of the aetiology causing ARDS onset, but the difference was not significant (respectively, 12.5% for COVID-19 and 16.7% for non-COVID-19 patients without CIPNM) (Table 2).

The proportion of patients who were discharged from the ICU requiring ventilatory support was significantly higher in patients with CIPNM (16 of 20) compared to patient without CIPNM (5 of 12) (Chi-square, p = .04), and there was no difference according to ARDS aetiology.

4 | DISCUSSION

According to our analysis, a high incidence of CIPNM was observed in critically ill patients with ARDS from all the aetiologies with a

TABLE 2 Demographic, anamnestic and clinical findings in patients with (+) or without (-) critical illness polyneuropathy and myopathy

	COVID–19		*ARDS*	
	CIPNM-	CIPNM+	CIPNM-	CIPNM+
***N* (%)**	**8 (35)**	**15 (65)**	**6 (29)**	**15 (71)**
Mean age (range) years	64 (45–80)	67 (47–84)	52 (36–62)	58 (43–83)
MRC, median (IQR)	36 (24–40)	16 (12–24)	36 (24–40)	16 (12–24)
Length of ICU stay median (IQR)	35 (18–82)	38 (16–62)	36 (20–76)	48 (28–96)
Outcome at ICU Discharge				
Dead *n* (%)	1 (12.5)	5 (33)	1 (16.7)	5 (33)
CK (U/l) mean (range)	202 (55–389)	367 (21–3413)	253 (45–457)	266 (42–783)
LDH (U/l) mean(range)	434 (249–967)	466 (231–981)	415 (231–615)	391 (143–1143)
Glycaemia (mg/dl)*mean (range)	126 (111–150)	179 (101–364)	211 (148–245)	197 (128–279)

Note: Descriptive data are reported as mean/standard deviation or median/interquartile range and number/percentages.

Abbreviations: *, mean morning glycaemia; ARDS, acute respiratory distress syndrome; CIPNM, critical illness polyneuropathy and myopathy; ICU, intensive care unit; IQR, interquartile range; MRC, Medical Research Council.

TABLE 3 Electromyographic features in patients with (+) or without (-) critical illness polyneuropathy and myopathy

	COVID–19		*ARDS*	
	CIPNM-	CIPNM+	CIPNM-	CIPNM+
MCV studies				
Peroneal MCV(m/s)	43.8 (39.2–49.3)	42.2 (36.9–46.4)	46.9 (43.0–53.3)	43.9 (40.9–46.6)
Tibial MCV(m/s)	40.2 (39.0–44.6)	42.4 (38.9–44.9)	42.7 (39.9–47.7)	42.5 (39.5–45.7)
Ulnar MCV(m/s)	51.9 (44.3–57.2)	46.7 (42.1–53.8)	50.1 (46.5–55.1)	49.5 (45.9–51.1)
CMAP amplitude (mV)				
EDB	1.8 (1.0–2.8)	0.5 (0.2–1.0)	2.0 (1.1–2.5)	1.0 (0.6–1.2)
AH	9.1 (1.5–11.7)	5.3 (2.3–6.3)°	12.1 (9.6–19.7)	3.4 (2.0–4.6)*
Tibial anterior	6.9 (3.7–11.8)	2.5 (1.8–4.2)#	8.4 (6.7–12.2)	1.9 (1.2–3.0)*
Soleus	15.9 (7.3–18.8)	3.7 (2.7–6.1)*	16.4 (12.5–24.7)	4.0 (1.1–6.4)°
ADM	8.6 (4.7–9.3)	3.4 (2.4–4.5)°	10.1 (5.8–10.6)	3.4 (2.3–3.9)°
Antidromic SCV studies				
Sural SCV(m/s)	47.7 (42.6–51.0)	43.9 (41.0–47.2)	46.5 (45.7–50.3)	47.3 (41.7–50.8)
Ulnar SCV(m/s)	53.5 (45.8–59.5)	47.6 (42.7–51.5)	52.0 (48.2–57.7)	49.0 (44.0–51.7)
Sural SNAP amp (μV)	5.4 (3.7–10.8)	4.8 (2.0–6.4)	5.1 (3.9–10.5)	4.1 (1.8–5.7)
Ulnar SNAP amp (μV)	18.8 (8.1–29)	13.0 (9.5–18.5)	16.1 (11.8–35.0)	12.0 (6.7–19.0)

Note: All values are reported as median and interquartile range.

Abbreviations: ADM, abductor digiti minimi; AH, abductor hallucis; amp, amplitude; CMAP, compound muscle action potential; EDB, extensor digitorum brevis; MCV, motor conduction velocity; SCV, sensory conduction velocity; SNAP, sensory nerve action potential.

Mann-Whitney *U* test results in bold type: °$p < 001$; #$p < .0001$; *$p < .00001$.

similar percentage in patients with ARDS from COVID-19 infection and ARDS from other aetiologies (65% of patients with COVID-19 infection and 71% of patients with ARDS from other aetiologies). Moreover, similar short-term clinical outcomes across the two groups of ARDS patients imply that both neuropathy and myopathy were not more strongly related to COVID-19 infection.

CIPNM is the most frequent neurological disease in COVID-19 patients who develop neuromuscular complications.[7–10,18,19] CIPNM is characterized by different clinical, instrumental and biochemical features such as muscle wasting, impaired contractility, reduced deep tendon reflexes, neuropathy and muscle protein degradation (preferential loss of myosin is a distinct feature of this condition).[9] CIPNM represents a common neurological disease frequently observed in critically ill patients admitted to ICUs for different causes,[12] including ARDS from different aetiologies.[13,14] Despite that, consensus among authors about the mechanism of action that leads to CIPNM onset is still lacking. An example of this was represented by CIPNM observed in patients with ARDS from H1N1 infection.[14–16] In fact, in this case, some authors suggested a direct invasion of the muscle by the virus, while other studies reported findings of non-specific changes in skeletal muscle biopsies.[14–16] In particular, these non-specific degenerative changes could be related to toxic myopathy (i.e., use of oseltamivir) or to poor clinical condition (critical illness), as well as to the direct action of the H1N1 virus.[14]

Concerning other viral diseases, such as in the case of coronavirus SARS-CoV infection, a virus sharing the same receptors as COVID-19, an affinity of the virus to the angiotensin-converting enzyme2 (ACE2) receptors in the mechanism underlying muscle tropism and injury has been hypothesized.[32] However, in some cases, coronavirus SARS-CoV, using the same receptor, was not detected in skeletal muscle on post-mortem examination.[33] Concerning COVID-19 infection, in support of the hypothesis of direct muscle injury by the virus, evidence of literature for both ACE2 expression and COVID-19 viral infiltration in the diaphragm of a subset of COVID-19 ICU patients was provided.[34] However, another explanation for muscle damage during COVID-19 infection might be the activation of a harmful immune response causing nervous system abnormalities: in particular, elevated pro-inflammatory cytokines in serum might cause skeletal muscle injury.[5] Therefore, it can be deduced that the data of current literature are still few and showing conflicting results. Thus, further studies are needed to identify a reliable mechanism that may underlie direct COVID-19 muscle injury.

In addition, in most of the studies conducted on patients with COVID-19,[5,9–11] the detection of CIPNM was limited to the evaluation of clinical parameters based on the assessment of strength of both the upper and lower limbs, using the MRC scale. This clinical assessment may be subject to confounding factors often present in critically ill patients (such as impaired consciousness level due to different causes, i.e., the use of sedation drugs or poor patient cooperation) that could under- or overestimate the presence of CIPNM. Among the instrumental/biochemical tests (i.e., ultrasound or nerve and muscle biopsy to detect the loss of myosin thick filaments) that could be associated with the clinical evaluation, the ENG/EMG has gained favour over the years. This is because, comparable to other neurophysiological tests (i.e., electroencephalogram-EEG and somatosensory evoked potentials-SEPs),[35–37] ENG/EMG is fast, easily reproducible and it does not require patient cooperation. In addition, it has the advantage of not being subject to confounding factors and gives a quantitative result, allowing standardization in the diagnosis of CIPNM among physicians. However, to date, only a few previous studies[7,8,18–20] have investigated the presence of CIPNM in patients with ARDS from COVID-19 with a neurophysiological evaluation. The limitations reported mainly concerned the limited sample of patients and the lack of well-defined criteria for the selection of patients to be investigated. In particular, in the reports by Cabanes-Martinez et al.[19] and of Madia et al.,[20] the authors found neurophysiological data for CIPNM in 11/12 and 6/6 patients, respectively. In our sample of patients, in whom, according to our local clinical practice, an ENG/EMG investigation is performed in subjects showing marked hyposthenia, before the reduction of ventilator mechanical support, incidence of CIPNM has been observed in 65% of ARDS patients due to COVID-19 infection. This percentage was very similar to that previously reported by Van Aerde et al.[9] At last, there is still no evidence of literature about an instrumental neurophysiological comparison of the presence of CIPNM in ARDS patients of different aetiologies including COVID-19. In particular, only in the study by Cabanes-Martinez et al.,[19] authors proposed to analyse whether CIPNM associated with COVID-19 differs from CIPNM observed in ARDS patients of other aetiologies. However, in their paper, authors suggested only indirectly the absence of differences limiting their statement on the basis of having not found distinctive features of muscle involvement in patients with COVID-19 but only non-specific changes of the skeletal muscle on the biopsy preparation.

In our sample of ARDS patients, CIPNM incidence rate was similar in patients with COVID-19 infection (65%) compared to ARDS from other aetiologies (71%). This result, limited to our cohort of ARDS patients, may be interpreted as indirect evidence of absence of increased correlation between COVID-19 infection and CIPNM onset. Therefore, it is more likely that the involvement of muscular tissue and peripheral nerves in COVID-19 patients might be secondary to critical illness rather than a result of a direct viral mechanism of action.

According to our results, we found no difference in the incidence of CIPNM in patients with ARDS from COVID-19 infection compared to ARDS from other aetiologies. However, the overall percentage of this neuromuscular disease in all critically ill ARDS patients, whatever the aetiology, was high.

CIPNM occurring in critically ill patients is known to complicate recovery, increasing the duration of both mechanical ventilation and length of hospital stay.[38–40] Thus, the importance of its early identification is even more evident during the outbreak of COVID-19, when a great number of patients require intensive treatments. In this context, it would be useful to propose updates to existing guidelines[41] concerning the optimal timing for ENG/EMG recording and the standardized protocol for the collection of the neurophysiological parameters,[42,43] as already done for other neurophysiological tests (EEG),[44] in order to improve the diagnostic-therapeutic management of critically ill COVID-19 patients.

In addition, the identification of neuropathy in CIPNM represents another important point of focus, because it may affect the neurological outcome. Several neurophysiological tools have previously been proposed to help in distinguishing neuropathy from

myopathy, especially in non-cooperative patients.[43] According to our results, a slight reduction of both MCV and SCV was observed in some patients even with median values that were not statistically different in patients with or without CIPNM. In addition, the discrepancy in the reduction of median values of SNAP amplitudes between the sural and ulnar nerves (with a reduction of sural SNAP amplitude compared to the ulnar SNAP amplitude), observed in all ARDS patients regardless of the presence of CIPNM, at first suggests a technical problem in the sural SNAP recording. Thus, at least limited to our sample of patients with CIPNM, neurophysiological findings supporting the presence of a neuropathy were not frequently associated with the findings supporting the myopathic involvement.

Considering the continuing increase in patients requiring mechanical ventilation, the epidemiological persistence of COVID-19 cases and considering the shortage of ICU beds, the reduction of timing of mechanical ventilation would be one of the main objectives of treatment. For this reason, the prevention and treatment of CIPNM is of great importance, based on early mobilization of the patient, short cycles of corticosteroid administration, protective ventilation strategy and increase in days free from mechanical ventilation.[10] Respiratory failure and CIPNM have a bidirectional relationship, and the presence of CIPNM can affect the outcomes of COVID-19 patients both during the ICU stay and after discharge. It is well known that in the acute phase the presence of neuromuscular complication increases in-hospital mortality[45] of critical patients and negatively affect weaning from mechanical ventilation long-term outcome.[9] In our patient population, we found no difference in mortality during ICU stay between patients with or without CIPNM; however, at ICU discharge, patients with neurophysiological findings of CIPNM required ventilatory support more frequently than patients without CIPNM. Thus, if the weaning strategies should be tailored on the basis of respiratory muscle monitoring before stopping mechanical ventilation, the presence of CIPNM should be investigated.[46]

Finally, concerning the post-acute phase in the Intensive Rehabilitative Unit, patients with CIPMN could benefit from rehabilitation but may achieve lower functional outcomes.[47,48] Thus, in addition to pulmonary rehabilitation, a physical motor rehabilitation should also be recommended to reduce symptoms of respiratory failure and distress and to restore the pre-illness functionality.[49,50]

4.1 | Limitations

This study has some limitations. Firstly, since it was a retrospective study, the clinical and biochemical data were collected from patient charts and in some cases were incomplete (for example, there was a lack of information on markers of inflammation). Secondly, despite being the first study comparing ENG/EMG data of patients with ARDS of different aetiologies and analysing neurophysiological data from a greater number of patients compared to other previous studies,[7,8,18–20] a main limitation of our paper is the small sample size. In addition, the exact incidence of CIPNM is difficult to calculate for several reasons. For example, some non-essential studies were delayed or cancelled, or due to the severity of the disease, some patients died before the neurophysiological evaluation could be performed. Moreover, the similarities in mortality rate in patients with CIPNM (irrelevant of ARDS aetiology) compared to patients without CIPNM were probably due to both the small number of enrolled patients and the selection bias of them, because of the study's retrospective design. Another main limitation of our study concerns the lack of availability of muscle biopsy. Moreover, we are aware that in order to differentiate critical illness myopathy (CIM) from critical illness polyneuropathy (CIP), standard electrodiagnostic parameters would be not sufficient. The distinction between CIM and CIP would be useful for prognostic long-term purpose, because of the longer time of functional recovery in patients with CIP. Unfortunately, in our cohort of patients, several factors have hindered the collection of parameters useful for the distinction between CIM and CIP. First of all, we were not able to perform quantitative EMG analysis because of about two thirds (73%) of patients were not cooperative and in the remainder of subjects, weakness level hampered the performance of a quantitative EMG. In addition, since muscle direct stimulation was not available in the cohort of patients with non-COVID-ARDS and considering the presence of individual protection devices and the necessity to reduce timing of contact stay with COVID-19 patients, we did not include muscle direct stimulation in our neurophysiological protocol. We also did not perform repetitive stimulation since post- or pre-synaptic transmission defect was not clinically suspected in any of the patients and because neurophysiological evaluation was performed at least 48 h after the suspension of neuromuscular blockade agent administration.

Finally, being a monocentric study, the generalizability of the results may be questionable; thus, further multicentric studies are needed to confirm our preliminary results.

5 | CONCLUSION

As the COVID-19 infection continues to spread, our understanding of the neurological manifestations in affected patients is also evolving. Considering the existing knowledge of other coronaviruses and respiratory viral infection pathogeneses, the extensive association of both central nervous system and peripheral nervous system manifestations with COVID-19 is not surprising. In particular, in the exploration of potential COVID-19-associated neurological diseases, the statistical probability of unique disease occurrence in the context of a pandemic is the data required to investigate causation appropriately. On the basis of a similar CIPNM incidence rate in our patient cohort between patients with COVID-19 infection compared to patients with ARDS from other aetiologies (65% of patients with COVID-19 infection and 71% of patients with ARDS from other aetiologies), we indirectly suggested the lack of increased correlation between COVID-19 infection and CIPNM onset. Therefore, we assume that the involvement of muscular tissue and peripheral nerves in COVID-19 patients might be secondary to critical illness; however, the problem relating to the interpretation of the possible different

physiopathologies that lead to the development of the critical illness remains unclear about the possible viral mechanism. Therefore, further prospective multicentre trials, also based on quantitative ENG/EMG, a more complete stratification of patients and the careful use of muscle biopsy are needed to provide a foundation for the data reported in our work.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Maenia Scarpino and Chiara Lazzeri wrote the manuscript. Chiara Lazzeri, Maenia Scarpino and Giovanni Lanzo collected clinical and neurophysiological data. Francesco Lolli did statistical analysis. Marco Ciapetti and Bahia Hakiki conducted literature research and articles screening. Manuela Bonizzoli, Antonello Grippo and Adriano Peris revised the manuscript. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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APPENDIX

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