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REVIEW ARTICLE

CRITICAL ILLNESS POLYNEUROPATHY AND FUNCTIONAL OUTCOME IN SUBJECTS WITH COVID-19: REPORT ON FOUR PATIENTS AND A SCOPING REVIEW OF THE LITERATURE

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Patients with COVID-19 may develop a range of neurological disorders. We report here 4 COVID-19 subjects with intensive care unit-acquired weakness and their functional outcome. In addition, a scoping review of COVID-19 literature was performed to investigate this issue. Of the post-COVID-19 patients admitted to our Neuro-Rehabilitation Unit, 4 (3 males, 1 female; mean age 59.2±8.62 years) had intensive care unit-acquired weakness, diagnosed with electromyography. Muscle strength and functional evaluation were performed on all patients with Medical Research Council, Disability Rating Scale and Functional Independence Measure, respectively, at admission, discharge and 6-month follow-up after discharge. Electromyography revealed that 3 subjects had critical illness polyneuropathy and 1 had critical illness polyneuropathy/critical illness myopathy. At follow-up, the 3 subjects with critical illness polyneuropathy reached full recovery. The patient with critical illness polyneuropathy/critical illness myopathy showed moderate disability requiring bilateral ankle foot-orthosis and support for ambulation. The scoping review retrieved 11 studies of COVID-19 patients with intensive care unit-acquired weakness, concerning a total of 80 patients: 23 with critical illness myopathy (7 probable), 21 with critical illness polyneuropathy (8 possible), 15 with critical illness polyneuropathy and myopathy (CIPNM) and 21 with intensive care unit-acquired weakness. Of 35 patients who survived, only 3 (8.5%) reached full recovery. All 3 had critical illness myopathy, but 2 of these had a diagnosis of probable critical illness myopathy. Intensive care unit-acquired weakness commonly occurred in subjects with COVID-19. Recovery was variable and a low percentage reached full recovery. However, the heterogeneity of studies did not allow definitive conclusions to be drawn.

Key words: COVID-19; critical illness polyneuropathy; intensive care unit-acquired weakness; outcome; rehabilitation; critical illness myopathy.

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LAY ABSTRACT

Patients with COVID-19 may develop a range of neurological disorders. We report here 4 cases of COVID-19 patients with intensive care unit-acquired weakness and their functional outcome. In addition, a scoping review of the COVID-19 literature was performed to investigate the occurrence of, and recovery from, intensive care unit-acquired weakness and sub-types (critical illness polyneuropathy, critical illness myopathy and critical illness polyneuropathy/critical illness myopathy) in subjects with COVID-19. Of these 4 patients, the 3 patients with critical illness polyneuropathy reached full recovery. The patient with critical illness polyneuropathy/critical illness myopathy showed moderate disability, requiring use of a bilateral device (ankle foot-orthosis). The scoping review of studies of COVID-19 patients with intensive care unit-acquired weakness retrieved a total of 80 patients: 21 with intensive care unit-acquired weakness, 23 with critical illness myopathy, 21 with critical illness polyneuropathy, and 15 with critical illness polyneuropathy/critical illness myopathy. Intensive care unit-acquired weakness commonly occurred in COVID-19 subjects, but the outcome was variable and a low percentage reached full recovery. COVID-19 subjects can develop long-term consequences and limitations, particularly those with intensive care unit-acquired weakness, who need more rehabilitation. New rehabilitative strategies and well-designed studies investigating the benefit of rehabilitation are necessary.

Since the emergence of coronavirus disease COVID-19 (SARS-CoV-2) in China (1), it has spread rapidly to become a severe worldwide pandemic. To date, epidemiological data show more than 277 million people have been infected and more than 5 million have died (2). COVID-19 is a complex disease that predominantly affects the lungs, producing characteristic interstitial pneumonia with respiratory failure and critical conditions, which can require mechanical ventilation (MV) and admission to the intensive care unit (ICU). The large number of people requiring hospital or ICU admission has produced a health "tsunami", stressing health systems worldwide and resulting in organizational disciplinary changes (3). A severe effect of the pandemic is the saturation of intensive care capacity.

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During ICU stay and after discharge critically ill subjects can develop a common neuromuscular complication, defined as ICU-acquired weakness (ICUAW), which includes a spectrum of disorders including critical illness polyneuropathy (CIP), critical illness myopathy (CIM) and overlapping forms (CIP/CIM or CIPNM) (4–6). The occurrence of this neurological complication has been variously detected, with a range of 45–80% (7–8). The types of ICUAW show characteristic histological and electrophysiological features, but are clinically indistinguishable, since all forms produce weakness and bilateral limb paresis with an absence of tendon reflexes. Although several studies have been published about the disorders affecting the central nervous system (CNS) and the peripheral nervous system (PNS) in patients with COVID-19 (9–11), few reports investigating the occurrence of, and recovery from, ICUAW types have been reported.

The aim of this study is to describe the case reports and functional outcomes of 4 COVID-19 patients with ICUAW admitted to our Neuro-Rehabilitation Unit. In addition, a systematic review of the COVID-19 literature was performed to investigate occurrence of, and recovery from, ICUAW in subjects with COVID-19.

CASE REPORTS OF PATIENTS WITH COVID-19 AND ICUAW

After approval from the local Ethics Committee (Sezione Giovanni Paolo II- IRCCS Casa Sollievo della Sofferenza) and informed consent, patients admitted to our Neuro-Rehabilitation Unit between June 2020 and February 2021 with post-COVID-19 were investigated. Ten post-COVID-19 patients (6 males, 4 females) with neuromuscular disorders were found. Of these, 2 subjects had Guillain-Barré syndrome, 4 had bilateral plexus brachial lesion, and 4 (3 males, 1 female; mean age 59.2 years (standard deviation (SD) 8.62) had ICUAW. All post-COVID-19 patients with ICUAW were transferred from the ICU, where they had undergone endotracheal intubation, mechanical ventilation and, subsequently, tracheostomy. During the ICU stay, they had received a pharmacological therapeutic protocol for COVID-19, including antiretroviral drugs and steroids. Furthermore, they had developed infections with multi-drug resistant germs (MDR), including *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and had undergone multiple antibiotic therapy. At admission to our Neuro-Rehabilitation Unit, all subjects were breathing spontaneously, but needed a variable oxygen level treatment. Furthermore, all had a tracheal tube and nasal-gastric tube for nutrition. Clinical characteristics of the post-COVID-19 subjects are reported in Table I. All subjects were evaluated by electromyography (EMG) at admission. ICUAW and sub-types were diagnosed in the neuro-rehabilitation setting, apart from 1 subject who received a diagnosis of ICUAW by EMG during the ICU stay, due to severe weakness involving the upper and lower limbs. Furthermore, quantification of strength was performed for all subjects by means of the Medical Research Council (MRC) scale according to De Jonghe's method (12). Functional evaluation was performed through the Disability Rating Scale (DRS) and the Functional Independence Measure (FIM). All measurements were performed at admission, at discharge and at 6 months of follow-up. At admission, post-COVID-19 subjects with ICUAW showed variable grades of muscular weakness from paresis to tetraplegia. One of these (patient #3) had severe paralysis of the upper and lower limbs and a global MRC score of 10. No subjects had involvement of cranial nerves.

Electrophysiological examination

EMG was performed as described previously (13). Briefly, all patients underwent conventional orthodromic motor and antidromic sensory nerve conduction studies, performed bilaterally on 8 motor nerves (median, ulnar, common peroneal and tibial nerves)

Table I. Clinical characteristics of subjects with COVID-19 and intensive care unit-acquired weakness (ICUAW)

Characteristics	#1	#2	#3	#4	Mean (SD)
Sex	M	M	M	F	
Age, years	47	62	64	64	59.2 (8.62)
Comorbidities		Hypertension	Diabetes mellitus, hypertension, obesity	Diabetes mellitus	
SAPS II	32	35	38	34	34.7 (2.5)
Sepsis	+	+	+	+	
	Corynebacterium	Pseudomonas; Klebsiella pneumoniae; Acinetobacter baumannii; Enterococcus; Staphylococcus capitis	Klebsiella pneumoniae; Acinetobacter baumannii; Pseudomonas	Pseudomonas	
Tracheal tube	+	+	+	+	
Nasogastric tube	+	+	+	+	
ICU stay	40	32	35	28	33.7 (5.05)
Neuro-rehabilitation stay	15	30	105	65	58.7 (34.5)

SAPS II: Simplified Acute Physiology Score 35 (29–40); ICU: intensive care unit; SD: standard deviation.

and 6 sensory nerves (median, ulnar and sural nerves). Muscular activity at rest and, when possible, during contraction, was assessed with concentric needle electrodes. Sensory nerve action potential (SNAP), distal motor latencies, F wave, compound muscle action potential (CMAP) and nerve conduction velocities were recorded. Abnormal CMAP or SNAP amplitudes were considered significant when found in at least 2 nerves. Spontaneous activity, recruitment and interference patterns were detected bilaterally by needle EMG from deltoid, first dorsal interosseus, tibial anterior and abductor hallucis muscles. CIP was recognized if electrophysiological results revealed very low amplitude or absent sensory responses and low motor amplitudes with normal or mildly reduced conduction velocities. Patients were diagnosed as having myopathy in the setting of low or normal motor amplitudes, with relatively normal sensory responses. Overlapping electrophysiological findings of CIP and CIM were considered as defining the CIP/CIM subtype. Of 4 patients with ICUAW, 3 (patients #1, #2 and #4) had CIP and 1 (patient #3) had CIP/CIM type. A summary of EMG data for the study sample is shown in Table II.

Rehabilitation interventions

All post-COVID patients underwent an individualized and tailored rehabilitation treatment for 3 h per day, 6 days a week. The rehabilitation programme comprised joint mobilization, proprioceptive neuromuscular facilitation according to neuro-developmental techniques, flexibility and strength exercises. The patients underwent 2 h of electrical muscular stimulation daily on the lower limbs, by placing surface electrodes on the quadriceps and anterior tibial muscles, bilaterally. Electrical stimuli involved biphasic rectangular square

Table II. Summary of electrophysiological data

	#1		#2		#3		#4	
Nerve	A	V	A	V	A	V	A	V
Upper limb								
L ulnar motor								
• distal	3.5		4.6		0.8		3.8	
• proximal	3	47.1	3.2	46.2	0.7	36.8	3.5	52.2
R ulnar motor								
• distal	4.9		4.4		0.9		4,3	
• proximal	4.0	49.7	3.8	45.0	0.8	34.7	4.0	50.1
L ulnar sensory	3	44.0	–	–	–	–	5	46.0
R ulnar sensory	4	46.0	2.3	44.0	–	–	4	47.0
L median motor								
• distal	4.4		4.8		0.8		4.1	
• proximal	4.1	45.8	3.7	47.0	0.8	35.4	3.7	47.0
R median motor								
• distal	4		4.1		2		3.5	
• proximal	3.5	46.0	3	45.0	1.5	36.0	3.0	47.0
R median sensory	4	45.0	–	–	–	–	7	48.0
L median sensory	3	43.0	1.5	43	–	–	8	46.0
Lower limb								
R peroneal								
• distal	2.3		< 0.2		< 0.2		1.2	
• proximal	1.9	39.2	< 0.2	35.5	< 0.2	32.0	0.9	50.0
L peroneal								
• distal	1.5		< 0.2		< 0.2		0.6	
• proximal	1	38.0	< 0.2	40.0	< 0.2	30.0-	0.5	44.0
R tibialis								
• distal	1.0		< 0.2		< 0.2		1.5	
• proximal	0.9	37.0	< 0.2	33.0	< 0.2	35.3	1.0	40.3
L tibialis								
• distal	3.6		< 0.2		< 0.2		1.3	
• proximal	2.4	40.1	< 0.2	37.8	< 0.2	34.2	0.9	41.2
Sural								
right	5.7	37.2	–	–	–	–	8.4	40.0
left	6.3	37.5	–	–	–	–	9.3	52.4

	#1		#2		#3		#4	
EMG	SA	IP	SA	IP	SA	IP	SA	IP
Upper limb proximal	–	Submaximal	–	Submaximal	+	Poor	–	Submaximal
Upper limb distal	+	Poor	+	Poor	+	Absent	+	Poor
Lower limb proximal	–	Submaximal	–	Submaximal	+	Myopathic recruitment	+	Submaximal
Lower limb distal	+	Poor	++	Poor	++	Absent	++	Poor

EMG: electromyography; A: amplitude (motor: mV, sensory: mcV); V: velocity (m/s); SA: spontaneous activity (+: rare, ++: moderate); IP: interference pattern; – no response (absent).

Table III. Strength and functional measures scores of COVID-19 patients with intensive care unit-acquired weakness (ICUAW) at admission, discharge and follow-up

Patients	EN/EMG	MRC admission	MRC discharge	MRC follow-up	DRS admission	DRS discharge	DRS follow-up	FIM tot admission	FIM discharge	FIM follow-up
#1	CIP	46	58	60	8	1	0	76	126	126
#2	CIP	26	50	58	10	4	0	48	115	126
#3	CIP/CIM	8	38	48	18	8	8	41	86	105
#4	CIP	40	50	60	12	5	0	62	110	126

CIP: critical illness polyneuropathy; CIM: critical illness myopathy; MRC: Medical Research Council scale; DRS: Disability Rating Scale; FIM: Functional Independence Measure.

pulses with a 20-ms duration at a rate of 20 Hz every 25 s. Amplitude of pulses was variable and based on the elicitation of visible muscular contraction (100–100 mA) (14).

Functional outcome

At discharge, only 1 subject (patient #1) had reached full recovery and ability in activities of daily living. Two subjects had incomplete recovery with minor disability (patients #2 and #4). Of these, 1 (patient #2) showed persistent left foot drop that required application of a foot-ankle orthosis, and 1 (patient #4) reported fatigue and mild weakness involving the lower limbs that limited performance and endurance in motor activity. However, she was able to ambulate without support. Patient #2 reached independent ambulation after application of the device. All of these subjects had CIP type according to EMG. Patient #3 showed CIP/CIM according to EMG. At discharge, he had moderate disability and motor limitations due to leg paresis with bilateral foot drop that was reduced with foot-ankle orthosis. However, he was able to stand up and to ambulate with bilateral support. At follow-up, 6 months after discharge, 3 subjects (patients #1, #2 and #4) had full recovery and 1 (patient #3) showed bilateral foot drop still requiring ankle foot-orthosis. Strength evaluation and functional scale scores of admission, discharge and follow-up are reported in Table III.

LITERATURE REVIEW

Methods

To evaluate COVID-19 subjects with ICUAW, a search of the studies was conducted using MEDLINE/PubMed, CINAHL, EMBASE, Web of Science, Scopus databases and Google Scholar. The search was restricted to English language reports published between 1 December 2019 and 31 March 2021. The search terms included "COVID-19", "critically ill patients", "intensive care unit acquired weakness", "ICUAW", "critical illness polyneuropathy", "CIP", "critical illness myopathy", "CIM", "critical polyneuropathy and myopathy", "CIPNM", "CIP and CIM"; "CIP/CIM", "acute tetraplegia", "functional outcome" and "COVID-19". The search was made either by using MeSH terms, keywords or subject headings. Related terms were combined using the Boolean operators "OR" and "AND". Search limits included only adults. Abstracts/posters or articles that were not peer-reviewed were excluded. The literature search was conducted by 3 independent authors (AMC, AG, and FDR). Inclusion criteria were: patient age $\geq$18 years; COVID-19 diagnosis; COVID-19 subjects with ICUAW, or the following types: CIP, CIM and CIP/CIM.

The research was conducted according to the Preferred Reporting Items for Systematic Reviews and the Meta-Analyses (PRISMA) diagram, depicting the selection of articles searched for the study (Fig. 1).

Results

The review resulted in 11 studies being included, based on inclusion criteria (15–25) (Table IV). Studies were widely heterogeneous. Of these, 2 were case reports describing single subjects (15–16), 5 were case series with small samples ranging from 3 to 11 patients (17–11), and 4 cohort studies (22–25). Of these, 2 studies investigated neurological manifestations in large cohorts of COVID-19 patients (22–23) and among these, subjects with CIP or CIM were also detected. One was a retrospective study that ascertained COVID-19 subjects with MV who developed ICUAW (24) and 1 study that, with the use of a prospective method design, investigated the incidence of ICUAW in COVID-19 subjects during ICU stay (25).

A total of 80 patients, age range 51–81 years, was reported. Of these, 23 were diagnosed with CIM (7 probable), 21 with CIP (8 possible), 15 with CIP/CIM, and 21 with ICUAW. Twelve (15%) patients died. ICUAW was diagnosed by EMG in all studies except the study by Van Aerde et al. (24), in which ICUAW was diagnosed on MRC scale, and the study by Nersesian et al. (22), in which ICUAW diagnosis was performed clinically. In this study, the authors detected 8 subjects with possible CIP and only 1 was diagnosed by EMG. Biopsy was performed in 1 study (20) involving, globally, 3 subjects. Of these, 1 subject revealed scattered necrotic and regenerative fibres in the absence of inflammatory infiltrates and 2 subjects showed non-specific findings, consisting of very occasional atrophic and regenerative fibres (20).

Five studies did not report the outcome of COVID-19 subjects with ICUAW because they addressed different issues, such as occurrence (25), electrophysiological parameters (20, 25), neurological manifestations of COVID-19 patients (23), or described the clinical phenomenon (15, 16). Recovery was reported in 6 studies (15, 17, 19, 21, 22, 24). Of these, 1 was a case report, by Bagnato et al. (15), who described a 62-year-old woman with COVID-19 diagnosed with CIM. After discharge, she had a mild weakness in the lower limb proximal muscles and was able to walk without assistance. Of the remaining studies, 4 were case series (17, 19, 21, 22), with samples ranging from 3 to 8 subjects, and 1 was a cohort study that investigated COVID-19 patients with ICUAW compared with no ICUAW

subjects (24). Globally, the outcome was reported for 42 (52.5%) subjects: 10 with CIM (6 had probable CIM), 8 with probable CIP, 4 with CIP/CIM, and 20 with ICUAW. Seven (16.6%) patients died. In detail, Madia et al. reported 6 subjects with probable CIM. Of these, 2 patients reached full recovery and 3 (51.2%) showed disability due to CNS lesions (17). Yildiz et al. described 3 women with COVID-19 with severe weakness and tetraparesis due to CIM. Of these, 2 subjects died after 60 and 200 days, respectively, during ICU stay and only 1, who had MV weaning after 57 days from ICU admission, recovered slowly with intensive physiotherapy. However, the level of functional outcome was not specified (21). Nasuelli et al. described 4 subjects with CIP/CIM. Of these, 3 subjects died after 3 weeks and only 1 had a positive outcome, but showed slow recovery of motor skills, in particular due to foot flexion deficit that improved after intensive rehabilitation (19). Nersesjan et al. described 8 subjects with definite or possible CIP. At discharge, all patients were tetraparetic and had muscle atrophy and hyporeflexia (22). Finally, Van Aerde et al. performed a retrospective, observational study to detect COVID-19 patients with MV who developed ICUAW. At discharge, COVID-19 subjects with ICUAW had significantly poorer functional outcome than those without ICUAW: Barthel 8 (2.5–11.5) vs 10.5 (8–18), ($p=0.040$) for COVID subjects with and without ICUAW, respectively.

Of 35 COVID-19 patients with ICUAW who survived, and for whom it was possible to detect the outcome, only 3 (8.5%) subjects reached full recovery. All 3 of these had CIM, although 2 of the 3 subjects had a diagnosis of probable CIM. On the other hand, the majority of COVID-19 patients with ICUAW reported a variable disability. No measure was employed to evaluate functional outcome, except in the study by Nersesjan et al. (22), which used mRS, and that by Van Aerde et al. (24), which used the mobility score and the Barthel scale. Muscle weakness was quantified by the MRC scale in only 2 studies (16, 18). It was not possible to compare our post-COVID-19 subjects with a matched group of post-COVID-19 patients published in the literature, due to the heterogeneity of enrolled samples, including sitting, timing of neuro-muscular disorder ascertainment, functional measures, demographics (mean age 73.6 ± 8.7 vs 59.2 ± 8.62 years, respectively, in subjects reported in the literature and our sample) and rehabilitative treatment.

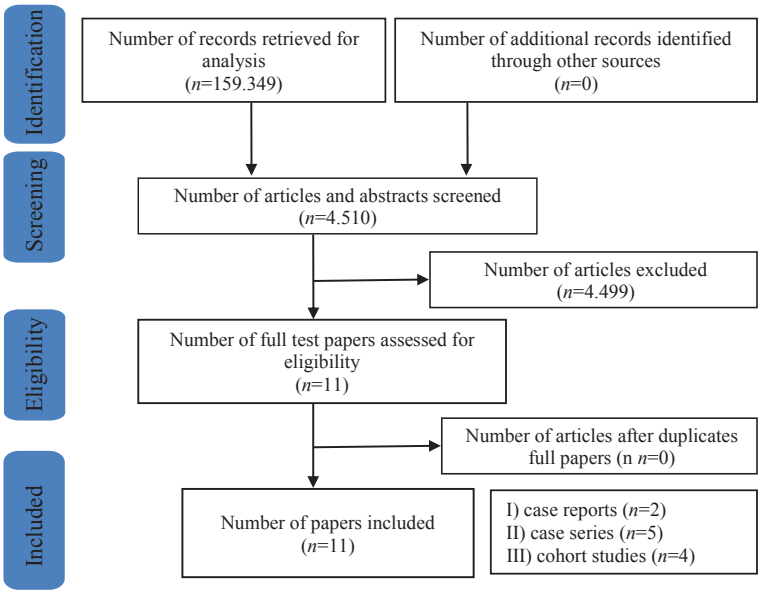

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram depicting the selection of articles for the study.

DISCUSSION

ICUAW is a common neurological complication in COVID-19 subjects during ICU stay and after discharge, which requires intensive rehabilitation. Recovery was found to be variable, but, unlike the general ICUAW population, a low percentage of COVID-19 patients reached full functional recovery. COVID-19 infection can result in characteristic interstitial pneumonia with severe respiratory failure, which may involve multi-organ systems. An increasing number of studies are being published on the role and pathophysiological mechanisms of COVID-19 (9) in producing and favouring neurological manifestations that affect the central (CNS) and peripheral nervous system (PNS). Among the disorders of PNS, variable conditions and neuropathies have been described, including Guillain-Barré syndrome and its variants (26, 27), cranial multifocal neuropathy, dysautonomia (28) and brachial plexus lesion (29). Likewise, neuromuscular disorders, such as myalgia, myositis and, in particular, myasthenia gravis, have also been described (30). Our experience and the current review show that ICUAW is also a common neurological disorder in critically ill COVID-19 subjects who require ICU stay.

Among COVID-19 patients admitted to neurorehabilitation in our department, we detected 4 subjects with ICUAW. A scoping review of the COVID-19 literature showed that a total of 80 COVID-19 patients with ICUAW were reported in the literature between 1 December 2019 and 31 March 2021. ICUAW can cause variable disabling conditions and, consequently, an important aspect to consider concerns rehabilitation interventions in order to obtain full recovery and a good quality of life (31, 32). In this respect, despite the lack of treatments and the limitations of rehabilitative strategies (33), subjects with ICUAW can achieve recovery with variable functional outcomes. An extensive literature review of the neuromuscular sequelae of ICU subjects with critical illness revealed that 68.8% made a complete recovery and regained the ability to walk independently (31). It was reported that the outcome depended on the type of ICUAW, as confirmed by the fact that CIM had an earlier and better functional outcome than CIP (34, 35). However, the current review shows that the outcome

Table IV. Critical illness polyneuropathy and myopathy in subjects with COVID-19; from literature review

Authors	Study; Setting	CIPNM type	Neurological features	Follow-up	Functional measures	Other measures	Outcome
Bagnato S et al. (15) 2020	Case report neuro-rehabilitation	A 62-year-old woman; CIM	Cardiac or pulmonary diseases	2 months	None	EMG,	At discharge, the patient had a mild weakness in her lower limb proximal muscles and was able to walk without assistance
Tankisi A (16) 2020	Case report; ICU	A 68-year-old man; CIM	Severe symmetrical proximal and distal weakness, diffuse muscle wasting and absent deep tendon reflexes	Not reported	None	MRC (2/5)	Not reported
Madia F et al. (17) 2020	Case series; ICU	5 M, 1 F; ranged from 51 to 72 years CIM = 6 probably	Acute flaccid quadriplegia	14–20 days	None	ENG/EMG	2 (28.5%) patients gained complete recovery; 3 (42.8%) patients showed disability due to CNS lesions; 2 patients died
Bax F et al. (18) 2020	Case series; Post-ICU	8 pts (6 with ICUAW): CIP = 2 CIM = 1 (possible) CIPNM = 2 ICUAW* = 1	Diffuse weakness		None	MRC; ENG/EMG	Not reported
Nasuelli NA et al. (19) 2020	Case series; ICU	4 pts; 3 M, 1 F; age from 60 to 74 years CIPNM = 4	Tetraplegia with diffuse hypotonia, and hypotrophy	1 month Time in ICU >3 weeks	None	EMG	1 patient had positive outcome but slow recovery of motor skills, in particular due to foot flexion deficit. He improved after intensive rehabilitation. 3 (75%) patients died
Cabañes-Martínez L et al. (20) 2020	Retrospective study; clinical neurophysiology department;	12 patients; 10 M, 2 F; mean age 65 years (52–75); 11 pts CIM = 7 CIP = 4	General weakness and/or difficulty to wean from the ventilator	n/a	None	NCS/EMG; biopsy (3 patients)	5 (45.4%) patients died and 7 were discharged from the ICU, but outcome was not reported
Nersesjan V et al. (22) 2020	Cohort study; prospective observational study; tertiary referral centre	Total 61 patients; 63% males, mean age 62.7 years; CIP = 8 (possible), alone 1 patient was diagnosed by ENG/EMG	Tetraparesis with hyporeflexia and atrophy	3 months; follow-up available for 45	mRS	ENG/EMG; re-admissions (if any), death after discharge, and new-onset neurological and psychiatric diagnoses	all patients were tetraparetic at discharge, had muscle atrophy and hyporeflexia and had been admitted to ICU 10 (16.3%) patients died
Rifino N et al. (23) 2020	Cohort study; retrospective, observational analysis	1,760 COVID-19 patients, 137 presented neurological manifestations; CIPNM = 9 pts; 8 M, 1 F, mean age 60.7 years	Not reported	n/a	None	ENG/EMG	Not reported
Van Aerde N et al. (24) 2020	Cohort study; retrospective; observational study; ICU	74 subjects with IMV; 20 = ICUAW	Not reported	30 (19–42) days	Barthel scale; mobility score	MCR-sum score	Handgrip-strength 43% (28–59%) vs 64% (36–80%), (p = 0.045), and Barthel: 8 (2.5–11.5) vs 10.5 (8–18), (p = 0.040) remained lower in COVID-19 subjects with ICUAW at discharge
Frithiof R et al. (25) 2021	Prospective observational intensive care unit cohort study; incidence and ES parameters	11 M; mean age 64 years; CIM = 4 CIP = 7	Muscular weakness	n/a	None	ENG/EMG	Not reported
Yildiz OK et al. (21) 21	Case series; ICU	3 patients; 3 F (64, 76 and 81 years old, respectively) CIM = 3;	Diffuse muscle weakness and tetraparesis	2–16 months	None	ENG/EMG	1 patient recovered slowly with intensive physiotherapy. 2 subjects died

pts: patients; ICU: intensive care unit; CIP: critical illness polyneuropathy; CIM: critical illness myopathy; CIP/CIM or CIPNM: overlapping CIP and CIM or critical illness polyneuropathy and myopathy; ICUAW: intensive care unit acquired weakness; IMV: invasive mechanical ventilation; MRC: Medical Research Council scale; NCS: nerve conduction study; ENG: electroneurography; EMG: electromyography; n/a: not applicable.
*Clinically evident weakness, but equivocal ENG/EMG findings.

was described in a low number of COVID-19 subjects, consisting of 35 (43.7%) survivals, of whom only 3 (8.5%) reached full recovery. This finding is much lower than that of general critically ill subjects with ICUAW. On the other hand, the functional outcome in our COVID-19 subjects with ICUAW was in line with the findings reported in the literature. Indeed, after rehabilitation, 2 (50%) subjects reached full recovery and, after 6 months, only 1 showed mild disability and limitation of gait. This contrasting finding has several possible reasons. Almost all studies did not use proper functional scales to quantify disability, and the evaluation of functional outcome was based on the neurological examination or on the improvement in muscle strength on the MCR scale. Furthermore, the studies were performed by ICU specialists, who might have preferentially described this neurological complication in COVID-19 subjects during the ICU stay or at discharge and overlooked reporting the recovery. Furthermore, our patients underwent intensive rehabilitative treatment, which might have produced some benefit and improved the outcome. All 3 subjects in the current review who reached full recovery had CIM, but 2 of these had a diagnosis of probable CIM. However, in considering only COVID-19 patients with CIM who survived, full recovery was detected in 22.3% of subjects. Conversely, it was observed that 3 COVID-19 patients with CIP reached full recovery, whereas 1 subject with overlapping CIP/CIM had disability at 6 months after discharge. Although some of the studies analysed in the current review differentiated the ICUAW types, no conclusion can be drawn regarding recovery from different forms of ICUAW, due to the lack of data addressing this issue. Nevertheless, the outcome of COVID-19 subjects with ICUAW, regardless of type, appeared poorer than that of subjects with general ICUAW, although on the basis of the number and quality of published studies, the level of recovery remains unclear.

Likewise, whether occurrence of ICUAW in ICU COVID-19 subjects is higher than in the ICU general population also remains unclear. The occurrence of this disorder has been variously detected, and a systematic review reported a median prevalence of 43% (36). Frithiof et al. investigated the occurrence of ICUAW in adult subjects with COVID-19 admitted to ICU between 13 March and 8 June 2020. The ICUAW incidence was higher in COVID-19 patients compared with a general ICU population treated during 2019 (9.9% vs 3.4%). In particular, CIP was more frequent in the COVID-19 ICU cohort (50%) than in the non-COVID-19 ICU cohort (0%, $p=0.008$) (25). On the other hand, Cabañes-Martínez et al. described, out of a total of 225 patients treated in the ICU, 11 patients with a clinical and neurophysiological diagnosis of CIM or CIP, but they stated that it was not possible to calculate the exact incidence of the presence of neuropathy or myopathy (20). It is well known that several risk factors can result in ICUAW in critically ill patients, including sepsis, ICU length of stay, and multiple organ failure (7, 8), as well as the use of neuromuscular blocking and several drugs. In this respect, Neresian et al. (22) compared COVID-19 ICU patients with ICUAW to COVID-19 ICU patients without neuromuscular complications. Interestingly, those with ICUAW had a significantly longer stay (median 49.5 vs 23 days, $p<0.001$), had been admitted to ICU more frequently (100% vs 40%, $p=0.002$), were more often treated with renal replacement therapy (62% vs 14%, $p=0.008$), and were more often delirious (75% vs 30%, $p=0.02$) (22). Likewise, Van Aerde et al. noticed that COVID-19 subjects with ICUAW had significantly longer ICU stays (days) ($p=0.008$), lower mobility scores at ICU discharge ($p<0.001$), compared with those without ICUAW (24). Therefore, the same risk factors and the severity of systemic disease itself might favour the occurrence of ICUAW in COVID-19 subjects. In this respect, Bax et al. suggested a possible association with the duration of intubation and with increased IL-6 levels at admission (18).

Another factor to take into account when considering ICUAW in COVID-19 is the possible direct damage to nerves and muscles caused by the virus. It has been reported that some neurological disorders are caused by the direct action of COVID-19 on the brain tissue, such as encephalitis and myelitis (37). Even without evidence of viral invasion of the nervous system, immune-mediated events, through the cytokine or chemokine pathways, may lead to vascular leakage, demyelination, activation of complement and organ damage. Indeed, the dominant characteristics of COVID-19 infection are the excessive immune response of the host to virus invasion of the organs, through the production of inflammation factors, in particular cytokines (38, 39). Therefore, it is possible that the same underlying pathological conditions in critically ill subjects characterize COVID-19 patients and may represent an environment that favours neuromuscular disorders (20).

The current study has some limitations. We report here 4 post-COVID-19 patients with ICUAW among those with neuromuscular disorders admitted to a neuro-rehabilitation setting. Therefore, the results concern a single centre and are not generalizable. The review of the COVID-19 literature aimed to determine the occurrence and recovery of ICUAW subjects with COVID-19, but the cohort studies and case series were highly heterogeneous. A further limitation concerns the recovery of subjects with ICUAW types due to the lack

of functional measurements and of trials focusing on rehabilitative interventions.

Suggestions and implications for future research

After discharge COVID-19 subjects may have long-term consequences and limitations. A recent study showed that, 6 months after acute infection, COVID-19 survivors were mainly affected by fatigue or muscle weakness, sleep difficulties, and anxiety or depression (40). Therefore, multi-component rehabilitative interventions and new approach strategies are being applied to address the respiratory, muscular, psychological and affective disorders that can persist in these patients. In this respect, COVID-19 subjects with ICUAW need more intensive rehabilitation, but, at present, rehabilitative interventions and proper investigations concerning ICUAW recovery are scant. Therefore, there is a strong need to find new rehabilitative strategies and plan well-designed studies investigating the efficacy and the benefit of rehabilitation. Further research is needed into the following aspects of neurological manifestations occurring in COVID-19 patients:

- whether the occurrence of ICUAW in COVID-19 subjects is higher than that in the critically ill population without COVID;
- whether COVID-19 causes direct damage to the peripheral nerves, or if such damage is due to inflammation factors that favour nerve lesions;
- whether COVID-19 subjects with ICUAW may have a different type of recovery;
- rehabilitation interventions and their effect on functional outcome and quality of life.

CONCLUSION

This review found that ICUAW is common in COVID-19 patients, producing disabling conditions for which rehabilitation is required. Recovery is variable, but a low percentage of COVID-19 patients with ICUAW gain a full functional outcome. However, the small size of samples and the heterogeneity of studies in this review do not permit definitive conclusions to be drawn. Rehabilitation interventions and further detailed studies should be carried out to improve functional outcome and to answer unsolved questions.

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