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ORIGINAL ARTICLE

Comparative features and outcomes of major neurological complications of COVID-19

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Abstract

Background and purpose: The aim of this study was to assess the neurological complications of SARS-CoV-2 infection and compare phenotypes and outcomes in infected patients with and without selected neurological manifestations.

Methods: The data source was a registry established by the European Academy of Neurology during the first wave of the COVID-19 pandemic. Neurologists collected data on patients with COVID-19 seen as in- and outpatients and in emergency rooms in 23 European and seven non-European countries. Prospective and retrospective data included patient demographics, lifestyle habits, comorbidities, main COVID-19 complications, hospital and intensive care unit admissions, diagnostic tests, and outcome. Acute/subacute selected neurological manifestations in patients with COVID-19 were analysed, comparing individuals with and without each condition for several risk factors.

Results: By July 31, 2021, 1523 patients (758 men, 756 women, and nine intersex/unknown, aged 16–101 years) were registered. Neurological manifestations were diagnosed in 1213 infected patients (79.6%). At study entry, 978 patients (64.2%) had one or more chronic general or neurological comorbidities. Predominant acute/subacute neurological manifestations were cognitive dysfunction (N = 449, 29.5%), stroke (N = 392, 25.7%), sleep–wake disturbances (N = 250, 16.4%), dysautonomia (N = 224, 14.7%), peripheral neuropathy (N = 145, 9.5%), movement disorders (N = 142, 9.3%), ataxia (N = 134, 8.8%), and seizures (N = 126, 8.3%). These manifestations tended to differ with regard to age, general and neurological comorbidities, infection severity and non-neurological manifestations, extent of association with other acute/subacute neurological manifestations, and outcome.

Conclusions: Patients with COVID-19 and neurological manifestations present with distinct phenotypes. Differences in age, general and neurological comorbidities, and infection severity characterize the various neurological manifestations of COVID-19.

KEYWORDS
coronavirus, COVID-19, neurological complications, neurology

INTRODUCTION

The spectrum of acute and chronic neurological complications of coronavirus disease 2019 (COVID-19) has been illustrated in an increasing number of reports and summarized in several systematic reviews [1–3]. Cognitive impairment, stroke, headache, and sleep disorders are likely the most common findings, although other manifestations have been frequently documented. Some neurological disorders occurring during the acute phase are associated with a more extensive inflammatory reaction and carry a worse prognosis in terms of death, sequelae, and overall functional impairment [4–6]. However, most available data have been obtained in varying circumstances (single centers, small and selected samples, case reports) and in divergent and dissimilar populations of origin. Limitations also include the use of different diagnostic criteria and assessment of the course of the disease in variable and often too short periods of follow-up [7]. In addition, several studies have focused only on specific clinical conditions, such as delirium [8], dementia [9], cerebrovascular disease [10–12] or Guillain–Barré syndrome [13].

With this background, it is difficult to predict the type of neurological complications that patients might have, based on their baseline demographic and clinical profile. The European Academy of Neurology (EAN) set up a registry for the study of the neurological complications of COVID-19 early during the first wave of the COVID-19 pandemic. The aim was to promote international collaboration and standardized assessments of these important complications [14]. Using the data collected in this registry, we have compared infected patients with and without several key neurological manifestations to provide the demographic and clinical profile of each major neurological complication and define risk factors, comorbidities, acute complications of infection, and outcome.

PATIENTS AND METHODS

The EAN NEuro-covid ReGistrY (ENERGY) was started in May 2020 to provide data on neurological signs and symptoms in adult patients with COVID-19 infection seen by neurologists in outpatient services,

emergency rooms, and hospital departments (including intensive care units [ICUs]) in various European and non-European countries. Details of the structure and organization of ENERGY have been published elsewhere [14]. Briefly, neurologists who are members of the EAN and agree to participate in the registry are asked to record neurological symptoms, signs and diagnoses reported in neurological consultation in clinically or laboratory-confirmed COVID-19 patients. Data are collected prospectively or retrospectively and recorded in an electronic case record form (e-CRF). Included variables are patient demographics and lifestyle habits, chronic comorbidities, date of first symptoms of infection, hospital and ICU admission, incident general (non-neurological) and neurological manifestations during the acute phase, diagnostic tests, and outcome (recovery, improvement, sequelae, death). Non-neurological manifestations of COVID-19 include dyspnea, pneumonia, cardiovascular symptoms/signs, renal insufficiency, coagulation disorders and refractory shock. The occurrence of any of those manifestations define "severe" COVID-19 infection. All adult patients with symptoms and/or signs and/or diseases requiring neurological consultation are eligible for inclusion. A guide including the definitions of all collected variables is included in the e-CRF (Appendix S1) to facilitate data collection at study entry and during follow-up. At study entry (corresponding to the time of neurological evaluation), and at hospital discharge, the patient's modified Rankin Scale (mRS) score and new neurological manifestations are noted. For patients who have died, date of death and, if performed, autopsy is noted. Only laboratory-confirmed COVID-19 cases were included in the analyses. Descriptive statistics were used for variables collected during the acute phase (defined by the interval from onset to the recovery of symptoms of infection) in the entire sample.

The outcome of the infection, in terms of functional impairment, was defined as "stable/improved" if mRS score at discharge was equal to or lower than the baseline score and "worse" if mRS score at discharge was higher than the baseline score.

For selected acute/subacute neurological manifestations (cognitive dysfunction—including dysexecutive syndrome—stroke, sleep–wake disturbances, dysautonomia, peripheral neuropathy, movement disorders, ataxia, seizures), patients with and without that clinical condition were compared on the same variables included in the descriptive statistics.

The same variables, except for neurological manifestations, occurred in the acute/subacute phase, were evaluated as potential risk factors for the occurrence of each selected neurological manifestation. The association of potential risk factors with the occurrence of each neurological manifestation was evaluated using univariable logistic regression models, with the neurological complication as a dependent variable and potential risk factors as independent variables. A stepwise selection was also applied in a multivariable model including all variables evaluated in univariable analysis, to identify those that were more strongly associated with the occurrence of each neurological sign or disease. Stepwise selection was applied using the following criteria: a significance level of 0.05 was required to enter variables into the model and a significance level of 0.05 was also required for a variable to be retained in the model. The results of the univariable and multivariable logistic regression models are presented as odds ratios (ORs) and adjusted (adj.) ORs with 95% confidence intervals (CIs). Statistical significance was set at the 5% level ($p = 0.05$). Missing data were handled using the listwise deletion method. The number of missing data is reported for categorical variables. The proportion of missing data in the entire sample for each variable included in the analyses is also reported. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

The study was approved by the ethics committees of all participating sites and informed consent was obtained from all eligible patients in line with each participating country's legal requirements.

RESULTS

As of July 31, 2021, a total of 1523 laboratory-confirmed COVID-19 patients were included in the registry. The general characteristics of the sample are illustrated in Table 1. Included were 756 women, 758 men and nine intersex/unknown sex patients, aged from 16 to 101 years (median 63 years). Patients were registered in 23 countries (including seven outside Europe). A total of 978 patients (64.2%) had one or more chronic general comorbidities at study entry. Hypertension (51.3%), cardiovascular diseases (30.1%) and diabetes (22.3%) were the predominant diseases. At baseline, registered patients exhibited several neurological comorbidities, the commonest being, in decreasing order, stroke (16.9%), dementia (7.4%), and multiple sclerosis (4.5%).

Non-neurological manifestations of COVID-19 infection were present in 55.0% of cases, mainly represented by pneumonia (54.8%) and dyspnea (47.8%). Acute/subacute neurological manifestations were diagnosed by consulting neurologists in 1213 infected patients (79.6%). These included differing symptoms, signs, or diseases. Neurological manifestations were differentiated into self-reported symptoms and diagnoses captured by clinical evaluation. The most common symptoms were headache (41.4%), followed by hyposmia/hypogeusia (31.5%), myalgia (30.1%), vertigo (21.6%), sleep–wake disturbances (including sleepiness/hypersomnia; 16.4%), and ataxia (8.8%). Cognitive dysfunction (29.5%), stroke (25.7%), dysautonomia (14.7%), peripheral neuropathies (9.5%), movement disorders (9.3%) and seizures (including status epilepticus; 8.3%) were the predominant clinical diagnoses.

Details of the commonest neurological signs and diseases are given in Tables S1–S4.

Cognitive dysfunction

Patients exhibiting cognitive dysfunction during the acute phase of COVID-19 ($N = 449$; Table S1) were 10 years older than patients without cognitive dysfunction. In this cohort, general comorbidities were present in 77.1% of cases (vs. 58.8% in patients without cognitive dysfunction; $p < 0.0001$). Hypertension, cardiovascular

TABLE 1 General characteristics of the sample ($N = 1523$), stratified by setting (outpatients, hospitalized)

	Total[a]			Outpatients ($n = 274$)		Hospitalized not in ICU ($n = 819$)		Hospitalized in ICU ($n = 328$)	
	n	%	% missing or unknown	*n*	%	*n*	%	*n*	%
Country									
Austria	72	4.73	0	3	1.09	44	5.37	24	7.32
Brazil	66	4.33		41	14.96	21	2.56	4	1.22
Croatia	36	2.36		26	9.49	4	0.49	5	1.52
Egypt	7	0.46		1	0.36	5	0.61	1	0.30
Estonia	13	0.85		0	0.00	10	1.22	3	0.91
France	22	1.44		3	1.09	16	1.95	3	0.91
Germany	7	0.46		0	0.00	7	0.85	0	0.00
Honduras	2	0.13		2	0.73	0	0.00	0	0.00
Hungary	105	6.89		16	5.84	88	10.74	1	0.30
Israel	66	4.33		0	0.00	55	6.72	11	3.35
Italy	233	15.3		80	29.20	131	16.00	22	6.71
Macedonia	68	4.46		18	6.57	40	4.88	10	3.05
Mexico	22	1.44		1	0.36	0	0.00	21	6.40
Moldova	169	11.1		3	1.09	63	7.69	99	30.18
Norway	50	3.28		11	4.01	26	3.17	13	3.96
Poland	62	4.07		37	13.50	25	3.05	0	0.00
Portugal	59	3.87		0	0.00	33	4.03	23	7.01
Romania	177	11.62		0	0.00	151	18.44	26	7.93
Russia	51	3.35		7	2.55	39	4.76	5	1.52
Switzerland	48	3.15		19	6.93	17	2.08	10	3.05
Tunisia	19	1.25		5	1.82	11	1.34	3	0.91
Turkey	145	9.52		1	0.36	19	2.32	34	10.37
Ukraine	24	1.58		0	0.00	14	1.71	10	3.05
Sex									
Male	758	49.77	1	101	36.86	430	52.50	175	53.35
Female	756	49.64		173	63.14	384	46.89	151	46.04
Intersex	2	0.13		0	0.00	1	0.12	1	0.30
Unknown	7	0.46		0	0.00	4	0.49	1	0.30
Smoking									
Yes	195	12.8	11	30	10.95	86	10.50	44	13.41
No	1153	75.71		217	79.20	644	78.63	235	71.65
Unknown	175	11.49		27	9.85	89	10.87	49	14.94
Source of COVID-19 contact									
Occupation	120	7.88	56	55	20.07	56	6.84	9	2.74
Family member	309	20.29		90	32.85	156	19.05	45	13.72
Social	130	8.54		29	10.58	64	7.81	19	5.79
Travel	22	1.44		3	1.09	10	1.22	5	1.52
Other	92	6.04		1	0.36	65	7.94	25	7.62
Unknown	850	55.81		96	35.04	468	57.14	225	68.60

TABLE 1 (Continued)

	Median	IQR	% missing or unknown	Median	IQR	Median	IQR	Median	IQR
Age at COVID onset	63	47–74	4	47	32–57	66	52–77	66	56–74
Age at inclusion	63	47–74	1	47	33–58	66	52–77	66	56–74
Age at admission	65	51–75	3	43	31–55	67	52–77	66	56–74
BMI	26	23–29	11	24	22–28	25	23–29	27	24–30
Comorbidities	***n***	**%**	**% missing or unknown**	***n***	**%**	***n***	**%**	***n***	**%**
Any comorbidity	978	64.22	1	94	34.31	585	71.43	252	76.83
Hypertension	782	51.35	2	60	21.90	459	56.04	224	68.29
Type 1 diabetes	9	0.59	1	0	0.00	2	0.24	4	1.22
Type 2 diabetes	331	21.73	4	18	6.57	205	25.03	96	29.27
Cardiovascular disease	458	30.07	1	33	12.04	297	36.26	121	36.89
Chronic kidney disease	133	8.73	2	2	0.73	80	9.77	48	14.63
Chronic liver disease	51	3.35	2	1	0.36	33	4.03	16	4.88
Chronic pulmonary disease	139	9.13	2	16	5.84	85	10.38	31	9.45
Anemia	81	5.32	3	6	2.19	55	6.72	19	5.79
Cancer	121	7.94	1	7	2.55	80	9.77	31	9.45
Immunosuppressed state	72	4.73	2	12	4.38	38	4.64	20	6.10
Other non-neurological comorbidity	369	24.23	1	35	12.77	239	29.18	92	28.05
Dementia	113	7.42	0	7	2.55	79	9.65	20	6.10
Parkinson's disease	52	3.41	0	19	6.93	20	2.44	7	2.13
Stroke: ICH, ischemic stroke, TIA	258	16.94	0	12	4.38	170	20.76	70	21.34
Multiple sclerosis	68	4.46	0	37	13.50	23	2.81	5	1.52
Motor neuron disease	10	0.66	0	1	0.36	9	1.10	0	0.00
Neuromuscular disorder	20	1.31	0	7	2.55	9	1.10	4	1.22
Neuropathy	44	2.89	0	5	1.82	25	3.05	6	1.83
Other neurological disease	150	9.85	0	30	10.95	89	10.87	28	8.54
COVID systemic complications	837	54.96	2	33	12.04	523	63.86	266	81.10
Dyspnea	728	47.8	2	63	22.99	404	49.33	216	65.85
Pneumonia	835	54.83	2	35	12.77	509	62.15	255	77.74
Cardiovascular	171	11.23	6	7	2.55	85	10.38	78	23.78
Kidney failure/dialysis	100	6.57	3	0	0.00	55	6.72	43	13.11
Coagulation disorder/disseminated intravascular coagulation	80	5.25	3	3	1.09	36	4.40	41	12.50
Refractory shock	73	4.79	2	0	0.00	30	3.66	43	13.11
Extracorporeal membrane oxygenation	7	0.46	2	0	0.00	0	0.00	7	2.13
Mechanical ventilation	198	13	1	0	0.00	40	4.88	156	47.56
Neurological manifestations (symptoms)	1213	79.65	0	181	66.06	686	83.76	280	85.37
Headache	631	41.43	8	156	56.93	290	35.41	127	38.72
Hyposmia/hypogeusia	480	31.52	14	174	63.50	209	25.52	59	17.99
Vertigo	329	21.6	9	75	27.37	173	21.12	70	21.34
Myalgia	458	30.07	10	145	52.92	208	25.40	73	22.26
Sleep–wake disturbances	250	16.41	7	86	31.39	173	21.12	70	21.34
Ataxia	134	8.8	1	15	5.47	77	9.40	36	10.98

(Continues)

TABLE 1 (Continued)

Comorbidities	*n*	%	% missing or unknown	*n*	%	*n*	%	*n*	%
Neurological manifestations (diagnoses)									
Dysautonomia	224	14.71	7	57	20.80	102	12.45	46	14.02
Cognitive dysfunction	449	29.48	4	73	26.64	248	30.28	113	34.45
Hyperactive delirium	157	10.31	2	15	5.47	79	9.65	58	17.68
Hypoactive delirium/ acute encephalopathy	149	9.78	2	10	3.65	67	8.18	67	20.43
Stupor/coma	181	11.88	1	8	2.92	70	8.55	99	30.18
Syncope	83	5.45	2	11	4.01	46	5.62	19	5.79
Seizures/status epilepticus	126	8.27	1	12	4.38	74	9.04	36	10.98
Meningitis/encephalitis	53	3.48	2	8	2.92	26	3.17	15	4.57
Stroke	392	25.74	1	11	4.01	236	28.82	134	40.85
Movement disorders[a]	142	9.32	4	17	6.20	71	8.67	31	9.45
Tremor	96	6.3	1	16	5.84	41	5.01	20	6.10
Chorea	2	0.13	1	0	0.00	1	0.12	0	0.00
Dystonia	23	1.51	4	0	0.00	17	2.08	5	1.52
Myoclonus	21	1.38	1	0	0.00	13	1.59	7	2.13
Dyskinesia	16	1.05	1	6	2.19	5	0.61	2	0.61
Spinal cord disorder	57	3.74	1	2	0.73	34	4.15	17	5.18
Peripheral neuropathy	145	9.52	2	18	6.57	74	9.04	49	14.94
Other neurological manifestations	215	14.12	5	26	9.49	133	16.24	56	17.07
Hospital admission	1242	81.55	0.5	0	0.00	819	100.00	324	98.78
ICU admission	328	21.54	7	0	0.00	0	0.00	328	100.00
Pre-morbid mRS score									
0	802	55.62	5	207	81.50	366	47.41	171	54.29
1	238	16.5		32	12.60	143	18.52	40	12.70
2	130	9.02		10	3.94	75	9.72	34	10.79
3	143	9.92		5	1.97	98	12.69	33	10.48
4	85	5.89		0	0.00	61	7.90	23	7.30
5	44	3.05		0	0.00	29	3.76	14	4.44
Missing	81			20		47		13	
Discharge mRS score									
0	431	29	2	198	74.72	166	20.78	20	6.17
1	233	15.68		45	16.98	143	17.90	23	7.10
2	166	11.17		15	5.66	98	12.27	38	11.73
3	207	13.93		7	2.64	132	16.52	58	17.90
4	157	10.57		0	0.00	114	14.27	43	13.27
5	81	5.45		0	0.00	49	6.13	29	8.95
6	211	14.2		0	0.00	97	12.14	113	34.88
Missing	37			9		20		4	
Outcome at discharge									
Worse	727	50.49	5	17	6.61	427	55.53	265	83.86
Stable/improved	713	49.51		240	93.39	342	44.47	51	16.14
Missing	83			17		50		12	

TABLE 1 (Continued)

Comorbidities	*n*	%	% missing or unknown	*n*	%	*n*	%	*n*	%
Death									
No	1275	85.8	2	265	100.00	702	87.86	211	65.12
Yes	211	14.2		0	0.00	97	12.14	113	34.88
Missing	37			9		20		4	

Abbreviations: BMI, body mass index; ICU, intensive care unit; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; TIA, transient ischemic attack.

[a]At least one of: tremor, chorea, dystonia, myoclonus, dyskinesia and parkinsonism.

diseases, cancer and, to a lesser extent, chronic kidney disease and anaemia prevailed in patients with cognitive dysfunction. Along with history of dementia, other neurological comorbidities, such as cerebrovascular diseases and Parkinson's disease, were also more common in patients with than in patients without cognitive dysfunction. Among COVID-19 complications, dyspnea, pneumonia and, to a lesser extent, cardiovascular manifestations prevailed in patients with cognitive dysfunction. Neurological manifestations occurred during the acute phase of the infection in 87.7% of cases with cognitive dysfunction and in 76.3% of cognitively unaffected individuals ($p < 0.0001$). These included, among others, dysautonomia, vertigo, sleep–wake disturbances, dysexecutive syndrome, delirium, stupor/coma, syncope, seizures, central nervous system (CNS) infection, stroke, and movement disorders. Patients with cognitive dysfunction were most disabled (higher mRS scores) at study entry and at discharge. A worse outcome at discharge was found in 58.0% of patients presenting cognitive dysfunction and in 47.3% of patients with normal cognition ($p = 0.0002$). In-hospital deaths occurred in 21.9% versus 11.0% ($p < 0.0001$), respectively. The only variables confirmed by stepwise selection to characterize the phenotype of patients with cognitive dysfunction were older age at study entry (adj. OR 1.02, 95% CI 1.01–1.03), history of hypertension (adj. OR 1.66, 95% CI 1.17–2.35), history of dementia (adj. OR 12.46, 95% CI 6.18–25.13), dyspnea (adj. OR 1.68, 95% CI 1.25–2.27) and premorbid functional disability (mRS score 5; adj. OR 5.80, 95% CI 3.07–10.95 (Table 2)).

Stroke

Patients experiencing stroke ($N = 392$; Table S1) were significantly older than patients without stroke (13-year difference in median), had a higher body mass index, and presented one or more general comorbidities (81.2% vs. 58.4%; $p < 0.0001$), largely represented by hypertension, type 2 diabetes, cardiovascular disease, chronic kidney disease and, to a lesser extent, chronic pulmonary disease. COVID-19 non-neurological complications were more frequent in this cohort (70.4% vs. 49.6%; $p < 0.0001$), mostly represented by pneumonia, cardiovascular disorders, and refractory shock. Other neurological manifestations also prevailed in patients with stroke (93.1% vs. 75.0%; $p < 0.0001$), such as cognitive dysfunction, dysexecutive syndrome, delirium, stupor/coma, seizures, CNS infection, tremor, dystonia, and ataxia. Patients with stroke were most frequently hospitalized and admitted to the ICU. Outcome at discharge was worse than in patients without stroke in terms of greater functional disability and death. However, the only variables whose association with stroke was confirmed by stepwise selection were older age (adj. OR 1.04, 95% CI 1.02–1.05), history of hypertension (adj. OR 2.65, 95% CI 1.77–3.98), history of Parkinson's disease (adj. OR 11.57, 95% CI 7.43–18.01), and viral infection complicated by cardiovascular disease (adj. OR 2.15, 95% CI 1.33–3.47 (Table 2)).

Sleep–wake disturbances

Sleep–wake disorders ($N = 250$; Table S2) included, among others, hypersomnia, and daytime somnolence. Other than Parkinson's disease, no neurological disorder was present in the history of patients reporting sleep–wake disturbances during COVID-19. Dyspnea and cardiovascular symptoms were more frequently reported by this cohort than in the remaining study population. Several other neurological manifestations with the infection were concurrently present, including headache, hyposmia/hypogeusia, myalgia, vertigo, cognitive dysfunction, dysexecutive syndrome, dysautonomia, delirium, stupor/coma, syncope, seizures, CNS infection, movement disorders (in addition to parkinsonism, tremor, and myoclonus), ataxia, spinal cord disorders and peripheral neuropathies. Functional abilities at study entry and discharge and overall outcome were not worse in those patients than in the rest of the cohort. Only history of Parkinson's disease (adj. OR 3.31, 95% CI 1.53–7.17), dyspnea (adj. OR 1.98, 95% CI 1.36–2.89) and cardiovascular COVID-19 complications (adj. OR 1.90, 95% CI 1.20–3.02) were confirmed to be associated with sleep–wake disturbances by stepwise selection (Table 3).

Dysautonomia

Compared to patients without altered autonomic function, patients with dysautonomia ($N = 224$; Table S2) more often had a history of Parkinson's disease, concurrent headache, hyposmia/hypogeusia, vertigo, myalgia, sleep–wake disturbances, cognitive dysfunction,

TABLE 2 Demographic and clinical predictors of cognitive impairment and stroke

	Cognitive dysfunction								Stroke							
	Univariable analysis				Stepwise selection				Univariable analysis				Stepwise selection			
	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value
Sex				0.0715				–				0.8288				–
Male	1 (ref.)				1 (ref.)	–	–		1 (ref.)				1 (ref.)	–	–	
Female	1.20	0.96	1.50		–	–	–		1.04	0.83	1.31		–	–	–	
Intersex/unknown	3.31	0.88	12.43		–	–	–		1.47	0.37	5.95		–	–	–	
Smoking				0.0847				–				<0.0001				–
Yes	0.67	0.47	0.96		–	–	–		0.89	0.62	1.28		–	–	–	
No	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
Unknown	0.87	0.61	1.24		–	–	–		2.09	1.50	2.91		–	–	–	
Source of COVID-19 contact				0.1148				–				<0.0001				–
Family member	1.16	0.88	1.53		–	–	–		0.41	0.30	0.57		–	–	–	
Occupation	0.59	0.37	0.94		–	–	–		0.19	0.10	0.37		–	–	–	
Social	0.87	0.57	1.31		–	–	–		0.47	0.30	0.75		–	–	–	
Travel	1.10	0.44	2.72		–	–	–		0.10	0.01	0.74		–	–	–	
Other/unknown	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
Age at admission (1-year increase)	1.03	1.02	1.04	<0.0001	1.02	1.01	1.03	0.0006	1.04	1.03	1.05	<0.0001	1.04	1.02	1.05	<0.0001
BMI (1-unit increase)	1.00	1.00	1.01	0.0972	–	–	–	–	1.00	0.99	1.00	0.6407	–	–	–	–
Non neurological comorbidities																
Hypertension	1.84	1.47	2.30	<0.0001	1.66	1.17	2.35	0.0044	4.24	3.27	5.50	<0.0001	2.65	1.77	3.98	<0.0001
Type 1/type 2 diabetes	0.98	0.75	1.28	0.8678	0.55	0.38	0.79	0.0013	2.07	1.60	2.68	<0.0001	–	–	–	–
Cardiovascular disease	1.94	1.54	2.45	<0.0001	–	–	–	–	2.69	2.11	3.42	<0.0001	–	–	–	–
Chronic kidney disease	1.61	1.11	2.32	0.0115	–	–	–	–	1.91	1.32	2.77	0.0006	–	–	–	–
Chronic liver disease	1.32	0.73	2.37	0.3557	–	–	–	–	1.10	0.59	2.05	0.7761	–	–	–	–
Chronic pulmonary disease	0.96	0.66	1.42	0.8494	–	–	–	–	0.61	0.39	0.95	0.0297	–	–	–	–
Anemia	1.70	1.07	2.68	0.0237	–	–	–	–	1.08	0.65	1.79	0.7636	–	–	–	–
Cancer	1.77	1.21	2.59	0.0032	–	–	–	–	0.70	0.44	1.10	0.1235	–	–	–	–
Immunosuppressed state	0.62	0.35	1.10	0.1026	–	–	–	–	0.75	0.42	1.34	0.3310	–	–	–	–
Neurological comorbidities																
Dementia	13.77	8.37	22.65	<0.0001	12.46	6.18	25.13	<0.0001	0.68	0.42	1.10	0.1153	0.22	0.10	0.46	<0.0001

TABLE 2 (Continued)

	Cognitive dysfunction								Stroke							
	Univariable analysis				Stepwise selection				Univariable analysis				Stepwise selection			
	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value
Parkinson's disease	1.95	1.11	3.40	0.0195	–	–	–	–	0.30	0.12	0.76	0.0107	11.57	7.43	18.01	<0.0001
Stroke: ICH, ischemic stroke, TIA	1.50	1.13	1.99	0.0047	–	–	–	–	9.08	6.75	12.19	<0.0001	–	–	–	–
Multiple sclerosis	0.40	0.20	0.79	0.0081	–	–	–	–	<0.001	<0.001	>999.999	0.9739	–	–	–	–
Motor neuron disease	0.26	0.03	2.09	0.2074	–	–	–	–	<0.001	<0.001	>999.999	0.9763	–	–	–	–
Neuromuscular disorder	0.60	0.20	1.79	0.3553	–	–	–	–	<0.001	<0.001	>999.999	0.9782	–	–	–	–
Neuropathy	0.79	0.40	1.58	0.5092	–	–	–	–	0.07	0.01	0.47	0.0069	0.07	0.01	0.58	0.0131
COVID systemic complications																
Dyspnea	2.08	1.66	2.61	<0.0001	1.68	1.25	2.27	0.0006	0.84	0.67	1.06	0.1466	0.58	0.41	0.83	0.0025
Pneumonia	1.87	1.49	2.35	<0.0001	–	–	–	–	1.46	1.16	1.85	0.0015	–	–	–	–
Cardiovascular	1.46	1.05	2.04	0.0257	–	–	–	–	2.85	2.06	3.95	<0.0001	2.15	1.33	3.47	0.0017
Kidney failure/dialysis	1.25	0.82	1.92	0.3061	–	–	–	–	1.26	0.81	1.96	0.3141	–	–	–	–
Coagulation disorder/ disseminated intravascular coagulation	1.16	0.72	1.88	0.5433	–	–	–	–	1.42	0.87	2.30	0.1570	–	–	–	–
Refractory shock	1.43	0.88	2.33	0.1513	–	–	–	–	2.36	1.47	3.81	0.0004	–	–	–	–
Extracorporeal membrane oxygenation	0.40	0.05	3.31	0.3935	–	–	–	–	<0.001	<0.001	>999.999	0.9802	–	–	–	–
Mechanical ventilation	1.26	0.92	1.73	0.1500	–	–	–	–	1.00	0.71	1.41	0.9948	0.27	0.16	0.48	<0.0001
Hospital admission	1.24	0.92	1.66	0.1544	0.38	0.21	0.70	0.0019	8.34	4.81	14.47	<0.0001	–	–	–	–
ICU admission	1.34	1.04	1.74	0.0261	–	–	–	–	2.51	1.94	3.25	<0.0001	2.69	1.77	4.09	<0.0001
Pre-morbid mRS score				<0.0001				0.0143				0.0001				0.0001
0	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
1	1.27	0.92	1.76		1.01	0.67	1.52		1.39	1.00	1.93		0.32	0.19	0.55	–
2	1.64	1.10	2.44		1.28	0.78	2.08		1.64	1.09	2.47		0.38	0.20	0.73	–
3	2.46	1.70	3.57		0.83	0.50	1.38		1.75	1.19	2.58		0.29	0.16	0.55	–
4	3.39	2.15	5.35		1.75	0.98	3.12		2.58	1.62	4.11		0.49	0.24	1.01	–
5	5.80	3.07	10.95		3.32	1.50	7.35		1.91	1.00	3.64		0.48	0.18	1.26	–

Abbreviations: adj., adjusted; BMI, body mass index; ICU, intensive care unit; LCL, lower confidence limit; OR, odds ratio; mRS, modified Rankin Scale; TIA, transient ischemic attack; UCL, upper confidence limit.

TABLE 3 Demographic and clinical predictors of sleep disorders and dysautonomia

	Sleep disorders								Dysautonomia							
	Univariable analysis				Stepwise selection				Univariable analysis				Stepwise selection			
	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value
Sex				0.4438				–				0.7575				–
Male	1 (ref.)				1 (ref.)	–	–		1 (ref.)				1 (ref.)	–	–	
Female	1.18	0.90	1.55		–	–	–		1.48	1.48	1.48		–	–	–	
Intersex/unknown	0.69	0.09	5.59		–	–	–		<0.001	<0.001	>999.999		–	–	–	
Smoking				0.9619				–				0.2118				–
Yes	1.01	0.67	1.52		–	–	–		1.06	0.70	1.60		–	–	–	
No	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
Unknown	1.06	0.70	1.62		–	–	–		0.64	0.38	1.07		–	–	–	
Source of COVID-19 contact				<0.0001				0.0034				<0.0001				<0.0001
Family member	1.60	1.15	2.23		1.63	1.06	2.48		2.54	1.82	3.53		2.95	1.99	4.39	
Occupation	2.78	1.81	4.28		2.69	1.41	5.11		2.23	1.38	3.60		2.66	1.39	5.07	
Social	0.88	0.50	1.53		0.63	0.29	1.36		1.47	0.87	2.46		1.62	0.90	2.92	
Travel	1.39	0.46	4.17		2.02	0.55	7.41		<0.001	<0.001	>999.999		<0.001	<0.001	>999.999	
Other/unknown	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
Age at admission (1-year increase)	1.00	0.99	1.01	0.7404	–	–	–	–	1.00	0.99	1.01	0.6025	–	–	–	–
BMI (1-unit increase)	1.00	1.00	1.01	0.9839	–	–	–	–	1.00	1.00	1.01	0.8941	–	–	–	–
Non-neurological comorbidities																
Hypertension	0.87	0.66	1.14	0.3083	–	–	–	–	0.94	0.71	1.25	0.6626	–	–	–	–
Type 1/type 2 diabetes	1.24	0.91	1.70	0.1742	–	–	–	–	0.83	0.58	1.18	0.2973	0.59	0.38	0.92	0.0203
Cardiovascular disease	1.00	0.74	1.34	0.9783	–	–	–	–	1.52	1.13	2.04	0.0056	–	–	–	–
Chronic kidney disease	0.68	0.39	1.16	0.1560	–	–	–	–	0.96	0.58	1.60	0.8868	–	–	–	–
Chronic liver disease	0.67	0.28	1.59	0.3657	–	–	–	–	1.63	0.82	3.22	0.1632	–	–	–	–
Chronic pulmonary disease	1.13	0.72	1.78	0.6002	–	–	–	–	0.85	0.51	1.43	0.5397	–	–	–	–
Anemia	1.17	0.66	2.08	0.5997	–	–	–	–	1.23	0.68	2.22	0.5017	–	–	–	–

TABLE 3 (Continued)

	Sleep disorders								Dysautonomia							
	Univariable analysis				Stepwise selection				Univariable analysis				Stepwise selection			
	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value
Cancer	0.70	0.40	1.23	0.2163	–	–	–	–	0.94	0.55	1.61	0.8313	–	–	–	–
Immunosuppressed state	1.02	0.54	1.92	0.9526	–	–	–	–	1.05	0.54	2.03	0.8871	–	–	–	–
Neurological comorbidities																
Dementia	1.33	0.83	2.15	0.2412	–	–	–	–	1.19	0.71	1.99	0.5116	–	–	–	–
Parkinson's disease	2.13	1.15	3.95	0.0160	3.31	1.53	7.17	0.0024	2.70	1.47	4.95	0.0013	2.39	1.06	5.38	0.0356
Stroke: ICH, ischemic stroke, TIA	0.57	0.38	0.87	0.0088	–	–	–	–	0.73	0.48	1.10	0.1269	–	–	–	–
Multiple sclerosis	1.22	0.65	2.26	0.5387	–	–	–	–	1.54	0.84	2.82	0.1643	2.43	1.02	5.76	0.0446
Motor neuron disease	1.28	0.27	6.04	0.7592	–	–	–	–	2.51	0.64	9.76	0.1856	–	–	–	–
Neuromuscular disorder	1.28	0.42	3.85	0.6637	–	–	–	–	0.64	0.15	2.78	0.5540	–	–	–	–
Neuropathy	1.52	0.74	3.12	0.2535	–	–	–	–	1.51	0.72	3.19	0.2780	–	–	–	–
COVID systemic complications																
Dyspnea	1.54	1.17	2.03	0.0019	1.98	1.36	2.89	0.0004	1.52	1.14	2.02	0.0041	2.12	1.48	3.05	<0.0001
Pneumonia	0.82	0.63	1.08	0.1622	–	–	–	–	1.07	0.80	1.42	0.6429	–	–	–	–
Cardiovascular	1.60	1.09	2.35	0.0174	1.90	1.20	3.02	0.0064	1.45	0.97	2.19	0.0730	–	–	–	–
Kidney failure/dialysis	1.30	0.78	2.16	0.3177	–	–	–	–	0.86	0.47	1.57	0.6182	–	–	–	–
Coagulation disorder/ disseminated intravascular coagulation	1.19	0.67	2.12	0.5628	–	–	–	–	1.36	0.76	2.44	0.2956	–	–	–	–
Refractory shock	0.80	0.41	1.58	0.5217	–	–	–	–	0.41	0.17	1.04	0.0597	–	–	–	–
Extracorporeal membrane oxygenation	0.85	0.10	7.08	0.8790	–	–	–	–	<0.001	<0.001	>999.999	0.9766	–	–	–	–
Mechanical ventilation	1.15	0.78	1.70	0.4720	–	–	–	–	1.24	0.83	1.85	0.2946	–	–	–	–
Hospital admission	0.47	0.35	0.65	<0.0001	0.40	0.21	0.75	0.0046	0.59	0.43	0.83	0.0020	–	–	–	–
ICU admission	0.92	0.66	1.29	0.6326	–	–	–	–	0.93	0.66	1.32	0.6932	–	–	–	–
Pre-morbid mRS score				0.3228				–				0.3899				–

(Continues)

TABLE 3 (Continued)

	Sleep disorders								Dysautonomia							
	Univariable analysis				Stepwise selection				Univariable analysis				Stepwise selection			
	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value
0	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
1	0.83	0.56	1.24		–	–	–	–	0.96	0.63	1.46		–	–	–	–
2	0.87	0.53	1.44		–	–	–	–	1.42	0.88	2.30		–	–	–	–
3	0.87	0.54	1.41		–	–	–	–	1.39	0.88	2.21		–	–	–	–
4	0.41	0.18	0.90		–	–	–	–	0.98	0.52	1.87		–	–	–	–
5	0.72	0.30	1.72		–	–	–	–	0.60	0.21	1.70		–	–	–	–

Abbreviations: adj., adjusted; BMI, body mass index; ICU, intensive care unit; LCL, lower confidence limit; OR, odds ratio; mRS, modified Rankin Scale; TIA, transient ischemic attack; UCL, upper confidence limit.

dysexecutive syndrome, delirium, seizures, CNS infection, dystonia, myoclonus, syncope, dyskinesia, movement disorders, ataxia, and spinal cord disease. Patients with dysautonomia tended to exhibit more premorbid functional impairment, were more frequently hospitalized, and had a worse outcome at discharge and higher in-hospital deaths. After stepwise selection, the only variables retained in the model as significantly associated with dysautonomia were history of Parkinson's disease (adj. OR 2.39, 95% CI 1.06–5.38), history of multiple sclerosis (adj. OR 2.43, 95% CI 1.02–5.76) and dyspnea (adj. OR 2.12, 95% CI 1.48–3.05 (Table 3)).

Peripheral neuropathy

Patients experiencing peripheral neuropathies ($N = 145$; Table S3) tended to present a history of type 2 diabetes ($p = 0.0009$) and presented more COVID-19 complications ($p < 0.0001$) than patients without neuropathy. These included renal insufficiency, refractory shock, and disseminated intravascular coagulation and other coagulation disorders. Peripheral neuropathies were associated with need for ICU admission and mechanical ventilation. Other neurological manifestations were associated with peripheral neuropathies. These included myalgia, sleep–wake disturbances, delirium, stupor/coma, syncope, chorea, seizures, CNS infection, ataxia, and spinal cord disorders. Outcome at discharge was worse with greater functional impairment. History of peripheral neuropathy, disseminated intravascular coagulation (adj. OR 4.76, 95% CI 2.50–9.07), and need for mechanical ventilation were confirmed by stepwise selection to be associated with peripheral neuropathy (Table 4).

Movement disorders

A wide array of movement disorders ($N = 142$; Table S3) were present during the acute phase of COVID-19. These included tremor, chorea, dystonia, myoclonus, dyskinesia, and parkinsonism. Patients with movement disorders at onset of COVID-19 infection were older than patients without (median age 68 vs. 62 years), were more commonly smokers, and had a history of hypertension and cardiovascular disease. Dementia ($p = 0.0297$) and peripheral neuropathy ($p = 0.0403$) predominated at baseline. Acute infection tended to be complicated by symptoms of cardiovascular origin ($p < 0.0001$) and required extracorporeal membrane oxygenation ($p = 0.0210$). The acute phase was accompanied by several other neurological manifestations. Included were headache, vertigo, myalgia, cognitive dysfunction, dysautonomia, dysexecutive syndrome, and sleep–wake disturbances. Patients with movement disorders were more commonly functionally disabled at baseline, but not at discharge. In that cohort, the outcome was better than in patients without movement disorders. Stepwise selection confirmed the association of movement disorders with history of smoking (adj. OR 2.09, 95% CI 1.23–3.57), history of Parkinson's disease (adj. OR 11.69, 95% CI

TABLE 4 Demographic and clinical predictors of peripheral neuropathy and movement disorders

	Peripheral neuropathy								Movement disorders							
	Univariable analysis				Stepwise selection				Univariable analysis				Stepwise selection			
	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value
Sex				0.4760				–				0.0152				0.0314
Male	1 (ref.)				1 (ref.)	–	–		1 (ref.)				1 (ref.)	–	–	
Female	0.81	0.57	1.14		–	–	–		0.72	0.50	1.02		0.94	0.60	1.47	
Intersex/unknown	1.07	0.13	8.70		–	–	–		4.24	1.04	17.28		7.78	1.62	37.31	
Smoking				0.0039				–				0.0037				0.0086
Yes	1.10	0.65	1.86		–	–	–		2.04	1.32	3.15		2.09	1.23	3.57	
No	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
Unknown	2.14	1.37	3.35		–	–	–		0.86	0.47	1.58		0.62	0.25	1.52	
Source of COVID-19 contact				0.7961				–				0.0731				–
Family member	0.81	0.51	1.28		–	–	–		1.34	0.90	2.01		–	–	–	
Occupation	0.72	0.35	1.46		–	–	–		0.33	0.12	0.92		–	–	–	
Social	1.06	0.59	1.93		–	–	–		0.71	0.35	1.45		–	–	–	
Travel	<0.001	<0.001	>999.999		–	–	–		0.96	0.22	4.17		–	–	–	
Other/unknown	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
Age at admission (1-year increase)	1.00	0.99	1.01	0.4276	–	–	–	–	1.01	1.00	1.02	0.0536	–	–	–	–
BMI (1-unit increase)	0.99	0.97	1.02	0.4938	–	–	–	–	0.99	0.98	1.01	0.5238	–	–	–	–
Non neurological comorbidities																
Hypertension	0.90	0.64	1.27	0.5467	–	–	–	–	1.51	1.06	2.15	0.0217	–	–	–	–
Type 1/type 2 diabetes	1.98	1.37	2.85	0.0003	–	–	–	–	1.15	0.77	1.73	0.4853	–	–	–	–
Cardiovascular disease	0.88	0.60	1.28	0.4928	–	–	–	–	1.93	1.36	2.74	0.0003	–	–	–	–
Chronic kidney disease	1.03	0.57	1.88	0.9160	–	–	–	–	1.48	0.86	2.55	0.1534	–	–	–	–
Chronic liver disease	0.80	0.29	2.26	0.6788	–	–	–	–	1.06	0.41	2.71	0.9045	–	–	–	–
Chronic pulmonary disease	1.37	0.80	2.35	0.2546	–	–	–	–	0.82	0.43	1.56	0.5494	–	–	–	–
Anemia	1.36	0.69	2.71	0.3743	–	–	–	–	1.57	0.81	3.04	0.1792	–	–	–	–
Cancer	0.65	0.31	1.37	0.2592	–	–	–	–	0.87	0.44	1.70	0.6765	–	–	–	–
Immunosuppressed state	0.86	0.37	2.02	0.7254	–	–	–	–	0.88	0.37	2.07	0.7673	–	–	–	–
Neurological comorbidities																
Dementia	0.16	0.04	0.65	0.0107	–	–	–	–	1.82	1.05	3.15	0.0320	–	–	–	–

(Continues)

TABLE 4 (Continued)

	Peripheral neuropathy								Movement disorders							
	Univariable analysis				Stepwise selection				Univariable analysis				Stepwise selection			
	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value
Parkinson's disease	0.79	0.28	2.21	0.6486	–	–	–	–	9.01	5.06	16.08	<0.0001	11.69	5.55	24.65	<0.0001
Stroke: ICH, ischemic stroke, TIA	0.42	0.23	0.76	0.0045	–	–	–	–	0.74	0.45	1.22	0.2369	–	–	–	–
Multiple sclerosis	0.28	0.07	1.15	0.0767	–	–	–	–	0.76	0.30	1.93	0.5689	–	–	–	–
Motor neuron disease	1.06	0.13	8.40	0.9577	–	–	–	–	2.45	0.52	11.66	0.2594	–	–	–	–
Neuromuscular disorder	2.42	0.80	7.32	0.1191	–	–	–	–	0.51	0.07	3.83	0.5113	–	–	–	–
Neuropathy	12.18	6.55	22.64	<0.0001	13.03	5.96	28.46	<0.0001	2.23	1.02	4.90	0.0455	–	–	–	–
COVID systemic complications																
Dyspnea	1.27	0.90	1.78	0.1797	–	–	–	–	1.10	0.78	1.56	0.5817	–	–	–	–
Pneumonia	1.19	0.84	1.68	0.3349	–	–	–	–	1.26	0.88	1.78	0.2064	–	–	–	–
Cardiovascular	1.30	0.79	2.15	0.3045	–	–	–	–	3.14	2.06	4.76	<0.0001	3.28	2.00	5.38	<0.0001
Kidney failure/dialysis	1.91	1.09	3.36	0.0246	–	–	–	–	0.96	0.47	1.95	0.9096	–	–	–	–
Coagulation disorder/ disseminated intravascular coagulation	3.79	2.23	6.44	<0.0001	4.76	2.50	9.07	<0.0001	1.78	0.94	3.38	0.0766	2.09	1.02	4.28	0.0442
Refractory shock	0.26	0.06	1.06	0.0603	0.18	0.04	0.81	0.0254	0.71	0.28	1.78	0.4592	–	–	–	–
Extracorporeal membrane oxygenation	3.84	0.74	19.98	0.1095	–	–	–	–	7.43	1.65	33.54	0.0091	–	–	–	–
Mechanical ventilation	2.59	1.72	3.90	<0.0001	2.69	1.56	4.65	0.0004	0.71	0.40	1.26	0.2451	–	–	–	–
Hospital admission	1.66	1.00	2.78	0.0510	–	–	–	–	1.74	1.03	2.94	0.0388	–	–	–	–
ICU admission	2.01	1.39	2.91	0.0002	–	–	–	–	1.02	0.67	1.55	0.9282	–	–	–	–
Pre-morbid mRS score				0.0790				–				0.0026				–
0	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
1	1.11	0.70	1.76		–	–	–	–	2.08	1.29	3.35		–	–	–	–
2	0.72	0.36	1.43		–	–	–	–	2.47	1.41	4.33		–	–	–	–
3	0.45	0.20	0.99		–	–	–	–	1.82	1.01	3.28		–	–	–	–
4	0.43	0.15	1.20		–	–	–	–	2.14	1.07	4.29		–	–	–	–
5	0.20	0.03	1.48		–	–	–	–	2.73	1.16	6.42		–	–	–	–

Abbreviations: adj., adjusted; BMI, body mass index; ICU, intensive care unit; LCL, lower confidence limit; OR, odds ratio; mRS, modified Rankin Scale; TIA, transient ischemic attack; UCL, upper confidence limit.

5.55–24.65) and complications of COVID-19: cardiovascular symptoms (adj. OR 3.28, 95% CI 2.00–5.38) and disseminated intravascular coagulation (adj. OR 2.09, 95% CI 1.02–4.28 (Table 4)).

Ataxia

Patients developing ataxia ($N = 134$; Table S4) were slightly younger than the rest of the study population, had a more frequent history of type 1 diabetes ($p = 0.0051$), chronic pulmonary disease ($p = 0.0004$) and immunosuppressed state ($p = 0.0045$). Neurological comorbidities included history of dementia ($p = 0.0143$) and multiple sclerosis ($p < 0.0001$). COVID-19 non-neurological complications included pneumonia ($p = 0.0371$) and cardiovascular diseases ($p = 0.0017$). Other neurological manifestations most commonly present during the acute phase of COVID-19 included headache, hyposmia/hypogeusia, dysautonomia, vertigo, myalgia and sleep–wake disturbances, hypoactive delirium, syncope, seizures, CNS infection, stroke, movement disorders other than Parkinsonism, spinal cord disease and peripheral neuropathy. Course and outcome were not worse, but even better than the rest of the study population. History of multiple sclerosis (adj. OR 20.31, 95% CI 9.15–45.10) and cardiovascular complications of COVID-19 (adj. OR 3.25, 95% CI 1.93–5.46) were the only variables confirmed by stepwise selection to be associated with ataxia (Table 5).

Seizures/status epilepticus

Compared to patients who did not have seizures, patients presenting seizures at the time of COVID-19 infection ($N = 126$; Table S4) had type 1 ($p = 0.0062$) and 2 diabetes ($p = 0.0167$), history of anemia ($p = 0.0281$) and cancer ($p = 0.0006$), and COVID-19 non-neurological complications (acute renal insufficiency and refractory shock; $p < 0.0001$) and required mechanical ventilation. Other acute neurological manifestations were most common in patients with seizures and included dysautonomia, vertigo, sleep–wake disturbances, cognitive dysfunction, dysexecutive syndrome, delirium, stupor/coma, syncope, CNS infection, stroke, ataxia, peripheral neuropathies, and spinal cord disease. Although patients with seizures were most commonly hospitalized and, to a lesser extent, admitted to the ICU, their outcome was not necessarily worse, and they were less prone to die. The only variables whose association with seizures/status epilepticus was confirmed by stepwise selection were history of cancer (adj. OR 3.16, 95% CI 1.72–5.81) and high premorbid functional disability (mRS score 5: adj. OR 4.98, 95% CI 2.28–10.86 (Table 5)).

DISCUSSION

In this international multicenter cohort study, we found that various acute/subacute neurological manifestations were present in patients with COVID-19 seen in neurological consultation during the acute phase of infection. The frequency of some neurological manifestations (cognitive disturbances, stroke, peripheral neuropathies, and delirium) was similar to the largest series published to dae [15], which included 1979 patients, whereas hyposmia/hypogeusia, dysautonomia, and coma were more frequent in our sample. This is likely due to the peculiar assessment by neurologists in our study.

We identified eight main clinical phenotypes, which only partly overlapped and tended to differ in terms of general and neurological comorbidities, severity and complications of SARS-CoV-2, and outcome. These findings suggest that, for some acute neurological manifestations, specific profiles can be identified based on the personal history and the characteristics of the clinical picture of COVID-19 at the time of infection.

Patients with COVID-19-related cognitive dysfunction are generally older than the average COVID-19 population referred to neurologists. As expected, they might present with a history of dementia and functional disability. Infection severity, marked by the presence of dyspnea, might also add to the worse outcome at discharge and the higher risk of in-hospital death. Our data are in keeping with the higher-than-expected mortality of older patients diagnosed with SARS-CoV-2 who lived in institutions or were hospitalized with the disease [16]. In that study, dementia, diabetes, chronic kidney disease and hypertension were the main risk factors for death. In another systematic review of cohort and case–control studies, previous dementia was the main factor associated with poor health outcomes, including mortality, in older adults with COVID-19 infection [17]. Elderly individuals are thus at high risk of developing severe forms of COVID-19 due to factors associated with aging and a higher prevalence of medical comorbidities [18].

We found that stroke tends to occur in older patients with history of hypertension and Parkinson's disease, and the presence of cardiovascular manifestations. In those individuals, the well-known adverse effects of underlying infection (documented here by cardiovascular complications) might interact with other vascular risk factors (e.g., hypertension) or comorbidities (e.g., parkinsonism), followed by vascular complications, as they have some risk factors in common and even several shared genes [19]. In a systematic review of studies on the prevalence of nervous system diseases during the COVID-19 outbreak, patients with cerebrovascular disease who had been infected had a threefold increased risk of severity and mortality [5]. In the same study, no significant differences were found for the prevalence of epilepsy and dementia between non-severe and severe COVID-19 patients. There was no significant association between stroke, epilepsy, and COVID-19 mortality.

The occurrence of sleep–wake disturbances was associated with history of Parkinson's disease. This is not unexpected because sleep disturbance is a well-known non-motor feature in patients with Parkinson's disease [20]. The association of sleep–wake disturbances with dyspnea and/or cardiovascular COVID-19 complications supports the suggested association between COVID-19 and sleep-disordered breathing [21, 22]. However, the high frequency of sleep–wake disturbances may also reflect other factors, including brainstem tropism of SARS-CoV-2 [23].

TABLE 5 Demographic and clinical predictors of ataxia and seizures/status epilepticus

	Ataxia								Seizures/status epilepticus							
	Univariable analysis				Stepwise selection				Univariable analysis				Stepwise selection			
	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value
Sex				0.0654				–				0.9383				–
Male	1 (ref.)				1 (ref.)	–	–		1 (ref.)				1 (ref.)	–	–	
Female	5.33	1.30	21.81		–	–	–		0.94	0.65	1.35		–	–	–	
Intersex/unknown	1.02	0.71	1.46		–	–	–		<0.001	<0.001	>999.999		–	–	–	
Smoking				0.0743				–				0.0416				–
Yes	1.25	0.74	2.09		–	–	–		1.19	0.69	2.04		–	–	–	
No	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
Unknown	1.75	1.07	2.84		–	–	–		1.88	1.15	3.07		–	–	–	
Source of COVID-19 contact				0.8164				–				0.0801				–
Family member	1.18	0.76	1.83		–	–	–		0.58	0.34	0.98		–	–	–	
Occupation	1.21	0.64	2.30		–	–	–		0.41	0.16	1.02		–	–	–	
Social	0.91	0.46	1.81		–	–	–		0.70	0.34	1.42		–	–	–	
Travel	1.73	0.50	5.96		–	–	–		1.48	0.43	5.09		–	–	–	
Other/unknown	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
Age at admission (1-year increase)	0.99	0.98	1.00	0.1248	–	–	–	–	1.00	0.99	1.01	0.6966	–	–	–	–
BMI (1-unit increase)	0.98	0.94	1.02	0.3150	–	–	–	–	1.00	1.00	1.01	0.5544	–	–	–	–
Non-neurological comorbidities																
Hypertension	0.91	0.64	1.30	0.6120	–	–	–	–	1.05	0.73	1.51	0.8083	–	–	–	–
Type 1/type 2 diabetes	1.31	0.88	1.96	0.1871	–	–	–	–	1.77	1.19	2.63	0.0045	–	–	–	–
Cardiovascular disease	1.07	0.73	1.57	0.7369	–	–	–	–	0.78	0.51	1.18	0.2333	–	–	–	–
Chronic kidney disease	1.03	0.55	1.92	0.9231	–	–	–	–	1.22	0.67	2.24	0.5111	–	–	–	–
Chronic liver disease	0.41	0.10	1.72	0.2257	–	–	–	–	1.50	0.63	3.59	0.3604	–	–	–	–
Chronic pulmonary disease	0.07	0.01	0.49	0.0077	–	–	–	–	1.16	0.64	2.12	0.6282	–	–	–	–
Anemia	0.82	0.35	1.92	0.6503	–	–	–	–	2.03	1.07	3.85	0.0312	–	–	–	–

TABLE 5 (Continued)

	Ataxia								Seizures/status epilepticus							
	Univariable analysis				Stepwise selection				Univariable analysis				Stepwise selection			
	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value
Cancer	0.82	0.41	1.66	0.5826	–	–	–	–	2.42	1.44	4.07	0.0008	3.16	1.72	5.81	0.0002
Immunosuppressed state	2.42	1.29	4.54	0.0058	–	–	–	–	1.41	0.66	3.02	0.3727	–	–	–	–
Neurological comorbidities																
Dementia	0.27	0.08	0.85	0.0255	–	–	–	–	1.49	0.81	2.74	0.1977	–	–	–	–
Parkinson's disease	0.20	0.03	1.44	0.1094	–	–	–	–	0.92	0.33	2.60	0.8771	–	–	–	–
Stroke: ICH, ischemic stroke, TIA	1.27	0.81	1.97	0.3005	–	–	–	–	0.98	0.60	1.60	0.9323	–	–	–	–
Multiple sclerosis	8.91	5.29	15.02	<0.0001	20.31	9.15	45.10	<0.0001	0.50	0.16	1.61	0.2462	–	–	–	–
Motor neuron disease	1.15	0.15	9.17	0.8930	–	–	–	–	1.23	0.16	9.82	0.8425	–	–	–	–
Neuromuscular disorder	0.54	0.07	4.08	0.5523	–	–	–	–	<0.001	<0.001	>999.999	0.9802	–	–	–	–
Neuropathy	0.49	0.12	2.03	0.3225	–	–	–	–	0.52	0.12	2.18	0.3708	–	–	–	–
COVID systemic complications																
Dyspnea	0.69	0.48	0.99	0.0463	–	–	–	–	0.86	0.60	1.25	0.4314	–	–	–	–
Pneumonia	0.69	0.48	0.98	0.0380	–	–	–	–	1.00	0.69	1.44	0.9880	–	–	–	–
Cardiovascular	2.07	1.30	3.28	0.0021	3.25	1.93	5.46	<0.0001	1.17	0.67	2.02	0.5854	–	–	–	–
Kidney failure/ dialysis	0.65	0.28	1.50	0.3105	–	–	–	–	2.27	1.29	4.02	0.0047	–	–	–	–
Coagulation disorder/ disseminated intravascular coagulation	1.52	0.76	3.02	0.2330	–	–	–	–	0.89	0.38	2.10	0.7966	–	–	–	–
Refractory shock	0.28	0.07	1.16	0.0793	–	–	–	–	2.31	1.21	4.41	0.0115	–	–	–	–
Extracorporeal membrane oxygenation	<0.001	<0.001	>999.999	0.9816	–	–	–	–	1.86	0.22	15.53	0.5688	–	–	–	–
Mechanical ventilation	0.58	0.30	1.09	0.0879	–	–	–	–	1.65	1.03	2.65	0.0368	–	–	–	–

(Continues)

TABLE 5 (Continued)

	Ataxia							Seizures/status epilepticus						
	Univariable analysis				Stepwise selection			Univariable analysis				Stepwise selection		
	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value	OR	95% LCL	95% UCL	*p* value	adj. OR	95% LCL	95% UCL	*p* value
Hospital admission	1.88	1.08	3.27	0.0255	–	–	–	–	2.27	1.23	4.17	0.0085	–	–	–	–
ICU admission	1.38	0.92	2.07	0.1170	–	–	–	–	1.51	1.01	2.28	0.0461	–	–	–	–
Pre-morbid mRS score				0.0331				–				<0.0001				0.0007
0	1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–		1 (ref.)	–	–	
1	1.74	1.08	2.81		–	–	–	–	0.62	0.32	1.20		0.59	0.27	1.31	–
2	2.10	1.19	3.70		–	–	–	–	1.43	0.76	2.68		1.31	0.62	2.78	–
3	1.20	0.63	2.29		–	–	–	–	1.62	0.90	2.90		0.93	0.43	1.99	–
4	2.15	1.10	4.19		–	–	–	–	1.52	0.72	3.19		1.14	0.48	2.74	–
5	0.96	0.29	3.18		–	–	–	–	5.99	3.01	11.92		4.98	2.28	10.86	-

Abbreviations: adj., adjusted; BMI, body mass index; ICU, intensive care unit; LCL, lower confidence limit; OR, odds ratio; mRS, modified Rankin Scale; TIA, transient ischemic attack; UCL, upper confidence limit.

History of Parkinson's disease or multiple sclerosis has been associated with the occurrence of dysautonomia. Non-motor symptoms (including dysautonomia) are frequently present in the premotor stage of Parkinson's disease [24]. Autonomic dysfunction is a common finding also in patients with multiple sclerosis [25]. These observations and the corresponding hypotheses support the concept that patients who experience symptoms of autonomic dysfunction might be individuals with predisposing diseases who, in the presence of COVID-19, present an exacerbation of their baseline clinical condition [26].

History of peripheral neuropathy, intravascular coagulation, and need for mechanical ventilation at the time of infection were associated with peripheral neuropathy. Disseminated intravascular coagulation is a common complication of severe COVID-19 infection [27]. However, the association between disseminated intravascular coagulation and peripheral neuropathy has been rarely reported as a complication of diabetic ketoacidosis [28] or because of cancer and chemotherapy in cancer patients [29]. We cannot exclude that patients with COVID-19 develop peripheral neuropathy because of critical illness, as shown by the frequent report of neuropathies in subjects with prolonged stay in the ICU [30]. The occurrence of refractory shock and greatest use of mechanical ventilation in this cohort support this interpretation.

The association of movement disorders with history of Parkinson's disease is not unexpected. In a meta-analysis of 12 studies including 103,874 COVID-19 patients, Parkinson's disease was associated with poor in-hospital outcome and mortality as a consequence of acute infection [31]. The association was influenced by age and history of smoking. As movement disorders are a group of diseases with differing underlying mechanisms, an association of smoking with diseases other than Parkinson's disease cannot be excluded. As movement disorders were associated with cardiovascular complications of COVID-19 and coagulation defects, we can speculate that smoking, a well-known risk factor for cardiovascular and cerebrovascular disease, can also affect movement disorders of vascular origin.

History of multiple sclerosis and cardiovascular complications of COVID-19 were associated with ataxia. While ataxia is a common finding in patients with multiple sclerosis, the association of this sign with cardiovascular complications is less intuitive. A possible explanation is that severe infection (marked by cardiovascular complications) leads to brainstem dysfunction [22], leading to severe standing and gait impairment.

Except for history of cancer and premorbid functional disability, we failed to find specific risk factors for patients who developed seizures during COVID-19 infection. Seizures are the symptom of several CNS disorders and, as such, may occur in the presence of a variety of clinical conditions. The effects of the infection in patients with a history of epilepsy (not documented here) are still controversial. The frequency of seizures and status epilepticus did not increase during the pandemic [32]. The association between seizures/status epilepticus and premorbid functional disability cannot be easily explained, except for stating that individuals experiencing seizures are

prone to the development of acute symptomatic seizures caused by differing neurological complications.

Our findings seem to support the assertion that specific acute/subacute neurological manifestations are only in part the result of the severity of COVID-19 infection (as shown by its respiratory and cardiovascular complications), and they may also represent the worsening of a pre-existing clinical neurological condition or a de novo neurological symptom, sign or disease in predisposed individuals.

Major strengths of this study include the large sample size and the reasonably accurate ascertainment of neurological manifestations. All patients were seen in neurological consultation, and, for this reason, we can assume that all neurological symptoms, signs and diseases were accurately diagnosed.

Several limitations must be also acknowledged. The first and most important is represented by the difficulty in separating the neurological manifestations caused by COVID-19 from those that result from the underlying neurological comorbidities. This limitation cannot be easily overcome because SARS-CoV-2 acts on individuals who can be affected by or at least predisposed to the occurrence of neurological symptoms, signs, or diseases of the central or the peripheral nervous system. Our findings, when comparing infected patients with and without a given neurological sign or disease, support this assertion as several neurological complications in patients with COVID-19 are simply the worsening of a pre-existing disease. Importantly, 41% of patients (n = 627/1523) reported pre-existing neurological comorbidities.

The second limitation is selection bias. Although we asked study participants to register all patients consecutively seen in consultation in the emergency room, during hospital stay, or in outpatient services, as data collection was performed within the time constraints of the pandemic, some patients, perhaps those less severely affected, may have been omitted, leaving just the most severe cases in the registry. In addition, cases and controls were only individuals seen by neurologists. Nevertheless, we collected patients and disease-specific characteristics and outcome in 310 cases (20.4%) in whom no neurological manifestation was confirmed. This sample might represent, at least in part, the general (non-neurological) COVID-19 population.

The third limitation is the focus on neurological manifestations. Although we did our best to collect information on all comorbidities with an impact on patients' health and the major complications of COVID-19, the baseline phenotype of registered patients and the full spectrum of the disease are perhaps incomplete.

The last limitation is the possible use of different diagnostic criteria and the application of different methods for case ascertainment by investigators who were not assessed for inter-rater agreement. The use of a guide including the definitions of all collected variables might have been insufficient to stardardize data collection. We should also mention the absence of systematic assessments of the different phenoytpes with current tools (e.g., questionnaires) and the fact that our otherwise broad approach did not assess some symptoms/clinical manifestation (e.g., fatigue).

Despite these limitations, our exploratory study can lead to several important conclusions. First, patients with COVID-19 seen in neurological consultation presented with a high proportion of acute/subacute neurological symptoms, signs or diseases which contribute to the detection of different phenotypes. Each phenotype was characterized by the combination of selected demographic and clinical variables, the latter represented by specific baseline comorbidities and by various complications of COVID-19 infection. The different profiles that result from these combinations help identify individuals who might develop one or another neurological manifestation and highlight the importance of contextualizing the spectrum of acute manifestations of COVID-19.

AUTHOR CONTRIBUTIONS

Concept and design: Ettore Beghi, Elena Moro, Raimuld Helbok, Claudio Bassetti. Acquisition, analysis or interpretation of data: all Authors. Drafting of manuscript: Ettore Beghi, Maurizio Leone. Critical revision of the manuscript for important intellectual content: Main authors. Statistical analysis: Elisa Bianchi. Obtaining of funding: Claudio Bassetti. Supervision: Main authors. Acquisition of data and critical review of manuscript: ENERGY Study Group.

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CONFLICT OF INTEREST

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bureaus, manuscript writing or educational events from TEVA, Krka and Novartis, and is President of the Ethics Committee of *UHC Sestre milosrdnice*. Due to the conflict of interest, she did not participate in the discussion or decision-making on the proposed research. Elena Moro reports grants or contracts from any entity (if not indicated in item #1 above) as follows: research grant from Ipsen; honoraria for consulting from Medtronic, Abbott and Kyowa; and participation on a data safety monitoring board or advisory board for Newronika. Clarissa Lin Yasuda reports support for the present manuscript from FAPESP2013/07559–3; FAPESP 2019/11457–8, and payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events from UCB, ZODIAC and TORRENT. Carmel Armon reports royalties or licenses: UpToDate co-author on two chapters, payment for expert testimony as a neurology consultant to Inbal, Inc. and the Israeli government insurance company. Luís Maia reports support for the present manuscript from Research4COVID – FCT grant n°229 Project grant for institution, and Bial Foundation Grant Project grant for institution. Waldemar Brola reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Biogen, Merck, Novartis, Sanofi Genzyme and Roche, and support for attending meetings and/or travel from Biogen, Sanofi and Roche.

DATA AVAILABILITY STATEMENT

Data can only be shared with the permission of individual countries.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

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