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ORIGINAL ARTICLE

Short- and long-term outcome and predictors in an international cohort of patients with neuro-COVID-19

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[Correction added on 12 March 2022 after first online publication: Serefnur Ozturk's name and third affiliation was corrected.]

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Abstract

Background and purpose: Despite the increasing number of reports on the spectrum of neurological manifestations of COVID-19 (neuro-COVID), few studies have assessed short- and long-term outcome of the disease.

Methods: This is a cohort study enrolling adult patients with neuro-COVID seen in neurological consultation. Data were collected prospectively or retrospectively in the European Academy of Neurology NEuro-covid ReGistrY ((ENERGY). The outcome at discharge was measured using the modified Rankin Scale and defined as 'stable/improved' if the modified Rankin Scale score was equal to or lower than the pre-morbid score, 'worse' if the score was higher than the pre-morbid score. Status at 6 months was also recorded. Demographic and clinical variables were assessed as predictors of outcome at discharge and 6 months.

Results: From July 2020 to March 2021, 971 patients from 19 countries were included. 810 (83.4%) were hospitalized. 432 (53.3%) were discharged with worse functional status. Older age, stupor/coma, stroke and intensive care unit (ICU) admission were predictors of worse outcome at discharge. 132 (16.3%) died in hospital. Older age, cancer, cardiovascular complications, refractory shock, stupor/coma and ICU admission were associated with death. 262 were followed for 6 months. Acute stroke or ataxia, ICU admission and degree of functional impairment at discharge were predictors of worse outcome. 65/221 hospitalized patients (29.4%) and 10/32 non-hospitalized patients (24.4%) experienced persisting neurological symptoms/signs. 10/262 patients (3.8%) developed new neurological complaints during the 6 months of follow-up.

Conclusions: Neuro-COVID is a severe disease associated with worse functional status at discharge, particularly in older subjects and those with comorbidities and acute complications of infection.

KEYWORDS
COVID-19, neurological disorders, outcome, predictors, SARS-CoV-2

INTRODUCTION

The spectrum of coronavirus disease 2019 (COVID-19) includes several neurological manifestations that, when present, are associated with higher severity and worse outcome [1–4]. However, neurological symptoms, signs and diagnoses in patients with COVID-19 (neuro-COVID) vary according to the target populations, setting (inpatients vs. outpatients), diagnostic criteria and the background of those in charge of data collection [5]. At present, there are only few publications with follow-up, mainly from single centre studies [6] or non-hospitalized patients [7], or based on self-reports [8], electronic databases [9,10], small samples [11], or with short follow-up [12,13] or high attrition rates [14]. Thus, available evidence is insufficient to define the full spectrum of neuro-COVID and verify how patients' profile (demographics, baseline clinical features) and acute manifestations of infection predict the outcome of the disease.

On this background, an international registry of patients with COVID-19 and neurological symptoms, signs or diagnoses was established for a better understanding of the disease spectrum, along with risk factors, comorbidities and outcome [15]. The advantage of such a registry is the investigation of a large sample of patients from various countries, from which data on neuro-COVID are collected using uniform diagnostic criteria and standardized methods.

The aims of this study were (1) to compare the outcome of neuro-COVID at hospital discharge and at 6 months with patients' profile (comorbidities, general and neurological findings during the

acute phase) and find outcome predictors; (2) to illustrate the demographic and clinical features of inpatients and outpatients with neuro-COVID from different countries; (3) to define incidence and types of new neurological manifestations after the acute phase.

PATIENTS AND METHODS

A multinational registry of patients with neuro-COVID was activated in May 2020 by the European Academy of Neurology (EAN) to provide epidemiological data on neurological signs and symptoms in patients with COVID-19 infection reported by neurologists in outpatient services, emergency rooms and hospital departments (the EAN NEuro-covid ReGistrY, ENERGY). Details on the ENERGY structure and organization have been published [15]. Briefly, all neurologists participating in the registry were asked to record neurological symptoms, signs and diagnoses in clinically or laboratory-confirmed COVID-19 patients in an electronic case record form (e-CRF) (Appendix S1). Data were collected prospectively or retrospectively and included patients' demographics and lifestyle habits, comorbidities, date of first symptoms of infection, hospital and intensive care unit (ICU) admission, incident general and neurological manifestations during the acute phase, diagnostic tests and outcome. Each variable was reported as 'Yes', 'No' or 'Unknown'. In addition, for each documented neurological manifestation, the local investigator was asked to indicate whether or not it was associated with COVID-19.

All adult patients with symptoms and/or signs and/or diseases requiring neurological consultation were eligible for inclusion. A guide is included in the e-CRF (Appendix S2) to define each variable and facilitate data collection in the e-CRF at study entry and during follow-up. Registration and follow-up of eligible patients is ongoing.

All registered patients were followed through telephone contacts at 6 and 12 months. At each contact, the modified Rankin Scale (mRS) score was assigned and new neurological manifestations were noted; for patients who died, date of death and, if performed, autopsy were noted. As the mRS is reliable even when applied by telephone [16], in addition to follow-up, functional disability at baseline was measured enquiring of patients or caregivers their pre-morbid functional status.

Descriptive statistics were performed on all variables collected during the acute phase in the entire sample and comparing hospitalized and non-hospitalized patients and prospective and retrospective observations. The outcome of the infection, in terms of functional impairment, was defined as 'stable/improved' if mRS at discharge was equal to or lower than the baseline score; 'worse' if mRS score at discharge was higher than the baseline score. Stable/improved and worse outcome were also assessed in patients who died during hospital stay compared to those discharged alive.

Neurological symptoms, signs and diagnoses persisting at 6 months were listed. The demographic and clinical profile of patients with new neurological manifestations occurring during follow-up was illustrated. The same methods were used to assess the effect of variables collected during the acute phase or at discharge on the 6-month outcome.

The association of all variables included in the registry with outcome (worse vs. stable/improved) and status (dead vs. alive) at hospital discharge was evaluated using univariable logistic regression models. Variables identified as statistically significant in univariable models were included in multivariable models, and a stepwise selection (with $p < 0.05$ as the criterion for entering and removing effects) was applied to identify variables most strongly associated with the outcome and status at discharge. Results of univariable and multivariable logistic regression models are presented as odds ratios (ORs) and adjusted odds ratios with 95% confidence intervals (CIs). Significance was set at the 5% level (0.05).

For demographic and lifestyle variables, mRS and outcome, the number of missing data was reported in the tables and indicated as unknown or missing. For all other variables, 'unknown' values were grouped with 'No'. For neurological findings, the categories 'present, not COVID associated' and 'present, likely COVID associated' were combined. Data presented as numbers with percentages or as means with standard deviations or medians and ranges were calculated only in subjects with the corresponding values.

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 31 March 2021, 1004 patients were enrolled. COVID-19 infection was not laboratory-confirmed in 33 cases, which were excluded from further analyses. The final sample included 971 patients from 19 countries (Europe 14; Asia 2; Africa 2; South America 1) (Table 1). A flowchart of the study is illustrated in Figure 1.

With few exceptions, there were no major differences in the general characteristics of prospective compared to retrospective cases (Table S1). There were 497 men and 466 women (plus eight intersex or unknown) aged 16–101 years (median 63; interquartile range [IQR] 48–74). One or more comorbidities were present in 619 cases (63.75%). The most frequent was hypertension (52.0%), followed by cardiovascular disease (29.8%) and diabetes (22.0%). A history of transient ischaemic attacks or stroke (154 cases, 15.9%), dementia (86 cases, 8.9%) and Parkinson's disease (35 cases, 3.6%) were the commonest neurological comorbidities.

In all, 810 patients (83.4%) were hospitalized. Compared to non-hospitalized patients, hospitalized patients were older, more often men, with one or more baseline comorbidities, and with functional impairment at baseline (Table 1). Functional disability at admission (mRS 2+) was present in 34.1% of hospitalized patients and 10.6% of non-hospitalized cases. Hospitalized patients experienced more systemic COVID-19 complications and had more neurological manifestations during the acute phase. The most common neurological complaints/manifestations during the acute phase included

TABLE 1 Confirmed COVID-19 cases, hospitalized and not hospitalized cases

	All COVID-19 confirmed ($n = 971$)[a]		Hospitalized ($n = 810$)		Not hospitalized ($n = 154$)		
	n	%	*n*	%	*n*	%	*p* value
Country							
Austria	66	6.80	64	7.90	2	1.30	<0.0001
Brazil	3	0.31	1	0.12	2	1.30	
Egypt	6	0.62	5	0.62	1	0.65	
Estonia	0	0.00	0	0.00	0	0.00	
France	22	2.27	19	2.35	3	1.95	
Hungary	101	10.40	85	10.49	16	10.39	
Israel	30	3.09	30	3.70	0	0.00	
Italy	165	16.99	96	11.85	69	44.81	
Macedonia	1	0.10	1	0.12	0	0.00	
Moldova	118	12.15	116	14.32	2	1.30	
Norway	50	5.15	39	4.81	11	7.14	
Poland	26	2.68	9	1.11	17	11.04	
Portugal	56	5.77	53	6.54	0	0.00	
Romania	84	8.65	84	10.37	0	0.00	
Russia	13	1.34	7	0.86	6	3.90	
Switzerland	42	4.33	22	2.72	19	12.34	
Tunisia	19	1.96	14	1.73	5	3.25	
Turkey	145	14.93	141	17.41	1	0.65	
Ukraine	24	2.47	24	2.96	0	0.00	
Sex							
Male	497	51.18	434	53.58	59	38.31	0.0033
Female	466	47.99	368	45.43	95	61.69	
Intersex	2	0.21	2	0.25	0	0.00	
Unknown	6	0.62	6	0.74	0	0.00	
Smoking							
Yes	122	12.56	109	13.46	13	8.44	0.0949
No	729	75.08	606	74.81	120	77.92	
Unknown	120	12.36	95	11.73	21	13.64	
Source of COVID-19 contact							
Occupation	75	7.72	42	5.19	33	21.43	<0.0001
Family member	168	17.30	119	14.69	46	29.87	
Social	86	8.86	66	8.15	18	11.69	
Travel	17	1.75	16	1.98	1	0.65	
Other	61	6.28	61	7.53	0	0.00	
Unknown	564	58.08	506	62.47	56	36.36	
	Median (*n*)	**IQR**	**Median (*n*)**	**IQR**	**Median (*n*)**	**IQR**	
Age at COVID onset	63 (909)	48–74	66 (751)	52–76	48 (151)	34–61	<0.0001
BMI	25 (840)	23–28	26 (706)	23–29	24 (130)	22–28	0.0455
	n	%	*n*	%	*n*	%	
Any comorbidity	619	63.75	565	69.75	49	31.82	<0.0001
Hypertension	505	52.01	464	57.28	36	23.38	<0.0001
Diabetes type 1	8	0.82	8	0.99	0	0.00	0.2054
Diabetes type 2	206	21.22	191	23.58	14	9.09	<0.0001
Cardiovascular disease	289	29.76	269	33.21	17	11.04	<0.0001

TABLE 1 (Continued)

	n	%	*n*	%	*n*	%	
Chronic kidney disease	88	9.06	87	10.74	1	0.65	<0.0001
Chronic liver disease	37	3.81	37	4.57	0	0.00	0.0057
Chronic pulmonary disease	93	9.58	86	10.62	6	3.90	0.0136
Anaemia	50	5.15	47	5.80	3	1.95	0.0389
Cancer	85	8.75	80	9.88	4	2.60	0.0055
Immunosuppressed state	50	5.15	44	5.43	6	3.90	0.3712
Other non-neurological comorbidity	232	23.89	216	26.67	15	9.74	<0.0001
Dementia	86	8.86	79	9.75	6	3.90	0.0275
Parkinson's disease	35	3.60	21	2.59	14	9.09	0.0001
Stroke: ICH, ischaemic stroke, TIA	154	15.86	147	18.15	6	3.90	<0.0001
Multiple sclerosis	47	4.84	19	2.35	28	18.18	<0.0001
Motor neuron disease	4	0.41	3	0.37	1	0.65	0.6501
Neuromuscular disorder	12	1.24	11	1.36	1	0.65	0.4395
Neuropathy	34	3.50	31	3.83	3	1.95	0.2157
Other neurological disease	99	10.20	82	10.12	16	10.39	0.8675
COVID systemic complications	501	51.60	480	59.26	17	11.04	<0.0001
Dyspnoea	503	51.80	453	55.93	46	29.87	<0.0001
Pneumonia	528	54.38	501	61.85	22	14.29	<0.0001
Cardiovascular	121	12.46	117	14.44	1	0.65	<0.0001
Renal insufficiency/ dialysis	65	6.69	65	8.02	0	0.00	0.0002
Coagulation disorder/ disseminated intravascular coagulation	45	4.63	44	5.43	1	0.65	0.0080
Refractory shock	38	3.91	37	4.57	0	0.00	0.0183
Extra-corporeal membrane oxygenation (ECMO)	5	0.51	5	0.62	0	0.00	0.3176
Mechanical ventilation	121	12.46	116	14.32	0	0.00	<0.0001
Neurological findings	747	76.93	633	78.15	107	69.48	0.0434
Headache	394	40.58	310	38.27	81	52.60	0.0010
Hyposmia/hypogeusia	291	29.97	199	24.57	90	58.44	<0.0001
Dysautonomia	139	14.32	107	13.21	31	20.13	0.0274
Vertigo	194	19.98	159	19.63	32	20.78	0.5409
Myalgia	284	29.25	202	24.94	80	51.95	<0.0001
Sleep disorders	161	16.58	120	14.81	39	25.39	0.0009
Cognitive impairment (including dysexecutive syndrome)	288	29.66	256	31.60	32	20.78	0.0029
Hyperactive delirium	122	12.56	111	13.70	10	6.49	0.0163
Hypoactive delirium/ acute encephalopathy	112	11.53	106	13.09	6	3.90	0.0007
Stupor/coma	124	12.77	119	14.69	4	2.60	<0.0001

(Continues)

TABLE 1 (Continued)

	n	%	*n*	%	*n*	%	
Syncope	51	5.25	46	5.68	5	3.25	0.1813
Seizures/status epilepticus	81	8.34	76	9.38	5	3.25	0.0085
Meningitis/encephalitis	42	4.33	38	4.69	4	2.60	0.2087
Stroke	253	26.06	244	30.12	6	3.90	<0.0001
Tremor	68	7.00	60	7.41	8	5.19	0.2681
Chorea	1	0.10	1	0.12	0	0.00	0.6556
Dystonia	18	1.85	18	2.22	0	0.00	0.0562
Myoclonus	15	1.54	15	1.85	0	0.00	0.0818
Dyskinesia	12	1.24	9	1.11	3	1.95	0.4301
Parkinsonism	26	2.68	21	2.59	5	3.25	0.7217
Ataxia	86	8.86	78	9.63	8	5.19	0.0573
Spinal cord disorder	38	3.91	36	4.44	2	1.30	0.0557
Peripheral neuropathy	92	9.47	85	10.49	7	4.55	0.0150
Other neurological findings	121	12.46	106	13.09	15	9.74	0.1859
Hospital admission	810	83.42	810	100.00	0	0.00	<0.0001
ICU admission	227	23.38	224	27.65	0	0.00	<0.0001
Pre-morbid mRS							
0	488	52.87	381	48.97	104	75.36	<0.0001
1	153	16.58	132	16.97	20	14.49	
2	95	10.29	84	10.80	10	7.25	
3	96	10.40	90	11.57	4	2.90	
4	64	6.93	64	8.23	0	0.00	
5	27	2.93	27	3.47	0	0.00	
Missing	48		32		16		
Discharge mRS							
0	264	28.12	170	21.49	94	64.83	<0.0001
1	158	16.83	128	16.18	30	20.69	
2	116	12.35	101	12.77	15	10.34	
3	130	13.84	123	15.55	6	4.14	
4	88	9.37	87	11.00	0	0.00	
5	51	5.43	50	6.32	0	0.00	
6	132	14.06	132	16.69	0	0.00	
Missing	32		19		9		
Outcome							
Worse[b]	448	49.12	432	56.10	14	10.07	<0.0001
Stable/improved[b]	464	50.88	338	43.90	125	89.93	
Not available	59		40		19		

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

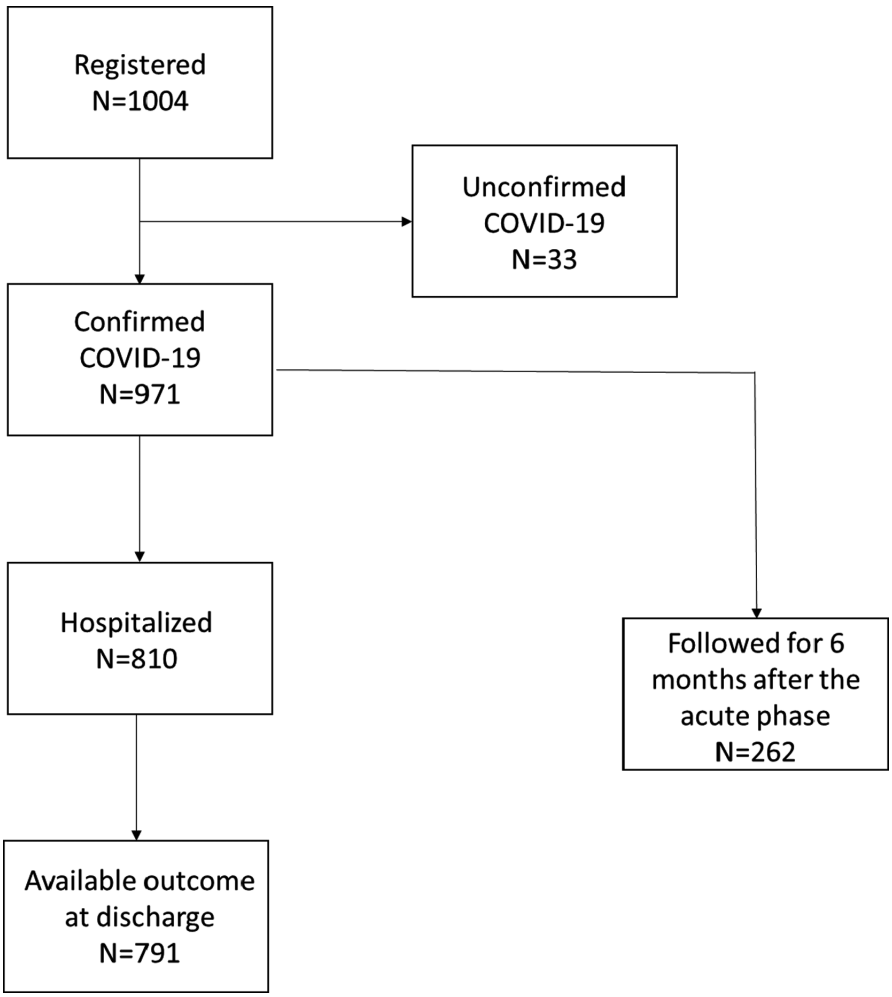
[a]Setting was unknown in seven cases: Portugal three, Switzerland one, Turkey three.

[b]Worse outcome, mRS score at discharge higher than pre-morbid mRS score; stable/improved outcome, mRS score at discharge equal to or lower than pre-morbid mRS score.

headache (38.2% in hospitalized and 52.6.9% in non-hospitalized patients), cognitive impairment (31.6% vs. 20.8%), stroke (30.1% vs. 3.9%), delirium (26.7% vs. 10.4%), hyposmia/hypogeusia (24.6% vs. 58.4%), sleep disorders (14.8% vs. 25.4%), myalgias (24.9% vs. 51.9%) and stupor/coma (14.7% vs. 2.6%). 224 patients (27.6%) were admitted to the ICU.

At discharge, the proportion of hospitalized patients with functional impairment (mRS 2+) increased to 62.3% (vs. 14.5% of

FIGURE 1 Study flowchart



non-hospitalized subjects). 432 hospitalized patients (53.3%) were discharged with a worse functional status compared to admission (Table 2, columns A). Compared to patients who improved or were stable, patients with worse outcome were older, had more non-neurological (hypertension, cardiovascular and renal diseases) and neurological comorbidities (history of transient ischaemic attacks or stroke, dementia) and presented more systemic complications during the acute phase. Stroke was the most common neurological manifestation in patients with worse outcome (40.7%) followed by cognitive impairment (34.0%), headache (31.0%), stupor/coma (23.6%) and myalgia (20.8%). In contrast, in patients with stable/improved outcome the commonest manifestations were, in decreasing order, headache (48.2%), hyposmia/hypogeusia (32.3%), myalgias (30.5%), vertigo (23.4%) and cognitive impairment (20.7%).

In all, 132 patients died in hospital (Table 2, columns B). Compared to those discharged alive, patients who died were older (median age at COVID-19 onset 76 years, IQR 67–85), with more comorbidities (hypertension, cardiovascular and renal diseases, cancer and, amongst neurological diseases, stroke, dementia and Parkinson's disease). Stupor/coma, stroke and cognitive disturbances were the commonest neurological manifestations/complaints in patients who died in hospital (59.1%, 47.7% and 49.2%, respectively) along with dysexecutive syndrome (23.5%) and hypoactive delirium (24.2%). Almost all deceased patients presented systemic COVID-19 complications (predominantly pneumonia, 84.9% of cases), 48.5% were admitted in ICU and 36.4% required mechanical ventilation. Refractory shock occurred in 27.3% of in-hospital deaths.

The variable most highly associated with worse outcome was refractory shock (OR 30.6; 95% CI 4.2–224.5) (Table 3, columns A). Increasing age also predicted worse outcome (OR 1.04 for each additional year; 95% CI 1.03–1.05). Amongst neurological manifestations, stupor/coma (OR 6.2; 95% CI 3.6–10.8) and stroke (OR 3.1; 95% CI 2.2–4.3) showed the highest risk for worse outcome. The need for mechanical ventilation (OR 8.1; 95% CI 4.35–15.0) and ICU admission (OR 5.8; 95% CI 3.9–8.6) indicated worse outcome. Older age, stupor/coma, stroke and ICU admission were confirmed as predictors of worse outcome at discharge in a multivariable model, whilst syncope and dystonia were predictors of stable/improved outcome. In univariable models, stupor/coma carried the highest death risk (OR 21.8; 95% CI 13.6–34.8), followed by cognitive impairment (3.05; 95% CI 2.1–4.5), hypoactive delirium (OR 2.5; 95% CI 1.6–4.0) and stroke (OR 2.4; 95% CI 1.7–3.56). Use of mechanical ventilation (OR 5.1; 95% CI 3.3–7.9), pneumonia (OR 4.3; 95% CI 2.6–7.0), ICU admission (OR 3.0; 95%

TABLE 2 Outcome at discharge (only confirmed and hospitalized COVID-19 cases)

	A					B				
	Worse outcome[a] (*n* = 432)		Stable/improved outcome[a] (*n* = 338)		*p* value	Alive (*n* = 659)		Dead (*n* = 132)		*p* value
	n	%	*n*	%		*n*	%	*n*	%	
Country										
Austria	35	8.10	22	6.51	<0.0001	52	7.89	10	7.58	<0.0001
Brazil	0	0.00	1	0.30		1	0.15	0	0.00	
Egypt	0	0.00	1	0.30		5	0.76	0	0.00	
Estonia	0	0.00	0	0.00		0	0.00	0	0.00	
France	15	3.47	3	0.89		14	2.12	4	3.03	
Hungary	28	6.48	56	16.57		75	11.38	10	7.58	
Israel	8	1.85	22	6.51		24	3.64	6	4.55	
Italy	70	16.20	23	6.80		69	10.47	26	19.70	
Macedonia	0	0.00	1	0.30		1	0.15	0	0.00	
Moldova	97	22.45	19	5.62		89	13.51	27	20.45	
Norway	23	5.32	7	2.07		31	4.70	0	0.00	
Poland	4	0.93	3	0.89		7	1.06	0	0.00	
Portugal	35	8.10	18	5.33		44	6.68	9	6.82	
Romania	51	11.81	33	9.76		56	8.50	28	21.21	
Russia	2	0.46	5	1.48		7	1.06	0	0.00	
Switzerland	6	1.39	5	1.48		17	2.58	1	0.76	
Tunisia	10	2.31	4	1.18		11	1.67	3	2.27	
Turkey	48	11.11	92	27.22		132	20.03	8	6.06	
Ukraine	0	0.00	23	6.80		24	3.64	0	0.00	
Sex										
Male	237	54.86	170	50.30	0.1716	349	52.96	69	52.27	0.6373
Female	193	44.68	162	47.93		302	45.83	63	47.73	
Intersex	1	0.23	1	0.30		2	0.30	0	0.00	
Unknown	1	0.23	5	1.48		6	0.91	0	0.00	
Smoking										
Yes	40	9.26	67	19.82	<0.0001	100	15.17	8	6.06	0.0027
No	336	77.78	240	71.01		492	74.66	101	76.52	
Unknown	56	12.96	31	9.17		67	10.17	23	17.42	

TABLE 2 (Continued)

	A					B				
	Worse outcome[a] (n = 432)		Stable/improved outcome[a] (n = 338)		p value	Alive (n = 659)		Dead (n = 132)		p value
	n	%	*n*	%		*n*	%	*n*	%	
Source of COVID-19 contact										
Occupation	13	3.01	25	7.40	0.0002	39	5.92	1	0.76	<0.0001
Family member	50	11.57	61	18.05		103	15.63	12	9.09	
Social	31	7.18	34	10.06		51	7.74	14	10.61	
Travel	9	2.08	6	1.78		15	2.28	0	0.00	
Other	44	10.19	16	4.73		38	5.77	22	16.67	
Unknown	285	65.97	196	57.99		413	62.67	83	62.88	
	Median (*n*)	**IQR**	**Median (*n*)**	**IQR**		**Median (*n*)**	**IQR**	**Median (*n*)**	**IQR**	
Age at COVID onset	70 (405)	60–79	58 (308)	43–71	<0.0001	63 (606)	49–73	76 (127)	67–85	<0.0001
BMI	26 (379)	23–29	25 (302)	23–28	0.0135	26 (573)	23–28	25 (117)	22–29	0.6456
	n	%	*n*	%		*n*	%	*n*	%	
Any comorbidity	335	77.55	202	59.76	<0.0001	434	65.86	118	89.39	<0.0001
Hypertension	289	66.90	158	46.75	<0.0001	348	52.81	107	81.06	<0.0001
Diabetes type 1	3	0.69	5	1.48	0.2865	8	1.21	0	0.00	0.2033
Diabetes type 2	112	25.93	71	21.01	0.1114	149	22.61	40	30.30	0.0585
Cardiovascular disease	165	38.19	92	27.22	0.0014	195	29.59	68	51.52	<0.0001
Chronic kidney disease	57	13.19	28	8.28	0.0309	54	8.19	32	24.24	<0.0001
Chronic liver disease	14	3.24	20	5.92	0.0728	30	4.55	7	5.30	0.7093
Chronic pulmonary disease	47	10.88	35	10.36	0.8148	68	10.32	15	11.36	0.7207
Anaemia	22	5.09	20	5.92	0.6171	34	5.16	13	9.85	0.0375
Cancer	46	10.65	29	8.58	0.3368	53	8.04	24	18.18	0.0003
Immunosuppressed state	20	4.63	19	5.62	0.5334	33	5.01	8	6.06	0.6184
Other non-neurological comorbidity	145	33.56	63	18.64	<0.0001	153	23.22	60	45.45	<0.0001
Dementia	49	11.34	27	7.99	0.1214	53	8.04	26	19.70	<0.0001

(Continues)

TABLE 2 (Continued)

	n	%	*n*	%		*n*	%	*n*	%	
Parkinson's disease	14	3.24	7	2.07	0.3227	14	2.12	7	5.30	0.0381
Stroke: ICH, ischaemic stroke, TIA	98	22.69	44	13.02	0.0006	102	15.48	43	32.58	<0.0001
Multiple sclerosis	3	0.69	13	3.85	0.0023	18	2.73	1	0.76	0.1764
Motor neuron disease	0	0.00	2	0.59	0.1094	3	0.46	0	0.00	0.4374
Neuromuscular disorder	5	1.16	4	1.18	0.9734	9	1.37	1	0.76	0.5681
Neuropathy	15	3.47	13	3.85	0.7833	26	3.95	5	3.79	0.9322
Other neurological disease	38	8.80	37	10.95	0.3179	60	9.10	17	12.88	0.1818
COVID systemic complications	312	72.22	151	44.67	<0.0001	350	53.11	122	92.42	<0.0001
Dyspnoea	270	62.50	163	48.22	<0.0001	335	50.83	105	79.55	<0.0001
Pneumonia	306	70.83	172	50.89	<0.0001	374	56.75	112	84.85	<0.0001
Cardiovascular	76	17.59	39	11.54	0.0193	79	11.99	38	28.79	<0.0001
Renal insufficiency/ dialysis	46	10.65	17	5.03	0.0048	42	6.37	22	16.67	<0.0001
Coagulation disorder/ disseminated intravascular coagulation	28	6.48	13	3.85	0.106	33	5.01	9	6.82	0.3971
Refractory shock	36	8.33	1	0.30	<0.0001	1	0.15	36	27.27	<0.0001
Extra-corporeal membrane oxygenation (ECMO)	4	0.93	0	0.00	0.0761	4	0.61	0	0.00	0.3695
Mechanical ventilation	99	22.92	12	3.55	<0.0001	66	10.02	48	36.36	<0.0001
Neurological findings	377	87.27	230	68.05	<0.0001	498	75.57	125	94.70	<0.0001
Headache	134	31.02	163	48.22	<0.0001	279	42.34	23	17.42	<0.0001
Hyposmia/hypogeusia	79	18.29	109	32.25	<0.0001	184	27.92	7	5.30	<0.0001
Dysautonomia	50	11.57	54	15.98	0.0761	93	14.11	13	9.85	0.1893
Vertigo	72	16.67	79	23.37	0.02	140	21.24	14	10.61	0.0048
Myalgia	90	20.83	103	30.47	0.0022	184	27.92	12	9.09	<0.0001
Sleep disorders	63	14.58	51	15.09	0.8446	105	15.93	14	10.61	0.1181

TABLE 2 (Continued)

	n	%	*n*	%		*n*	%	*n*	%	
Cognitive impairment (including dysexecutive syndrome)	157	36.34	86	25.44	0.0012	183	27.77	67	50.76	<0.0001
Hyperactive delirium	76	17.59	32	9.47	0.0013	86	13.05	23	17.42	0.1833
Hypoactive delirium/acute encephalopathy	76	17.59	29	8.58	0.0003	74	11.23	32	24.24	<0.0001
Stupor/coma	102	23.61	16	4.73	<0.0001	41	6.22	78	59.09	<0.0001
Syncope	14	3.24	30	8.88	0.0008	41	6.22	4	3.03	0.1485
Seizures/status epilepticus	37	8.56	38	11.24	0.2136	62	9.41	14	10.61	0.6699
Meningitis/encephalitis	19	4.40	19	5.62	0.4368	33	5.01	5	3.79	0.5498
Stroke	176	40.74	62	18.34	<0.0001	180	27.31	63	47.73	<0.0001
Tremor	24	5.56	32	9.47	0.038	54	8.19	5	3.79	0.0786
Chorea	0	0.00	1	0.30	0.2579	1	0.15	0	0.00	0.6543
Dystonia	2	0.46	15	4.44	0.0002	17	2.58	1	0.76	0.2001
Myoclonus	8	1.85	7	2.07	0.8271	12	1.82	3	2.27	0.7283
Dyskinesia	2	0.46	7	2.07	0.0394	7	1.06	2	1.52	0.6543
Parkinsonism	9	2.08	12	3.55	0.2149	20	3.03	1	0.76	0.1374
Ataxia	34	7.87	43	12.72	0.026	72	10.93	6	4.55	0.0248
Spinal cord disorder	19	4.40	16	4.73	0.8244	34	5.16	2	1.52	0.0667
Peripheral neuropathy	49	11.34	26	7.69	0.09	73	11.08	7	5.30	0.0466
Other neurological findings	62	14.35	37	10.95	0.1613	88	13.35	16	12.12	0.7021
ICU admission	180	41.67	37	10.95	<0.0001	157	23.82	64	48.48	<0.0001
Pre-morbid mRS										
0	206	48.02	163	48.95	0.6792	331	52.29	38	29.46	<0.0001
1	78	18.18	53	15.92		118	18.64	13	10.08	
2	50	11.66	32	9.61		64	10.11	18	13.95	
3	48	11.19	41	12.31		66	10.43	23	17.83	
4	35	8.16	29	8.71		39	6.16	25	19.38	
5	12	2.80	15	4.50		15	2.37	12	9.30	
Missing	3		5			26		3		

(Continues)

TABLE 2 (Continued)

	n	%	*n*	%		*n*	%	*n*	%	
Discharge mRS					<0.0001					<0.0001
0	0	0.00	170	50.30		170	25.80	0	0.00	
1	58	13.43	62	18.34		128	19.42	0	0.00	
2	57	13.19	38	11.24		101	15.33	0	0.00	
3	88	20.37	35	10.36		123	18.66	0	0.00	
4	61	14.12	22	6.51		87	13.20	0	0.00	
5	36	8.33	11	3.25		50	7.59	0	0.00	
6	132	30.56	0	0.00		0	0.00	132	100.00	

Abbreviations: BMI, body mass index; ICH, intracerebral haemorrhage; ICU, intensive care unit; IQR, interquartile range; mRS, modified Rankin Score; TIA, transient ischaemic attack.
[a]Worse outcome, mRS score at discharge higher than pre-morbid mRS score; stable/improved outcome, mRS score at discharge equal to or lower than pre-morbid mRS score.

CI 2.05–4.4), cardiovascular complications (OR 3.0; 95% CI 1.9–4.6) and renal insufficiency (OR 2.9; 95% CI 1.7–5.1) also predicted in-hospital mortality. Amongst pre-existing comorbidities, hypertension (OR 3.8; 95% CI 2.4–6.1), chronic kidney diseases (OR 3.6; 95% CI 2.2–5.8), cardiovascular diseases (OR 2.5; 95% 1.7–3.7) and cancer (OR 2.5; 95% CI 1.5–4.3) were the variables most highly associated with in-hospital death. Amongst pre-existing neurological comorbidities, stroke (OR 2.6; 95% CI 1.7–4.0) and Parkinson's disease (OR 2.6; 95% CI 1.02–6.5) carried the highest risk. Premorbid mRS score was significantly associated with in-hospital mortality, showing an increasing risk with increase of the disability score (Table 3, columns B). Older age, cancer, cardiovascular complications, refractory shock, stupor/coma and ICU admission were predictors of death in the multivariable model, whilst hyposmia/hypogeusia predicted a lower risk of death.

At the time of data collection, a total of 269 patients (224 hospitalized and 45 non-hospitalized) had been followed for 6 months. Of them, 262 had laboratory-confirmed COVID-19 infection. This sample included 131 men and 130 women (unknown sex in 1) aged 19 through 91 years (IQR 47–71) (Table S2). 199 patients (76.0%) had neurological manifestations during the acute phase of the COVID-19 infection, predominantly headache (40.8%), hyposmia/hypogeusia (34.7%), myalgia (29.1%), delirium (25.2%), cognitive impairment (23.3%), stroke sequelae (21.0%) and sleep disorders (17.1%). A mild-to-severe functional impairment (mRS 2+) was present in 48 patients (18.9%) before the onset of symptoms, in 133 patients (53.8%) at the end of the acute phase of the infection, and in 118 patients (46.1%) at the 6-month follow-up. Almost all the variables associated with worse outcome at discharge were negative prognostic predictors for outcome at 6 months (Table 4). Experiencing stroke or ataxia during the acute phase (OR 8.5, 95% CI 2.8–26.1; and, respectively, OR 6.9, 95% CI 1.2–40.7) and ICU admission (OR 3.6; 95% CI 1.5–8.7) were confirmed as predictors of worse outcome at 6 months, along with functional impairment at discharge. In contrast, history of stroke was associated with stable/improved outcome (OR 0.3; 95% CI 0.1–0.9).

At 6 months, 65/221 hospitalized patients (29.4%) and 10/41 non-hospitalized patients (24.4%) experienced persisting neurological symptoms/signs, the commonest being hemiparesis/plegia (11 patients), cognitive impairment (10 cases), anosmia/ageusia (10 cases), para/tetraparesis (six cases) and fatigue (five cases) (Figure 2).

Ten patients (3.8%) developed new neurological complications during follow-up. Two were not hospitalized during the acute phase. The general characteristics of these patients are illustrated in Table S3. Incident neurological manifestations varied in type and severity. The majority of patients had one or more comorbidities and complications of COVID-19 (mostly pneumonia). Three patients had severe functional impairment at 6 months. These patients developed vertical diplopia and, respectively, status epilepticus and recurrent stroke during follow-up. New neurological complaints were more severe in patients with sequelae at hospital discharge.

TABLE 3 Predictors of outcome at discharge ($N = 971$)

	A Worse outcome vs. stable/improved outcome[a]						B Dead vs. alive at discharge					
	Univariable model			Multivariable model			Univariable model			Multivariable model		
	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value
Sex												
Male	1 (ref.)		0.1432				1 (ref.)		0.9611			
Female	0.86	0.64–1.14					1.05	0.73–1.54				
Intersex/unknown	0.24	0.05–1.20					ne	ne				
Smoking												
Yes	0.43	0.28–0.65	0.0001				0.39	0.18–0.83	0.0039			
No	1 (ref.)	–					1 (ref.)	–				
Unknown	1.29	0.81–2.06					1.67	0.99–2.81				
Source of COVID-19 contact												
Occupation	0.53	0.35–0.80	0.0007				0.50	0.27–0.94	0.0471			
Family member	0.33	0.16–0.67					0.11	0.02–0.81				
Social	0.59	0.35–0.99					1.18	0.63–2.21				
Travel	0.97	0.34–2.76					ne	ne				
Other/unknown	1 (ref.)	–					1 (ref.)	–				
Age at admission (1-year increase)	1.04	1.03–1.05	<0.0001	1.03	1.02–1.04	<0.0001	1.06	1.05–1.08	<0.0001	1.05	1.03–1.07	<0.0001
BMI (1-unit increase)	1.01	0.99–1.03	0.2869				0.99	0.97–1.02	0.5206			
Non-neurological comorbidities												
Hypertension	2.30	1.72–3.09	<0.0001				3.82	2.41–6.07	<0.0001			
Diabetes type 1/type 2	1.25	0.90–1.74	0.1878				1.39	0.92–2.10	0.1171			
Cardiovascular disease	1.65	1.21–2.25	0.0014				2.53	1.73–3.70	<0.0001			
Chronic kidney disease	1.68	1.05–2.71	0.0324				3.59	2.21–5.83	<0.0001			
Chronic liver disease	0.53	0.27–1.07	0.0770				1.17	0.50–2.73	0.7095			
Chronic pulmonary disease	1.06	0.67–1.68	0.8154				1.11	0.61–2.02	0.7208			
Anaemia	0.85	0.46–1.59	0.6174				2.01	1.03–3.92	0.0409			

(Continues)

TABLE 3 (Continued)

	A Worse outcome vs. stable/improved outcome[a]						B Dead vs. alive at discharge					
	Univariable model			Multivariable model			Univariable model			Multivariable model		
	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value
Cancer	1.27	0.78–2.07	0.3345				2.54	1.51–4.29	0.0005	2.57	1.23–5.34	0.0117
Immunosuppressed state	0.82	0.43–1.55	0.5341				1.22	0.55–2.71	0.6189			
Neurological comorbidities												
Dementia	1.47	0.90–2.41	0.1232				2.81	1.68–4.68	<0.0001			
Parkinson's disease	1.58	0.63–3.97	0.3267				2.58	1.02–6.52	0.0451			
Stroke: ICH, ischaemic stroke, TIA	1.96	1.33–2.89	0.0007				2.64	1.73–4.02	<0.0001			
Multiple sclerosis	0.18	0.05–0.62	0.0068				0.27	0.04–2.05	0.2068			
Motor neuron disease	ne	ne	0.9796				ne	ne	0.9837			
Neuromuscular disorder	0.97	0.26–3.67	0.9734				0.55	0.07–4.39	0.5737			
Neuropathy	0.90	0.42–1.92	0.7822				0.96	0.36–2.54	0.9330			
COVID systemic complications												
Dyspnoea	1.79	1.34–2.39	<0.0001				3.76	2.40–5.90	<0.0001			
Pneumonia	2.34	1.74–3.16	<0.0001				4.27	2.59–7.04	<0.0001			
Cardiovascular	1.64	1.08–2.48	0.0201				2.97	1.90–4.63	<0.0001	2.08	1.07–4.06	0.0311
Renal insufficiency/ dialysis	2.25	1.27–4.00	0.0058				2.94	1.69–5.11	0.0001			
Coagulation disorder/ disseminated intravascular coagulation	1.73	0.88–3.40	0.1099				1.39	0.65–2.98	0.3986			
Refractory shock	30.63	4.18–224.56	0.0008				ne	ne	<0.0001	44.72	5.68–352.5	0.0003
Extra-corporeal membrane oxygenation (ECMO)	ne	ne	0.9818				ne	ne	0.9877			

TABLE 3 (Continued)

	A Worse outcome vs. stable/improved outcome[a]						B Dead vs. alive at discharge					
	Univariable model			Multivariable model			Univariable model			Multivariable model		
	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value
Mechanical ventilation	8.08	4.35–14.99	<0.0001				5.13	3.31–7.94	<0.0001			
Neurological findings												
Headache	0.48	0.36–0.65	<0.0001				0.29	0.18–0.46	<0.0001			
Hyposmia/ hypogeusia	0.47	0.34–0.66	<0.0001				0.15	0.07–0.32	<0.0001	0.12	0.04–0.40	0.0006
Dysautonomia	0.69	0.46–1.04	0.0772				0.67	0.36–1.23	0.1919			
Vertigo	0.66	0.46–0.94	0.0205				0.44	0.25–0.79	0.0059			
Myalgia	0.60	0.43–0.83	0.0023				0.26	0.14–0.48	<0.0001			
Sleep disorders	0.96	0.64–1.43	0.8444				0.63	0.35–1.13	0.1209			
Cognitive impairment (including dysexecutive syndrome)	1.67	1.22–2.29	0.0013				2.68	1.83–3.93	<0.0001			
Hyperactive delirium	2.04	1.31–3.17	0.0015				1.40	0.85–2.33	0.1846			
Hypoactive delirium/acute encephalopathy	2.28	1.44–3.58	0.0004				2.53	1.59–4.03	<0.0001			
Stupor/coma	6.22	3.59–10.77	<0.0001	12.01	4.35–33.11	<0.0001	21.77	13.62–34.81	<0.0001	22.77	12.1–42.86	<0.0001
Syncope	0.34	0.18–0.66	0.0013	0.10	0.03–0.31	<0.0001	0.47	0.17–1.34	0.1576			
Seizures/status epilepticus	0.74	0.46–1.19	0.2149				1.14	0.62–2.11	0.6701			
Meningitis/ encephalitis	0.77	0.40–1.48	0.4379				0.75	0.29–1.95	0.5514			
Stroke	3.06	2.19–4.28	<0.0001	2.89	1.88–4.44	<0.0001	2.43	1.66–3.56	<0.0001			
Tremor	0.56	0.33–0.98	0.0402				0.44	0.17–1.13	0.0865			
Chorea	ne	ne	0.9780				ne	ne	0.9858			
Dystonia	0.10	0.02–0.44	0.0024	0.02	0.00–0.14	<0.0001	0.29	0.04–2.19	0.2288			
Myoclonus	0.89	0.32–2.48	0.8263				1.25	0.35–4.51	0.7288			
Dyskinesia	0.22	0.05–1.07	0.0600				1.43	0.30–6.98	0.6555			

(Continues)

TABLE 3 (Continued)

	A Worse outcome vs. stable/improved outcome[a]						B Dead vs. alive at discharge					
	Univariable model			Multivariable model			Univariable model			Multivariable model		
	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value
Parkinsonism	0.58	0.24–1.39	0.2202				0.24	0.03–1.83	0.1704			
Ataxia	0.59	0.37–0.94	0.0273				0.39	0.17–0.91	0.0301			
Spinal cord disorder	0.93	0.47–1.83	0.8238				0.28	0.07–1.19	0.0853			
Peripheral neuropathy	1.54	0.93–2.53	0.0919				0.45	0.20–1.00	0.0499			
ICU admission	5.81	3.93–8.59	<0.0001	5.62	3.54–8.95	<0.0001	3.01	2.05–4.43	<0.0001	2.17	1.18–4.00	0.0130
Pre-morbid mRS												
0	1 (ref.)	–	0.6842				1 (ref.)	–	<0.0001			
1	1.16	0.77–1.75					0.96	0.49–1.86				
2	1.24	0.76–2.02					2.45	1.32–4.56				
3	0.93	0.58–1.47					3.04	1.70–5.43				
4	0.96	0.56–1.63					5.58	3.06–10.22				
5	0.63	0.29–1.39					6.97	3.04–15.98				

Abbreviations: Adj. OR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; ICH, intracerebral haemorrhage; ICU, intensive care unit; mRS, modified Rankin Scale; OR, odds ratio; ne, not estimable; TIA, transient ischaemic attack.

[a]Worse outcome, mRS score at discharge higher than pre-morbid mRS score; stable/improved outcome, mRS score at discharge equal to or lower than pre-morbid mRS score.

DISCUSSION

This is the largest international cohort study including 6-month follow-up in adult patients with neuro-COVID seen by neurologists. It was found that neurological complications are highly prevalent and have a dramatic impact on the outcome of hospitalized patients. Further strengthening the relevance of neurological involvement, a 76% persistence of neurological involvement was found with mild-to-severe functional impact in 68%.

At admission, one or more comorbidities were present in 63.7% of cases and functional disability was documented in 34.1%; 51.6% of patients experienced systemic complications of SARS-CoV-2 infection, 83.4% were hospitalized, 23.4% were admitted to the ICU, 56.1% had worsening of their functional abilities at discharge, and 16.7% died whilst in hospital. Stupor or coma, ICU admission and stroke carried a worse outcome at discharge whereas history of cancer, development of cardiovascular complications and refractory shock were associated with increased mortality. Older age and coma were negative prognostic predictors (increased functional disability and death) but did not predict worse outcome at 6 months amongst survivors at discharge. ICU admission was a negative prognostic factor both at discharge and at 6 months.

At 6 months, 28.6% of patients still presented persistent neurological sequelae of the acute phase, the commonest being focal or generalized motor weakness and cognitive impairment. The development of stroke or ataxia, ICU admission and functional impairment at discharge were predictive of worse 6-month outcome. These findings support the dispute that only the severity of the acute COVID-19 spectrum and some neurological complications, rather than older age, the presence of comorbidities and the baseline functional impairment, are significant long-term prognostic predictors.

A number of neurological symptoms or signs (hyposmia/hypogeusia, syncope, dystonia, history of stroke) were associated with stable/improved outcome. However, for some of them (hyposmia/hypogeusia, syncope, dystonia) interview bias is a possible explanation (as more severe cases were perhaps unable to report those symptoms). The protective role of history of stroke cannot be easily interpreted. Although the mechanisms of previous strokes might have been different from COVID-19's mechanism of action, a coincidental finding cannot be excluded.

Another study assessed incident neurological symptoms, signs and diagnoses in 4491 hospitalized patients seen in neurological consultation [17]. In that study, 88% of patients had new neurological manifestations. The most common were toxic/metabolic encephalopathy (51%), stroke (14%), seizures (12%) and hypoxic/ischaemic brain injury (11%). In line with our study, those patients were older, more severely ill and less likely to be discharged home.

Our findings differ from other reports. In a large retrospective cohort (N = 236,379) using data from an electronic health records network [9], the estimated incidence of neurological or psychiatric diagnoses at 6 months following the acute phase of COVID-19 was 33.6% (first diagnosis, 12.8%). The commonest neurological diseases were, in decreasing order, stroke (2.7%), dementia (0.7%) and parkinsonism (0.1%). Our higher rates can be explained by the source of our cases (80% hospitalized) and by patients seen in neurological consultation. However, in line with us, the incidence of stroke and dementia were significantly higher in patients with more severe disease.

In a prospective study of 4182 incident cases of COVID-19 who self-reported their symptoms using a mobile application, 558 participants (13.3%) experienced symptoms lasting ≥28 days, 189 (4.5%) for ≥8 weeks and 95 (2.3%) for ≥12 weeks [8]. The commonest were fatigue, headache, dyspnoea and anosmia and they were more frequent with increasing age, body mass index and female sex. The presence of more than five symptoms during the first week of illness was associated with prolonged complaints during follow-up. This is in line with our study and suggests that the higher severity of the disease is the consequence of a multisystem involvement by the virus, as shown by others [18]

Post-hospital persistent symptoms (including memory loss [34%], concentration and sleep disorders [28% and 30%]) were reported during phone calls by 279 patients who had COVID-19 [6]. Although some study limitations (single centre, inclusion of patients without neurological complaints, high attrition rate) can explain the differences with our findings, the frequent report of cognitive impairment and sleep disorders indicated similarities.

In a study including 1733 of 2469 discharged patients with a median follow-up of 6 months, fatigue or muscle weakness (63%) and sleep difficulties (26%) were the commonest persistent symptoms [13]. Twenty-four per cent of cases reported a median 6-min walking distance less than the lower limit of the normal range. Compared to our study, these higher rates might be explained by high attrition (736 patients, perhaps the least severe cases, did not attend follow-up appointments).

In a population-based cohort study including non-hospitalized subjects, 938 subjects were invited to participate in a postal survey and 48% responded. Although the interviewees reported reduction of symptoms 1.5–6 months after the acute phase, 16% manifested persisting dyspnoea, 12% dysosmia and 10% dysgeusia [7]. The differences between this study and ours are reflected, on one side, by our longer follow-up and, on the other side, by the possible under-ascertainment of non-neurological manifestations in our study or under-ascertainment of neurological complaints in that study.

Sequelae at 6 months were reported in a prospective cohort study by 32.8% of 177 adults recovering from COVID-19 [11]. The commonest persistent symptoms included fatigue and loss of smell or taste. The lower prevalence of sequelae in our study might reflect the focus on neurological manifestations.

Our study has strengths and limitations. The major strength is the large sample, which includes data from different countries and settings. Another strength is the accurate search and diagnostic assessment of neurological manifestations. All patients were examined by a neurologist and, to optimize inter-rater agreement, diagnoses were guided by standard definitions. Although each neurological manifestation was investigated based on the findings available at the time of the interview, the e-CRF included precise questions and

TABLE 4 Predictors of outcome at 6 months ($N = 262$)

	Worse outcome vs. stable/improved outcome[a]					
	Univariable model			Multivariable model		
	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value
Sex						
Male	1 (ref.)		0.9979			
Female	1.02	0.62–1.67				
Intersex/unknown	ne	ne				
Smoking						
Yes	0.80	0.35–1.84	0.5947			
No	1 (ref.)	–				
Unknown	1.63	0.52–5.14				
Source of COVID-19 contact						
Occupation	0.23	0.10–0.50	0.0008			
Family member	0.36	0.17–0.78				
Social	0.36	0.13–1.02				
Travel	0.79	0.23–2.71				
Other/unknown	1 (ref.)	–				
Age at admission (1-year increase)	1.03	1.02–1.05	0.0001			
BMI (1-unit increase)	0.99	0.99–1.00	0.6458			
Non-neurological comorbidities						
Hypertension	1.96	1.19–3.23	0.0085			
Diabetes type 1/type 2	1.26	0.66–2.40	0.4771			
Cardiovascular disease	2.25	1.22–4.15	0.0095			
Chronic kidney disease	7.88	1.75–35.45	0.0071			
Chronic liver disease	0.76	0.17–3–45	0.7181			
Chronic pulmonary disease	0.95	0.45–2.01	0.8851			
Anaemia	2.08	0.51–8.52	0.3070			
Cancer	0.47	0.19–1.15	0.0996			
Immunosuppressed state	1.02	0.29–3.60	0.9796			
Neurological comorbidities						
Dementia	0.32	0.08–1.22	0.0955			
Parkinson's disease	0.67	0.11–4–09	0.6664			
Stroke: ICH, ischaemic stroke, TIA	2.08	1.01–4.31	0.0475	0.27	0.08–0.91	0.0302
Multiple sclerosis	0.25	0.03–2.25	0.2153			
Motor neuron disease	ne	ne	–			
Neuromuscular disorder	1.54	0.25–9.36	0.6410			
Neuropathy	0.33	0.03–3.25	0.3443			
COVID-19 systemic complications						
Dyspnoea	1.13	0.69–1.86	0.6225			
Pneumonia	1.34	0.81–2.20	0.2501			
Cardiovascular	3.84	1.37–10.76	0.0105			
Renal insufficiency/dialysis	4.19	1.35–13.01	0.0131			
Coagulation disorder/disseminated intravascular coagulation	2.83	0.73–10.91	0.1317			
Refractory shock	ne	ne	0.9907			
Extra-corporeal membrane oxygenation (ECMO)	1.02	0.14–7.33	0.9872			
Mechanical ventilation	2.77	1.30–5.88	0.0081			

TABLE 4 (Continued)

	Worse outcome vs. stable/improved outcome[a]					
	Univariable model			Multivariable model		
	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value
Neurological findings						
Headache	0.71	0.43–1.18	0.1925			
Hyposmia/hypogeusia	0.52	0.30–0.88	0.0152			
Dysautonomia	1.22	0.53–2.84	0.6393			
Vertigo	1.27	0.66–2.44	0.4711			
Myalgia	0.95	0.55–1.63	0.8451			
Sleep disorders	1.14	0.59–2.18	0.1209			
Cognitive impairment (including dysexecutive syndrome)	2.09	1.17–3.74	0.0125			
Hyperactive delirium	1.65	0.83–3.28	0.1542			
Hypoactive delirium/acute encephalopathy	3.07	1.24–7.60	0.0151			
Stupor/coma	5.43	1.17–25.32	0.0311			
Syncope	0.67	0.11–4.09	0.6664			
Seizures/status epilepticus	0.74	0.30–1.83	0.5196			
Meningitis/encephalitis	1.37	0.30–6.23	0.6869			
Stroke	6.35	3.02–13.36	<0.0001	8.51	2.77–26.13	0.0007
Tremor	1.82	0.52–6.39	0.3475			
Chorea	ne	ne	0.8997			
Dystonia	ne	ne	0.9906			
Myoclonus	1.02	0.06–16.43	0.9910			
Dyskinesia	ne	ne	0.9907			
Parkinsonism	ne	ne	0.9790			
Ataxia	6.03	1.31–27.78	0.0212	6.94	1.18–40.68	0.0180
Spinal cord disorder	1.72	0.40–7.36	0.4635			
Peripheral neuropathy	1.84	0.81–4.20	0.1462			
ICU admission	6.39	3.19–12.79	<0.0001	3.59	1.49–8.66	0.0017
Pre-morbid mRS						
0	1 (ref.)	–	0.8153			
1	1.01	0.53–1.92				
2	0.65	0.23–1–79				
3	0.82	0.30–2.24				
4	0.37	0.07–1.97				
5	0.69	0.15–3.20				
Discharge mRS						
0	1 (ref.)	–	<0.0001	1 (ref)	–	<0.0001
1	11.60	3.96–33.97		6.71	2.03–22.15	
2	19.33	6.34–58.98		12.96	3.60–46.66	
3	39.44	12.44–125.0		21.46	5.92–77.73	
4	28.35	8.55–93.98		19.38	4.87–77.14	
5	50.26	10.64–237.4		23.64	4.32–129.3	

Abbreviations: Adj. OR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; ICH, intracerebral haemorrhage; ICU, intensive care unit; mRS, modified Rankin Scale; OR, odds ratio; TIA, transient ischaemic attack.

[a]Worse outcome, mRS score at discharge higher than pre-morbid mRS score; stable/improved outcome, mRS score at discharge equal to or lower than pre-morbid mRS score.

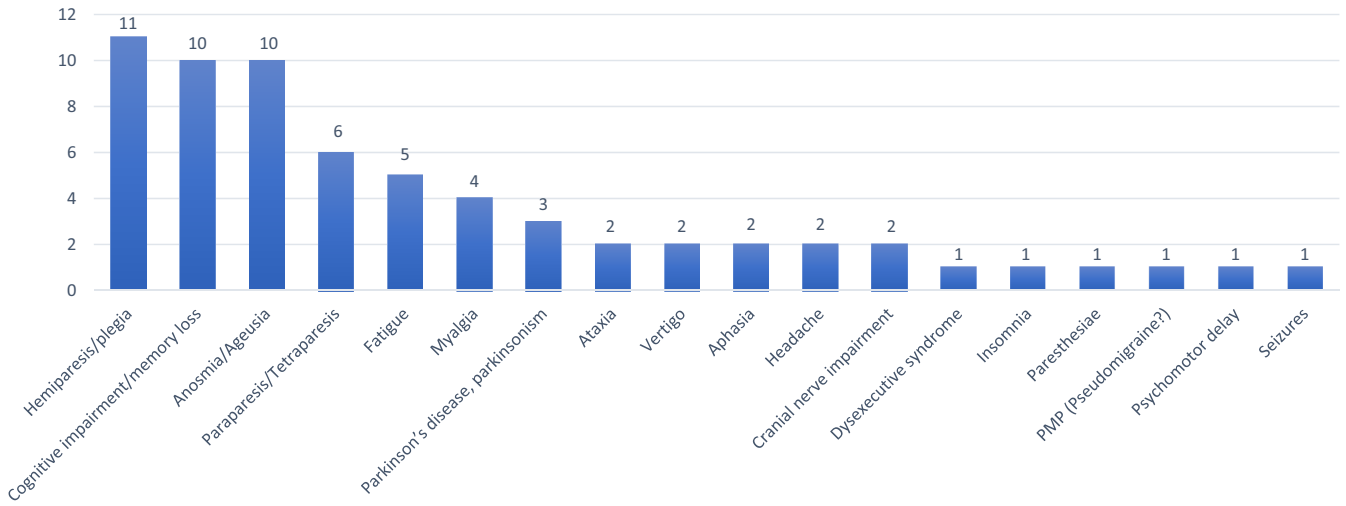


FIGURE 2 List of neurological symptoms, signs and diseases persisting at 6 months [Colour figure can be viewed at wileyonlinelibrary.com]

clinical assessment of the patient was to be completed according to a detailed checklist (Appendix S1). The major limitation of our study is the lack of a population base. It was attempted to define the reference population to estimate incidence and prevalence of the various neurological manifestations. However, the differing catchment areas served by the participating sites did not consent precise calculations. Another important limitation is the focus on neurological manifestations. Eligible patients were those seen in neurological consultation. Although efforts were made to collect information on all comorbidities with impact on patients' health and the major complications of COVID-19, our investigation of the full spectrum of the disease has been incomplete. Then, diagnostic accuracy was not always high as a more detailed assessment of registered patients (results of neuropsychological and imaging tests, treatments) was not required to avoid a time consuming data collection, given the emergency context in which neurological consultation was performed. It was also chosen not to collect data on treatments as they were rarely supported by evidence-based recommendations. Finally, the use of mRS at discharge to predict functional disability at home or in residential or rehabilitation settings could be debated.

In conclusion, in a multinational cohort of patients with neuro-COVID undergoing structured neurological consultation, a severe disease was found in a high proportion of patients. The presence of severe infection with complications predicted worse outcome at discharge, persistence of functional disability, and a number of sequelae at 6 months follow-up, some of those occurring after the remission or stabilization of the acute phase of the disease. Patients with neurological manifestations during the acute phase of COVID-19 infection should be carefully monitored to prevent the occurrence of long-term complications and premature mortality.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data can only be shared with permission of individual countries.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX 1

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