

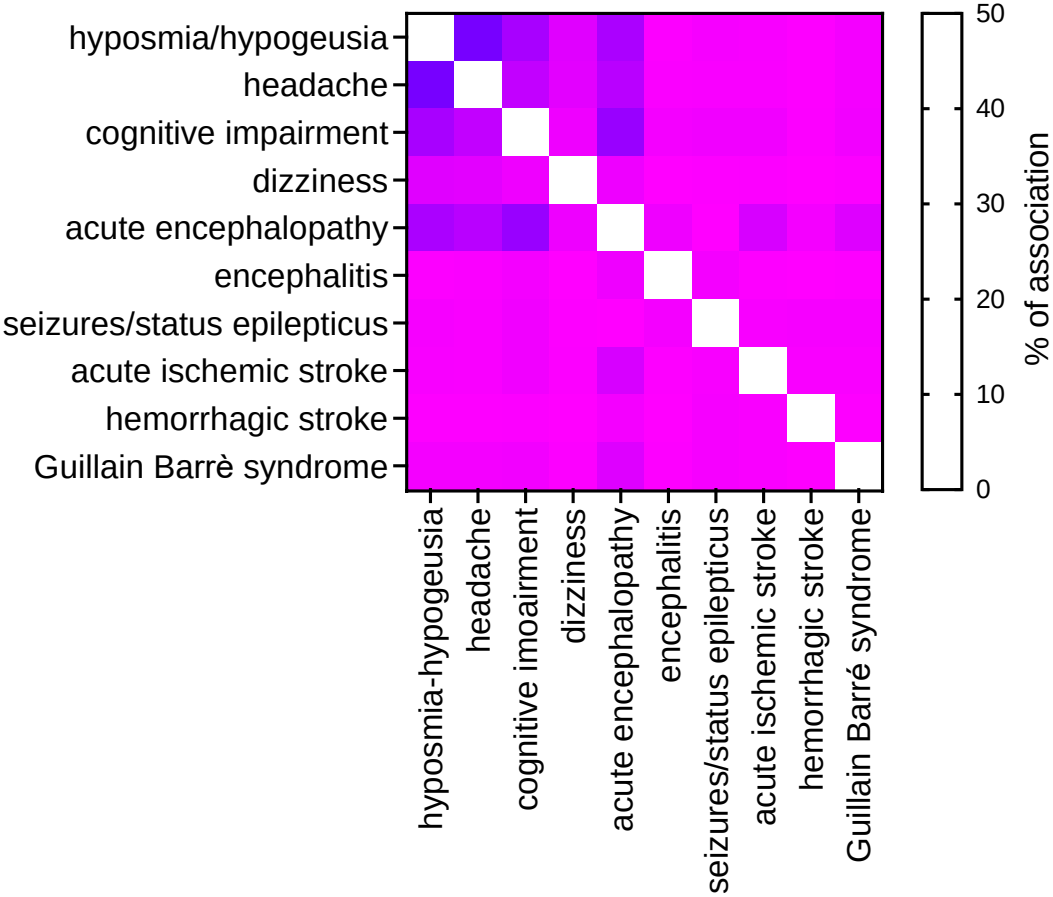
Incidence and long-term functional outcome of neurological disorders in hospitalized COVID-19 patients infected with pre-Omicron variants

From the Neuro-COVID Italy Investigators

Supplemental material

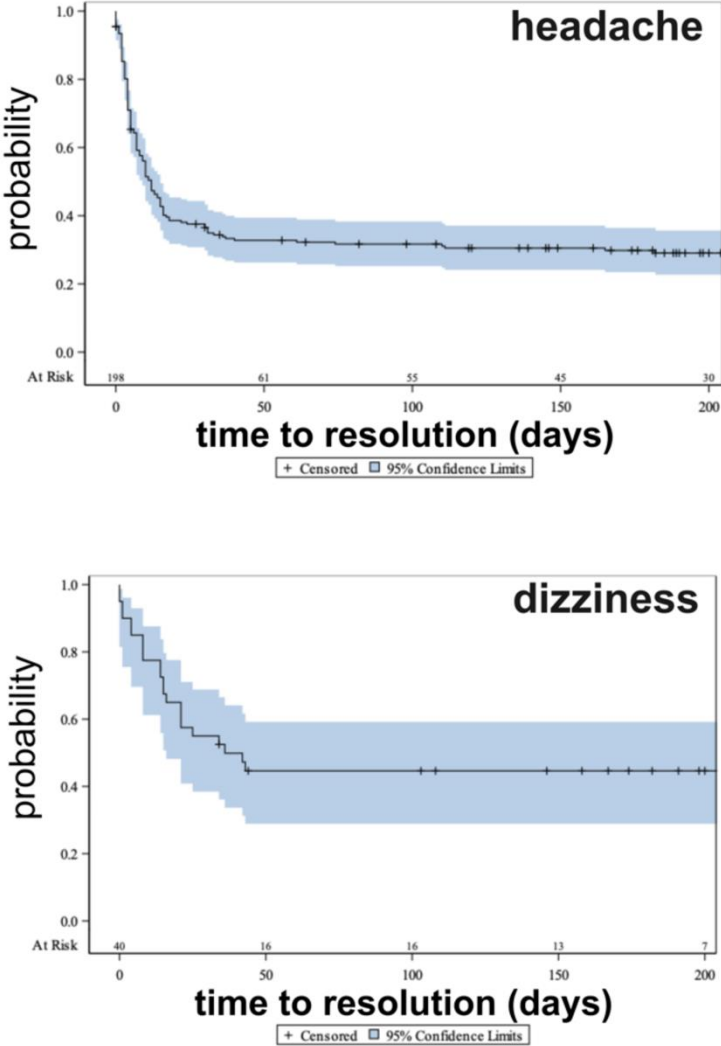
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eFigure 1
Clusters of neuro-COVID disorders.

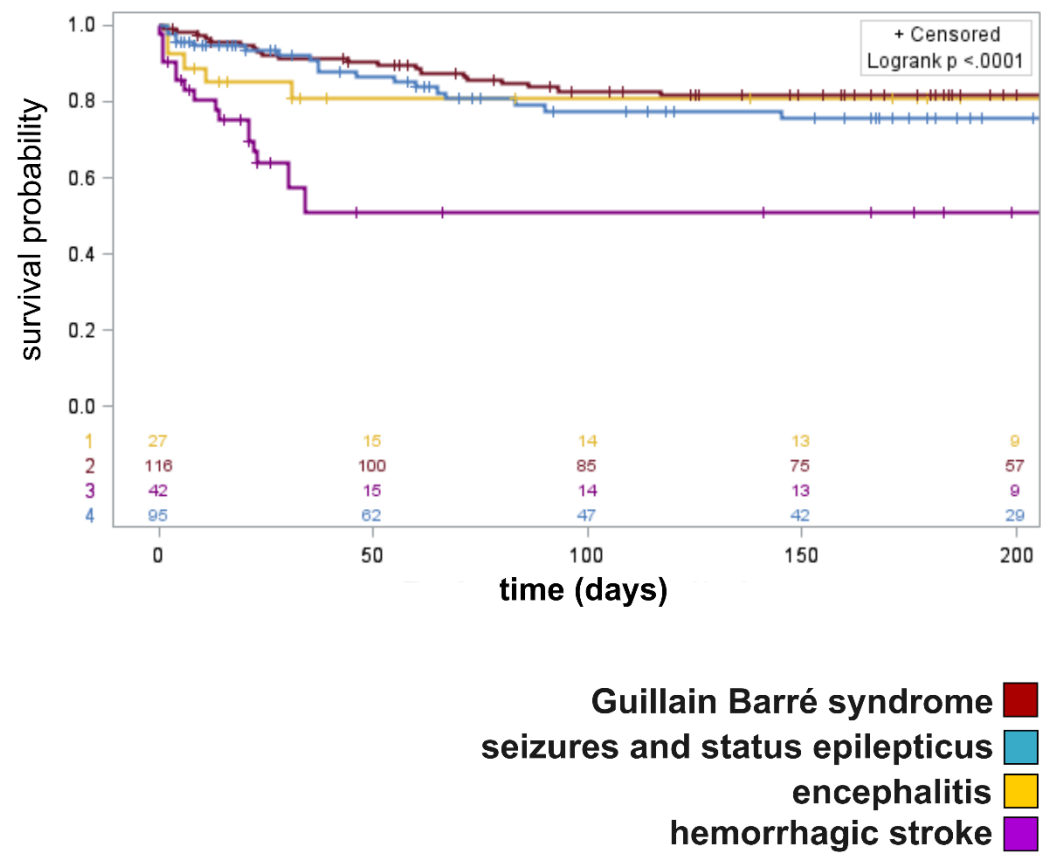


Cluster heat map of selected neuro-COVID disorders. The color scale indicates the percent of association between two disorders.

eFigure 2
Recovery curves for headache and dizziness

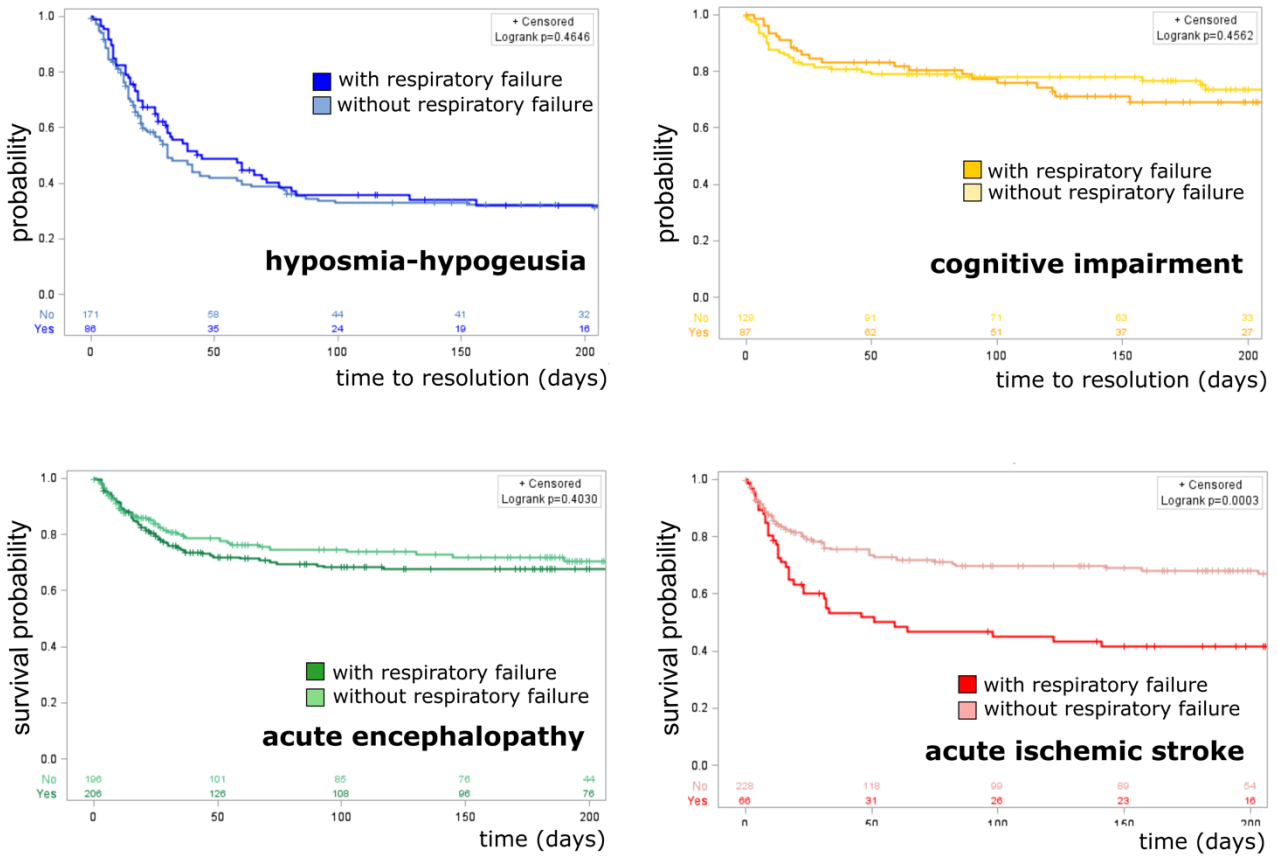


eFigure 3
Survival curves for Guillain Barrè syndrome, seizures and status epilepticus, encephalitis and hemorrhagic stroke



eFigure 4

Recovery and survival curves of the most common Neuro-COVID disorders, with and without severe respiratory failure during the acute phase



Respiratory failure = severe respiratory failure requiring continuous positive airway pressure (CPAP) or mechanical ventilation.

eTable 1. Complete list of neuro-COVID disorders

Disorders	No.	%
Acute encephalopathy	470	16.3
Hyposmia-hypogeusia	377	13.1
Acute ischemic stroke	343	11.9
Cognitive impairment	256	8.9
Peripheral neuropathy* (any, including focal neuropathy and critical illness neuropathy; excluding GBS)	248	8.6
Headache	220	7.6
Myalgia*	201	7.0
Seizures and status epilepticus	135	4.7
Guillain Barré syndrome (GBS)	135	4.7
Hemorrhagic stroke	56	1.9
Fatigue*	56	1.9
Dizziness	49	1.7
Transient ischemic attack (TIA)**	42	1.5
Encephalitis	36	1.2
Postural instability and gait disturbance	34	1.2
Syncope	29	1.0
Insomnia	27	0.9
Catatonia, mutism, bradykinesia	26	0.9
Upper cranial nerve palsy (diplopia, facial nerve, facial sensation)	23	0.8
Neuralgia	22	0.8
Tremor	21	0.7
Parkinsonism	12	0.4
Subjective sensory symptoms	12	0.4
Unvoluntary muscle contractions, muscle cramps, subcortical myoclonic jerks	11	0.4
Lower cranial nerve palsy (dysphonia, dysphagia, dysarthria)	7	0.2
Myelitis	6	0.2
Cerebral venous sinus thrombosis	6	0.2
Auditory symptoms, including tinnitus	5	0.2
Dysautonomia	5	0.1
Posterior reversible encephalopathy syndrome (PRES)	3	0.1
Migraine with aura	2	0.1
Nystagmus	2	0.1
Excessive daytime sleepiness	2	0.1
Hyperosmia	1	< 0.1
Corea	1	< 0.1
Total	2881	100

Analysis was patient-centered and focused on 10 major neuro-COVID disorders (on grey background). * not considered as major neuro-COVID disorders, since these disorders commonly occur as consequence of prolonged hospitalization or ICU admissions. ** not considered as a major neuro-COVID disorder, since diagnostic accuracy for TIA is low

eTable 2. Major diagnostic tests of selected neuro-COVID disorders (clinical neurological syndromes)

Disorder	Brain imaging (CT or MRI)		EEG			CSF		EMG & NCS	
	new focal lesion n/n (%)	new multifocal lesions n/n (%)	generalized or focal slowing n/n (%)	epileptiform discharges n/n (%)	status epilepticus n/n (%)	protein content > 60 mg/dL n/n (%)	cell content > 5 count/uL n/n (%)	axonal neuropathy n/n (%)	demyelinating neuropathy n/n (%)
Subsyndromal delirium*	5/71 (7.0)	9/71 (12.7)	15/38 (39.5)	5/38 (13.2)	0/36 (0)	10/24 (41.7)	0/23 (0)	-	-
Delirium*	22/121(18.2)	13/121 (10.7)	32/62 (51.6)	11/62 (17.7)	1/61 (1.6)	8/26 (30.8)	3/24 (12.5)	-	-
Coma*	10/49 (20.4)	12/49 (24.5)	19/32 (59.4)	2/32 (6.2)	1/32 (3.1)	4/11 (36.4)	1/11 (9.1)	-	-
Acute ischemic stroke	160/259 (61.8)	71/259 (27.4)	26/44 (59.1)	6/44 (13.6)	1/44 (2.3)	-	-	-	-
Guillain-Barré syndrome	-	-	-	-	-	15/26 (57.7)	7/26 (26.9)	24/92 (26.1)	47/92 (51.1)
Seizures and status epilepticus	22/110 (20.0)	15/110 (13.6)	31/103 (30.1)	35/103 (33.9)	20/103 (19.4)	8/23 (34.8)	3/25 (12.0)	-	-
Hemorrhagic stroke	30/41 (73.2)	9/41 (21.9)	6/16 (37.5)	3/16 (18.7)	2/16 (12.5)	-	-	-	-
Encephalitis	4/31 (12.9)	9/31 (29.0)	15/29 (51.7)	4/29 (13.8)	7/29 (24.1)	19/30 (63.3)	12/30 (40.1)	-	-

* pre-defined subtypes of acute encephalopathy. CT = computerized tomography. MRI = magnetic resonance imaging. EEG = electroencephalography. CSF = cerebrospinal fluid. EMG & NCS = electromyography and nerve conduction studies. n/n = number of patients with the indicated diagnostic finding divided by the number of patients with the indicated diagnostic test reported in the study dataset.

eTable 3. Outcome of neuro-COVID disorders in the working age population

Disorder	Long-term neurologic outcome				
	total n (%)	full recovery n (%)	mild symptoms n (%)	disabling symptoms n (%)	unknown n (%)
All neuro-COVID cases aged 18 to 64	781 (100)	244 (31.4)	321 (41.1)	101 (12.9)	115 (14.7)
<i>Selected disorders, participants aged 18 to 64:</i>					
Acute encephalopathy	141 (100)	60 (42.5)	38 (27.0)	22 (15.6)	21 (14.9)
Acute ischemic stroke	90 (100)	23 (25.6)	40 (44.4)	24 (26.7)	3 (3.3)
Guillain-Barré syndrome	71 (100)	11 (15.5)	39 (54.9)	12 (16.9)	9 (12.7)
Seizures and status epilepticus	47 (100)	37 (78.7)	3 (6.4)	2 (4.3)	5 (10.6)
Hemorrhagic stroke	21 (100)	9 (42.9)	4 (19.0)	7 (33.3)	1 (4.8)
Encephalitis	19 (100)	12 (63.2)	1 (5.3)	2 (10.5)	4 (21.0)
Hyposmia/hypogeusia	228 (100)	122 (53.5)	57 (25)	13 (5.7)	36 (15.8)
Cognitive impairment	109 (100)	24 (22.0)	64 (58.7)	6 (5.5)	15 (13.8)
Headache	171 (100)	107 (62.6)	36 (21.0)	2 (1.2)	26 (15.2)
Dizziness	28 (100)	9 (32.1)	14 (50)	0 (0)	5 (17.9)

eTable 4. Outcome predictors for selected neuro-COVID disorders

	unit	good functional outcome	poor functional outcome	crude OR (95% CI)	p value	adjusted OR (95% CI)	adjusted p value
Acute encephalopathy		No. = 299	No. = 115				
Age ^a	years	71 (61-79)	78 (67-84)	1.03 (1.01-1.04)	p < 0.001	1.03 (1.01-1.05)	p = 0.003
Sex	male (%) / female	173 (57.8)	74 (64.3)	1.31 (0.84-2.05)	p = 0.228	1.30 (0.81-2.09)	p = 0.273
Pre-existing neurological comorbidity	n (%)	87 (29.1)	47 (40.8)	1.68 (1.07-2.63)	p = 0.022	1.47 (0.87-2.49)	p = 0.146
Severe respiratory failure ^b	n (%)	139 (46.5)	73 (63.5)	2.00 (1.28-3.11)	p = 0.002	2.61 (1.57-4.33)	p < 0.001
Anticoagulants	n (%)	158 (52.3)	64 (55.6)	1.12 (0.72-1.72)	p = 0.607	0.68 (0.40-1.13)	p = 0.143
Steroids	n (%)	152 (50.1)	71 (61.2)	1.56 (1.00-2.42)	p = 0.047	1.31 (0.77-2.22)	p = 0.315
Remdesivir	n (%)	72 (24.1)	16 (13.9)	0.51 (0.28-0.92)	p = 0.025	0.60 (0.31-1.14)	p = 0.121
Acute ischemic stroke		No. = 178	No. = 143				
Age ^a	years	71 (60-79)	79 (69-86)	1.05 (1.03-1.06)	p < 0.001	1.05 (1.03-1.07)	p < 0.001
Sex	male (%) / female	106 (58.8)	90 (62.9)	1.13 (0.72-1.79)	p = 0.577	1.25 (0.75-2.08)	p = 0.387
Pre-existing neurological comorbidity	n (%)	40 (22.4)	42 (29.4)	1.43 (0.86-2.37)	p = 0.159	0.97 (0.55-1.69)	p = 0.922
Severe respiratory failure ^b	n (%)	25 (14.0)	46 (32.2)	2.92 (1.67-5.02)	p < 0.001	3.01 (1.63-5.51)	p < 0.001
Anticoagulants	n (%)	67 (37.6)	70 (48.9)	1.58 (1.01-2.48)	p = 0.042	1.29 (0.74-2.25)	p = 0.359
Steroids	n (%)	47 (26.4)	44 (30.8)	1.24 (0.76-2.01)	p = 0.388	0.78 (0.41-1.47)	p = 0.450
Remdesivir	n (%)	33 (18.5)	23 (16.1)	0.84 (0.46-1.51)	p = 0.564	0.78 (0.41-1.48)	p = 0.454
Hyposmia-hypogeusia		No. = 278	No. = 21				
Age ^a	years	58 (50-69)	59 (49-73)	1.00 (0.97-1.04)	p = 0.572	1.07 (0.97-1.04)	p = 0.707
Sex	male (%) / female	155 (55.7)	8 (38.1)	0.488 (0.19-1.2)	p = 0.123	0.49 (0.18-1.33)	p = 0.165
Pre-existing neurological comorbidity	n (%)	18 (6.5)	4 (19.0)	3.39 (1.03-11.16)	p = 0.043	2.57 (0.72-9.17)	p = 0.144
Severe respiratory failure ^b	n (%)	93 (33.4)	6 (28.6)	0.79 (0.29-2.11)	p = 0.647	1.08 (0.36-3.24)	p = 0.889
Anticoagulants	n (%)	127 (45.7)	12 (57.1)	1.58 (0.64-3.88)	p = 0.313	1.09 (0.34-3.46)	p = 0.878
Steroids	n (%)	112 (40.3)	12 (57.1)	1.97 (0.80-4.84)	p = 0.136	1.19 (0.36-3.93)	p = 0.775
Remdesivir	n (%)	94 (33.8)	2 (9.5)	0.20 (0.04-0.90)	p = 0.036	0.26 (0.05-1.23)	p = 0.090

Cognitive impairment		No. = 187	No. = 27				
Age ^a	years	66 (54-73)	75 (67-81)	1.07 (1.03-1.11)	p < 0.001	1.06 (1.01-1.10)	p = 0.006
Sex	male (%) / female	113 (60.4)	17 (62.9)	1.11 (0.48-2.56)	p = 0.801	0.95 (0.38-2.34)	p = 0.918
Pre-existing neurological comorbidity	n (%)	25 (13.4)	11 (40.7)	4.45 (1.85-10.69)	p < 0.001	2.48 (0.92-6.67)	p = 0.070
Severe respiratory failure ^b	n (%)	75 (40.1)	13 (48.1)	1.38 (0.61-3.11)	p = 0.428	1.45 (0.60-3.49)	p = 0.404
Anticoagulants	n (%)	111 (59.3)	14 (51.8)	0.73 (0.32-1.65)	p = 0.460	0.61 (0.23-1.56)	p = 0.305
Steroids	n (%)	105 (56.1)	17 (62.9)	1.32 (0.57-3.05)	p = 0.504	1.03 (0.37-2.87)	p = 0.946
Remdesivir	n (%)	44 (23.5)	3 (11.1)	0.40 (0.11-1.41)	p = 0.156	0.50 (0.12-1.97)	p = 0.323

OR = odds ratio. CI = confidence intervals. OR > 1 indicates higher probability of poor functional outcome. ^a per year of age; ^b requiring CPAP or mechanical ventilation.