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Neuro-COVID frequency and short-term outcome in the Northern Portuguese population

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Abstract

Background and purpose: COVID-19-related acute neurological phenotypes are being increasingly recognised, with neurological complications reported in more than 30% of hospitalised patients. However, multicentric studies providing a population-based perspective are lacking.

Methods: We conducted a retrospective multicentric study at five hospitals in Northern Portugal, representing 45.1% of all hospitalised patients in this region, between 1 March and 30 June 2020.

Results: Among 1261 hospitalised COVID-19 patients, 457 (36.2%) presented neurological manifestations, corresponding to a rate of 357 per 1000 in the North Region. Patients with neurologic manifestations were younger (68.0 vs. 71.2 years, p = 0.002), and the most frequent neurological symptoms were headache (13.4%), delirium (10.1%), and impairment of consciousness (9.7%). Acute well-defined central nervous system (CNS) involvement was found in 19.1% of patients, corresponding to a rate of 217 per 1000 hospitalised patients in the whole region. Assuming that all patients with severe neurological events were hospitalised, we extrapolated our results to all COVID-19 patients in the region, estimating that 116 will have a severe neurological event, corresponding to a rate of nine per 1000 (95% CI = 7–11). Overall case fatality in patients presenting neurological manifestations was 19.8%, increasing to 32.6% among those with acute well-defined CNS involvement.

Conclusions: We characterised the population of hospitalised COVID-19 patients in Northern Portugal and found that neurological symptoms are common and associated with a high degree of disability at discharge. CNS involvement with criteria for in-hospital admission was observed in a significant proportion of patients. This knowledge provides the tools for adequate health planning and for improving COVID-19 multidisciplinary patient care.

Vanessa Oliveira, Mafalda Seabra, Rita Rodrigues, Vanessa Carvalho, and Michel Mendes contributed equally to the article.

Luís F. Maia and Manuel Correia share last authorship.

INTRODUCTION

A novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 and is responsible for the coronavirus disease 2019 (COVID-19) pandemic, with more than 100 million diagnosed patients and more than 2.3 million deaths [1].

SARS-CoV-2 has been shown to attach to cell membranes by binding to angiotensin-converting enzyme 2 (ACE2) [2]. Human tissue studies revealed that this receptor can be found in epithelia of the lung and small intestine and in endothelial cells from arteries and veins across different organs, including the brain [3]. Furthermore, studies using animal models demonstrated that ACE2 is expressed at the neuronal level, in the cytoplasm of cell bodies [4,5]. Recent neuropathology studies of tissue samples have detected SARS-CoV-2 viral load in some of the evaluated brain sections, but without clear evidence of direct virus damage [6,7]. These studies also showed ischaemic lesions in the brain, as well as inflammation characterised by T lymphocyte infiltration (particularly in the brain stem and cerebellum) [7].

Consistently, over the course of the pandemic, neurological involvement in COVID-19 patients (NeuroCovid) has been increasingly recognised. In the acute phase of the disease, multiple neurological presentations have been described, such as anosmia, ageusia, encephalopathy, stroke, necrohaemorrhagic encephalitis, Guillain–Barré syndrome, polyneuritis cranialis, and posterior reversible encephalopathy syndrome [8–16]. Retrospective studies of hospitalised patients with COVID-19 have reported a rate of neurological complications ranging from 36.4% to 57.4% [13,14,17]. These manifestations can be considered as directly related to the effect of the virus, as para- or postinfectious immune-mediated, or as complications of the systemic manifestations of COVID-19 [18].

Despite the growing number of reports of acute neurological phenotypes and retrospective studies of hospitalised patients, studies providing a populational perspective are still lacking. Therefore, we performed a multicentric retrospective study, involving the hospitals of Northern Portugal, to characterise the neurological manifestations of a hospitalised population of patients with COVID-19.

METHODS

The 23 public hospitals in the North Region of Portugal are organised into 14 National Health System trusts, and one hospital per trust received COVID-19 patients (Figure 1). All of these hospitals made available the distribution by age and sex of hospitalised patients between 1 March and 30 June 2020, diagnosed by real-time reverse transcriptase polymerase chain reaction detection of

13144 cases in the Northern Region

2795 (21.3%) hospitalized patients

1261 (45.1%) reviewed patients

457 (36.2%) with neurological manifestations

♀ Centers included in the study
● Public COVID-19 hospitals
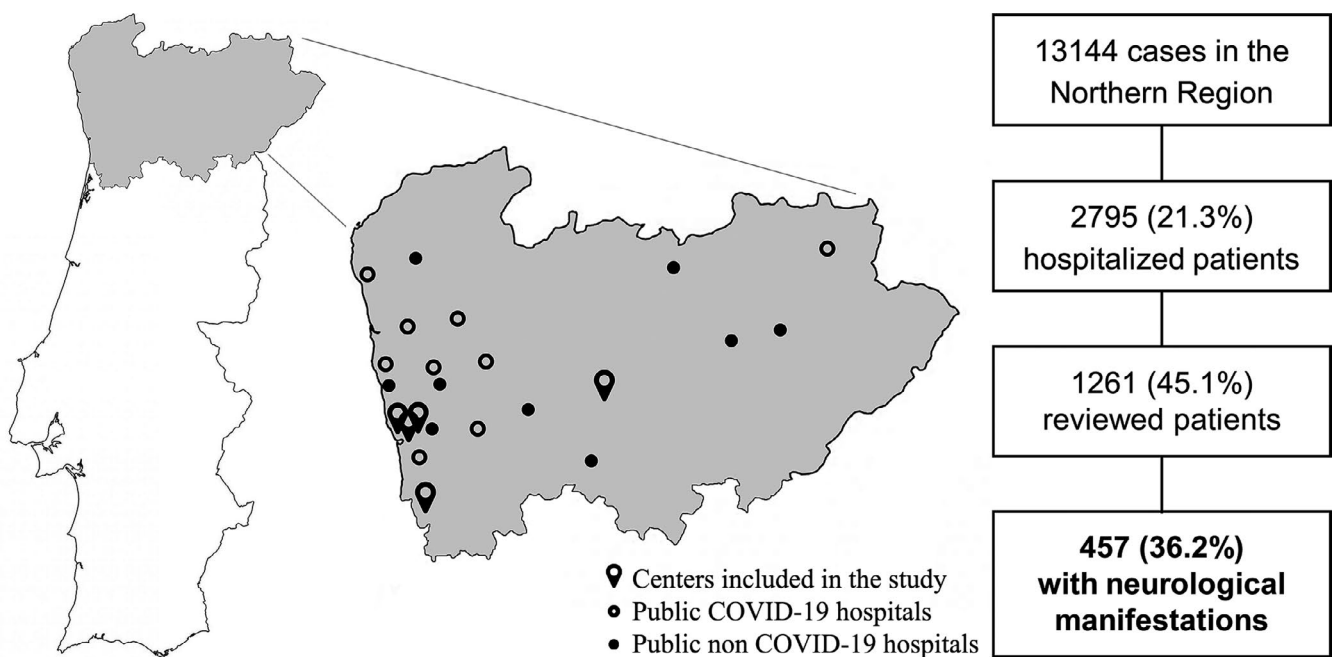● Public non COVID-19 hospitals

FIGURE 1 Left side: Map of Portugal. Centre: Map of Northern Portugal displaying the hospitals in the region. Right side: Fluxogram displaying the number of patients with COVID-19 diagnosis in Northern Portugal, the number of hospitalised patients, and the rate of neurological complications

SARS-CoV-2 RNA in nasopharyngeal or oropharyngeal swab. From this target population, five hospitals collaborated in this retrospective multicentric study, two tertiary hospitals in the city of Porto (Centro Hospitalar Universitário do Porto and Centro Hospitalar Universitário de São João), two hospitals in Porto's surrounding cities of Matosinhos (Unidade Local de Saúde de Matosinhos) and Santa Maria da Feira (Centro Hospitalar Entre-Douro e Vouga), and another in the inner-Portugal region (Centro Hospitalar Trás-os-Montes e Alto-Douro). The study was approved by the ethical committee of all institutions involved. A waiver of written informed consent was authorised.

Patients

At each hospital, electronic medical records were reviewed systematically by neurologists or experienced neurology residents to identify those presenting neurological manifestations during inpatient stay, utilizing a standardised form. Recorded neurological manifestations were acute cerebrovascular disorders, consciousness impairment (depressed level of consciousness), delirium (disturbance in the level of awareness, with attentional deficits, confusion, or disorientation), dizziness (including vertigo), dysgeusia, headache, hyposmia, movement disorders, myalgias, myelopathy (defined by clinical and imaging findings), myopathy (defined by clinical findings), seizures, peripheral nerve symptoms, sleep disorders, and visual symptoms. In the presence of neurological manifestations, further data were collected, including accompanying symptoms, previous comorbidities (diabetes, hypertension, pulmonary chronic obstructive disease, chronic kidney disease, cardiac disease, cerebrovascular disease, active cancer, and immunosuppression), laboratory parameters, treatments, and outcome. Functional outcome was determined using the modified Rankin Scale (mRS) at hospital discharge. Acute well-defined central nervous system (CNS) involvement was defined as the presence of acute cerebrovascular disorder, seizure, delirium, consciousness impairment, and myelopathy. Severe neurological

events directly or indirectly associated with COVID-19 included acute cerebrovascular disease, seizure, posterior reversible encephalopathy syndrome, Guillain–Barré syndrome, myelopathy, cranial multineuritis, and multiple sclerosis or myasthenia gravis exacerbations. Patients with severe neurological involvement met criteria for hospitalisation due to the neurological phenotype.

Data analysis

The goodness of fit chi-squared was used to test representativeness of sample according to population characteristics. Rates of neurological manifestations are described, and rate ratios by sex, age, and type of hospital (tertiary vs. others) were calculated using Poisson regression models. Patients with and without acute well-defined CNS involvement were compared using the qui-squared test. Statistical significance was set at $p < 0.05$.

We calculated the expected number of neurological manifestations in COVID-19 hospitalised patients in the North Region during the study period and respective rates, using known characteristics of the target population (sex, age, and type of hospital). Moreover, based on the age/sex distribution of patients with SARS-CoV-2 infections in Northern Portugal supplied by the Portuguese Directorate-General for Health, we projected the total number of patients with acute well-defined CNS involvement and severe neurological events in this region.

RESULTS

Between 1 March and 30 June 2020, a total of 42,523 cases of COVID-19 were diagnosed in Portugal. In Northern Portugal, 13,144 cases were diagnosed, including 2795 (21.3%) patients who required hospitalisation in the target population (Figure 1). We reviewed 1261 (45.1%) inpatient records at the five participating centres. Mean age of patients was 70.0 years (±17.2), with 66.9% older than 65 years,
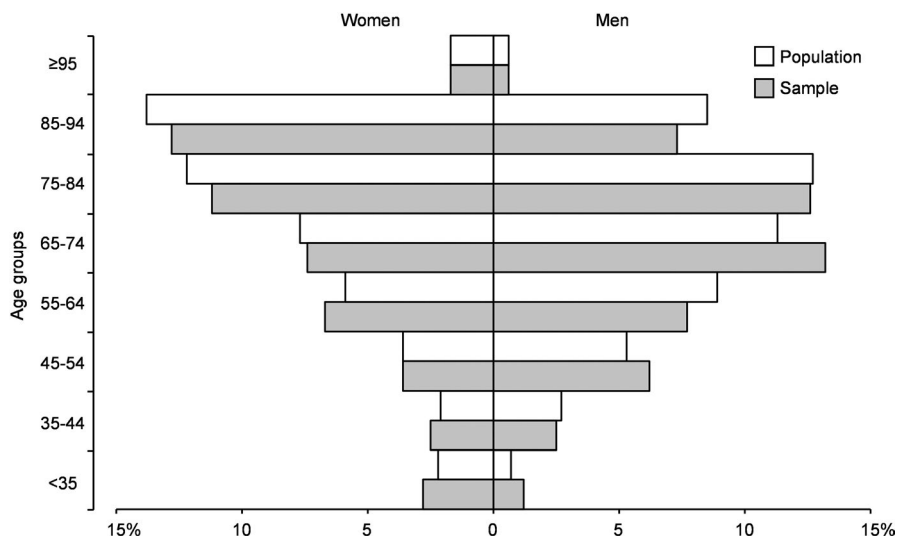

FIGURE 2 Distribution by sex and age in years of the target population and the sample of five hospitals

and 51.3% were males. Overall, there was an overrepresentation of patients at tertiary hospitals, 73.9% (662 of 892) compared to 31.5% at the other hospitals (599 of 1899; see Figure S1), but the distribution by sex and age of the sample was not significantly different from that of the target population ($p = 0.2$; Figure 2 and Figure S2).

In 457 (36.2%) patients, at least one neurological manifestation was registered, with no evidence of gender differences. However, patients with neurologic manifestations were younger than patients without (68.0 ± 18.2 vs. 71.2 ± 16.6 years, $p = 0.002$).

There were also no differences in registered neurological manifestations according to type of hospital (Table S1). The most frequently reported neurological symptoms were headache (13.4%), delirium (10.1%), and consciousness impairment (9.7%; Figure 3). Headache was more frequently reported in women (16.4% vs. 10.5%) and delirium in men (12.4% vs. 7.7%), with no other differences regarding gender (Table 1). The frequency of delirium, consciousness impairment, and acute cerebrovascular disease increased with age, whereas other symptoms (headache, myalgia, myopathy, hyposmia, dysgeusia, and sleep disorders) were more frequent in the younger population (Table 1). Male patients with neurological manifestations had more comorbidities (pulmonary chronic obstructive disease and cardiac disease), and more severe respiratory and systemic disease, with increased need for oxygen therapy, mechanical ventilation, intensive care admission, and higher lethality (Table S2).

Acute well-defined CNS involvement was reported in 19.1% of patients, more frequently in men (21.6% vs. 16.4%) and in older patients (24.0% vs. 9.3%). Acute cerebrovascular disorder was the final diagnosis in 23 (1.8%) patients: 15 ischaemic strokes, four haemorrhagic strokes, three transient ischaemic attacks, and one cerebral vein thrombosis. Seizures occurred in 19 (1.5%) patients: 16 acute symptomatic seizures (three cases evolving into nonconvulsive status epilepticus) and three patients with a previous epilepsy with a seizure triggered by the infection. One patient presented with a myelopathy. No encephalitis, meningitis, or vasculitis attributed to SARS-CoV-2 infection was reported (according to the attending clinician criteria).

Peripheral nerve symptoms were described in 11 patients, including one patient with a Guillain–Barré syndrome and one with a sensorimotor polyneuropathy. Less common diagnoses were reported in eight patients, including two cases of posterior reversible encephalopathy syndrome, one nonarteritic anterior ischaemic optic neuropathy, and one cranial multineuritis.

Among patients with neurological manifestations, acute well-defined CNS involvement was present in 52.7% (Table 2). These patients were older and predominantly men and presented more comorbidities compared to patients with other neurological manifestations. Typical COVID-19 symptoms such as cough, odynophagia, nausea/vomiting, and diarrhoea were less frequent in those with acute well-defined CNS involvement, whereas hypoxia and subsequent treatment (oxygen therapy and mechanical
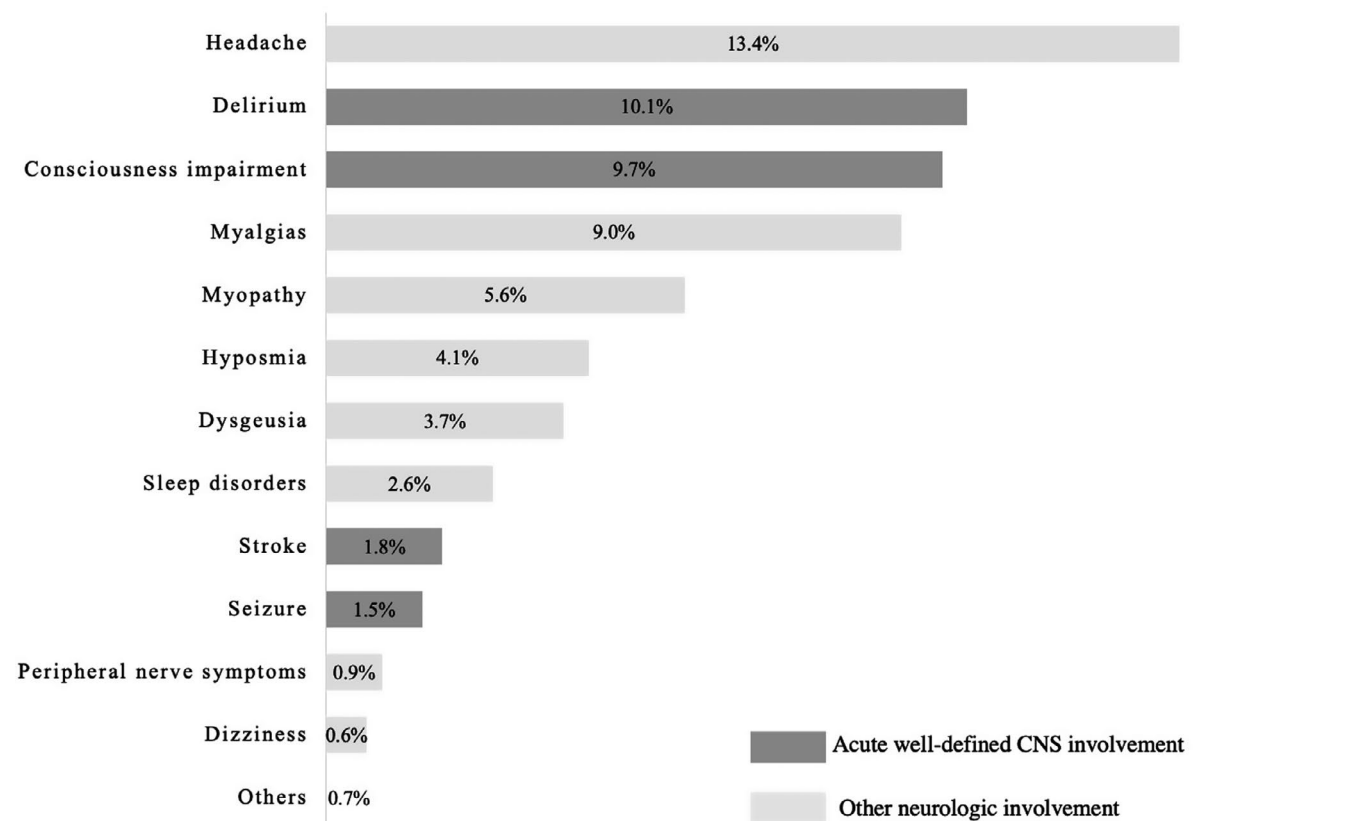

FIGURE 3 Spectrum of neurological symptoms in hospitalised patients. "Others" includes visual symptoms, myelopathy, myasthenia gravis, and multiple sclerosis exacerbation. CNS, central nervous system

TABLE 1 Neurological manifestations in 1261 hospitalised patients with laboratory-confirmed SARS-CoV-2 infection

| | Overall, n = 1261 | | Gender | | | | | Age | | | | |
| | | | Male, n = 647 | | Female, n = 614 | | Male vs. female, RR (95% CI) | <65 years, n = 418 | | ≥65 years, n = 843 | | By 10 years, RR (95% CI) |
	n	%	n	%	n	%		n	%	n	%	
Acute well-defined CNS involvement	241	19.1	140	21.6	101	16.4	1.48 (1.17–1.87)	39	9.3	202	24.0	1.33 (1.23–1.45)
Delirium	127	10.1	80	12.4	47	7.7	1.82 (1.28–2.59)	21	5.0	106	12.6	1.35 (1.20–1.51)
Consciousness impairment	122	9.7	65	10.0	57	9.3	1.36 (0.96–1.92)	11	2.6	111	13.2	1.66 (1.43–1.93)
Acute cerebrovascular disorder	23	1.8	12	1.9	11	1.8	1.04 (0.45–2.41)	6	1.4	17	2.0	1.01 (0.80–1.26)
Seizure	19	1.5	11	1.7	8	1.3	1.46 (0.59–3.61)	2	0.5	17	2.7	1.32 (0.91–1.92)
Myelopathy	1	0.1	1	0.2						1	0.1	
Other neurologic involvement	298 (216)	23.6	144	22.3	154	25.1	0.87 (0.71–1.05)	156	37.3	142	16.8	0.78 (0.75–0.81)
Headache	169 (140)	13.4	68	10.5	101	16.4	0.63 (0.48–0.84)	108	25.8	61	7.2	0.71 (0.67–0.75)
Myalgia	114 (94)	9.0	53	8.2	61	9.9	0.82 (0.58–1.16)	75	17.9	39	4.6	0.71 (0.66–0.77)
Myopathy	71 (34)	5.6	38	5.9	33	5.4	1.07 (0.68–1.68)	28	6.7	43	5.1	0.87 (0.80–0.95)
Hyposmia	52 (45)	4.1	20	3.1	32	5.2	0.59 (0.34–1.01)	32	7.7	20	2.4	0.72 (0.64–0.80)
Dysgeusia	47 (40)	3.7	23	3.6	24	3.9	0.91 (0.52–1.59)	27	6.5	20	2.4	0.69 (0.61–0.78)
Sleep disorders	33 (21)	2.6	18	2.8	15	2.4	1.11 (0.57–2.19)	16	3.8	17	2.0	0.88 (0.75–1.03)
Peripheral nerve symptoms	11 (6)	0.9	5	0.8	6	1.0		3	0.7	8	0.9	
Dizziness	8 (5)	0.6	2	0.3	6	1.0		3	0.7	5	0.6	
Others[a]	8 (5)	0.6	2	0.3	6	1.0		3	0.7	5	0.6	
Overall	457	36.2	235	36.3	222	36.2	0.99 (0.85–1.15)	170	40.7	287	34.0	0.94 (0.90–0.97)

Abbreviations: CI, confidence interval; CNS, central nervous system; RR, rate ratio.

aOthers include two posterior reversible encephalopathy syndrome, one myasthenia gravis exacerbation, one multiple sclerosis exacerbation, one autoimmune encephalitis, one nonarteritic anterior ischaemic optic neuropathy, one cranial multineuritis, and one dysphagia of undetermined cause.

ventilation) were more frequent in this group. At hospital discharge, 42.3% of these patients had an mRS ranging between 0 and 3 (ambulating unassisted), whereas 32.6% died during hospitalisation, compared to 89.4% and 5.6% in patients with other neurological manifestations, respectively. Regarding the cause of death, the majority of patients (61%) died due to respiratory complications of COVID-19.

NeuroCovid in the North Region of Portugal

Based on these results, we projected a total of 999 patients with neurological manifestations among hospitalised patients with COVID-19, corresponding to a rate of 357 per 1000 during the study period (4 months) in the whole North Region.

We also expected 605 patients with acute well-defined CNS involvement, corresponding to a rate of 217 per 1000 hospitalised patients, and 116 with severe neurological events, corresponding to a rate of 42 per 1000 admitted patients.

Assuming all patients with acute neurological involvement or severe neurological events were hospitalised, we may extrapolate our results to the whole population of COVID-19 patients in the North Region. We may expect that 46 per 1000 infected patients (95% confidence interval [CI] = 43–50) presented acute well-defined CNS involvement and nine per 1000 infected patients (95% CI = 7–11) presented a severe neurological event during the 4-month period.

TABLE 2 Clinical characteristics of all patients with neurological manifestations and those with acute well-defined CNS involvement

| Characteristics | Overall, n = 457 | | Acute well-defined CNS involvement | | | | |
| | | | Yes, n = 241[a] | | No, n = 216 | | |
	n	%	n	%	n	%	p
Mean age, years (SD)	68.0 (18.2)		76.7 (14.0)		58.4 (17.5)		<0.001
Gender, male	235	51.4	140	58.1	95	44.0	0.003
Preadmission mRS 0–3[b]	364	80.5	158	66.7	206	95.8	<0.001
Preadmission comorbidities							
Diabetes mellitus	130	28.4	81	33.6	49	22.7	0.010
Hypertension	262	57.3	164	68.0	98	45.4	<0.001
PCOD	40	8.8	20	8.3	20	9.3	0.7
Chronic kidney disease	63	13.8	44	18.3	19	8.8	0.003
Cardiac disease	119	26.0	83	34.4	36	16.7	<0.001
Cerebrovascular disease	71	15.5	58	24.1	13	6.0	<0.001
Active cancer	22	4.8	11	4.6	11	5.1	0.8
Neurologic disease	123	26.9	93	38.6	30	13.9	<0.001
Immunosuppression	29	6.3	12	5.0	17	7.9	0.2
COVID-19 symptoms							
Fever	322	70.5	164	68.0	158	73.1	0.2
Cough	311	68.1	133	55.2	178	82.4	<0.001
Odynophagia	45	9.8	11	4.6	34	15.7	<0.001
Dyspnea	242	53.0	129	53.5	113	52.3	0.8
Hypoxia	239	52.3	143	59.3	96	44.4	0.001
Nausea/vomiting	67	14.7	14	5.8	53	24.5	<0.001
Diarrheoa	87	19.0	33	13.7	54	25.0	0.002
Treatment							
Oxygen therapy	293	64.3	175	72.6	118	54.9	<0.001
Mechanical ventilation	75	16.4	47	19.5	28	13.0	0.060
Hydroxychloroquine	246	53.8	122	50.6	124	57.4	0.1
Corticotherapy	37	8.1	18	7.5	19	8.8	0.6
Antiviral agents[c]	40	8.8	22	9.2	18	8.3	0.7
Intensive care unit	91	19.9	49	20.3	42	19.4	0.8
mRS at discharge[d]							
0–3	294	64.6	101	42.3	193	89.4	<0.001
4–5	71	15.6	60	25.1	11	5.1	
6	90	19.8	78	32.6	12	5.6	

Abbreviations: CNS, central nervous system; mRS, modified Rankin Scale; PCOD, pulmonary chronic obstructive disease.

[a]"Yes" group includes patients with delirium/consciousness impairment, acute cerebrovascular disorder, seizure, and Myelopathy.

[b]Five patients without information.

[c]Includes 37 Lopinavir-Ritonavir and 3 Remdesivir (all women with acute well-defined CNS involvement).

[d]Two patients without information.

DISCUSSION

In this study, we characterised the full spectrum of neurological manifestations of COVID-19 patients admitted to hospitals within the North Region of Portugal. To the best of our knowledge, this is the first cohort to characterise an entire population admitted at several hospitals within a region, and therefore to provide a wider view of the problem.

This approach allowed us to project sample results to the entire hospitalised population, and to estimate that 999 COVID-19

patients exhibited associated neurological symptoms or diseases, during the first wave (March to June). To further illustrate the specific neurological impact and severity of the pandemic, we classified the patients according to the presence of acute well-defined CNS involvement based on Ellul et al. [18]. We then extrapolated from the target population to the entire population, estimating a rate of 46 per 1000 COVID-19-infected patients. When considering only severe neurological events, nearly nine per 1000 infected patients presented a condition that required specialised neurological evaluation and hospitalisation. Given the overall numbers of the ongoing pandemic, a large number of patients will present highly disabling neurological phenotypes. Hence, it is important to recognise this rate to prepare and structure COVID-19 health resources with adequate expertise in neurological care.

Our hospitalised COVID-19 population had a 36.2% rate of neurological involvement, similar to what was first described in China (36.4%) [17]. Since then, higher rates have been described in the United States (42.2%) and Spain (57.4%) [13,14]. The diverse definitions used for neurological manifestation may partially explain those differences. In some cohorts, as an example, the presence of an elevated creatine kinase or syncope alone was considered to be a neurological manifestation [13,14].

Consistently with previous studies, the most frequent neurological symptoms in our cohort were headache, delirium, consciousness impairment, and myalgias [13,14]. Moreover, our results are also in line with the perception of neurologists reported by the European Academy of Neurology NeuroCOVID-19 Task Force during the first wave of the pandemic [19]. Cases of altered consciousness and delirium were frequent, and although we cannot exclude other mechanisms directly related to the virus, most of these patients probably presented these symptoms in relation to systemic complications of COVID-19. However, the limited access to neuroimaging for COVID-19 patients during the pandemic may have led to an underdiagnosis of other neurological entities. The rates of acute cerebrovascular disorders and seizures in our series are also in line with previous descriptions [13,14,20]. Myelopathy is a rare diagnosis in the acute phase of the infection; one case was recognised in our cohort, and only three other cases were previously described in the literature [18,20]. Muscle complains including myopathy were frequent, with critical illness myopathy being the final diagnosis made by the assisting clinician in all patients. Nonetheless, it is difficult to exclude a direct role of the virus in the pathogenesis of these myopathies. In our series, we had one patient with Guillain–Barré syndrome. Although both the North American and Spanish cohorts also reported a low frequency of acute polyneuropathies [13,14] a higher rate of Guillain–Barré syndrome has been described at an Italian hospital, with 17 cases in a cohort of 1760 COVID-19 patients [20]. Hence, further data are still needed to clarify the true rate of acute polyneuropathies associated with COVID-19.

In Northern Portugal, hospitalised patients who presented any neurological symptoms were slightly younger than patients without neurological symptoms. This has been previously described by Liotta et al. [14] in a cohort of 509 hospitalised patients. The authors speculated that it could be explained by the clinical emphasis being focused on potential respiratory failure in older patients rather than on minor accompanying neurological manifestations. Furthermore, in our study, patients with milder symptoms such as headache, myalgias, hyposmia, and dysgeusia were more frequently younger, whereas delirium and consciousness disturbances were more frequent in older patients. It is also important to note that rates of milder symptoms particularly rely on the patient's recognition. Thus, besides a probable underreporting of those symptoms in older patients by the clinician, there may also be an interference of the consciousness level on the elderly's ability to recognise and report them.

In our cohort, few differences were found between genders. Headache was more frequently reported in women, which may partially be explained by common headache disorders being up to two times more prevalent in women [21]. In contrast, acute CNS involvement was found to be more frequent in men, mainly due to an increased rate of delirium. As male patients with neurological manifestations had more comorbidities and severe disease, they may be more susceptible to consciousness impairment.

The fatality in our hospitalised cohort was 19.8%, and 15.6% of patients were highly disabled at discharge, demonstrating the large functional impact of the infection.

The main limitation of our study was the retrospective nature of the data collection, which relied mainly on clinical records, and only reflects the neurological manifestations of hospitalised patients, who were not observed by neurologists in most of the cases. Ongoing initiatives such as the ENERGY registry will probably complement such limitation, as only patients observed by a neurologist are included [22]. We tried to overcome this by using a systematic and harmonised analysis of patient e-records. Most severe neurological phenotypes were hardly missed, but we acknowledge that minor phenotypes without systemic manifestations may not have been registered systematically across different hospitals. Particularly, the rate of headache, hyposmia, and dysgeusia were lower than expected. A series of 100 consecutive, unselected patients who were systematically and prospectively evaluated has shown a much higher rate (anosmia/dysgeusia and headache being found in 44% of patients each) [23]. The overrepresentation of younger patients at tertiary hospitals, more prone to present these phenotypes, might have portrayed an imbalance between the type of neurological manifestations presented. However, as a whole, our sample represented well the age/sex distribution of hospitalised COVID-19 patients, providing a fair approach to the target population. There may also be minor biases in the generalisation to the North Region, because 1.4% of all hospitalised patients were admitted to private care and were not considered in this study. The use of ancillary investigations was limited during this pandemic. This may have limited the accuracy and rates of some diagnosis (such as polyneuropathies and encephalitis) and supports that new solutions are needed to address this limitation.

Overall, neurological symptoms in hospitalised COVID-19 patients are common and often associated with a high degree of disability at discharge. Although most neurological manifestations were

minor, larger series have become important in describing new and more severe phenotypes associated with SARS-CoV-2 infection. A long-term follow-up should be carried out to determine the sequelae and impact of these manifestations, and to identify late onset neurological entities.

In conclusion, this collaborative work provides solid clinical, diagnostic, and epidemiological data to define the neurological spectrum of COVID-19 and estimate the impact of severe neurological phenotypes in the total COVID-19-infected population.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Vanessa Oliveira: conceptualisation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), writing–original draft (lead). **Mafalda Seabra:** data curation (equal), formal analysis (equal), investigation (equal), writing–review & editing (equal). **Rita Rodrigues:** data curation (equal), formal analysis (equal), investigation (equal), writing–review & editing (equal). **Vanessa Carvalho:** data curation (equal), formal analysis (equal), investigation (equal), writing–review & editing (equal). **Michel Mendes:** data curation (equal), formal analysis (equal), investigation (equal), writing–review & editing. **Diogo Pereira:** data curation (equal), investigation (equal), methodology, validation (equal). **Catarina Caldeiras:** data curation (equal), investigation (equal), validation (equal). **Bárbara Martins:** data curation (equal), investigation (equal), validation (equal). **Renata Silva:** data curation (equal), investigation (equal), validation (equal). **Ana Azevedo:** data curation (equal), investigation, validation. **Maria João Lima:** data curation (equal), investigation, validation. **Catarina Monteiro:** data curation (equal), investigation, methodology, validation. **Ricardo Varela:** formal analysis, investigation, methodology, validation. **Sofia Malheiro:** data curation (equal), investigation, validation. **Miguel Abreu:** data curation, investigation, validation.

Elsa Azevedo: data curation (equal), investigation, supervision, validation. **José Leal Loureiro:** formal analysis (equal), investigation (equal), supervision, validation (equal). **Vitor Tedim Cruz:** formal analysis (equal), investigation (equal), supervision, validation (equal). **Mário Rui Silva:** formal analysis (equal), investigation (equal), supervision, validation (equal). **Rui Magalhães:** data curation (equal), formal analysis (equal), validation (equal). **Carolina Silva:** data curation (equal), formal analysis (equal), validation (equal). **Luis F. Maia:** conceptualisation (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), project administration (equal), supervision (equal), writing–review & editing (equal). **Manuel Correia:** conceptualisation (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), supervision (equal), writing–review & editing (equal).

ETHICAL STATEMENT

This study was registered at all centres where the study was conducted, and it received approval from the institutional ethical standards committee. A waiver of written informed consent was obtained, after assessment of the public relevance of the study according to the Portuguese legislation that regulates data protection and clinical research. The authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.