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ORIGINAL ARTICLE

Neurological manifestations as prognostic factors in COVID-19: a retrospective cohort study

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Abstract

Background Neurological manifestations are frequent during COVID-19 but have been poorly studied as prognostic markers of COVID-19.

Objectives The aim of this study was to assess whether neurological manifestations are associated with a poor prognosis of COVID-19, and which patient and COVID-19 characteristics were associated with encephalopathy.

Methods This was a retrospective cohort study and included patients admitted with COVID-19 in four hospitals from Recife, Brazil. Data were collected by reviewing medical records.

Results 613 were included; 54.6% were male, the median age was 54 (41–68) years, 26.4% required mechanical ventilation, and 24.1% died. The neurological symptoms presented were: myalgia (25.6%), headache (22%), fatigue (22%), drowsiness (16%), anosmia (14%), disorientation (8.8%), ageusia (7.3%), seizures (2.8%), and dizziness (1.5%). Twelve patients (2%) had strokes (ischemic strokes: 9) and 149 (24.3%), encephalopathy. Older age, a prolonged hospitalization, diabetes mellitus, a previous history of stroke and having epileptic seizures during hospitalization were significantly associated with the occurrence of encephalopathy. Older age, smoking and requiring mechanical ventilation were associated with prolonged hospitalization. Older patients, those requiring mechanical ventilation and those with encephalopathy presented a significantly higher risk, while those who had anosmia presented a significantly lower risk of dying.

Conclusions Neurological symptoms are frequent among patients with COVID-19. Encephalopathy was the most frequent neurological complication and was associated with a higher mortality. Those with anosmia had a lower mortality.

Keywords Neurologic manifestations · Neurologic symptoms · COVID-19 · Encephalopathy · Mortality · Prognosis

Introduction

Neurological symptoms are frequent during COVID-19, and occur in 8–92% of hospitalized patients [1–5]. These include headache, anosmia, ageusia, myalgia, dizziness, fatigue, altered level of consciousness, mental confusion, agitation, and epileptic seizures. These symptoms are among those that most trouble patients during the course of the disease. Although respiratory symptoms are the main cause of hospitalization in COVID-19, neurological symptoms may also lead patients to seek hospital care [4].

Headache, anosmia and ageusia are symptoms that generally occur in patients with a milder form of the disease at the onset of clinical symptoms, and often occur grouped together [4, 6–13], while mental confusion, agitation and epileptic seizures are more frequent in more severe cases

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of the disease [4, 11, 14, 15]. Neurological symptoms have been poorly studied as prognostic markers of COVID-19.

While neurological complications are rare in terms of population [16], they are not infrequent among hospitalized patients, and are even more frequent in severe cases of COVID-19 [3, 12, 17–19]. The neurological complications described include cerebrovascular diseases, encephalopathies, encephalitis and meningitis, acute disseminated encephalomyelitis, myelitis, Guillain–Barré syndrome, multiple demyelinating sensory and motor mononeuropathy, and myopathies [3–5, 12, 18–24]. An Italian study that compared patients with and without COVID-19 admitted to a neurological unit with neurological complications reported mortality and length of hospital stay significantly higher among those with COVID-19. [25]

Several mechanisms may be involved in the genesis of symptoms and neurological complications in COVID-19. These include direct viral damage, a systemic inflammatory response, hypoxia, drugs used in patient management, and vascular complications [26]. Since there are different underlying mechanisms, our hypothesis is that different neurological manifestations may be used as prognostic markers of different risks.

The aim of this study was to assess whether neurological manifestations are associated with a poor prognosis of COVID-19 in hospitalized patients, and which patient and COVID-19 characteristics were associated with encephalopathy.

Methods

This was a retrospective cohort study conducted in the city of Recife, state capital of Pernambuco, located in Northeast Brazil, and involved four hospitals:

1. Hospital Universitário Oswaldo Cruz (HUOC-UPE). This hospital is linked to the Universidade de Pernambuco and attends patients from the public health system.
2. Hospital das Clínicas (HC-UFPE). This hospital is linked to the Universidade Federal de Pernambuco and attends patients from the public health system.
3. Instituto de Medicina Integral Professor Fernando Figueira (IMIP). This hospital attends patients from the public system and is linked to the Faculdade Pernambucana de Saúde.
4. Real Hospital Português de Beneficência de Pernambuco (RHP). This hospital attends patients from the private sector, generally with private health insurance.

Patients included in the study were those of both sexes, admitted with COVID–19 in April and May 2020, confirmed by reverse transcription polymerase chain reaction (RT-PCR) technique, with material collected from nasal and oropharynx swabs. Pregnant women and those aged under six years were excluded.

Data were collected by neurologists and neurology residents by reviewing medical records. For this, a specific form was developed, which contained: sociodemographic data; clinical data, such as the presence of comorbidities, laboratory tests performed, signs and symptoms presented, and the need for mechanical ventilation; the need for admission to the intensive care unit (ICU), the presence of neurological symptoms, such as dizziness, fatigue, headache, anosmia, ageusia, myalgia, seizures, altered level of consciousness and mental confusion; the presence of neurological complications; the occurrence of death and the days of hospitalization.

Patients presenting with a disturbance in attention and awareness (reduced orientation to the environment) developed over a short period and represented a change from baseline were considered to have delirium. [27]

Patients presenting with delirium and/or a decreased level of consciousness, which were not associated with the occurrence of stroke or another specific neurological diagnosis that justified these complaints were considered to have encephalopathy. [27]

Rhabdomyolysis was considered when the highest level of creatine kinase (CK) was greater than the 75th percentile for the sample.

A prolonged hospitalization was defined as a time greater than or equal to the 75th percentile.

Older patients were considered as those aged over 60 years.

Statistical analysis

The statistical analyses were performed using SPSS Statistics Software version 21.0 (IBM Corporation, Armonk, NY, USA).

Quantitative data were tested regarding normality of distribution, by the means of the Kolmogorov–Smirnov test. When the distribution was normal, the means and standard deviations were calculated. If not, the medians and the 25th and 75th percentiles were used (P_{25}; P_{75}).

The percentage distribution of the categorical variables was compared between the groups by means of the Chi-square test or Fisher's exact test. Numerical variables were compared using the Mann–Whitney test.

For the analyzes referring to death and length of hospital stay, if the patient presented with a neurological symptom that could be explained by a specific neurological diagnosis, the specific neurological diagnosis was used in the analysis.

Logistic regression models were used to assess what is associated with the presence of encephalopathy and whether neurological symptoms or complications were associated

with mortality and a prolonged hospitalization. Variables that presented some association with these prognostic factors in the univariate analysis (P value < 0.05) were initially included in the model using the stepwise method. Only those variables that caused no loss of stability remained in the model.

All tests were leveled by a 0.05 significance.

Ethical aspects

The research was approved by the Research Ethics Committees of the hospitals involved. Since data was collected through medical records, the informed consent form was waived by the Ethics Committees.

Results

A total of 701 medical records were reviewed, 82 patients were excluded for being pregnant and six for being aged under six years. Six hundred and thirteen patients were considered for analysis, 35.7% were patients from HUOC-UPE; 27.6%, from RHP; 22.7%, from IMIP; and 14%, from HC-UFPE. Three hundred and thirty-five (54.6%) were male, the median age was 54 (41–68) years, 248 (40.5%) were older patients; 239 patients (39%) needed to be admitted to ICU and 162 (26.4%) required mechanical ventilation. The median length of time on mechanical ventilation was 8 days (4–14).

These patients confirmed previous diseases: systemic arterial hypertension (47%), diabetes mellitus (29%), obesity (14.2%), smoking (8.5%), chronic kidney disease (8.3%), cancer (7.5%), stroke (2.9%); epilepsy (1.1%) and other diseases (< 5%).

Symptoms presented during COVID-19 were cough (83%), fever (79%), dyspnea (73%), diarrhea (14%) and runny nose (11%). Asthenia, chills, sore throat, joint pain, chest pain, abdominal pain, nausea or vomiting were reported by less than 10% of patients. The first pulse oximetry was recorded for 552 patients and presented a median of 95 (91–97%), but 229 patients (41.5%) presented $SpO_2 < 94\%$ and 100 patients (18.1%), $SpO_2 < 90\%$.

The neurological symptoms presented during COVID-19 were myalgia (25.6%), headache (22%), fatigue (22%), drowsiness (16%), anosmia (14%), disorientation (8.8%), ageusia (7.3%), and dizziness (1.5%).

Seventeen patients (2.8%) presented epileptic seizures, one of whom underwent cerebral magnetic resonance, cerebral magnetic resonance angiogram and cerebrospinal fluid test, which were normal. One of these patients had a previous history of epilepsy.

Twelve patients (2%) had strokes during COVID-19, of which, 9 were ischemic strokes and 3 were hemorrhagic. All patients with stroke were aged over 60 years, seven had hypertension, five had diabetes mellitus, one was a smoker, one had atrial fibrillation and one had heart failure. Five of those with stroke had suffered previous strokes.

Serum CK levels were recorded in 345 (56%) patients, which presented a median of 218.5 (73–516.5). Eighty of these patients (23.2%) presented a CK above the 75th percentile, indicating rhabdomyolysis.

One hundred and forty-nine (24.3%) patients presented encephalopathy. Table 1 demonstrates the laboratory profile of patients with encephalopathy. Those with encephalopathy presented significantly higher levels of neutrophils, C-reactive protein, urea, creatinin, aspartate aminotransferase and lactate dehydrogenase, and lower levels of hemoglobin and CK than those without encephalopathy.

Table 1 The laboratory data of those with and without encephalopathy

Laboratory tests	*N*	Total (median)	With encephalopathy (median)	Without encephalopathy (median)	*P* value
Hemoglobin (g/dL)	589	13.5 (11.4–14.4)	12.3 (9.8–14.8)	13.5 (13–14)	< 0.01
Neutrophil count (10^3/mcL)	581	6.47 (4.83–9.15)	9.15 (6.9–11.4)	4.83 (3.61–6.05)	< 0.01
Lymphocyte count (10^3/mcL)	581	1.27 (1.05–1.43)	1.27 (1.24–1.3)	1.21 (0.85–1.57)	0.24
Platelets (10^3/mcL)	581	217.5 (171.5–430.5)	385 (172–598)	217 (171–263)	0.60
C-Reactive protein (mg/dL)	515	70.5 (16.9–156.5)	156.5 (114–149)	16.9 (6.9–27)	< 0.01
D-Dimer (mcg/mL)	204	212.8 (3.6–496)	3.55 (1.6–5.5)	496 (420–572)	0.23
Urea (mg/dL)	574	40.5 (28–96)	90.5 (35–146)	33.5 (21–46)	< 0.01
Creatinin (mg/dL)	579	1.09 (0.85–2.09)	1.85 (0.7–3)	1.08 (1–1.17)	< 0.01
Aspartate aminotransferase (U/L)	541	47.5 (34.5–73.5)	73.5 (55–92)	34.5 (29–40)	< 0.01
Alanine aminotransferase (U/L)	541	32.5 (27.5–44.5)	44.5 (35–54)	27.5 (25–30)	0.94
Lactate dehydrogenase (U/L)	422	513 (316.5–693.5)	513 (436–590)	497 (197–797)	< 0.01
Ferritin (10^3 ng/mL)	371	1.39 (1.2–1.71)	1.68 (1.36–2)	1.23 (1.04–1.42)	0.24
Creatinine kinase (U/L)	345	218.5 (73–516.5)	205.5 (60–351)	384 (86–682)	< 0.01

Table 2 presents the sociodemographic and clinical characteristics which were associated with encephalopathy. After controlling for the variables of confusion, older age, a prolonged hospitalization, diabetes mellitus, a previous history of stroke and having epileptic seizures during hospitalization were significantly associated with the occurrence of encephalopathy.

The median length of hospital stay was 7 (4–13) days. One hundred and forty-two patients had prolonged hospitalization. Table 3 demonstrates that sociodemographic and clinical characteristics were associated with prolonged hospitalization. Older age, smoking, and requiring mechanical ventilation were associated with prolonged hospitalization. After repeating this analysis without the patients who had died, there was no change in these results (data not shown).

There were 148/613 (24.1%) hospital deaths. The variables associated with deaths are described in Table 4. After controlling for the confounding variables, older patients, and those requiring mechanical ventilation and with encephalopathy presented a significantly higher risk, while those who had anosmia presented a significantly lower risk of dying.

Table 2 Estimated risk for encephalopathy according to patient sociodemographic and clinical characteristics

Characteristics	Total ($N=613$)	With encephalopathy ($N=149$)	Without encephalopathy ($N=464$)	RR (95% CI)	P value	Adjusted RR (95% CI)
Aged > 60 years	248 (40.5)	100 (67.1)	148 (31.9)	1.45 (1.3–1.62)	< 0.01	3.59 (2.32–5.54)
Male	335 (54.6)	85 (57)	250 (54)	1.03 (0.94–1.13)	0.49	–
Comorbidity						
Smoking	52 (8.5)	13 (8.7)	39 (8.4)	1.01 (0.86–1.19)	0.9	–
Alcoholism	13 (2.1)	3 (2)	10 (2.2)	0.98 (0.73–1.33)	0.93	–
Obesity	87 (14.2)	14 (9.4)	73 (15.7)	0.89 (0.8–0.98)	0.05	–
Hypertension	288 (47)	90 (60.4)	198 (42.7)	1.19 (1.08–1.31)	< 0.01	–
Diabetes mellitus	178 (29)	68 (45.6)	110 (23.7)	1.32 (1.16–1.49)	< 0.01	1.95 (1.26–3.02)
Ischemic heart disease	27 (4.4)	10 (6.7)	17 (3.7)	1.21 (0.9–1.62)	0.12	–
Heart failure	26 (4.2)	12 (8.1)	14 (3)	1.42 (0.99–2.04)	< 0.01	–
Valvular heart disease	3 (0.5)	1 (0.7)	2 (0.4)	1.14 (0.51–2.53)	0.72	–
Atrial fibrillation	16 (2.6)	8 (5.4)	8 (1.7)	1.53 (0.93–2.5)	0.02	–
Asthma	29 (4.7)	2 (1.3)	27 (5.8)	0.8 (0.72–0.9)	0.03	–
Chronic obstructive pulmonary disease	24 (3.9)	8 (5.4)	16 (3.4)	1.14 (0.86–1.52)	0.29	–
Chronic renal disease	51 (8.3)	21 (14.1)	30 (6.5)	1.32 (1.04–1.66)	< 0.01	–
Chronic liver disease	10 (1.6)	4 (2.7)	6 (1.3)	1.27 (0.76–2.1)	0.24	–
Prior stroke	18 (2.9)	14 (9.4)	4 (0.9)	3.48 (1.46–8.27)	< 0.01	4.85 (1.38–17.02)
Epilepsy	7 (1.1)	2 (1.3)	5 (1.1)	1.06 (0.66–1.7)	0.79	–
Clinical data						
Fever	482 (78.6)	108 (72.5)	374 (80.6)	0.88 (0.78–1.0)	0.04	–
Dyspnoea	445 (72.6)	115 (77.2)	330 (71.1)	1.08 (0.98–1.18)	0.15	–
Mechanical ventilation	162 (26.4)	84 (56.4)	78 (16.8)	1.78 (1.51–2.1)	< 0.01	–
Seizure	17 (2.8)	15 (10.1)	2 (0.4)	6.59 (1.79–24.2)	< 0.01	37.3 (7.9–176.02)
Fatigue	135 (22)	24 (16.1)	111 (23.9)	0.9 (0.82–0.98)	0.04	–
Anosmia	86 (14)	5 (3.4)	81 (17.5)	0.77 (0.72–0.83)	< 0.01	–
Ageusia	45 (7.3)	2 (1.3)	43 (9.3)	0.78 (0.72–0.84)	0.01	–
Headache	135 (22)	11 (7.4)	124 (26.7)	0.77 (0.72–0.84)	< 0.01	–
Myalgia	157 (25.6)	16 (10.7)	141 (30.4)	0.79 (0.73–0.85)	< 0.01	–
Dizziness	9 (1.5)	3 (2)	6 (1.3)	1.14 (0.71–1.81)	0.52	–
Stroke	12 (2)	9 (6)	3 (0.6)	3.07 (1.15–8.18)	< 0.01	–
Ischemic stroke	9 (1.5)	7 (4.7)	2 (0.4)	3.44 (1.01–11.7)	< 0.01	–
Hemorrhagic stroke	3 (0.5)	2 (1.3)	1 (0.2)	2.28 (0.46–11.3)	0.08	–
Prolonged hospitalization	142 (23)	59 (39.6)	83 (17.9)	1.38 (1.19–1.6)	< 0.01	2.17 (1.38–3.41)

RR relative risk

Table 3 Estimated risk for prolonged hospitalization according to patient sociodemographic and clinical characteristics

Characteristics	Total ($N=613$)	Length of hospital stay (> 13 days) ($N=142$)	Length of hospital stay (< 14 days) ($N=471$)	RR (95% CI)	*P* value	Adjusted RR (95% CI)
Aged > 60 years	248 (40.5)	81 (57)	167 (35.5)	1.24 (1.12–1.36)	< 0.01	1.58 (1.03–2.43)
Male	335 (54.6)	79 (55.6)	256 (54.4)	1.01 (0.93–1.1)	0.79	–
Comorbidity						
Smoking	52 (8.5)	20 (14.1)	32 (6.8)	1.27 (1.02–1.58)	< 0.01	2.11 (1.1–4.05)
Alcoholism	13 (2.1)	4 (2.8)	9 (1.9)	1.11 (0.77–1.6)	0.51	–
Obesity	87 (14.2)	20 (14.1)	67 (14.2)	0.99 (0.88–1.13)	0.97	–
Hypertension	288 (47)	81 (57)	207 (44)	1.13 (1.03–1.24)	< 0.01	–
Diabetes mellitus	178 (29)	59 (41.5)	119 (25.3)	1.21 (1.08–1.35)	< 0.01	–
Ischemic heart disease	27 (4.4)	9 (6.3)	18 (3.8)	1.16 (0.88–1.52)	0.20	–
Heart failure	26 (4.2)	13 (9.2)	13 (2.8)	1.56 (1.06–2.29)	< 0.01	–
Valvular heart disease	3 (0.5)	1 (0.7)	2 (0.4)	1.15 (0.52–2.57)	0.68	–
Atrial fibrillation	16 (2.6)	6 (4.2)	10 (2.1)	1.24 (0.84–1.81)	0.17	–
Asthma	29 (4.7)	4 (2.8)	25 (5.3)	0.89 (0.76–1.03)	0.22	–
Chronic obstructive pulmonary disease	24 (3.9)	8 (5.6)	16 (3.4)	1.16 (0.87–1.54)	0.23	–
Chronic renal disease	51 (8.3)	19 (13.4)	32 (6.8)	1.24 (1.0–1.54)	0.01	–
Chronic liver disease	10 (1.6)	4 (2.8)	6 (1.3)	1.28 (0.77–2.14)	0.20	–
Prior stroke	18 (2.9)	9 (6.3)	9 (1.9)	1.55 (0.98–2.47)	< 0.01	–
Epilepsy	7 (1.1)	–	7 (1.5)	–	–	–
Clinical data						
Fever	482 (78.6)	113 (79.6)	369 (78.3)	1.02 (0.92–1.13)	0.75	–
Dyspnoea	445 (72.6)	107 (75.4)	38 (71.8)	1.04 (0.95–1.14)	0.40	–
Mechanical ventilation	162 (26.4)	70 (49.3)	92 (19.5)	1.48 (1.29–1.7)	< 0.01	3.58 (2.34–5.48)
Decreased level of consciousness	98 (16)	43 (30.3)	61 (13)	1.37 (1.16–1.62)	< 0.01	–
Disorientation	54 (8.8)	26 (18.3)	30 (6.4)	1.48 (1.15–1.89)	< 0.01	–
Encephalopathy	149 (24.3)	59 (41.5)	90 (19.1)	1.36 (1.19–1.56)	< 0.01	–
Seizure	17 (2.8)	6 (4.2)	11 (2.3)	1.19 (0.84–1.7)	0.23	–
Fatigue	135 (22)	31 (21.8)	104 (22.1)	0.99 (0.89–1.11)	0.95	–
Anosmia	86 (14)	12 (8.5)	74 (15.7)	0.87 (0.79–0.97)	0.03	–
Ageusia	45 (7.3)	7 (4.9)	38 (8.1)	0.9 (0.79–1.03)	0.21	–
Headache	135 (22)	23 (16.2)	112 (23.8)	0.91 (0.83–1.0)	0.05	–
Myalgia	157 (25.6)	17 (12)	40 (29.7)	0.81 (0.75–0.88)	< 0.01	–
Dizziness	9 (1.5)	3 (2.1)	6 (1.3)	1.15 (0.73–1.84)	0.47	–
Stroke	12 (2)	6 (4.2)	6 (1.3)	1.55 (0.88–2.73)	0.03	–
Ischemic stroke	9 (1.5)	4 (2.8)	5 (1.1)	1.39 (0.77–2.49)	0.13	–
Hemorrhagic stroke	3 (0.5)	2 (1.4)	1 (0.2)	2.31 (0.47–11.46)	0.07	–

RR relative risk

Discussion

Our patients presented with myalgia, headache, fatigue, drowsiness, anosmia, disorientation, and ageusia as the most frequent neurological symptoms. This is in agreement with the literature [1–5, 11, 12, 18].

We observed a stroke incidence of 2%, 75% of which were ischemic strokes. Most stroke patients presented with risk factors for vascular disease and 42% had a previously history of stroke. The hospital series that assessed neurological complications of COVID-19 reported a stroke frequency similar to ours (from 1 to 3.3%), with ischemic stroke being two to five times more frequent than hemorrhagic stroke [1, 3, 5, 11, 12, 18, 28]. A meta-analysis that included more than 100,000 patients with COVID-19 reported an incidence of cerebrovascular disease of 1.4% (1.0–1.9), with ischemic stroke being the most common

Table 4 Estimated risk for death according to patient sociodemographic and clinical characteristics

Characteristics	Total ($N=613$)	Death outcome: yes ($N=148$)	Death outcome: no ($N=465$)	RR (95% CI)	P value	Adjusted RR (95% CI)
Aged > 60 years	248 (40.5)	102 (68.9)	146 (31.4)	1.48 (1.33–1.66)	< 0.01	3.92 (2.17–7.08)
Male	335 (54.6)	87 (58.8)	248 (53.3)	1.05 (0.96–1.15)	0.25	–
Comorbidity						
Smoking	52 (8.5)	13 (8.8)	39 (8.4)	1.01 (0.86–1.19)	0.88	–
Alcoholism	13 (2.1)	4 (2.7)	9 (1.9)	1.09 (0.76–1.58)	0.57	–
Obesity	87 (14.2)	24 (16.2)	63 (13.5)	1.05 (0.92–1.21)	0.42	–
Hypertension	288 (47)	77 (52)	211 (45.4)	1.07 (0.97–1.17)	0.16	–
Diabetes mellitus	178 (29)	57 (38.5)	121 (26)	1.16 (1.04–1.3)	< 0.01	–
Ischemic heart disease	27 (4.4)	9 (6.1)	18 (3.9)	1.14 (0.87–1.5)	0.25	–
Heart failure	26 (4.2)	12 (8.1)	14 (3)	1.43 (1.0–2.04)	< 0.01	–
Valvular heart disease	3 (0.5)	2 (1.4)	1 (0.2)	2.28 (0.46–11.3)	0.08	–
Atrial fibrillation	16 (2.6)	11 (7.4)	5 (1.1)	2.47 (1.19–5.11)	< 0.01	–
Asthma	29 (4.7)	2 (1.4)	27 (5.8)	0.81 (0.72–0.9)	0.03	–
Chronic obstructive pulmonary disease	24 (3.9)	7 (4.7)	17 (3.7)	1.07 (0.83–1.39)	0.56	–
Chronic renal disease	51 (8.3)	26 (17.6)	25 (5.4)	1.6 (1.2–2.12)	< 0.01	–
Chronic liver disease	10 (1.6)	3 (2)	7 (1.5)	1.09 (0.72–1.63)	0.66	–
Prior stroke	18 (2.9)	8 (5.4)	10 (2.2)	1.38 (0.91–2.09)	0.04	–
Epilepsy	7 (1.1)	1 (0.7)	6 (1.3)	0.88 (0.65–1.2)	0.54	–
Clinical data						
Fever	482 (78.6)	106 (71.6)	376 (80.9)	0.87 (0.77–0.99)	0.02	–
Dyspnoea	445 (72.6)	125 (84.5)	320 (68.8)	1.2 (1.1–1.3)	< 0.01	–
Mechanical ventilation	162 (26.4)	117 (79.1)	45 (9.7)	3.35 (2.61–4.3)	< 0.01	27.4 (15.2–49.5)
Decreased level of consciousness	98 (16)	59 (39.9)	39 (8.4)	2.06 (1.62–2.61)	< 0.01	–
Disorientation	54 (8.8)	26 (17.6)	28 (6)	1.51 (1.17–1.95)	< 0.01	–
Encephalopathy	149 (24.3)	83 (56.1)	66 (14.2)	1.94 (1.62–2.33)	< 0.01	2.7 (1.51–4.83)
Seizure	17 (2.8)	8 (5.4)	9 (1.9)	1.44 (0.92–2.27)	0.03	–
Fatigue	135 (22)	26 (17.6)	109 (23.4)	0.92 (0.84–1.02)	0.13	–
Anosmia	86 (14)	2 (1.4)	84 (18.1)	0.74 (0.7–0.79)	< 0.01	0.17 (0.03–0.81)
Ageusia	45 (7.3)	3 (2)	42 (9)	0.8 (0.73–0.88)	< 0.01	–
Headache	135 (22)	13 (8.8)	122 (26.2)	0.79 (0.73–0.86)	< 0.01	–
Myalgia	157 (25.6)	14 (9.5)	143 (30.8)	0.77 (0.72–0.84)	< 0.01	–
Dizziness	9 (1.5)	1 (0.7)	8 (1.7)	0.85 (0.67–1.08)	0.36	–
Stroke	12 (2)	5 (3.4)	7 (1.5)	1.31 (0.81–2.11)	0.15	–
Ischemic stroke	9 (1.5)	3 (2)	6 (1.3)	1.14 (0.72–1.81)	0.52	–
Hemorrhagic Stroke	3 (0.5)	2 (1.4)	1 (0.2)	2.28 (0.46–11.3)	0.08	–
Prolonged hospitalization	142 (23)	43 (29.1)	99 (21.3)	1.12 (0.99–1.26)	0.04	–

RR relative risk

type. Those with stroke presented cardiovascular risk factors more often than those without stroke [29].

Almost a quarter of our patients who measured CK levels presented a significant increase in CK, indicating muscle damage. We cannot rule out that patients with muscle symptoms have dosed this enzyme more frequently, and that these levels are overestimated. However, a meta-analysis that included more than two thousand patients reported that 17% (11–22%) of the patients presented elevated levels of CK levels, which is close to ours. Elevated CK levels are associated with a threefold increase in the risk of a poor prognosis [30]. Since only 56% of patients measured CK levels, we decided not to include it in the prognostic analyses.

Encephalopathy was the most frequent neurological complication, occurring in 24% of our patients. The term encephalopathy refers to a brain dysfunction unexplained by any other neurological disease, which usually develops acutely and may have symptoms such as subsyndromal

delirium, delirium, or a decreased level of consciousness [27]. Unlike encephalitis, encephalopathy is not caused by the direct action of viral invasion and is multifactorial. Contributing factors for its appearance are the occurrence of hypoxic–ischemic alterations, toxic and metabolic alterations, the use of drugs for the treatment of these patients, the inflammatory response secondary to sepsis, and the failure of multiple organs [31]. The frequency of encephalopathy in different studies with patients hospitalized with COVID-19 ranged from 10 to 60% [1, 3–5, 11, 15, 32], and was higher in those studies that included more critically ill patients [31].

Our patients with encephalopathy presented higher levels of neutrophils and C-reactive protein, and greater changes in the liver enzymes and renal function. This suggests that sepsis and metabolic changes are associated with the development of encephalopathy. According to other studies, other factors may also be associated with its genesis, such as hypoxia, drugs used in the treatment of these patients and ischemic alterations [4, 14, 31].

Older patients, those with previous illnesses (diabetes mellitus and stroke), those who had epileptic seizures during hospitalization and those with prolonged hospitalization presented more encephalopathy. Liotta et al. reported a higher risk for encephalopathy in patients with COVID-19 who had some previous neurological disease, and encephalopathy was also associated with a longer length of hospital stay [3]. Other studies have reported that patients with COVID-19 who were older [15, 32] and with a higher number of chronic diseases [15] have a higher risk of delirium and older patients are more likely to have an altered level of consciousness [4].

Epileptic seizures may be part of the clinical condition of encephalopathy [31]. Since we do not record the temporal sequence of neurological symptoms, we are unable to determine whether these epileptic seizures are risk markers for the development of encephalopathy or its symptoms. We are also unable to rule out the fact that some of these patients had encephalitis, although this is rare in COVID-19, since most patients did not undergo imaging tests and none of them underwent a cerebrospinal fluid test.

Older age, smoking, and requiring mechanical ventilation were associated with a prolonged hospitalization. These conditions are associated with more severe forms of COVID-19 [12, 33]. None of the symptoms or neurological complications was associated with a prolonged length of hospital stay.

Older patients, those requiring mechanical ventilation and those with encephalopathy presented a significantly higher risk of dying. Older age and respiratory failure are well-established risk factors for death in COVID-19 [3, 33, 34], Only one previous study has assessed encephalopathy as a risk factor for death and reported the same results as ours [3]. Those with anosmia had a significantly lower risk of death. Our results corroborate what was reported by two other studies [12, 35]. We consider this to be of clinical importance, since anosmia is an easily measured marker of a good prognosis.

Anosmia occurs more frequently in patients with milder cases of COVID-19 and usually occurs at the onset of the disease, being more associated with viral invasion and the initial response to the virus than with systemic inflammatory conditions [4, 6, 11, 13]. Our results probably reflect the pathophysiological process underlying anosmia.

There is controversy in the literature as to whether headache is associated with a better prognosis [8, 9, 12]. However, studies on the subject have either not performed multivariate analysis to control the confounding variables or have not included other neurological symptoms in the analysis. Headache did not prove to be a prognostic marker in our study.

Our study has some limitations. The sample size was not calculated. Thus, we may not have been able to detect small differences. Data were obtained by reviewing medical records. This may have led to underestimating the presence of milder symptoms. The frequency of neurological symptoms is in agreement with that reported by other studies that have used the same methodology as ours, but it is lower than those that directly interviewed patients [1–5, 7, 11, 12, 18]. The sample was a convenience sample and the included patients were admitted to hospitals that treat more complex patients, which may have reduced the generalizability of the study.

Our study, however, has a number of strengths. Data were obtained by neurologists and neurology residents. This may have reduced misclassifications. An attempt was made to control for confounding variables related to poor prognosis in the analysis and all neurological symptoms and neurological complications were considered in the prognostic analysis.

Conclusions

Neurological symptoms are frequent among patients hospitalized with COVID-19. Encephalopathy was the most frequent neurological complication and was associated with older age, diabetes mellitus, previous stroke, a prolonged hospitalization, the presence of epileptic seizures and higher mortality. Those with anosmia had a lower mortality.

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Author contributions PASRF conceived the original idea. PASRF and JEM developed the theoretical framework. Acquisition of data: JEM, DFS, MCS, LMAB, MDPG, and FAAO. Analysis of data: PASRF and

JEM. Interpretation of the results: PASRF, JEM, DFS, MCS, LMAB, MDPG, and FAAO. All authors discussed the results and contributed to the final version of the manuscript. All authors read and approved the final manuscript.

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

Declarations

Conflict of interest The authors report that there were no conflicts of interest.

Ethics approval The research was approved by the Research Ethics Committees of the hospitals involved. Since data were collected through medical records, the informed consent form was waived by the Ethics Committees.

Consent for publication Not applicable.

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