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Neurological manifestations and clinical outcomes in hospitalized patients with COVID-19: Retrospective cohort in a Peruvian hospital

Manifestaciones neurológicas y desenlaces clínicos en pacientes hospitalizados con COVID-19: Cohorte retrospectiva en un hospital Peruano

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RESUMEN

Introducción: La mayoría de los pacientes hospitalizados por COVID-19 presentan una manifestación neurológica, pero los marcadores para manifestaciones neurológicas específicas y cómo estas afectan los resultados clínicos aún no están claros. **Objetivo:** Describir la frecuencia de manifestaciones neurológicas en pacientes hospitalizados con COVID-19 y analizar su relación con marcadores y desenlaces clínicos relevantes. **Métodos:** Estudio retrospectivo incluyendo adultos hospitalizados por COVID-19 con al menos una manifestación neurológica. Cefalea, anosmia, ageusia, y polineuromiopatia se clasificaron como manifestaciones neurológicas inespecíficas, mientras que crisis epilepticas, disminución del nivel de conciencia, delirio, ataxia, movimientos anormales, y eventos cerebrovasculares como específicas. Asociaciones evaluadas: a) covariables clínicas y de laboratorio con presentación de manifestación neurológica específica; b) manifestación neurológica específica con gravedad de COVID-19, ventilación mecánica y mortalidad; y c) duración de la ventilación mecánica y polineuromiopatia. **Resultados:** De 338 pacientes incluidos, 61,2% tenía COVID-19 grave, 25,2% estaba en ventilación mecánica y 23,7% murió. Las manifestaciones neurológicas más frecuentes fueron cefalea (68,3%), delirio (41,9%), disminución del nivel de conciencia (40,8%) y polineuromiopatia (21,8%). El dímero-D alto y la linfopenia se asociaron con manifestación neurológica específica. Se encontró al menos una manifestación neurológica específica en 39,9% de pacientes, y este grupo se asociación con COVID-19 grave, ventilación mecánica y mortalidad. Finalmente, una mayor duración en ventilación mecánica se asoció con mayor frecuencia de polineuromiopatia. **Conclusión:** Las manifestaciones neurológicas específicas fueron frecuentes en pacientes hospitalizados con COVID-19 y se asocian con mayor gravedad clínica y laboratorial.

Palabras claves: COVID-19; Sistema Nervioso; Mortalidad; Polineuropatías; Ventilación mecánica. (Fuente: DeCS)

ABSTRACT

Background: Most of hospitalized patients with COVID-19 have had neurological manifestations. However, biomarkers for specific neurological manifestations and how these affect clinical outcomes are still unclear. **Objective:** To describe the frequency of neurological manifestations in patients hospitalized with COVID-19 and analyze their relationship with biomarkers and relevant clinical outcomes. **Methods:** This retrospective cohort study included adult patients hospitalized due to COVID-19 with at least one neurological manifestation. Headache, anosmia, ageusia, and polyneuromyopathy were classified as nonspecific neurological manifestations, whereas epileptic seizures, decreased level of consciousness, delirium, encephalitis, abnormal movements, ataxia, and cerebrovascular events as specific. Assessed associations: a) clinical and laboratory covariates with the presentation of a specific neurological manifestation; b) the relationship between specific neurological manifestation and COVID-19 severity, mechanical ventilation, and mortality; and c) duration of mechanical ventilation and polyneuromyopathy. **Results:** Of the 338 patients included in the study, 61,2% had severe COVID-19, 25,2% required mechanical ventilation, and 23,7% died. The most frequent neurological manifestations were headache (68,3%), delirium (41,9%), decreased level of consciousness (40,8%), and polyneuromyopathy (21,8%). High serum D-dimer levels and lymphopenia were associated with a specific neurological manifestation. At least one specific neurological manifestation was found in 39,9% of patients, and these group was associated with mechanical ventilation and mortality. Finally, a longer duration on mechanical ventilation was associated with a higher frequency of polyneuromyopathy. **Conclusion:** Specific neurological manifestations were frequent in hospitalized patients with COVID-19 and are associated with greater clinical and laboratory severity.

Keywords: COVID-19; Nervous system; Mortality; Polyneuropathies; Respiration, Artifical. (Source: MeSH)

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can affect the central, peripheral, and neuromuscular nervous systems at any stage of coronavirus disease-2019 (COVID-19)[1]. The neuropathological characteristics of SARS-CoV-2, such as neuro-invasiveness and neuro-virulence[2], or the dysregulation of immunomodulation[3] could cause neurological manifestations in approximately 78% of hospitalized patients with COVID-19[4,5]. Severe cases of COVID-19 may also present thrombotic[6], hyperinflammatory and autoimmune processes[7], or those related to respiratory failure[8], which can affect the nervous system. Other neurological complications reported include cerebrovascular disease[9], encephalopathy[10], and Guillain-Barré syndrome[11], among others. Finally, patients who are critically ill with COVID-19 may experience weakness acquired in the intensive care unit[12] due to increased muscle catabolism, decreased muscle synthesis, or polyneuropathies[13].

Neurological manifestations or complications in patients with COVID-19 are associated with adverse clinical outcomes[5,14,15], increased morbidity, and mortality, independent of respiratory disease severity[16]. Otherwise, other studies have identified headache as an independent predictor of lower mortality risk in hospitalized patients with COVID-19[17]. Given the diversity of frequency, mechanisms, severity, and locations of neurological manifestations in patients with COVID-19, it is challenging to consider them all the same. Therefore, some studies have proposed differentiation between central and peripheric nervous system manifestations[18,19] or according to their pathophysiology origin[20,21]. However, biomarkers for neurological manifestations are still unclear[22].

The Latin American region has been one of the most affected by the pandemic worldwide, mainly due to the high levels of social, health, and economic inequality[23]. Particularly, Peru has registered one of the highest rates of in-hospital deaths worldwide[24]. In Peru, the frequency of different neurological manifestations has been reported in adult patients with COVID-19[25,26]. However, neurological manifestations are only differentiated as isolated or self-reported symptoms, thus bias their report and neglecting the different mechanisms that SARS-CoV-2 infection may have for their generation[27]. Additionally, the relationship between neurological manifestations and various inflammatory biomarkers that may predict them or their impact on clinical outcomes has not been thoroughly studied. Also, weakness in critically ill patients may result in impaired functional capacity, muscle strength, physical functions, and long-term mortality in survivors[28]; however, this has been inadequately described in patients with COVID-19.

Therefore, this study aimed to describe the frequency of neurological manifestations in hospitalized patients with COVID-19 and analyze their relationship with biomarkers and relevant clinical outcomes, considering the specificity of the neurological manifestations in the disease course of the analyzed cases. In addition, as secondary objective, we aimed to explore the association between the duration of mechanical ventilation and polyneuromyopathy.

METHODS

Study design

A retrospective cohort study was conducted at the Hospital Nacional Edgardo Rebagliati Martins, which belongs to the Peruvian Social Security health system (EsSalud). This is the third level of a healthcare center that adopted most of its hospital capacity to the care of patients with COVID-19.

Study population

Patients aged 15 years or older who had a respiratory clinical presentation and were admitted to a COVID-19 hospitalization area during three months (June to August 2020). Local hospital admission policies prioritize assessing patients 15 years or older by the adult neurology department. These patients had a very high suspected or confirmed COVID-19 diagnosis, and had any neurological manifestation during admission or hospitalization period.

COVID-19 confirmed diagnosis followed laboratory criteria with a positive test for the reverse transcriptase-polymerase chain reaction (RT-PCR). A patient with very high suspected COVID-19 diagnosis had a respiratory clinical criteria[29] and images criteria[30], without any other better diagnosis that explains the patient's clinical presentation, during the first COVID-19 outbreak. A neurological manifestation was considered as any symptom, sign, or pathology that involves the nervous system during COVID-19 infection. Patients who were admitted with a positive rapid chromatographic serological test but with a negative or absent RT-PCR and without reports of suggestive symptoms or images that are compatible with COVID-19 were excluded because these serological tests were considered as possible false-positive cases.

Variables

The neurological manifestations were collected from the registered evaluations in the medical records by physicians from the neurology department. In the absence of an assessment by a neurologist, the assessments of each patient's treating physician were considered. Only those neurological manifestations registered at admission or during the evolution of the hospitalized patient were considered. Independent authors collected all the data using a standardized data sheet for each identified patient.

Neurological manifestations were classified into two categories as in previous studies[31–33]: Those that only had nonspecific neurological manifestations, such as headache, anosmia, ageusia, abnormal extraocular movements and/or polyneuromyopathy affecting the peripheral nervous system or are miscellaneous; and those with at least one specific neurological manifestations affecting the central nervous system, such as epileptic seizures, decreased level of consciousness, delirium, encephalitis, abnormal movements, ataxia, and cerebrovascular events.

Delirium was defined as an acute disturbance of state of mind characterized by disorientation, hallucinations, psychosis, agitation, or inappropriate speech. In contrast, decreased level of consciousness was defined as somnolence or coma, different from delirium. Abnormal movements were defined as short and quick involuntary movements of any somatic muscle, and ataxia was defined as a lack of coordination during voluntary

movements. Polyneuromyopathy was any acute generalized weakness in any limb without evidence of mechanical or vascular etiology. Finally, laboratory evidence was necessary for the diagnosis of encephalitis (inflammation of cerebral parenchyma in computed tomography images or pleocytosis in cerebrospinal fluid) or cerebrovascular event (ischemic or hemorrhagic images in computed tomography images).

The severity criteria of the Infectious Diseases Society of America / American Thoracic Society were used to determine the severity of COVID-19 pneumonia[34]. Follow-up ended at hospital discharge or the death of the patient. The information was extracted from the clinical history (either physical or electronic) of the selected patients. Periodic reviews of medical records facilitated the identification of participants and reduced the potential losses in the study.

Ethics

The present study posed minimal risk to patients as no direct contact was made and no information was collected for their identity. Furthermore, only the researchers had access to the collected data. The research protocol was approved by the EsSalud Institutional Review Board for COVID-19 and is registered on the PRISA platform of the Peruvian National Institute of Health (Code: EI00000001457).

Statistical analysis

The information was recorded and stored in a Microsoft Excel 2016 program spreadsheet and then exported to the Stata v16 software. The percentage of missing data for each variable is reported. The proportion of lost data for most variables was small, and the lost data was considered to be random, thus the missing data was not treated.

Frequencies and percentages were used to summarize categorical variables, whereas median and interquartile ranges were used for quantitative variables, because they had a non-normal distribution. Some variables were categorized: the duration of mechanical ventilation was categorized into without, 1–14 days, 15–28 days, and >28 days. The following variables were dichotomized: serum C-reactive protein level as ≤15 mg/L and >15 mg/L[35]; serum D-dimer as <1 ug/mL and ≥1 ug/mL; serum ferritin and lactate dehydrogenase using the cutoff points of 723 ng/mL and 350 U/L, respectively[36]. Finally, the white blood cell and lymphocyte count were categorized using the cutoff points from 10 thousand/mm^3 to 500/mm^3, respectively. The cutoff points were a priori decided based on their ability to predict mortality or in-hospital complications in patients with COVID-19.

In dichotomous analysis, the association between each covariate with the type of neurological manifestation was evaluated using Chi-2 tests. Regression analyzes with generalized linear models with binomial family and link log were performed to calculate the Prevalence Ratios (PR) with their 95% confidence interval (95% CI). The calculated crude PR between covariables and a specific neurological manifestation was adjusted for COVID-19 severity. Contrarily, the PR was calculated to evaluate the association between the types of neurological manifestation with the following outcomes: COVID-19 severity, mechanical ventilation, and mortality. Each model was adjusted for the other two outcomes.

Finally, the association between the duration of mechanical ventilation and the presence of polyneuromyopathy was explored using the Chi-2 test and Poisson regression analysis with robust variances adjusted by COVID-19 severity using Stata MP v.16.0 statistical software for all analyses, and a *p*-value of <0,05 was considered statistically significant.

RESULTS

During the study period, 3329 patients with COVID-19 were admitted. A non-probabilistic sample of 1308 (39,3%) clinical records of patients who were hospitalized with a COVID-19 diagnosis from June to August 2020 was reviewed. Of these, 338 (25,8%) patients presented at least one neurological manifestation. 293 patients were included in the analysis because 45 of them had no COVID-19 diagnostic confirmation test or a highly suspected diagnosis of COVID-19. All patients had respiratory symptoms related to COVID-19 and had positivity confirmation test (39.2%) and/or fully tomographic patterns with an evolution and epidemiological contact consistent with COVID-19 (96.9%).

Most of patients were male (67,6%), with a mean age of 58,5 years old. Among the most frequent comorbidities were hypertension (31,7%), obesity (22,9%), diabetes mellitus (19,5%), and chronic lung disease (6,5%). The rest of the comorbidities did not exceed 5%. Patients on mechanical ventilation accounted for 29,7%, with a median of 18,5 days (interquartile range [IQR]: 12 to 33). The most frequent neurological manifestations were headache (65,9%), delirium (39,6%), altered alertness (40,5%), polyneuromyopathy (23,9%), anosmia (15.6%), ageusia (11,1%), seizures (7,6%), and cerebrovascular event (6,8%). In addition, three patients presented with abnormal movements (1,5%), and two with ataxia and encephalitis, each (1,0%). No patient was reported to had abnormal extraocular movements. Among the laboratory biomarkers, the median count of white blood cells and lymphocytes was 11 320 cells/mm^3 (IQR: 7 745–15 000) and 900 cells/mm^3 (IQR: 620–1310), respectively. The median C-reactive protein was 14,8 mg/L (IQR: 6,3–25,8), the median lactate dehydrogenase was 344 U/L (IQR: 265–436), the median D-dimer was 0,82 mg/L (IQR: 0,47–1,71), and the median ferritin was 793,5 ng/L (IQR: 438–1265). The rest of the sample characteristics are presented in Table 1.

Table 1. General characteristics of patients with COVID-19 who are hospitalized with some neurological manifestation (n = 293) †

Characteristics	n (%)
Age (years)*	58,5 (46 - 69)
Sex	
Male	198 (67,6)
Female	95 (32,4)
Comorbidity	
None	124 (42,3)
At least one	169 (57,7)
Mechanical ventilation	
No	194 (70,3)
1–14 days	34 (12,3)
15–28 days	18 (6,5)

>28 days	30 (10,9)
COVID-19 severity	
Nonsevere	96 (35,2)
Severe	177 (64,8)
Serum C-reactive protein	
Same or fewer than 15 mg/L	143 (51,8)
More than 15 mg/L	133 (48,2)
White blood cell count	
Fewer than 10,000 cells/mm^3	118 (40,4)
Same or more than 10,000 cells /mm^3	174 (59,6)
Lymphocyte count	
Same or more than 500 cells/mm^3	250 (86,2)
Fewer than 500 cells/mm^3	40 (13,8)
Serum D-dimer	
Fewer than 1 ug/mL	153 (58,0)
Same or more than 1 ug/mL	111 (42,0)
Serum ferritin	
Fewer than 723 ng/mL	112 (44,1)
Same or more than 723 ng/mL	142 (55,9)
Serum lactate dehydrogenase	
Fewer than 350 U/L	141 (52,2)
Same or more than 350 U/L	129 (47,8)
Neurological manifestation	
Specific	116 (39,6)
Nonspecific	177 (60,4)
Outcome	
Discharge	220 (75,1)
Death	73 (24,9)

† Some variables do not have 338 observations due to missing data; * Median and interquartile range

In the bivariate analysis, the association between each covariate and the neurological manifestation type outcome was evaluated. Age in quartiles, having at least one comorbidity, lymphocyte count, and serum D-dimer were found to be associated with the outcome. However, in the regression analysis, having at least one comorbidity, a D-dimer of ≥1 ug/mL and having a lymphocyte count of <500 cells/mm^3 were found to be associated with a higher frequency of a specific neurological manifestation. However, only D-dimer and lymphocytes associations were maintained in the analysis adjusted for COVID-19 severity (as shown in Table 2).

Table 2. Bivariate association between variables and type of neurological manifestation (n = 293) †

Characteristics	Neurological manifestation, n (%)		*p*-value *	cPR (95% CI)	*p*-value	aPR (95% CI)	*p*-value
	Nonspecific	Specific					
Sex			0,723				

Male	121 (61,1)	77 (38,9)		Ref,			
Female	56 (59,0)	39 (41,1)		0,95 (0,70 to 1,28)	0,721		
Age in quartiles			0,001				
15–46 years	43 (58,1)	31 (41,9)		Ref,			
47–59 years	52 (72,2)	20 (27,8)		0,66 (0,42 to 1,05)	0,079		
60–70 years	51 (68,0)	24 (32,0)		0,76 (0,50 to 1,17)	0,214		
71–101 years	30 (42,3)	41 (57,8)		1,38 (0,99 to 1,93)	0,060		
Comorbidity			0,028				
None	84 (67,7)	40 (32,3)		Ref,		Ref,	
At least one	93 (55,0)	76 (45,0)		1,39 (1,03 to 1,89)	0,033	1,24 (0,92 to 1,66)	0,153
Serum C-reactive protein			0,365				
Same or less than 15 mg/L	86 (60,1)	57 (39,9)		Ref,			
More than 15 mg/L	87 (65,4)	46 (34,6)		0,87 (0,64 to 1,18)	0,367		
White blood cell count			0,908				
Fewer than 10 000 cells/mm^3	72 (61,0)	46 (39,0)		Ref,			
Same or more than 10 000 cells /mm^3	105 (60,3)	69 (39,7)		1,02 (0,76 to 1,36)	0,908		
Lymphocyte count			0,015				
Same or more than 500 cells/mm^3	157 (62,8)	93 (37,2)		Ref,		Ref,	
Fewer than 500 cells/mm^3	17 (42,5)	23 (57,5)		1,55 (1,13 to 2,11)	0,006	1,39 (1,04 to 1,85)	0,027
Serum D-dimer			<0,001				
Fewer than 1 ug/mL	114 (74,5)	39 (25,5)		Ref,		Ref,	
Same or more than 1 ug/mL	49 (44,1)	62 (55,9)		2,19 (1,59 to 3,01)	<0,001	1,85 (1,36 to 2,52)	<0,001
Serum ferritin			0,078				
Fewer than 723 ng/mL	62 (55,4)	50 (44,6)		Ref,			
Same or more than 723 ng/mL	94 (66,2)	48 (33,8)		0,76 (0,56 to 1,03)	0,078		
Serum lactate dehydrogenase			0,232				
Fewer than 350 U/L	93 (66,0)	48 (34,0)		Ref,			
Same or more than 350 U/L	76 (58,9)	53 (41,1)		1,21 (0,89 to 1,64)	0,233		

† Some variables do not have 338 observations due to missing data; *Chi-square test; 95% CI: 95% Confidence Interval; cPR: crude prevalence ratio; aPR: Prevalence ratio adjusted by severity of COVID-19

Those with a specific neurological manifestation were more likely to be on mechanical ventilation and die, independently of COVID-19 severity, compared than those without specific neurological manifestations (Table 3). Finally, 1,5% of patients who were not on mechanical ventilation had polyneuromyopathy. Whereas, among those who were on mechanical ventilation for 1–14 days, 15–28 days, and >28 days, 58,6%, 66,7%, and 76,9% had a polyneuromyopathy, respectively. This association was maintained in the

regression analysis, obtaining PR adjusted for COVID-19 severity of 1,59 (95% CI: 1,42–1,78), 1,67 (95% CI: 1,44–1,92), and 1,77 (95% CI: 1,61–1,93) in the mechanical ventilation categories for 1–7 days, 15–28 days, and >28 days, respectively, taking as a reference not having been on mechanical ventilation.

Table 3. Association between specific neurological manifestation and three outcomes (n = 293) †

Outcomes	Neurological manifestation, n (%)		*p*-value*	cPR (95% CI)	*p*-value	aPR (95% CI)	*p*-value
	Nonspecific	Specific					
COVID-19 severity			<0,001				
Nonsevere	76 (46,9)	20 (18,0)		.		.	
Severe	86 (53,1)	91 (82,0)		1,54 (1,30 to 1,83)	<0,001	1,11 (0,86 to 1,44)	0,426
Mechanical ventilation			<0,001				
No	139 (83,2)	55 (49,1)		.		.	
Yes	28 (16,8)	57 (50,9)		3,04 (2,07 to 4,46)	<0,001	2,08 (1,51 to 2,85)	<0,001
Clinical outcome			<0,001				
Discharged	147 (83,1)	73 (62,9)		.		.	
Died	30 (17,0)	43 (37,1)		2,19 (1,46 to 3,27)	<0,001	2,06 (1,40 to 3,04)	<0,001

† Some variables do not have 338 observations due to missing data; *Chi-square test; 95% CI: 95% Confidence Interval; cPR: crude prevalence ratio; aRP: Prevalence ratio adjusted for COVID-19 severity, mechanical ventilation, and mortality

DISCUSSION

A quarter of patients with COVID-19 had at least one neurological manifestation and the most frequent were nonspecific, such as headache and polyneuromyopathy, and among the specific ones were decreased delirium and altered levels of consciousness. In addition, serum D-dimer of ≥1ug/mL and lymphocytes count of <500 cells/mm^3 were more frequently associated with a specific neurological manifestation, which was associated with worse clinical outcomes.

Various frequencies of neurological symptoms or manifestations have been reported in patients with COVID-19, ranging from 7,0% to 80,0%[20,37]. Headache is one of the manifestations reported in patients with COVID-19 with the highest frequency of 69%[37], along with hypogeusia (44,5 to 69,8%) and hyposmia (51,1% to 67,4)[1,38]. Similarly, the present study described a significant proportion of patients reporting nonspecific neurological manifestations. However, a significant proportion of less common but more specific neurological manifestations, such as delirium and decreased levels of consciousness, were also reported. This supports the hypothesis that COVID-19 has a direct influence on the peripheric and central nervous system.

Patients with neurological manifestations may be more severely affected by COVID-19, in comparison than those without neurological manifestations, as previous studies have shown[16,35]. However, it is important to differentiate the possible mechanisms by which the neurological manifestation occurs. Therefore, the proposed classification of nonspecific (peripherical and miscellaneous) and specific (central) neurological manifestations allows for a better distinction between the effects of a systemic condition and those of pre-existing neurological diseases or peripheric invasion of the peripheral nervous system.[36]

High values of various serum inflammatory biomarkers have been described as part of a pro-inflammatory and hypercoagulable state, which serve as predictors of severity and mortality in patients with COVID-19[39]. We described association between having inflammatory biomarkers of severity, such as a serum D-dimer level of ≥1ug/mL and a lymphocyte count of <500/mm^3, and the presentation of a specific neurological manifestation, after adjusting for COVID-19 severity. The systemic inflammatory caused by the SARS-CoV-2 infection activate the hypothalamus-pituitary-adrenocortical axis which may lead to lymphopenia[40]. In addition, it causes platelet activation and aggregation along with endothelial activation which ultimate develop a hypercoagulability and prothrombotic state, expressed in high levels of D-dimer[41]. Our results suggest that some systemic inflammatory biomarkers could be implicated into the appearance or presence of a specific neurological manifestation affecting the central nervous system. However, this finding needs to be confirmed in future studies.

Our results suggest that patients with only nonspecific neurological manifestations, such as headache, anosmia, and ageusia, are more likely to had non-severe forms of COVID-19. These results are consistent with a previous systematic review that found that peripheral neurological symptoms in patients with COVID-19 were associated to non-severe outcomes and better long-term disability[42]. These manifestations of the peripherical nervous system could be expressions of the direct virus entry into nerve cells

from cranial nerves through angiotensin-converting enzyme 2 and neurolopin-1 receptors[43,44]. However, it is unclear that the SARS-CoV-2 infiltrate the central nervous system using this method[45]. On the other hand, the specific neurological manifestations, such as cerebrovascular events, ataxia, seizures, and decreased levels of consciousness, are associated with higher mortality and mechanical ventilation rates. These findings are consistent with a systematic review that included ten studies, which described that decreased consciousness and acute cerebrovascular events were more frequent in patients with severe COVID-19, than in non-severe cases[46]. These manifestations might indicate an affection of the nervous system causes by the COVID-19. The progression of the infection through other mechanisms, besides that invasion, such as the prothrombotic state[47], activation of endothelium cells[48], the anterograde and retrograde migration[49], and the neuroinflammatory and neuroimmune modulations[7], could favor the appearance of specific neurological manifestations in the most severe cases of COVID-19 infection.

It appears that the relationship between polyneuromyopathy and the number of days on mechanical ventilation may be explained by the development of similar mechanisms to polyneuropathy in critically ill patients[13], because most of our patients with polyneuromyopathy were on mechanical ventilation. A study from Sweden reported 11 patients with COVID-19 who developed critically ill polyneuropathy, the incidence being higher compared to a general population treated in 2019 (9,9% vs, 3,4%)[50]. In the present study, 50 cases of polyneuromyopathy were reported in COVID-19 patients, with the majority being directly correlated with longer durations of mechanical ventilation. To date, this frequency appears to be the highest reported in patients with COVID-19[45]. Polyneuropathy has been described in patients with COVID-19[51] as an specific involvement of muscle or peripheral nerves due to SARS-CoV-2 mimetics molecular infection[52], but also as part of the context of critical patient polyneuromyopathy[53]. Although the study did not differentiate between the two, the progressive association with the duration of mechanical ventilation supports the latter hypothesis.

It's important to note that the study has some limitations. For example, it only included hospitalized patients with respiratory COVID-19 symptoms and a confirmatory PCR-RT test and/or a tomographic compatible pattern of lung, so patients without COVID-19 may have been missed. However, the sample study were hospitalized during the first outbreak of COVID-19 pandemic in Peru, with a very high transmission rate [54], so the possibility of selection bias is low. Additionally, due to limited contact between neurologists and patients and restrictions on complementary examinations, such as lumbar puncture, magnetic resonance imaging, electromyography, and conduction velocity, some neurological manifestations could not be fully studied. Therefore, the etiology of polyneuromyopathy could not be adequately assessed[12]. Furthermore, insufficient control for all possible confounding variables and the risk of underreporting due to the high flow of patients who are hospitalized could generate a bias. The time of presentation of the neurological manifestation as initial symptom or during hospitalization could bias its association with the clinical outcomes, because it is likely that if the neurological manifestation presented during the hospitalization. However, despite these limitations, the study provides relevant clinical associations that are compatible with observations of previous studies and could be further expanded in future research.

In conclusion, neurological manifestations are frequent in patients who are hospitalized with COVID-19, and inflammatory biomarkers such as serum D-dimer and lymphocyte count were associated with specific manifestations of the central nervous system. In contrast, these specific neurological manifestations are associated with mechanical ventilation and higher mortality. Therefore, central neurological manifestations in hospitalized COVID-19 patients may be related to the systemic inflammation process, and not to a invasion of SARS-CoV-2 into the central nervous system.

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