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Short Communication

Neurological manifestations of COVID-19 in Indonesia: Assessment of the role of sex and age

Andi W. Sompa[1,2], Hartina Harun[2], Riska A. Mimika[3] and Rolly Riksanto[3*]

[1]Department of Neurology, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Makassar, Makassar, Indonesia; [2]Department of Neurology, Pelamonia Hospital, Makassar, Indonesia; [3]Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Makassar, Makassar, Indonesia

*Corresponding author: rolly_riksanto@med.unismuh.ac.id

Abstract

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can manifest in multiple organs. While the primary manifestations of COVID-19 occur in the respiratory system, other organ systems are also involved, including nervous systems that cause neurological symptoms. The aim of this study was to determine the neurological manifestations of COVID-19 patients and to assess the role of age and sex on neurological manifestation incidence. A cross-sectional study was conducted at Pelamonia Hospital, Makassar, Indonesia, among inpatient COVID-19 cases, using a total sampling method. Demographic data and neurological manifestations of the COVID-19 patients were collected. The associations between age and sex with the incidence of neurological symptoms were analyzed using the Chi-squared test. Out of 424 inpatients with COVID-19 cases, 62.3% were females, with the highest age group was 20–40 years (42.7%). The neurological symptoms were reported in 232 patients, accounting for approximately 54.7%. The most frequently reported neurological symptom was headache (n=104, 44.8%), followed by anosmia (n=44, 18.9%), ageusia (n=48, 20.6%), myopathy (n=14, 6%), stroke (n=10, 4.3%), seizure (n=5, 2.1%), and altered consciousness (n=7, 3%). An association was found between sex and the incidence of headache, myopathy, stroke, and altered consciousness. There was also an association between age and the incidence of headache and stroke. The study highlights that COVID-19 patients commonly exhibit neurological implications affecting the central nervous system and peripheral nervous system. Therefore, it is crucial for the early detection of neurological symptoms in COVID-19 cases to have better management.

Keywords: COVID-19, outbreak, neurological manifestation, neurological symptom, headache

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a rapid outbreak across various regions [1,2]. On January 30, 2020, the World Health Organization (WHO) declared it a Public Health Emergency of International Concern (PHEIC), and on March 11, 2020, WHO officially categorized it as a pandemic due to its spread across multiple countries [3-6]. COVID-19 causes mild to severe symptoms, with common clinical manifestations including fever, cough, diarrhea, and fatigue [7]. However, COVID-19 also affects other organ systems, such as the nervous system causing patients to experience various types of neurological symptoms, involving the central nervous system

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(CNS) resulting in non-specific symptoms like headache, dizziness, muscle pain, fatigue, ageusia, anosmia, as well as specific symptoms such as meningitis, stroke, acute transverse myelitis, and Guillain-Barre syndrome [7,8].

Neurological manifestations can further be categorized into CNS and peripheral nervous system manifestations. CNS manifestations present in 25% of COVID-19 cases, which include meningoencephalitis, cerebrovascular events, seizures, and CNS neuro-immunological disorders [8]. Meanwhile, peripheral nervous system involvement occurs in 10% of COVID-19 cases and encompasses symptoms such as ageusia, anosmia, Guillain-Barré syndrome (GBS), myalgia, post-infectious myasthenia gravis, critically ill polyneuropathy (CIN), and critically ill myopathy (CIM) [8].

Although the precise mechanism by which SARS-CoV-2 penetrates the CNS remains elusive, two plausible explanations have emerged including the hematogenous spread of SARS-CoV-2 from the systemic circulation to the cerebral circulation, where slower blood flow may facilitate viral damage to the capillary endothelium and brain entry [9], and dissemination through the cribriform plate and olfactory bulb [10]. Previous experimental models have demonstrated that other coronaviruses can also harm the nervous system and that the virus may directly target neurons in the cardiorespiratory center [10-12]. Initial observations during the COVID-19 pandemic, suggest that the SARS-CoV-2 may exhibit a higher affinity for CNS targets. However, study on neurological manifestations among COVID-19 patients in Indonesia is limited. The aim of this study was to determine the neurological manifestations in COVID-19 patients and to assess the role of age and sex on the incidence of neurological manifestations.

Methods

Study design

A cross-sectional study was conducted at Pelamonia Hospital, Makassar, Indonesia, between September and December 2021. Ethical approval was obtained from the Ethics Commission of Universitas Muhammadiyah Makassar, and the study was conducted following the guidelines. All confirmed COVID-19 patients hospitalized at Pelamonia Hospital were included. A total sampling was employed in this study due to the relatively small population size.

Patients and inclusion criteria

All patients confirmed as having COVID-19 and hospitalized at Pelamonia Hospital met the inclusion criteria for this study. The study did not establish any specific exclusion criteria, which could potentially introduce bias in assessing the neurological manifestations of COVID-19 patients.

Study variables

The data collected included age, gender, and neurologic manifestations. Neurologic manifestations assessed and collected in this study included headache, anosmia, ageusia, myopathy, stroke, seizures, and consciousness impairment.

Statistical analysis

Sample characteristics are summarized using frequency (n) and percentage (%). The Chi-squared or Fisher's exact test was used to assess the associations between age and sex with the incidence of neurological manifestations among COVID-19 patients as appropriate. All analyses were conducted using SPSS version 25 (SPSS, IBM Inc., Chicago, USA).

Results

Characteristics of patients and the incidence of neurological manifestations

A total of 424 hospitalized COVID-19 patients were included and the demographic characteristics (sex and age) are presented in **Table 1**. Among the patients, 37.7% were male, while 62.3% were female. Out of the total patients, 9.3% were under the age of 20 years; 42.7% were aged 20–40 years, 33.1% were aged 40–60 years, and 15% were 60 years or older (**Table 1**).

Table 1. Characteristics of hospitalized COVID-19 patients included in this study (n=424)

Variable	Subgroup	Frequency	Neurological manifestation		*p*-value
			No (n=192)	Yes (n=232)	
Sex	Male	160	54 (28.1%)	106 (45.6%)	0.040
	Female	264	138 (71.9%)	126 (54.4%)	
Age (year)	<20	39	15 (7.8%)	24 (10.3%)	0.032
	20–40	181	86 (44.8%)	95 (41%)	
	40–60	140	71 (36.9%)	69 (29.7%)	
	>60	64	20 (10.5)	44 (19%)	

The distribution of neurological manifestations based on sex and age is presented in **Table 1**. Out of the 160 male patients, 54 (37.6%) exhibited neurological manifestations, while among the 264 female patients, 138 (62.4%) had neurological manifestations, suggesting that manifestations were significantly higher in females than in males (p=0.040) (**Table 1**). Among patients aged 40–60 years, 71 out of 140 patients experienced neurological manifestations, while 20 out of 64 patients aged 60 years and older exhibited neurological manifestations. Our data also suggested that age group was associated with the incidence of neurological manifestations (p=0.032) (**Table 1**).

Types of neurological manifestation

The neurological manifestations reported by the patients in this study are presented in **Table 2**. A total of 232 patients (54.8%) presented at least one neurological manifestation of which 44.8% had headache, 20.6% ageusia, 18.9% anosmia, and 6% had myopathy (**Table 2**). The neurological manifestations were not found in 192 patients (45.3%).

Table 2. Distribution of neurological manifestation of COVID-19 patients (n=232)

Neurological manifestation	Frequency	Percentage
Headache	104	44.8
Anosmia	44	18.9
Ageusia	48	20.6
Myopathy	14	6.0
Stroke	10	4.3
Seizure	5	2.1
Unconsciousness	7	3.0

Association between sex and neurological manifestations

The associations of sex and neurological manifestations in COVID-19 patients are presented in **Table 3**. Our analysis indicated a significant association between sex and the occurrence of headaches in COVID patients (p=0.013). Our study also suggested a significant association between sex and the occurrence of myopathy (p=0.001), stroke (p=0.032) and altered consciousness (p=0.014). However, no significant association was observed between sex and the incidence of anosmia, ageusia and seizure with p=0.170, p=0.137 and p=0.121, respectively (**Table 3**).

Table 3. Association between sex and the presence of neurological manifestations (n=232)

Neurological manifestation	Sex, n (%)		*p*-value
	Male	Female	
Headache			0.013
Yes	44 (42.3)	60 (57.7)	
No	38 (29.6)	90 (70.4)	
Anosmia			0.170
Yes	17 (38.6)	27 (61.4)	
No	43 (22.8)	145 (77.2)	
Ageusia			0.137
Yes	21 (43.75)	27 (56.25)	
No	64 (34.8)	120 (65.2)	
Myopathy			0.001
Yes	10 (71.4)	4 (28.6)	
No	39 (17.8)	179 (81.2)	
Stroke			0.032

Neurological manifestation	Sex, n (%)		*p*-value
	Male	Female	
Yes	6 (60)	4 (40)	
No	36 (16.3)	186 (83.7)	
Seizure			0.121
Yes	3 (60)	2 (40)	
No	102 (44.9)	125 (65.1)	
Altered consciousness			0.014
Yes	5 (71.4)	2 (28.6)	
No	72 (32)	153 (68)	

Association between age and neurological manifestations

The associations between age and the incidence of neurological manifestations in COVID-19 patients are presented in **Table 4**. Our Chi-squared test indicated a significant association between age and the presence of headache (p=0.004) and stroke (p=0.006) in hospitalized COVID patients. However, the data suggested that age was not associated with anosmia (p=0.100), ageusia (p=0.056), myopathy (p=0.145), and seizure (p=0.062), altered consciousness (p=0.215) in hospitalized COVID patients (**Table 4**).

Table 4. Association between age and the presence of neurological manifestations (n=232)

Neurological manifestation	Age group, n (%)				*p*-value
	<20 year	20–40 year	40–60 year	>60 year	
Headache					0.004
Yes	10 (9.6)	67 (64.5)	22 (21.1)	5 (4.8)	
No	15 (11.7)	70 (54.7)	31 (24.2)	12 (9.4)	
Anosmia					0.100
Yes	4 (9.1)	11 (25.0)	14 (31.8)	15 (34.1)	
No	32 (17)	59 (31.4)	72 (38.3)	25 (13.3)	
Ageusia					0.056
Yes	4 (8.4)	7 (14.6)	22 (45.8)	15 (31.2)	
No	21 (11.4)	65 (35.3)	68 (36.9)	30 (16.4)	
Myopathy					0.145
Yes	2 (14.2)	4 (28.6)	4 (28.6)	4 (28.6)	
No	57 (26.1)	54 (24.7)	60 (27.6)	47 (21.6)	
Stroke					0.006
Yes	0 (0.0)	2 (20.0)	5 (50.0)	3 (30.0)	
No	0 (0.0)	39 (17.6)	115 (51.8)	68 (30.6)	
Seizure					0.062
Yes	2 (40.0)	1 (20.0)	1 (20.0)	1 (20.0)	
No	50 (22.0)	35 (15.4)	104 (45.8)	38 (16.8)	
Altered consciousness					0.215
Yes	2 (28.6)	3 (42.8)	1 (14.3)	1 (14.3)	
No	30 (13.3)	35 (15.5)	90 (40.0)	70 (31.1)	

Discussion

This study reported neurological manifestations were more present in females, representing over 50% of the total cases. This finding aligns with a study that reported approximately 62.3% of COVID-19 patients were female [13]. This difference may be explained by the fact that females have stronger adaptive and innate immune systems due to the presence of dominant X chromosomes. Additionally, the X chromosome carries effectors that can regulate the activation of cytokine receptors, which are immune system regulators and mediators. Smoking, often in males, contributes to a higher risk of COVID-19 as nicotine in cigarettes can activate angiotensin-converting enzyme-2 (ACE-2) receptors in the lungs and may facilitate the attachment of SARS-CoV-2 to respiratory cells [14,15]. On the contrary, a study conducted on the Italian population, after implementing lockdown measures, reported a higher prevalence of COVID-19 among females. However, the increased infection rate among females post-lockdown might due to a higher number of females working in healthcare compared to males [16].

The majority of patients in this study were aged between 20–40 years old, which agrees with similar findings of a previous study that revealed that the majority of COVID-19 patients were in the 26–35 age range. This age group may be described by individuals who are typically more socially active, increasing their susceptibility to disease transmission [17]. In addition, a study

showed that those aged 60 and older have a higher risk of COVID-19 due to the prevalence of comorbidities such as hypertension [18]. Age and natural immunity levels are correlated; since natural immunity declines with age, older individuals are more likely to become infected [19]. Furthermore, polypharmacy is often seen in older individuals to manage comorbidities, resulting in a decline in organ function [20]. Recent studies explain that patients over 50 years of age are more likely to experience excessive ACE-2 expression due to decreased immunity, declining organ function, the presence of comorbidities, and other factors that increase the risk of death [21,22].

Almost one-quarter out of all COVID-19 patients in this study experienced symptoms of headache. In confirming the results, a study found that the most common neurological symptom among COVID-19 patients was headache, occurring in at least 6.5% of cases. Headaches can also manifest as the initial and only symptom in infected individuals [19,20,23-30]. Additionally, a study reported a prevalence of approximately 12% for headaches among COVID-19 patients, with many patients encountering headaches as their initial symptom. Headaches are related to the release of pro-inflammatory mediators and cytokines that stimulate the trigeminal perivascular nerve endings, leading to pain [20]. Significant associations were reported in this study between age and sex with the presence of headaches. This finding is in consonance with a study conducted in Nigeria, showing a prevalence of primary headaches at 39.3%, with a higher occurrence in women (p<0.0001), indicating significant results [31].

A study revealed myopathy was present in 3.1% of COVID-19 patients, often developing around the 12th day since symptom onset [23]. Myopathy can be influenced by severe respiratory problems, systemic inflammatory response, and sepsis. Additionally, the direct invasion of muscle cells by the virus through ACE-2 receptors is another mechanism for myopathy, as ACE-2 receptors are expressed in muscle cells [24]. A study reported the prevalence of altered consciousness in COVID-19 patients ranging from 1.4% to 6.9%, with a higher incidence in patients with comorbidities or critical conditions. Altered consciousness was associated with various causes such as encephalopathy, sepsis, and metabolic disorders [28]. This study demonstrated a relationship between sex with myopathy and altered consciousness, whereas there was no association between age with myopathy and altered consciousness. Unfortunately, there have not been any previous studies that have investigated these two aspects.

Stroke was reported in 2–6% of COVID-19 patients, especially among those over 60 years old with risk factors such as hypertension, diabetes, and vascular diseases [25]. Cerebrovascular diseases like ischemic stroke in COVID-19 patients may result from hypercoagulation and increased vascular thrombosis due to elevated ACE-2 receptor expression, ultimately leading to increased thrombus formation [26]. Based on the study results, it is evident that stroke occurrences were most observed in patients over 40 years of age, particularly in males. The study indicated a relationship between sex and age regarding stroke occurrences. This aligns with a study that revealed with a ratio of 2:1, males have a greater tendency to suffer strokes in adulthood compared to females. Although males are more vulnerable to stroke at a younger age, females catch up after reaching menopause due to a decrease in the estrogen hormone, which plays a protective role in females. Moreover, in early adulthood (18–40 years), males have a 20% higher risk of experiencing strokes compared to females. However, females of any age have a 50% higher risk of subarachnoid hemorrhage. Thus, both males and females have an equal likelihood of experiencing a stroke in early adulthood [32].

Conclusion

Our data indicated that 54.8% of hospitalized COVID-19 patients experienced neurological manifestations, including headache (44.8%), anosmia (18.9%), ageusia (20.6%), myopathy (6%), stroke (4.3%), seizure (2.1%), and consciousness impairment (3%). There was a relationship between sex and the incidence of headaches, myopathy, stroke, and unconsciousness. Age was associated with the incidence of headaches and stroke among the patients.

Ethics approval

Ethical approval was obtained from the Ethical Committee of Faculty of Medicine, Universitas Muhammadiyah Makassar, Indonesia (013/UM.PKE/X/43/2021).

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Conflict of interest

The authors declare no conflict of interest.

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Underlying data

All data underlying the results can be requested from the corresponding author.

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