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ORIGINAL ARTICLE

Clinical characteristics of 365 hospitalized COVID-19 patients with neurological symptoms: an observational study

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Abstract

Objective Since the beginning of the COVID-19 pandemic, a number of COVID-related neurological manifestations have been reported. We aimed to categorize the features of hospitalized COVID-19 patients who experienced neurological symptoms.

Methods In this descriptive, cross-sectional study, we enrolled all patients hospitalized with COVID-19 who experienced neurological symptoms in two hospitals in Tehran. Diagnosis of COVID-19 was established by PCR tests or computed tomography of the chest combined with COVID-19 clinical findings. The clinical characteristics, laboratory data, and imaging findings from 365 patients were analyzed.

Results The average patient age was 59.2 ± 16.7 years and included 213 males and 152 females. The most prevalent neurological symptoms were headache (56.2%), impaired consciousness (55%), and dizziness (20.5%). During hospitalization, most of the patients did not require mechanical ventilation (81.9%). The percentage of patients with end-organ damage was 9% and mortality was 15%. Regression analysis on the neurological symptoms indicated that the mortality rate of patients with headaches was 84% lower than for the other neurological symptoms. Hyperglycemia was significantly related with end-organ damage and mortality ($p = 0.029$, $p = 0.08$, respectively). New vascular lesions were evident on brain MRIs of 9 patients and brain CTs of 16 patients.

Conclusion Among the neurological symptoms of patients with COVID-19, headache appeared to indicate a protective factor against development of end-organ damage as well as mortality.

Keywords COVID-19 · Neurological manifestations · Headache · End-organ damage · Mortality · Unconsciousness

Introduction

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become the gravest pandemic of our generation [1]. The main clinical manifestations of COVID-19 are respiratory symptoms on the spectrum of mild flu to lethal acute respiratory distress syndrome (ARDS) [2]. Since the beginning of the outbreak, a growing number of reports have linked neurological manifestations such as cerebrovascular events, encephalitis, and

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acute polyneuropathy to COVID-19. One observational study reported that the frequency of neurologic symptoms among COVID-19 patients was approximately 36.4% [3].

Patients who demonstrate COVID-19-related neurological problems may exhibit a more severe disease course and worse outcomes [3]. Some of the neurological manifestations, such as cerebrovascular accidents and encephalitis, could have long-term complications that could have unfavorable effects on a COVID-19 survivor's life [4]. Furthermore, some COVID-19 patients have exclusively exhibited isolated neurological manifestations rather than the common respiratory or systemic features of this disease [5]. It is evident that physicians must be vigilant about the neurological aspects of this disease. This study reports on the clinical characteristics, laboratory results, and imaging findings and their association with disease mortality of hospitalized COVID-19 patients who exhibited neurological symptoms.

Methods

Study design

This descriptive, cross-sectional study was conducted in Sina and Ziaeian Hospitals from 20 February to 20 June 2020. Both hospitals are affiliated with Tehran University of Medical Sciences. The present study has been approved by the ethics committee of Tehran University of Medical Sciences (approval number: IR.TUMS.VCR.REC.1399.121).

Patients and data collection

We enrolled all COVID-19 patients with neurological symptoms who were hospitalized in the two hospitals during the specified time period. The COVID-19 diagnoses were based on positive reverse transcription-polymerase chain reaction (RT-PCR) of the oropharyngeal or clinical presentations compatible with COVID-19 (fever, cough, shortness of breath) and typical COVID-19 findings on chest computed tomography (CT). A radiologist interpreted the chest CT scans. The grading of lung involvement was according to a semi-quantitative scoring system where each lobe of the lung is scored visually from 0 to 5 as follows: (0) no involvement; (1) less than 5% involvement; (2) 5–25% involvement; (3) 26–50% involvement; (4) 51–75% involvement; (5) 76–100% involvement. The scores of all lobes were summed and severity scores of 1–5, 6–14, and 15–25 were denoted mild, moderate, and severe lung involvement, respectively [6].

Data regarding demographic features, clinical manifestations (both systemic and neurologic), past medical history, habitual history, laboratory results, imaging findings, and disease outcome were extracted from the medical records. The COVID-19 outcome was evaluated by the presence of end-organ damage (acute liver failure, acute renal failure, ARDS, acute cardiovascular damage, hematological abnormalities), ventilation support dependence, or mortality. The data were recorded by physicians and nurses on predesigned report forms and were further entered into an electronic database [7]. A neurologist reviewed all brain CT scans and brain MRI images.

Neurological manifestations included vertigo, dizziness, ataxia, headache, seizure, focal neurologic deficits, decreased level of consciousness, neck stiffness, and delirium. These were assessed carefully while collecting the patient history and during the physical examination. Focal neurological deficits were defined as one of the following types of impairment: aphasia, paresis, dysarthria, hemianopia, cranial nerve palsy, and hemisensory. Hemisensory deficit was defined as a loss of sensation on one side of the body.

A decreased level of consciousness was characterized by a reduction in the Glasgow coma scale. Based on DSM-5 criteria, delirium was considered to be a fluctuating disturbance of attention and awareness along with an additional cognitive impairment (e.g., perception, memory deficit, language, disorientation, visuospatial ability) which developed within a short period of time and could not be explained by a neurocognitive disorder or deep coma [8].

Statistical analysis

All statistical analyses were done in SPSS version 26. The descriptive data are presented as the mean of normally distributed variables and the median for non-normal variables. Categorical variables have been calculated as percentages. Two independent variables were analyzed by a *t* test or Mann–Whitney *U* test for non-parametric variables. Comparison between multiple groups was done by analysis of variance or the Kruskal–Wallis rank-sum test. The chi-squared test was performed to compare categorical variables data. Spearman's non-parametric correlation was used for the association between non-parametric variables and multivariable regression analysis was done to obtain a predictor factor. Regression was bivariable so that our dependent variables were prognostic factors such as mortality, mechanical ventilation, and end-organ damage. Covariates were classified as demographic, laboratory, and symptoms and were analyzed separately, with each dependent variable. The level of statistically significance was taken as $p < 0.05$.

Results

Demographic and baseline characteristics

Table 1 shows the demographic data as well as clinical characteristics of the selected patients. A total of 365 COVID-19

patients with neurological symptoms were recruited from the electronic database. The median age was 59.2 ± 16.7 years with 58.4% being male and 41.6% female. About 9.1% of patients developed end-organ damage and 15.2% of patients eventually died. Regression analysis of the demographic variables indicated that the risk of mortality was increased with higher age (OR: 1.03, $p = 0.001$). There was no meaningful relationship between gender, cigarette use, opium use and mortality ($p = 0.83$, $p = 0.065$, $p = 0.17$, respectively).

Upon admission, the average oxygen saturation percentage (SPO_2) was 90.4% and 47% of patients had fevers. Those patients with a higher SPO_2 values had lower rates of mortality ($p = 0.005$). The duration of hospitalization varied around an average of 5.9 days. Most patients did not require ventilation (81.9%). Patients who were ventilated showed more prevalent end-organ damage ($p \leq 0.001$ and $r = 0.439$) and an increased mortality rate ($p \leq 0.001$ and $r = 0.724$). The mortality rate in patients with tachycardia (pulse rate > 125) was about 5.6 times higher than in other patients ($p = 0.017$). There was no relationship between systolic blood pressure, diastolic blood pressure, respiratory rate, and fever and mortality ($p = 0.735$, $p = 0.62$, $p = 0.091$, $p = 0.198$, respectively).

Aside from the respiratory symptoms of COVID-19, the most common accompanying symptoms among these patients were gastrointestinal complaints (37.5%) followed by hypertension (34.3%).

Neurological signs and symptoms

The patients had diverse neurological manifestations, with headache being the most common (56.2%) (Table 1). Regression analysis of neurological symptoms upon admission indicated that patients with headache experienced an 84% lower mortality rate than the other patients ($p \leq 0.001$). Patients who were conscious upon arrival also had a 67% lower mortality rate than those who were not conscious ($p = 0.003$).

The presence of headache and being conscious reduced the need for ventilation by 76% and 60%, respectively ($p \leq 0.001$, $p = 0.007$). These two factors also decreased the risk of end-organ damage by 56% and 75%, respectively. Six percent of patients who presented were delirious and these patients had a 3.9 times higher risk of eventual mortality than the other patients. Five patients diagnosed with

Table 1 Demographic and clinical characteristics

	Number (*N*%) or mean (*M*) (SD)		Number (*N*%)	Mortality (%)
Sex		Past medical history		
Male	213 (58.4)	Comorbidity	219 (60)	
Female	152 (41.6)	GI	137 (37.5)	
Age (years old)		Hypertension	125 (34.3)	
Female	60.88 (16.6)	Diabetes	89 (24.5)	
Male	58.08 (16.7)	CVD	68 (18.7)	
Total	59.24 (16.7)	Liver disease	19 (5.2)	
Vital Sign		Asthma	10 (2.7)	
BP systolic (M)	122.66 (24.58)	Malignancy	9 (2.5)	
BP diastolic (M)	75.95 (16.61)	Lung disease	8 (2.2)	
Oxygen saturation (M)	90.44 (8.82)	Rheumatologic ESRD	6 (1.6) 5 (1.4)	
Respiratory rate (*N*) < 24	264 (85.2)	Neurological manifestations		
Respiratory rate (*N*) > 24	46 (14.8)	Headache	205 (56.2)	7.3
Pulse rate (*N*) < 125	336 (96.8)	Impaired consciousness	201 (55)	20.4
Pulse rate (*N*) > 125	11 (3.2)	Dizziness	75 (20.5)	12
Fever (*N*)	171 (47.5)	Vertigo	65 (17.8)	12.3
Level of consciousness		Ataxia	32 (8.8)	6.3
Conscious	153 (43.2)	Seizure	24 (6.6)	20.8
Decreased level of consciousness (GSC < 15)	201 (56.8)	Delirium	22 (6)	45.5
Habitual history		FND	17 (4.7)	17.6
Cigarette	28 (7.7)			
Opium	19 (5.2)			

SD standard deviation; *BP* blood pressure; *GSC* Glasgow coma scale; *GI* gastrointestinal; *CVD* cerebrovascular disease; *ESRD* end-stage renal disease; *FND* focal neurological deficits

delirium were less than 60 years of age and, among them, the mortality rate was 20%. In Table 2, binary regression analysis shows the relationship between all neurological symptoms and prognostic factors.

Paraclinical findings

The laboratory data and imaging findings are listed in Table 3. Regression analysis on the laboratory results showed that the risk of mortality was 3.6 times higher in patients who had leukocytosis (white blood cell (WBC) > 11,000; $p \leq 0.001$). Leukopenia (WBC < 4000) had no significant effect on mortality ($p = 0.32$). Hyperglycemia (blood sugar > 200 mg/dl) upon arrival had a significant relationship with end-organ damage and mortality ($p = 0.029$, $p = 0.08$, respectively). Patients with hyperglycemia recorded end-organ damage and mortality increases of 4.7 and 3 times, respectively, over the other patients. Among the laboratory findings, there was a significant relationship between headache and CPK and D-dimer levels, which the values were significantly lower in patients with headache ($p = 0.001$, $p = 0.015$, respectively).

Table 2 Binary regression analysis shows the relationship between all neurological symptoms and prognostic factors

Neurological symptoms	Mechanical ventilation	End-organ damage	Mortality
Impaired consciousness	**0.007**	**0.004**	**0.003**
Headache	**0.001**	**0.057**	**0.000**
Vertigo	0.793	0.945	0.583
Seizure	0.887	0.720	0.251
Delirium	**0.013**	0.422	**0.003**
Dizziness	0.305	0.278	0.594
Focal neurologic deficit	0.751	0.761	0.547
Ataxia	0.798	0.303	0.252

P value of < 0.05 was considered statistically significant. The bold formatting in the table means significant *p*-value

Lumbar puncture was performed on 30 patients with unexplained loss of consciousness that could not be justified by metabolic disorders, hypoxia, or sepsis. There was no evidence of SARS-CoV-2 RNA or pleocytosis (WBC > 5) in their cerebrospinal fluid (CSF). None of the patients had a positive oligoclonal band.

Table 3 Laboratory and imaging findings

Number (%)	Mean ± SD (mode)		
Chest CT findings			
Valid chest CT	273	WBC (10^3 /L)	8 ± 5.2
Mild	58 (15.9)	Lymphocyte (%)	21% ± 11.3
Moderate	111 (30.5)	Hemoglobin (g/dL)	13.5 ± 2.1
Severe	104 (28.6)	Platelet (10^3/L)	222.6 ± 96
Brain CT findings		Glucose (mg/dL)	151 ± 95.8
Valid CT scan	41 (100)	BUN (mg/dL)	37.6 ± 38.6
Normal CT	11 (26.8)	Creatinine (mg/dL)	1.3 ± 1.1
New ischemic event	16 (39)	Sodium (mEq/L)	135.3 ± 9.3
Nonspecific findings	10 (24.5)	Potassium (mEq/L)	4.3 ± 0.6
ICH	4 (9.7)	Calcium (mg/dL)	8.8 ± 0.8
Brain MRI findings		PT (s)	15.6 ± 9.7
Valid MRI	34 (100)	PTT (s)	35 ± 14.3
Normal MRI	16 (47)	INR	1.2 ± 0.4
New ischemic event	9 (26.5)	AST (U/L)	50.4 ± 31.9
Nonspecific findings	8 (23.5)	ALT (U/L)	40.1 ± 27.8
Small-ICH-Putamen	1 (3)	LH (U/L)	546 ± 260.2
Oropharyngeal sampling (COVID-19 PCR)		CPK (U/L)	245.8 ± 319.1
Valid number	341 (100)	D-dimer (ng/mL)	1353 ± 2080.6
Positive	195 (57.2)	Ferritin (ng/mL)	517.5 ± 543.5
Negative	146 (42.8)	Troponin (ng/L)	267 ± 2356.2
		ESR (mm/h)	49.7 ± 31.9
		CRP	50.7 ± 52.3

CT computed tomography; *SD* standard deviation; *ICH* intracranial hemorrhage; *MRI* magnetic resonance imaging; *PCR* polymerase chain reaction; *BUN* blood urea nitrogen; *PT* prothrombin time; *PTT* partial thromboplastin time; *INR* international normalized ratio; *AST* aspartate transaminase; *ALT* alanine transaminase; *LDH* lactate dehydrogenase; *CPK* creatine phosphokinase; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein

Before treatment initiation, 273 patients underwent chest CT scans and all showed some evidence of lung involvement. Sub-group analysis of individuals receiving chest CTs showed that those patients with severe lung involvement had a higher risk of end-organ damage (6.5 times), mortality (4 times), and requiring mechanical ventilation (3.8 times; $p=0.014$, $p=0.05$, and $p=0.05$, respectively). Amongst the neurological symptoms, there was a significant relationship between dizziness, vertigo, ataxia, and severity of lung involvement ($p=0.019$, $p=0.002$, and $p=0.022$, respectively). Analysis of brain magnetic resonance imaging (MRI) showed that those patients who presented in a delirious state on arrival were 9.2 times more likely to show acute vascular lesions on their MRI ($p=0.014$).

Data analysis on a subset of patients with the positive COVID-19 PCR test

The oropharyngeal PCR was positive in 195 patients. We found that the positive PCR test was not a predictor of mortality, end-organ damage, and need for mechanical ventilation ($p=0.70$, $p=0.07$, $p=0.63$, respectively). Upon admission, those patients with higher SPO2 values had lower rates of mortality ($p\leq0.001$). The mortality rate in patients with tachycardia (pulse rate > 125) was about 4.8 times higher than in other patients ($p=0.027$).

Regression analysis of neurological symptoms showed that patients with headache had an 85% lower mortality rate than the other patients ($p\leq0.001$). The presence of headache reduced the need for ventilation by 80% ($p\leq0.001$). Patients who were conscious upon admission also had a 63% lower mortality rate than those who were not conscious ($p=0.044$). Other neurological symptoms did not have a significant relationship with the prognostic factors.

Binary regression analysis on the laboratory findings showed that the risk of mortality was 3.3 times higher in patients who had leukocytosis ($p=0.004$). Leukopenia had no significant effect on mortality ($p=0.38$). Hyperglycemia upon arrival increased the mortality rate by 2.6 times ($p=0.019$). This factor also increased the risk of end-organ damage by 2.5 times and the risk of ventilation by 3.1 times ($p=0.041$, $p=0.003$, respectively).

Discussion

Since the beginning of the COVID-19 outbreak, neurologists have been curious about the neurological aspects of the disease. The more research is done on the neurological characteristics of COVID-19, the more we can learn about the exact behavior of SARS-CoV-2. Several potential mechanisms have been proposed for the development of neurological symptoms with COVID-19. Like other known respiratory viruses (measles, adenovirus, influenza), SARS-CoV-2 can invade the central nervous system (CNS) directly through retrograde axonal transport [9]. Detection of SARS-CoV-2 RNA in the CSF could be evidence of the neurotropism nature of this virus [10]. In our study, no evidence of the direct invasion of the CNS by the SARS-CoV-2 was detected. It also has been speculated that immune-mediated mechanisms, rather than direct involvement, are responsible for the neurological symptoms exhibited by COVID-19 patients [11], but we did not detect an oligoclonal band in the CSF studies of patients.

On the other side, systemic complications following COVID-19 can be attributed to neurological diseases. An initial report from Wuhan has shown that neurological symptoms were more prevalent in patients who had more severe COVID-19 symptoms [3]. It is known that SARS-CoV-2 can cause widespread systemic abnormalities, including electrolyte disturbances, hypercoagulation, cytokine storms, and disseminated intravascular coagulation which could result in multiple neurological complications [12]. The results of laboratory analysis indicated that a higher blood glucose level was linked with the worst rates for mortality and end-organ damage. Even COVID-19 patients who had never been diagnosed with diabetes developed hyperglycemia following insulin resistance induced by a cytokine storm. It has been shown that acute hyperglycemia can result in endothelial dysfunction, thrombosis, and inflammation by producing oxidative stress [13].

In our study, headache was the most frequently observed neurological symptom (56%). Although the frequency of headache in COVID-19 was lower in initial reports (8%), recent studies have shown that headache is quite common (64.4%) [3, 14]. It is likely that, at the beginning of the COVID-19 pandemic, neither physicians nor patients focused on extrapulmonary or less serious symptoms. In a recent multicenter prospective study conducted to evaluate the association between neurologic symptoms in COVID-19 patients and disease prognosis, headache had a negative correlation with severity (adjusted OR = 0.52, 95% CI = 0.32–0.85) and mortality (adjusted OR = 0.37, 95% CI = 0.75–0.92) [15].

Our findings were consistent with those of the previous study. They showed that, among the COVID-19-related neurological symptoms, headache appeared to be a protective factor, because patients who presented with headaches were 56% less likely to have end-organ damage. In addition, D-dimer values were significantly lower in patients with headaches, which could indicate a less severe systemic infection. Although the exact reason behind these COVID-19-related headaches is not clear, possible underlying mechanisms have been proposed. SARS-CoV-2 could invade the trigeminal nerve through the nasal or oral cavity. Frequent reports about the association of headache

and anosmia and ageusia could support this hypothesis [16]. Unfortunately, in the present study, the anosmia and ageusia were not recorded as symptoms.

Another likely cause of headache in COVID-19 is related to the gut–brain axis. Studies have shown an association between headache and gastrointestinal symptoms in COVID-19 patients [16]. In our study, 42.4% of patients with headaches exhibited concurrent gastrointestinal symptoms, which is a decisive percentage. Other systemic inflammatory responses following infection with SARS-CoV-2, including elevated levels of tumor necrosis factor-α (TNF-α), interleukin1β (IL-1β), interleukin-6 (IL-6), and interleukin IL-8, could cause headaches [17].

The second prevalent symptom in our study was the altered level of consciousness (55%). In a meta-analysis [18], the overall pooled prevalence of altered level of consciousness in COVID-19 patients from two studies with a total of 2848 cases were 3.8% (95% CIs: 0.16–12.04) with a high level of heterogeneity ($I^2 = 94.8\%$). When afflicted with COVID-19, patients can experience different degrees of decreased consciousness from reasons such as direct invasion of the virus into the CNS, inflammatory responses, cerebrovascular accidents, seizure, hypoxia, sepsis, and metabolic abnormalities [19]. Overall, the reasons behind the decreased level of consciousness could be explained by encephalitis or encephalopathy. In the present study, not only did patients not have brain lesions compatible with encephalitis on their brain imaging, but they also showed no evidence of infection of the CSF. This indicates that the decreased level of consciousness in our patients was more likely due to encephalopathy rather than encephalitis. In the present study, being completely conscious upon admission was associated with better outcomes.

As based on DSM-5 criteria, six percent of our patients were diagnosed with delirium. It has been shown that delirious COVID-19 patients experience more severe disease. Likewise, our delirious patients were more likely to experience in-hospital mortality. Of note, the possibility of new vascular lesions in the brain MRI was greater in patients who presented with delirium. A case report has shown that encephalopathy can present as a sentinel symptom of acute ischemic stroke in COVID-19 patients [20]. In another study, the administration of low molecular weight heparin to COVID-19 patients was associated with a decreased incidence of delirium [21]. It appears that inflammatory responses which occur in COVID-19 can lead to development of thrombosis; therefore, prescribing anticoagulants could potentially prevent thrombosis and subsequently decrease delirium.

Due to the high number of negative COVID-19 PCR tests in our study, we performed the same statistical analyses on a subset of patients with the positive COVID-19 PCR to confirm the validity of our results, and the results indicated consistency.

Given the population of this study was the hospitalized COVID-19 patients who might have a more severe course, the results of this study cannot be generalizable. Furthermore, we believe that our study has several limitations. First, as in other observational retrospective studies, we did not follow our patients for an extensive time. In the existing literature, several post-COVID-19 neurological manifestations have been reported. These include Guillain–Barre syndrome, NMDA encephalitis, and status epilepticus [22]. We only collected data about the acute phase of COVID-19; therefore, neurological disorders that developed after COVID-19 have not been included. Second, our data were collected from an electronic database, which might cause bias and decreased reliability and generalizability. Third, we did not include headache characteristics in our electronic database. In this study, headache was the most prevalent neurological symptom and was associated with a favorable prognosis compared to other symptoms. It would have been better to know more about the headache symptoms. Fourth, because the number of non-specific neurological symptoms was much higher than those for specific neurologic syndromes, we were unable to divide them into specific neurological categories of cerebrovascular events, encephalitis, and polyneuropathies for separate analysis.

In conclusion, we have found that multiple neurological symptoms could be associated with COVID-19 disease. Clinicians should bear in mind that neurological symptoms can be part of the COVID-19 spectrum and that not all these symptoms necessarily worsen the prognosis.

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Availability of data and materials All data not published within this article will be made available by request from any qualified investigator.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Lythgoe MP, Middleton P (2020) Ongoing clinical trials for the management of the COVID-19 pandemic. Trends Pharmacol Sci 41(6):363–382
2. Krishnan A, Hamilton JP, Alqahtani SA, Woreta TAA (2019) A narrative review of coronavirus disease 2019 (COVID-19): clinical, epidemiological characteristics, and systemic manifestations. Intern Emerg Med 2021:1–6
3. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X (2020) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 77(6):683–690

4. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T (2020) Neurological associations of COVID-19. Lancet Neurol. https://doi.org/10.2139/ssrn.3589350
5. Nepal G, Rehrig JH, Shrestha GS, Shing YK, Yadav JK, Ojha R, Pokhrel G, Tu ZL, Huang DY (2020) Neurological manifestations of COVID-19: a systematic review. Crit Care 24(1):1–1
6. Tabatabaei SM, Rajebi H, Moghaddas F, Ghasemiadl M, Talari H (2020) Chest CT in COVID-19 pneumonia: what are the findings in mid-term follow-up? Emerg Radiol 27(6):711–719
7. Talebpour M, Hadadi A, Oraii A, Ashraf H (2020) Rationale and design of a registry in a referral and educational medical center in Tehran, Iran: Sina Hospital Covid-19 Registry (SHCo-19R). Front Emerg Med 4(2s):e53
8. Adamis D, Rooney S, Meagher D, Mulligan O, McCarthy G (2015) A comparison of delirium diagnosis in elderly medical inpatients using the CAM, DRS-R98, DSM-IV and DSM-5 criteria. Int Psychogeriatr 27(6):883
9. Huang J, Zheng M, Tang X, Chen Y, Tong A, Zhou L (2020) Potential of SARS-CoV-2 to cause CNS infection: biologic fundamental and clinical experience. Front Neurol 11:659
10 Karvigh SA, Vahabizad F, Mirhadi MS, Banihashemi G, Montazeri M (2021) COVID-19-related refractory status epilepticus with the presence of SARS-CoV-2 (RNA) in the CSF: a case report. Neurol Sci 42:2611–2614
11. Guilmot A, Slootjes SM, Sellimi A, Bronchain M, Hanseeuw B, Belkhir L, Yombi JC, De Greef J, Pothen L, Yildiz H, Duprez T (2021) Immune-mediated neurological syndromes in SARS-CoV-2-infected patients. J Neurol 268(3):751–757
12. Tsivgoulis G, Palaiodimou L, Katsanos AH, Caso V, Köhrmann M, Molina C, Cordonnier C, Fischer U, Kelly P, Sharma VK, Chan AC (2020) Neurological manifestations and implications of COVID-19 pandemic. Ther Adv Neurol Disord 13:1756286420932036
13 Ceriello A (2020) Hyperglycemia and COVID-19: What was known and what is really new? Diabetes Res Clin Pract 167:108383
14. Sampaio Rocha-Filho PA, Magalhães JE (2020) Headache associated with COVID-19: Frequency, characteristics and association with anosmia and ageusia. Cephalalgia 40(13):1443–1451
15. Amanat M, Rezaei N, Roozbeh M, Shojaei M, Tafakhori A, Zoghi A, Darazam IA, Salehi M, Karimialavijeh E, Lima BS, Garakani A (2021) Neurological manifestations as the predictors of severity and mortality in hospitalized individuals with COVID-19: a multicenter prospective clinical study. BMC Neurol 21(1):1–2
16. Uygun Ö, Ertaş M, Ekizoğlu E, Bolay H, Özge A, Orhan EK, Çağatay AA, Baykan B (2020) Headache characteristics in COVID-19 pandemic-a survey study. J Headache Pain 21(1):1
17. Arzani M, Jahromi SR, Ghorbani Z, Vahabizad F, Martelletti P, Ghaemi A, Sacco S, Togha M (2020) Gut-brain axis and migraine headache: a comprehensive review. J Headache Pain 21(1):1–2
18. Pinzon RT, Wijaya VO, Buana RB, Al Jody A, Nunsio PN (2020) Neurologic characteristics in coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Front Neurol 11:565
19. Garg RK, Paliwal VK, Gupta A (2021) Encephalopathy in patients with COVID-19: a review. J Med Virol 93(1):206–222
20 Deliwala S, Abdulhamid S, Abusalih MF, Al-Qasmi MM, Bachuwa G (2020) Encephalopathy as the sentinel sign of a cortical stroke in a patient infected with coronavirus disease-19 (COVID-19). Cureus. https://doi.org/10.7759/cureus.8121
21. D'Ardes D, Carrarini C, Russo M, Dono F, Speranza R, Digiovanni A, Martinotti G, Di Iorio A, Onofrj M, Cipollone F, Bonanni L (2021) Low molecular weight heparin in COVID-19 patients prevents delirium and shortens hospitalization. Neurol Sci 42(4):1527–1530
22. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, Jayaseelan DL, Kumar G, Raftopoulos RE, Zambreanu L, Vivekanandam V (2020) The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain 143(10):3104–3120