

## ORIGINAL RESEARCH

# Clinical, Laboratory and Imaging Characteristics of Hospitalized COVID-19 Patients with Neurologic Involvement; a Cross-Sectional Study

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**Abstract:** **Introduction:** Although neurologic involvement and neuroimaging abnormalities have been frequently identified in COVID-19 patients, the underlying factors remain unclear. In this study, we assessed the association of the neurological manifestations and neuroimaging features of hospitalized COVID-19 patients with their clinical, laboratory, and imaging characteristics. **Methods:** This multicenter cross-sectional study was conducted between September 2020 and March 2021 at two large academic hospitals in Tehran, Iran. We used census sampling from medical records to enroll hospitalized patients with a positive COVID-19 Polymerase chain reaction (PCR) test who underwent brain imaging due to presenting any acute neurologic symptom during hospital stay. **Results:** Of the 4372 hospitalized patients with COVID-19, only 211 met the inclusion criteria (35.5% with severe infection). Central nervous system and psychiatric manifestations were significantly more common in severe cases ( $p \leq 0.044$ ). Approximately, 30% had a new abnormality on their neuroimaging, with ischemic (38/63) and hemorrhagic (16/63) insults being the most common. The most frequent reasons that provoked cranial imaging were headache (27%), altered consciousness (25.6%), focal neurologic signs (19.9%), and delirium (18%). Analysis revealed a positive correlation for age, neutrophilia, lymphopenia, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) with the emergence of neuroimaging abnormalities ( $p \leq 0.018$ ). In addition, patients with new neuroimaging abnormalities had a significantly higher lung CT score than those without any pathologic findings ( $11.1 \pm 4.8$  vs.  $5.9 \pm 4.8$ ,  $p < 0.001$ ). **Conclusion:** Approximately 30% of the study population had various acute neuroimaging findings. The lung CT score, neutrophil count, and age were strong predictors of acute neuroimaging abnormalities in hospitalized COVID-19 patients.

**Keywords:** COVID-19; Neurology; Neurologic Manifestations; Neuroimaging; Tomography, X-ray computed; Magnetic Resonance Imaging; Risk Factors

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## 1. Introduction

COVID-19 has been declared a public health emergency of international concern by the World Health Organization (WHO)(1). According to WHO statistics, to date (December 20, 2021), this disease has infected roughly 272 million people worldwide and has led to more than 5 million deaths (2). According to WHO statistics, Iran is one of the top 20 nations with the highest prevalence of COVID-19, with approximately 6.2 million individuals infected and 130,000 deaths documented so far (December 20, 2021) (2). COVID-19 can have a variety of clinical manifestations, from asymptomatic to death (3). With the increase in COVID-19 cases globally, many extra-pulmonary manifestations of this disease, such as neurologic ones, have been documented (3, 4). Different investigations have found that the prevalence of at least one new-onset neurological manifestation linked to COVID-19 infection is highly variable, ranging from around 10% to more than 80% (5-7). In addition, neuropsychiatric problems such as delirium have been frequently documented in hospitalized patients, and linked to a higher mortality rate in COVID-19 cases (8, 9). Several studies have also documented neuroimaging abnormalities in patients with COVID-19, including ischemic and hemorrhagic infarction, cerebral venous thrombosis, demyelinating disorders such as acute disseminated encephalomyelitis (ADEM), meningitis, encephalomyelitis, acute hemorrhagic necrotizing encephalopathy (ANE), and hemorrhagic posterior reversible encephalopathy syndrome (PRES)(4, 10-12).

Due to the neurological symptoms that emerge throughout the disease period, the potential effects of SARS-COV-2 on the nervous system has attracted remarkable attention, and several possible mechanisms of neurological injury have been postulated (13). This virus can affect the central nervous system via olfactory nerves or, enter brain cells by binding to angiotensin-converting enzyme-2 (ACE-2) or cause neuroinflammation following a cytokine storm (3, 14). COVID-19 can affect the central nervous system, peripheral nervous system, and musculoskeletal system, leading to various neurological manifestations including headache, anosmia, ageusia, dizziness, altered consciousness, myalgia, myelopathy, encephalopathy, meningitis, seizure, syncope, hemorrhage, and stroke (15, 16).

Despite the rapidly growing literature on this subject, correlations between neurological symptoms and/or neuroimaging findings in COVID-19 and other variables are still mostly unknown. Only a few studies have investigated the association between neurological symptoms and other variables. Our objective in this study is to evaluate COVID-19-related neurological and neuroimaging findings in hospitalized patients, while investigating their relationship with var-

ious clinical, laboratory, and lung CT score characteristics.

## 2. Methods

### 2.1. Study design and setting

This cross-sectional study was conducted between September 22, 2020 and March 30, 2021 at Imam Khomeini Hospital Complex and Shohadaye Tajrish Medical Center in Tehran, Iran. We used the STROBE checklist as the reporting guideline for this study. This was a retrospective study and all admission, discharge, diagnostic, and therapeutic decisions were made based on the latest version of the national COVID-19 protocol during the study, and we did not interfere with the patient's diagnostic process and didn't charge the patient or the system anything. The study protocol was approved by the ethics committee of AJA University of Medical Sciences, receiving the ethics code number (IR.AJAUMS.REC.1399.163).

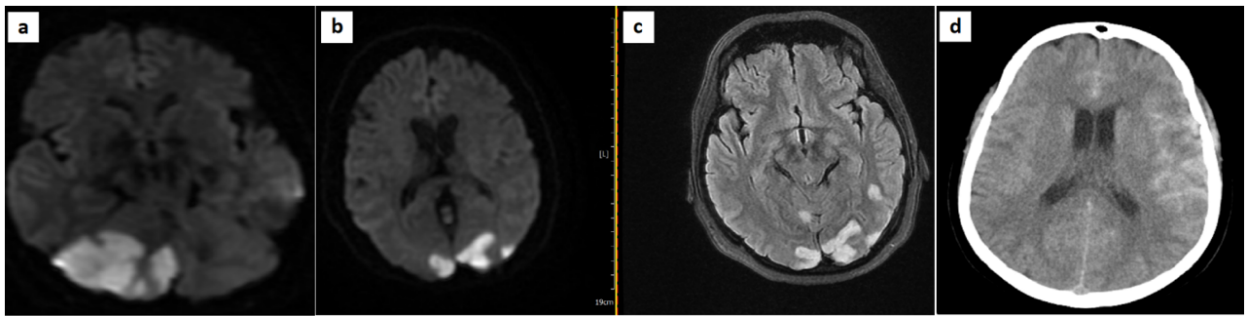
### 2.2. Study population

All adult ( $\geq 18$  years old) hospitalized COVID-19 patients with positive real-time reverse transcription-polymerase chain reaction (RT-PCR) test and a neuroimaging study (including brain and/or spine imaging) following the emergence of any acute neurologic manifestation during hospital stay were included in the study. Exclusion criteria were: (a) known history of previous neurological disorders; (b) previous neuroimaging abnormalities; (c) neurologic manifestation with non-COVID-19 etiology; and (d) incomplete medical records, which failed to meet the requirements for our checklist. Acute neurologic manifestations included: headache, dizziness, altered consciousness, seizure, any focal neurologic symptoms, delirium, psychosis, and any other type of neuropathy.

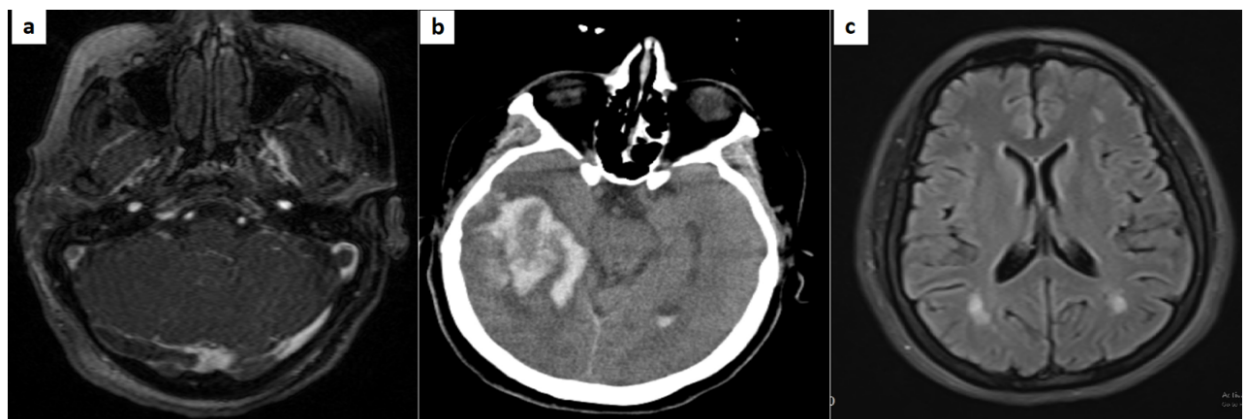
### 2.3. Outcomes and measurements

A checklist was designed and developed to extract patients' data. The collected data included demographic characteristics (age, gender, and underlying disease), clinical features (degree of severity on admission (measured using American Thoracic Society guidelines for community-acquired pneumonia (17), severe or non-severe), outcome (death or discharge), neurologic/psychiatric manifestations, and indication for neuroimaging), initial laboratory data (included a complete blood cell count (CBC), and assessment of renal function, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatine kinase (CK), and lactate dehydrogenase (LDH) according to the clinical care needs of the patient), chest CT scan, and neuroimaging findings. All neurological symptoms in this study were evaluated by an expert neurologist after suspicion of a clinician during daily routine practice in the mentioned centres. Neurologic man-





**Figure 1:** (a, b, c) Acute infarct in posterior cerebral artery (PCA) territory with restriction on diffusion-weighted magnetic resonance imaging (DWI) in a 53-year-old female with COVID-19 on the ninth day of admission; (d) hyper dense materials in brain sulci more prominent on left peritoneal lobe in favor of Subarachnoid hemorrhage (SAH).



**Figure 2:** (a, b) Large hyper dense heterogeneous lesion in right temporal lobe with peripheral edema, more evaluated with brain magnetic resonance imaging/venography (MRI/MRV), which showed abnormal signal in right sigmoid sinus compatible with cerebral venous thrombosis; (c) T2 Flair images in a 39-year-old female with COVID-19 shows some hyper intense predominantly subcortical and deep white matter lesions without periventricular and corpus callosum involvement suggestive of acute disseminated encephalomyelitis (ADEM).

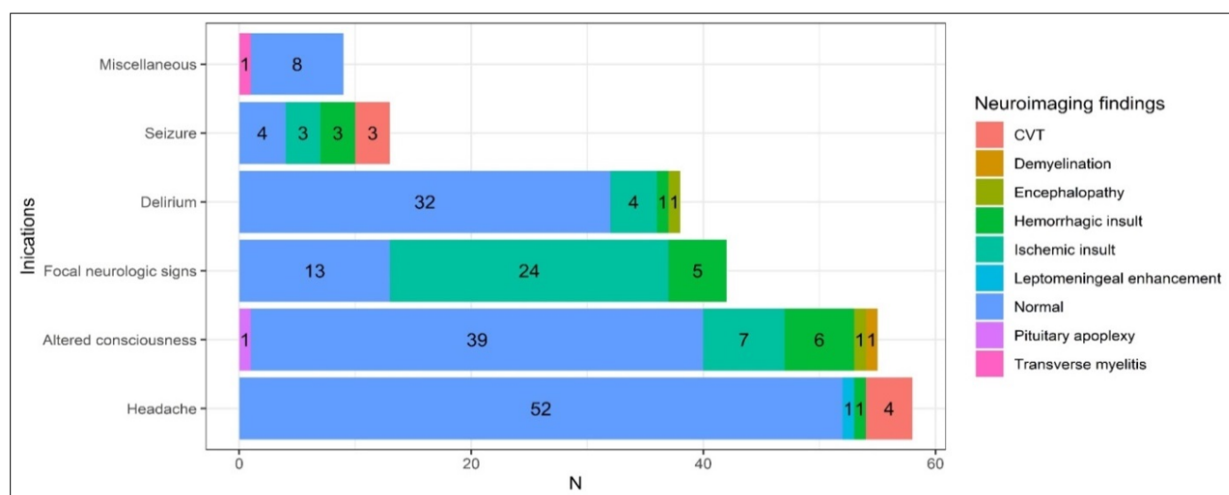
ifestations were divided into three groups: central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system (PNS) manifestations (taste impairment, smell impairment, vision impairment, and nerve pain), and acute psychiatric manifestations (psychosis and delirium). Both neurological and psychiatric symptoms were extracted from the consultation notes of experienced neurologists and psychiatrists. Acute cerebrovascular disorders including ischemic or hemorrhagic insults were diagnosed by clinical symptoms and brain imaging. Seizure was diagnosed based on clinical symptoms at the time of presentation. Indications for neuroimaging were also extracted from medical records and were categorized into six groups: 1) focal neurologic signs (including stroke, transient ischemic attack (TIA) and all possible forms); 2) altered consciousness / reduced GCS; 3) delirium; 4) headache; 5) seizure; and 6) miscellaneous.

#### 2.4. Image acquisition and interpretation

We obtained all the images in our study as per standard of care protocols. 1.5-T scanners (Siemens Avanto, Germany) with standardized protocols were utilized for brain and spine magnetic resonance imaging (MRI) scans. All CT and MRI images were initially reviewed by two experienced neuroradiologists (each having at least ten years of neuroradiology experience), and any disagreements were settled by consensus.

All available chest CT scans were evaluated for CT lung severity score via lobar based assessment (18). Each of the five lung lobes was subjectively graded from 0 to 5 (0, no involvement; 1, involvement <5%; 2, involvement 6–25%; 3, involvement 26–50%; 4, involvement 51–75%; 5, involvement >75%) in lobar based evaluation. The total score was the sum of the individual lobar scores and ranged from 0 to 25. All neuroimaging was analysed for the following characteristics: 1) ischemic insults; 2) haemorrhagic insults; 3) leptomeningeal or cranial nerves enhancement; 4) cerebral venous throm-





**Figure 3:** Distribution of neuroimaging findings based on neuroimaging indications. CVT: cerebral venous thrombosis.

bosis; 5) acute encephalopathy; 6) white matter involvement and any other new abnormal findings.

### 2.5. Statistical analysis

All statistical analyses were conducted using SPSS version 20. Mean and standard deviation were used for reporting normally distributed quantitative variables; Median and interquartile range (IQR) were used for reporting quantitative variables that were not normally distributed, and frequency (percentage) was used to report categorical variables. Independent sample t-test or Mann Whitney test was used for comparing two quantitative groups based on the result of Shapiro-Wilks for normality. Chi square test, and if needed Fisher's exact test was used to evaluate the association between two categorical variables. We also performed multivariate binary logistic regression analysis on factors that significantly correlated with neuroimaging abnormality. P-values < 0.05 were considered statistically significant.

## 3. Results

### 3.1. Demographic, clinical and laboratory characteristics

During the study period, a total of 4372 hospitalized patients with SARS-CoV-2 infection were identified. Of these, 211 patients met our inclusion criteria (52.6% male). Their mean age was 60.7 (standard deviation (SD) =15.8) years (age range, 18-94 years). Based on American Thoracic Society guidelines for community-acquired pneumonia, 75 (35.5%) of cases were categorized as severe COVID-19 infections and 136 (64.5%) of them were non-severe. Patients' characteristics are presented in Table 1.

84.4%, 19.4%, and 35.1% of the patients showed at least one

CNS, PNS, and neuropsychiatric manifestation, respectively. CNS findings were the most prevalent neurologic symptoms overall, with a significantly higher prevalence in the severe group (93.3% vs.

80.1%,  $p = 0.011$ ). The most frequently recorded CNS manifestations were: headache (40.3%), reduced consciousness (36%), and focal neurologic symptoms (18%). Altered consciousness, focal neurologic findings, and seizures were more prevalent in severe infections compared to non-severe infections; headache was significantly higher in non-severe infections (29.3% vs. 46.3%,  $p = 0.016$ ). Neuropsychiatric manifestations were also fairly common, with a total prevalence of around 35%, and were significantly associated with infection severity (severe (44.0%) vs. non-severe (30.1%),  $p = 0.044$ ). PNS manifestations were the least common among these three categories, with an overall prevalence of about 20% and no remarkable difference between severe and non-severe groups. In the PNS group, 2 cases were also diagnosed with Guillain-Barre syndrome. Clinical manifestations of patients are detailed in Table 1.

In the comparison of various factors between severe and non-severe cases, patients with severe infection were significantly older ( $64.5 \pm 14.2$  vs.  $58.6 \pm 16.4$ ,  $p = 0.010$ ), and had a higher mortality rate ( $p < 0.001$ ). In addition, past medical history of hypertension (54.7% vs. 39.7%,  $p = 0.037$ ) also associated with severity. However, no other difference was observed between these two groups. Regarding laboratory tests, patients with a severe infection had a higher inflammatory response, including higher neutrophil counts, lower lymphocyte counts, increased C-reactive protein levels, elevated erythrocyte sedimentation rate, and higher lactate dehydrogenase levels ( $p \leq 0.010$ ) compared to those with non-severe infection. During the study, 13 patients underwent lumbar

**Table 1:** Clinical and laboratory findings of patients based on severity of infection

Characteristics	Total (N= 211)	Severity of infection		P		
		Severe n=75	Non-severe n=136			
Age (year)	60.7±15.8	64.5±14.2	58.6±16.4	0.010		
Neuroimaging abnormality	63(29.9)	39(52)	24(17.6)	<0.001		
Gender	Male	111(52.6)	39 (52)	72(52.9)	0.896	
	Female	100 (47.4)	36 (48)	64(47.1)		
Comorbidities	Hypertension	95(45)	41(54.7)	54(39.7)	0.037	
	Diabetes mellitus	81(38.4)	26(34.7)	55(40.4)	0.409	
	Heart disease	51(24.2)	17(22.7)	34(25.0)	0.705	
	COPD	10(4.7)	4(5.3)	6(4.4)	0.763	
	CKD	14(6.6)	8(10.7)	6(4.4)	0.081	
	Liver disease	7(3.3)	3(4.0)	4(2.9)	0.681	
	Malignancy	18(8.5)	8(10.7)	10(7.4)	0.409	
Tobacco smoking		26(12.3)	9(12.2)	17(12.5)	0.916	
Outcome	Discharged	158(74.9)	38(50.7)	120(88.2)	<0.001	
	Expired	53(25.1)	37(49.3)	16(11.8)		
CNS	Total	179(84.4)	70(93.3)	109(80.1)	0.011	
	Dizziness	33(15.7)	15(20)	18(13.2)	0.195	
	Headache	85(40.3)	22(29.3)	63(46.3)	0.016	
	LOC	76(36.0)	46(61.3)	30(22.1)	<0.001	
	Ataxia	22(10.4)	9(12.0)	13(9.6)	0.579	
	Seizure	11(5.2)	9(12.0)	2(1.5)	0.001	
	Focal neurologic findings	38(18.0)	23(30.7)	15(11.0)	<0.001	
	Encephalopathy	4(1.9)	3(4.0)	1(0.7)	0.096	
	PNS	Taste impairment	23(10.9)	3(4.0)	20(14.7)	0.017
		Smell impairment	24(11.4)	3(4.0)	21(15.4)	0.012
Visual impairment		10(4.7)	5(6.7)	5(3.7)	0.328	
Guillain-Barre syndrome		2(0.9)	1(1.3)	1(0.7)	0.668	
Psychiatric	Total	74(35.1)	33(44.0)	41(30.1)	0.044	
Laboratory	WBC (cells /μL)	10219±4932	10930±6344	9827±3917	0.174	
	Neutrophil (cells /μL)	7904±4353	9271±5569	7150±3295	0.003	
	Lymphocyte (cells /μL)	1586±963	933±643	1945±921	<0.001	
	Platelet (cells /μL)	235004±114506	212413±102995	247463±118935	0.033	
	ESR (mm/hr)	43.0±33.1	62.1±26.9	32.4±31.4	<0.001	
	C-reactive protein (mg/L)	37.4±29.0	55.4±23.9	28.0±27.3	<0.001	
	CPK (U/L)	151.1±345.9	192.8±183.7	128.6±406.3	0.001	
	Lactate dehydrogenase (U/L)	543.2±436.9	661.3±585.4	478.7±313.7	0.01	
	Blood urea nitrogen (mg/dL)	56.3±49.2	70.8±53.1	48.3±45.2	0.002	
	Creatinine (mg/dL)	1.5±1.0	1.6±1.1	1.3±0.9	0.075	
	CSF	High WBC (cells/mm <sup>3</sup> )	4/13	---	---	
Increased Protein (mg/dL)		5/13	---	---		

Data presented as mean ± standard deviation (SD) or number (%). ESR: Erythrocyte sedimentation rate; LOC: loss of consciousness; CPK: Creatine phosphor Kinase; WBC: White blood cell; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.

puncture and their cerebrospinal fluid findings are shown in Table 1.

### 3.2. Neuroimaging findings

In the study population, 160 (75.8%) were examined using brain CT, 5 (2.4%) underwent brain and/or spine MRI, and 46 (21.8%) underwent both CT and MRI. Apart from changes commonly found in elderly patients, neuroimaging indicated no major abnormalities in 148 (70.1%) participants. Abnormal findings were seen in 63 (29.9%) cases, with the rate of

abnormality being significantly higher in patients with severe COVID-19 infection (52 % (severe) vs. 17.6% (non-severe), p < 0.001).

The main neurologic imaging hallmark was acute ischemic infarcts, found in 38 (18%) of the 211 individuals. Of these, 35 (92%) had territorial infarction and 3 (8%) had non-territorial infarcts. Ischemia in the territory supplied by the middle cerebral artery (MCA) (27/35, 77%) was the most prevalent among territorial infarcts. The rest included: 3 posterior cerebral artery (PCA), 1 anterior cerebral artery (ACA), 2 in-



**Table 2:** Summary of patients' neuroimaging (computed tomography scan or magnetic resonance imaging) findings

Variables	Values n (%)
<b>Indication for neuroimaging</b>	
Headache	57 (27.0)
Altered consciousness	54 (25.6)
Focal neurologic signs	42 (19.9)
Delirium	38 (18.0)
Seizure	11 (5.2)
Miscellaneous	9 (4.3)
<b>Ischemic insult</b>	
Territorial	35 (16.6)
Non-territorial	3 (1.4)
<b>Hemorrhagic insult</b>	
Large intracranial and intraventricular	5 (2.4)
Microhemorrhage	8 (3.8)
Subarachnoid hemorrhage (SAH)	3 (1.4)
<b>Territory of ischemic insult</b>	
Middle cerebellar artery (MCA)	27 (12.8)
Posterior cerebellar artery (PCA)	5 (2.4)
Anterior cerebellar artery (ACA)	2 (0.9)
Infratentorial	3 (1.4)
<b>Other findings</b>	
Acute encephalopathy	2 (0.9)
Leptomeningeal enhancement	1 (0.5)
Pituitary apoplexy	1 (0.5)
Cranial nerves	0 (0.00)
Cerebral venous thrombosis (CVT)	7 (3.3)
Transverse myelitis	1 (0.5)
Demyelination (white matter involvement)	1 (0.5)

fratentorial, 1 PCA+ACA, and 1 PCA +infratentorial (figure 1). Intracranial hemorrhages (ICHs) were the second most common finding (16/211), with micro-hemorrhages being the most common (8/16, 50%), followed by 5 large cranial hemorrhages and 3 cases of subarachnoid hemorrhage (SAH) (figure 1). Of these, one was a 27-year-old female with no remarkable past medical history surveyed with complaints of severe headache and altered mental status approximately one week after the beginning of COVID-19 symptoms who underwent brain CT and MRI. Cranial imaging revealed brain edema and a 12×9×8mm mass in the left aspect of the pituitary fossa with a hemorrhagic appearance suggestive of pituitary adenoma apoplexy.

Seven cases were diagnosed with cerebral venous thrombosis (CVT), one of which had superior sagittal sinus thrombosis accompanied by leptomeningeal enhancement. Another case was a 66-year-old man with hypertension, classified as a severe infection, who underwent cranial imaging due to decreased consciousness and seizure. His brain MRI showed an abnormal signal area with hemorrhagic change in the right temporal lobe and an abnormal signal in the right sigmoid sinus favoring venous infarct due to dural venous si-

nus thrombosis. In MRV (Magnetic Resonance Venography), transverse and sigmoid sinus was not seen, and abnormal signals in T2/W sequences consistent with venous thrombosis were present (figure2). Details of neuroimaging characteristics are summarized in Table 2.

### 3.3. Neuroimaging indications

Among reasons for undergoing imaging, the most common indications were headache (27%), impaired mental status (25.6%), and focal neurologic signs (19.9%) (Table2). Indications for neuroimaging matched with neuroimaging characteristics are presented in figure 3. Most of the patients with headache (52/57, 91%) and delirium (32/38, 84%) had no abnormal findings on neuroimaging, but most of those who had seizures (7/11, 64%) had pathologic findings on neuroimaging. Most ischemic or hemorrhagic insults were seen among patients who underwent neuroimaging due to altered consciousness or focal neurology (42/55, 76%). On the other hand, all CVT cases were detected in people who had headaches and/or seizures.

### 3.4. Association of neuroimaging with clinical, laboratory features, and lung CT score

Table 3 presents the characteristics of patients with and without neuroimaging abnormalities. We found that individuals with abnormal findings in neuroimaging studies were significantly older ( $p = 0.009$ ) and had a higher level of ESR, CRP, and neutrophil count ( $p \leq 0.018$ ). The analysis also revealed that chest CT score of patients with COVID-19 who had new abnormalities on neuroimaging was significantly higher than those who didn't have any pathologic neuroimaging findings (mean CT score±SD, 11.1±4.8 vs. 5.9±4.8,  $p < 0.001$ ). However, no other related factor was detected.

### 3.5. Predictors of neuroimaging abnormality

The multivariate logistic regression on the factors influencing neuroimaging abnormality is presented in Table 4. This analysis showed that age ( $B=0.041$ ,  $SE=0.013$ ,  $Exp(B)=1.042$ ,  $p = 0.002$ ), neutrophil count ( $B=0.000$ ,  $SE=0.000$ ,  $Exp(B)=1$ ,  $p = 0.039$ ) and lung CT Score ( $B=-0.181$ ,  $SE=0.045$ ,  $Exp(B)=0.834$ ,  $p = 0.000$ ) were strong predictors of neuroimaging abnormality. However, ESR, CRP, and lymphocyte count showed no significant prediction ability for neuroimaging abnormality ( $p \geq 0.116$ ).

## 4. Discussion

In this study, we surveyed hospitalized patients with COVID-19-related neurologic symptoms requiring neuroimaging, focusing on their clinical, laboratory, and chest CT scan characteristics. Our patients had a wide range of neurologic symptoms as well as neuroimaging indications and findings. We

**Table 3:** Comparing the patients' characteristics between cases with and without acute neuroimaging abnormality

Characteristics	Total (n= 211)	Neuroimaging abnormality		P
		With n=63	Without n=148	
<b>Age (years)</b>				
Mean ± SD	60.7 ± 15.8	56.3 ± 16.1	62.6 ± 15.4	0.009
<b>Gender</b>				
Male	111 (52.6)	28 (44.4)	83 (56.1)	0.121
Female	100 (47.4)	35 (55.6)	65 (43.9)	
<b>Comorbidities</b>				
Hypertension	95 (45.0)	30 (47.6)	65 (43.9)	0.621
Diabetes	81 (38.4)	22 (34.9)	59 (39.9)	0.499
Heart disease	51 (24.2)	13 (20.6)	38 (25.7)	0.434
COPD	10 (4.7)	1 (1.6)	9 (6.1)	0.160
Chronic kidney disease	14 (6.6)	6 (9.5)	8 (5.4)	0.271
Liver disease	7 (3.3)	0 (0.0)	7 (4.6)	0.079
Malignancy	18 (8.5)	4 (6.3)	14 (9.5)	0.459
Tobacco smoking	26 (12.3)	10 (15.9)	16 (10.8)	0.306
<b>Outcome</b>				
Discharged	158 (74.9)	42 (66.7)	116 (78.4)	0.073
Expired	53 (25.1)	21 (33.3)	32 (21.6)	
<b>Laboratory findings</b>				
WBC (cells/μL)	10219±4932	11090±5806	9849±4480	0.094
Neutrophil (cells /μL)	7904 ± 4353	9158 ± 5094	7371 ± 3894	0.006
Lymphocyte (cells /μL)	1586 ± 963	1238 ± 714	1733 ± 1017	<0.001
Platelet (cells /μL)	235004±114506	247349±105979	229750±117901	0.308
ESR (mm/hr)	43.0 ± 33.1	52.7 ± 27.5	39.0 ± 34.3	<0.001
CRP (mg/L)	37.4 ± 29.0	44.3±26.3	34.4 ± 29.7	0.018
CPK (U/L)	151.1 ± 345.9	214.7±592.2	121.5 ± 107.3	0.235
LDH (U/L)	543.2 ± 436.9	518.1±358.0	554.0 ± 467.5	0.632
BUN (mg/dL)	56.3 ± 49.2	50.0±37.3	59.0 ± 53.4	0.166
Creatinine (mg/dL)	1.5 ± 1.0	1.2 ± 0.6	1.5 ± 1.1	0.027
<b>CT lung severity score (0-25)</b>				
Mean ± SD	7.4 ± 5.3	11.1 ± 4.8	5.9 ± 4.8	<0.001

Data presented as mean ± standard deviation (SD) or number (%). WBC: White blood cell; CT: computed tomography scan; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; CPK: Creatine Phosphokinase; LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen; COPD: Chronic obstructive pulmonary disease.

**Table 4:** The multivariate binary logistic regression of the potential factors predicting neuroimaging abnormality

Parameters	B	Standard error	EXP (B)	P value
Constant	-0.175	0.954	0.839	0.854
Age	0.041	0.013	1.042	0.002
Neutrophil	0.000	0.000	1.000	0.039
Lymphocyte	0.000	0.000	1.000	0.116
Erythrocyte sedimentation rate (ESR)	-0.006	0.009	0.994	0.486
C reactive protein (CRP)	0.004	0.010	1.004	0.685
Creatinine	0.369	0.318	1.446	0.246
CT lung severity score	-0.181	0.045	0.834	0.000

CT: computed tomography.

discovered that nearly 30% of COVID-19 patients with neurological involvement had an abnormality in their neuroimaging, with the most commonly reported abnormality being acute ischemic infarcts, followed by ICH. Analysis showed

that the emergence of acute neuroimaging findings was related to a higher lung CT severity score as well as age, neutrophil count, lymphocyte count, ESR, and CRP level. Multivariate logistic regression on the factors influencing neu-



roimaging abnormality identified age, neutrophil count, and lung CT score as strong predictors of new abnormal neuroimaging findings. We also found that being old; having a past medical history of HTN, having a CNS manifestation, and having neuropsychiatric symptoms are associated with disease severity.

Patients with hypertension in our study were more likely to have severe COVID-19 infection; similar to the findings of several previous papers (19-22) which found that hypertension is related to a greater risk of mortality. So, this underlying condition should be considered by clinicians as a predictor of progression of COVID-19 to severe status and poor outcome. Patients with severe infection were found to be older. According to some studies (19, 21, 22), older patients had a greater mortality rate. Patients with abnormal neuroimaging were also found to be older, which is consistent with the findings of Chen et al., who reported that age is associated with acute cerebrovascular events in COVID-19 patients (20). This is important because in elderly patients with COVID-19, who have nonspecific symptoms of neurological involvement, the likelihood of neurological involvement should always be considered, and the threshold for neurological imaging should be lower. However, in contrast to some investigations that found a higher prevalence of severe cases in men, no gender difference was observed between these two groups in our study (23-25). CNS manifestations were shown to be the most prevalent neurological manifestation, with headache being the most common (40.3%). This finding is in agreement with previous studies, which found headache to be one of the most common neurological manifestations, with a frequency ranging from 4 to more than 40% (6, 7, 16, 19, 21, 22, 26). We found that almost 30% of COVID-19 patients with neurologic manifestations had abnormal neuroimaging. This number has been observed to range from 20% to more than 80% in different studies (26-32). The disparities could be due to the lower threshold for undergoing brain imaging in Iran's health system setting, sample-size differences, or differences in the characteristics of the sample groups. For example, in the study that reported this number to be above 80%, a greater percentage of the sample experienced more serious neurological symptoms, such as paresis or loss of consciousness, or had more comorbidities. Like Mahammedi et al. (32), we observed that patients who had acute abnormalities on neuroimaging had a significantly higher CT lung severity score. Although further research is needed to verify this association, it suggests that any neurological symptoms in COVID-19 patients with a high CT lung severity score should be taken seriously. In addition, we can employ the CT lung severity score as a prognostic tool in managing COVID-19 patients with neurological manifestations.

Ischemia and infarction were the most common imaging abnormalities, as they had been in many earlier studies (19, 28,

30, 33, 34). However, we have an inadequate understanding of the mechanisms of the neurologic manifestations presented in COVID-19 patients, and we don't know whether they were caused by direct invasion of the coronavirus to the central nervous system (35). SARS-CoV-2 has been demonstrated to enhance coagulopathy in previous investigations (36, 37), thus finding ischemia and infarction in neuroimaging appears to be a possibility that should be considered. We also reported four cases of encephalopathy, two of which displayed encephalopathy features on brain imaging. Both were in the severe group and had to undergo neuroimaging due to delirium and focal neurologic signs; tragically, one of them passed away during the hospital stay. We also described a case of pituitary apoplexy in a young woman, which has been recorded in only a few cases in the COVID-19 setting (38).

There are some limitations to this study that should be highlighted. Even though our sample was large and multi-center, we only investigated hospitalized patients in two large hospitals. Our study was retrospective, which can contribute to an underestimation of variable frequency. Multinational and outpatient studies on long-term outcomes as well as other study designs should be considered. Due to the subjective nature of neuroimaging and chest CT scan findings, it was challenging to standardize them. We overcame this constraint by having two expert neuroradiologists review all CT and MRI images and reaching a consensus on any disputes. Another major limitation was that we only enrolled COVID-19 patients with neurologic manifestations who underwent neuroimaging. Because performing neuroimaging on all patients as a routine is unnecessary and immoral, increasing the probability of exposure to the virus during a pandemic, imaging was done selectively in patients with more serious and significant neurologic symptoms.

## 5. Conclusion

Our study demonstrates that roughly 30% of the studied cases had various new neuroimaging abnormalities, which should not be dismissed during the COVID-19 pandemic. Furthermore, age, neutrophil count, and lung CT score were shown to be strong predictors for the emergence of neuroimaging pathologic findings.

## 6. Declarations

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## 6.2. Authors' contributions

Design of the study by AZ, MS, A.R and F.A; Data acquisition by AZ, MA, MR and A.T; Images review by HH, NA, and MA, Data analysis and interpretation by MHA; AR, FA, and RH; drafting the manuscript by AZ, MHA, HS, and AB; Revision of the manuscript by MS, AR, FA, MA, and AT; the final version of the manuscript is approved by all the authors.

## 6.3. Funding and supports

None.

## 6.4. Conflict of Interest

The authors declare no conflict of interest

## 6.5. Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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