Neurological Complications of COVID-19

PAYAM SAADAT

NEUROLOGIST

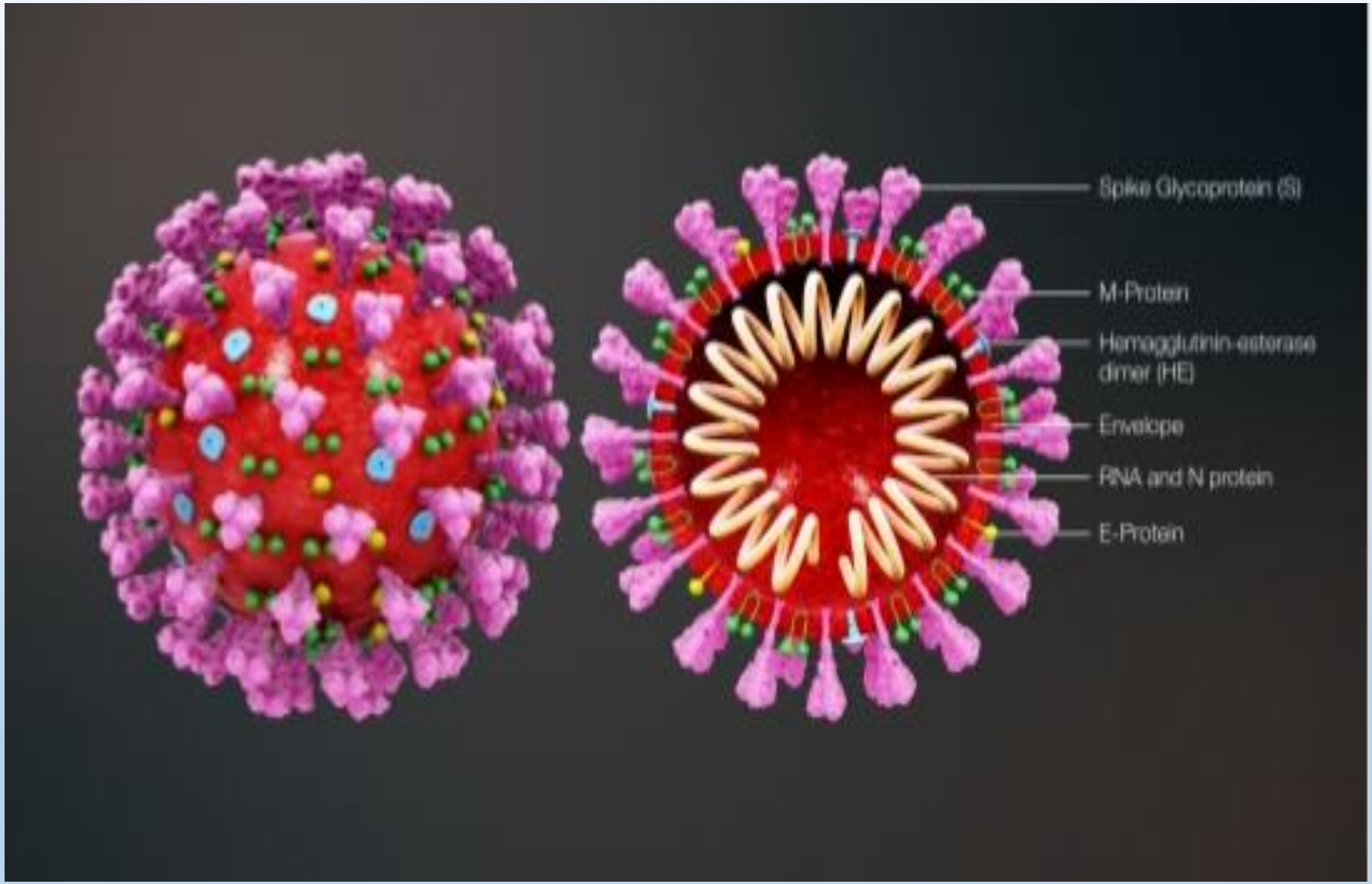
What are Coronaviruses?

- Coronaviruses (CoVs), which are large enveloped non-segmented positive-sense RNA viruses, generally cause enteric and respiratory diseases in animals and humans. Most human CoVs, such as hCoV-229E, OC43, NL63, and HKU1 cause mild respiratory diseases, but the worldwide spread of two previously unrecognized CoVs, the severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) have called global attention to the lethal potential of human CoVs.

DEFINITION

Coronavirus: Coronaviruses are a large family of viruses that are known to cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).

(According to World Health Organization)


Spike Glycoprotein (S)
M-Protein
Hemagglutinin-esterase dimer (HE)
Envelope
RNA and N protein
E-Protein

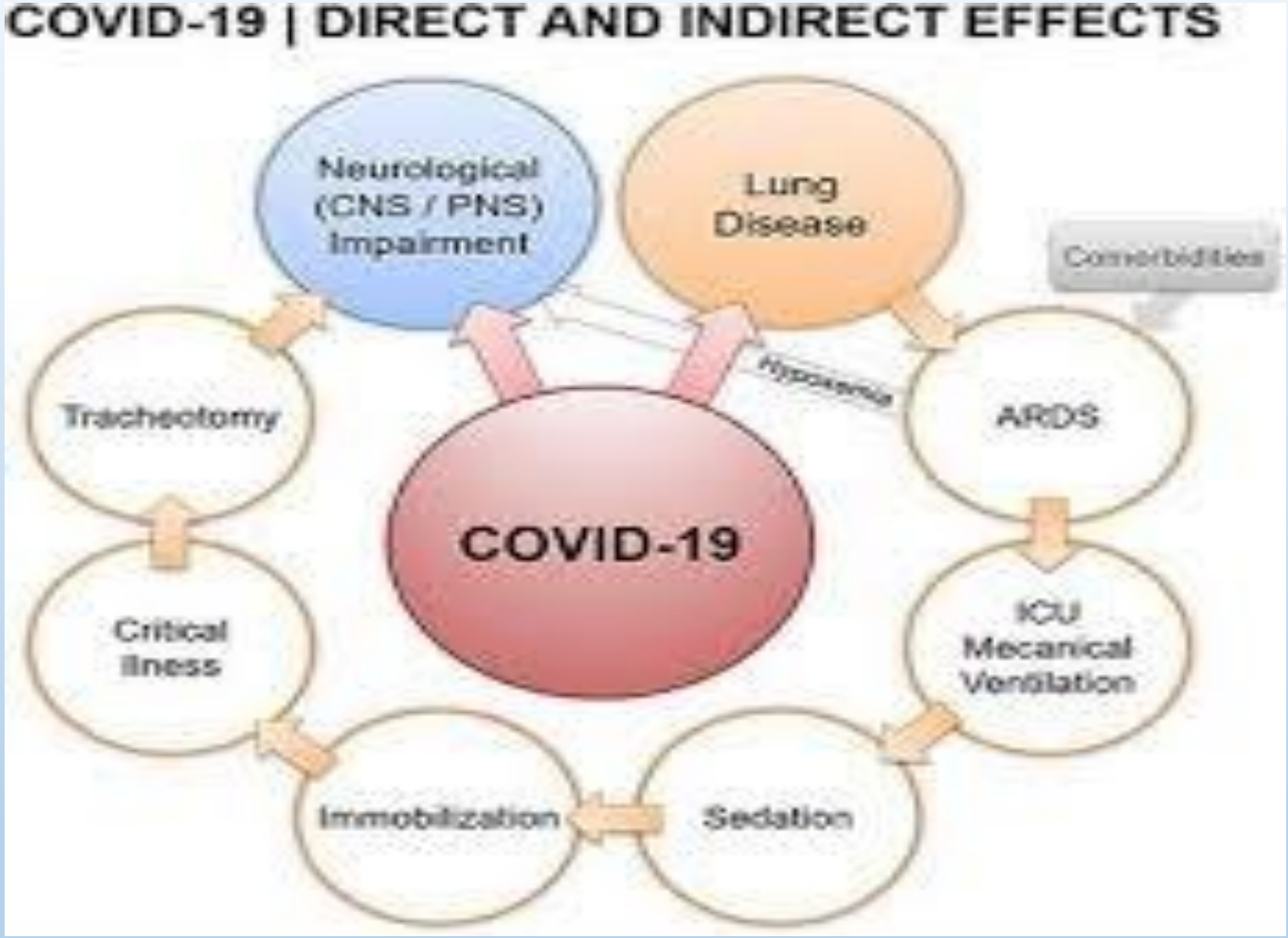
Coronavirus contains four structural proteins, including the spike protein (S), envelope protein (E), membrane protein (M), and the nucleocapsid protein (N). Among them, the S protein plays the most important role in virus attachment, fusion, and entry. SARS-CoV-2, like SARS-CoV, recognizes the angiotensin-converting enzyme 2 (ACE2) as a host cell entry receptor . High expression of the ACE2 receptor is seen in type II alveolar cells of the lung, intestine, esophagus, cardiomyocytes, proximal tubular cells, and urothelial cells. Glial cells and neurons have been reported to express ACE2 receptors, making the brain a potential target of COVID-19 infection.

Clinical Features of COVID-19.

- SARS-CoV-2 causes acute, highly lethal pneumonia with clinical symptoms like those reported for SARS-CoV and MERS-CoV. Imaging examination revealed that most patients with fever, dry cough, and dyspnea showed bilateral ground-glass opacities on chest computerized tomography scans.

Clinical Features of COVID-19.

- different from SARS-CoV, SARS-CoV-2-infected patients rarely showed prominent upper respiratory tract signs and symptoms, indicating that the target cells of SARS-CoV-2 may be located in the lower airway.


COVID-19 | DIRECT AND INDIRECT EFFECTS
Neurological (CNS / PNS) Impairment
Lung Disease
Comorbidities
Hypoxemia
Tracheotomy
ARDS
COVID-19
Critical Illness
ICU Mecanical Ventilation
Immobilization
Sedation

SYMPTOMS

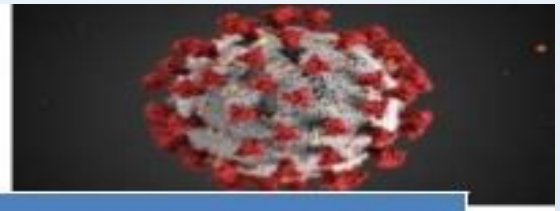
Most common symptoms:

-Fever
-Dry cough
-Tiredness

Less common symptoms:

-Aches and pains
-Sore throat
-Diarrhea
-Conjunctivitis
-Headache
-Loss of taste or smell
-A rash on skin, or discoloration of fingers or toes

Signs and Symptoms...



Symptom	%
Fever	87.9%
Dry cough	67.7%
Fatigue	38.1%
Sputum production	33.4%
Shortness of breath	18.6%
Muscle pain or joint pain	14.8%
Sore throat	13.9%
Headache	13.6%

Chills	11.4%
Nausea or vomiting	5.0%
Nasal congestion	4.8%
Diarrhoea	3.7%
Haemoptysis	0.9%
Conjunctival congestion	0.8%

Pathways of Viral Infection

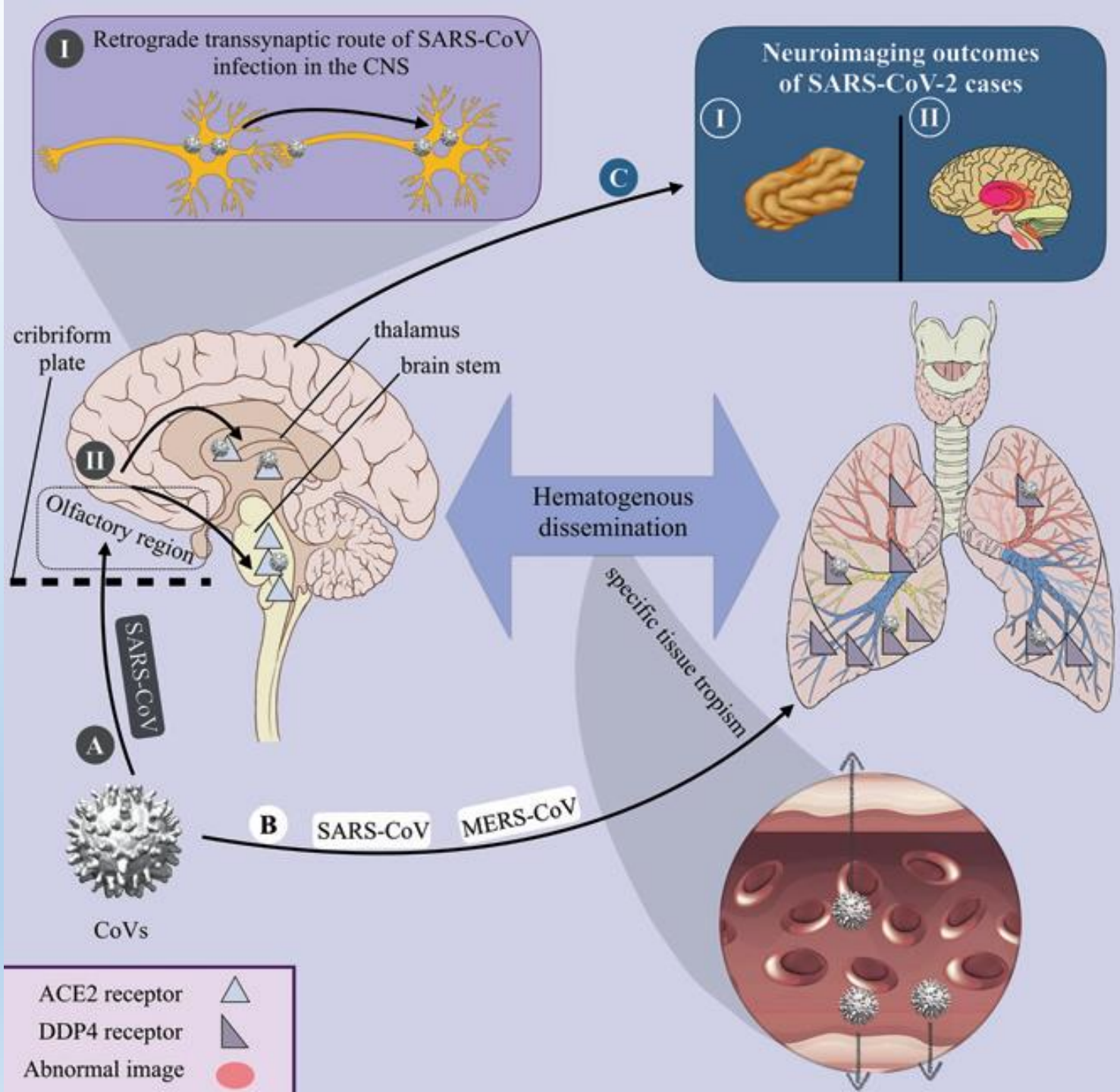
- On the one hand, it has been reported that SARS has the ability to directly infect the BBB epithelium, representing 1 avenue of hematogenous spread. Additionally, several strains of CoVs, including SARS, have shown the ability to infect multiple types of leukocytes both in vitro and in vivo. This feature represents a potential second avenue of hematogenous spread, akin to the “Trojan Horse” model exhibited by HIV, by which the virus is covertly introduced to the CNS by a host’s infected immune cells.

Pathways of Viral Infection

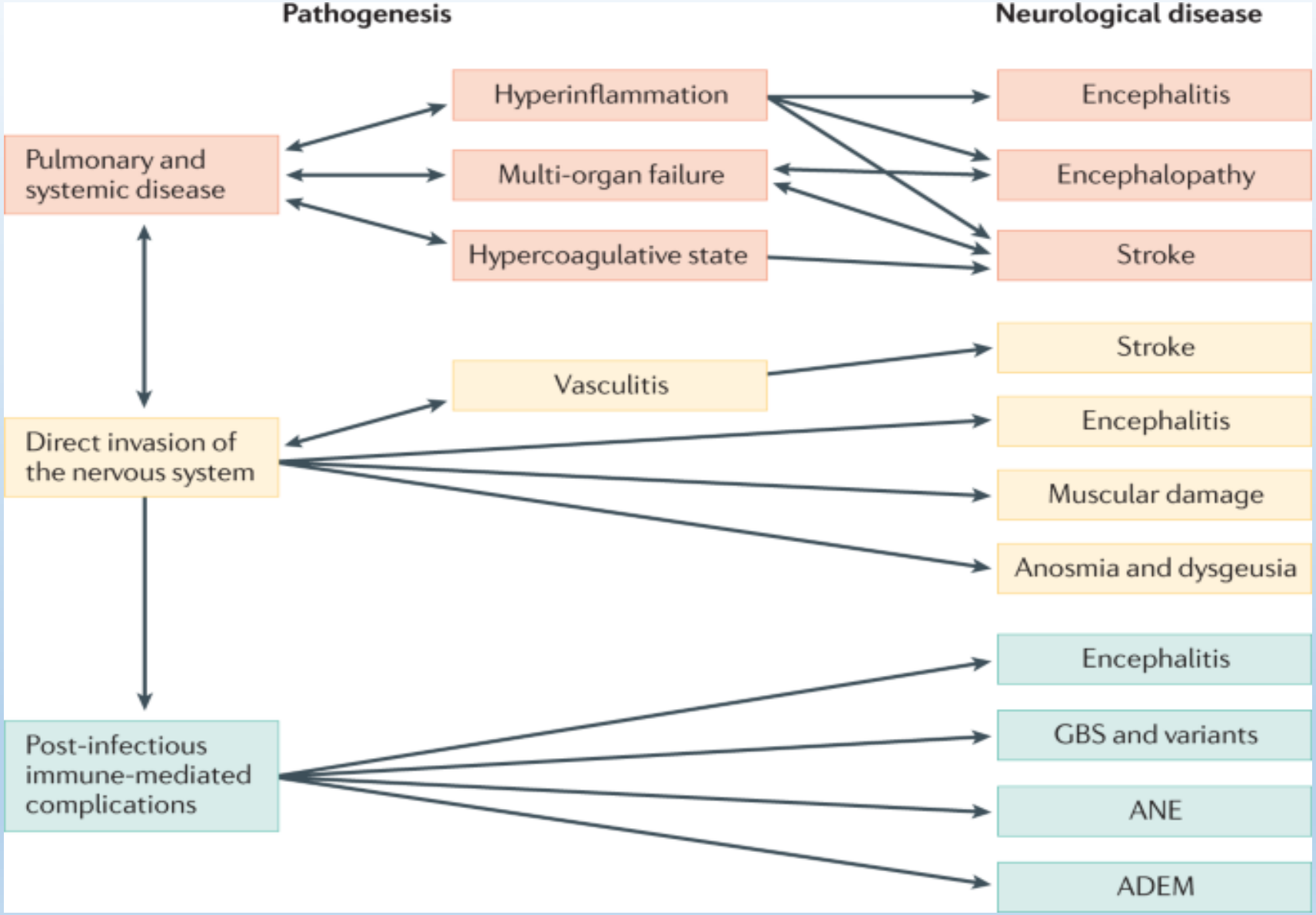
- In the hematogenous route, the virus may pass through the BBB by transcytosis across brain microvascular endothelial cells and pericytes by endocytic vesicles or, rather, directly infect endothelial or epithelial cells to pass across the BBB or blood-CSF barrier in the choroid plexus of the ventricular system, respectively. Alternatively, the virus could be transported intracellularly in a concealed manner by leukocytes. There is mixed evidence regarding the viability of the hematogenous route in the neuroinvasiveness of CoVs.

Potential neuroinvasive mechanisms of SARS-CoV-2 and associated imaging abnormalities. Pathways that may be responsible for the neuroinvasive capability of SARS- and MERS-CoV are demonstrated briefly. Neuronal damage induced by SARS-CoV-2 may act through docking on ACE 2 receptors. This novel CoV may function through pathways, similar to that of SARS-CoV. Moreover, hematogenous dissemination facilitates

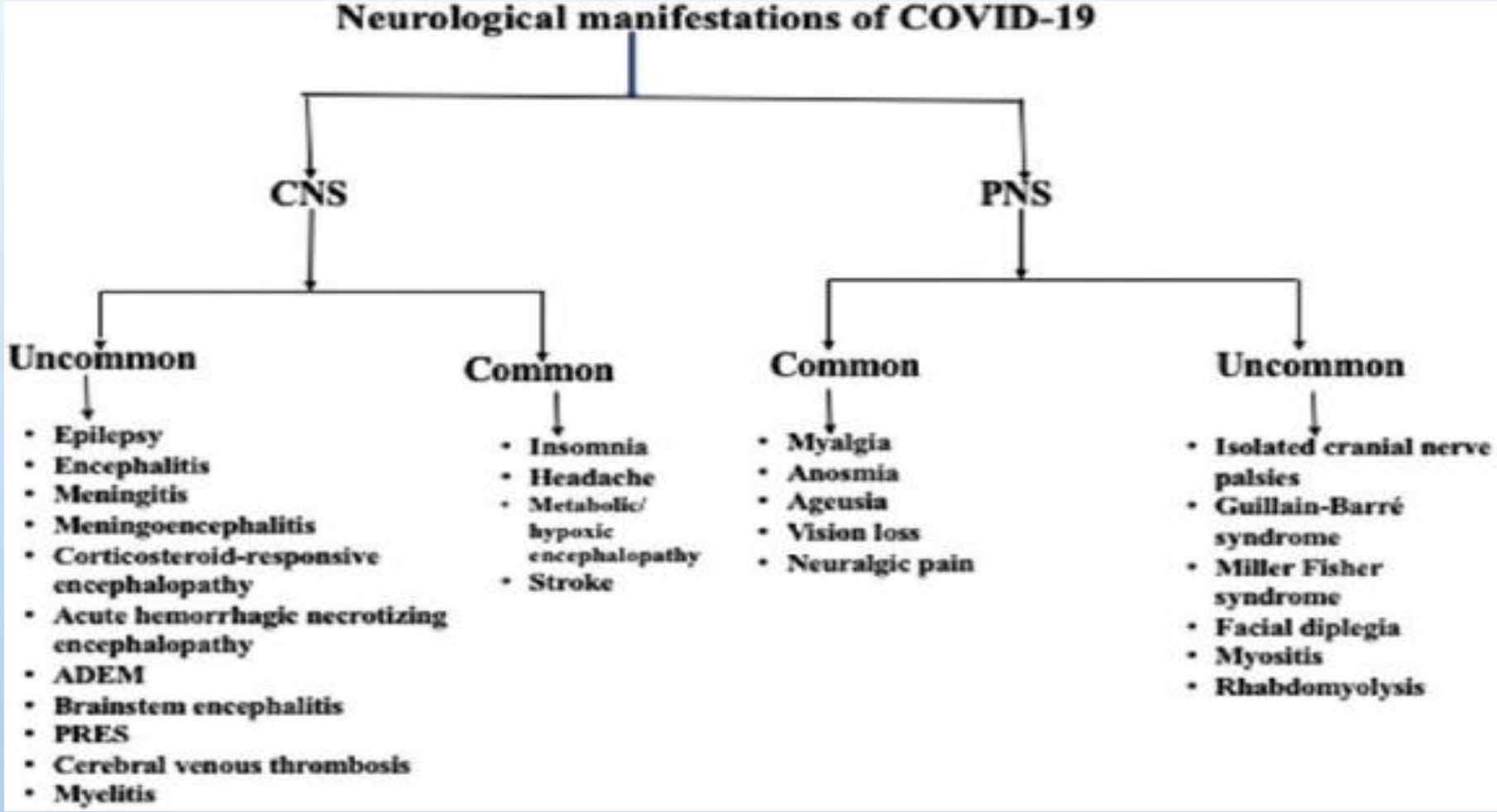
tissue tropism. (A) (I) SARS-CoVs can infect neurons via a retrograde transsynaptic route via ACE 2 receptors, (II) infecting the thalamus and brain stem considerably. (B)Further, MERS-CoV binds to dipeptidyl peptidase (DPP4), which is known as the MERS-CoV receptor. Both SARS- and MERSCoVs invade the lung following respiration.(C) (I) Temporal lobe, (II) basal ganglia, and periventricular region abnormalities have been found in the imaging of COVID-19 patients. These regions are similar to SARSCoV infection areas.



SARS-CoV-2 could also cause damage to the central nervous system indirectly. Viruses do not have to enter the brain to cause damage; they can activate an immune response that triggers subsequent damage within neuronal tissue. SARS-CoV-2 has been reported to cause a massive release of cytokines, a syndrome known as “cytokine storm” downstream effects of this immune response include endothelial damage, disseminated intravascular coagulation, and disrupted cerebral autoregulation.


Pathogenesis
Neurological disease
Pulmonary and systemic disease
Hyperinflammation
Multi-organ failure
Hypercoagulative state
Encephalitis
Encephalopathy
Stroke
Direct invasion of the nervous system
Vasculitis
Stroke
Encephalitis
Muscular damage
Anosmia and dysgeusia
Post-infectious immune-mediated complications
Encephalitis
GBS and variants
ANE
ADEM

COVID-19 pandemic is the largest and the most severe outbreak since the 1918 Spanish flu. Most of its early symptoms are related to the respiratory system but there seems to be a noticeable number of patients who develop symptoms related to the Nervous system, both central and peripheral. Large series from Wuhan, China has shown that 36% of hospitalized patients developed neurological manifestations and these can include the following:


Neurological manifestations of COVID-19
CNS
PNS
Uncommon
Epilepsy
Encephalitis
Meningitis
Meningoencephalitis
Corticosteroid-responsive encephalopathy
Acute hemorrhagic necrotizing encephalopathy
ADEM
Brainstem encephalitis
PRES
Cerebral venous thrombosis
Myelitis
Common
Insomnia
Headache
Metabolic/ hypoxic encephalopathy
Stroke
Common
Myalgia
Anosmia
Ageusia
Vision loss
Neuralgic pain
Uncommon
Isolated cranial nerve palsies
Guillain-Barré syndrome
Miller Fisher syndrome
Facial diplegia
Myositis
Rhabdomyolysis

Anosmia and Aguesia:

Loss of sense of smell (Anosmia) and taste (Augesia) has been seen as an initial presentation in the presence of or absence of other symptoms of COVID-19. The fact that it can occur without other classical COVID-19 manifestations makes it unique and has been used as a screening test for otherwise asymptomatic COVID-19 patients. This is most likely due to the direct involvement of the olfactory nerve by the Coronavirus. These symptoms, however, are short-lived and most patients regain their sense of smell and taste as they recover from Coronavirus.

Headache:

is the key symptom and can be attributed to low oxygen levels in the brain; secondary to involvement of the lungs or maybe a virus related to swelling or inflammation of brain tissue and meninges (covering of the brain). Headache has been seen in 13% of patients with COVID-19. Those patients who have pre-existing primary headaches like migraine and tension-type headaches also have worsened in COVID times mainly attributed to stress/panic created by the pandemic. So, it's difficult to differentiate primary headaches from COVID-19 symptoms; however, any new onset of headache with fever, cough, body aches, loss of taste, and smell should be evaluated for COVID-19.

Brain stroke:

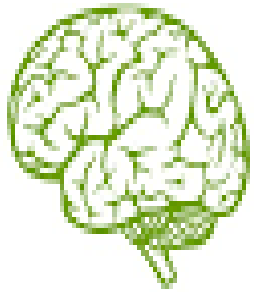
Ischemic stroke is another clinical entity which can present in patients with COVID-19 infection .The incidence is more eminent in patients with comorbidities (hypertension, diabetes,and high cholesterol). It’s been postulated that the virus binds to the receptors where drugs to lower blood pressure bind, thus predisposing to uncontrolled hypertension and brain hemorrhage. This presentation may arise secondary to a cytokine storm syndrome , which can cause endothelial damage ,disseminated intravascular coagulation, and disrupted cerebral auto-regulation . Through the ACE2 receptor of the vascular endothelium, the virus's extensive invasion of the vascular endothelium obviously may cause extensive endotheliitis, increasing the risk of thrombosis leading to ischemic stroke. Critically ill patients with severe SARS-CoV-2 infection often show elevated levels of D-dimer, a fibrin-degraded product which serves as a marker of dysfunctional activation of the coagulation system, such as in acute ischemic stroke . However, it is observed that the stroke prevalence in COVID-19 patients and non-COVID-19 patients are similar.

.

Variables associated with increased mortality risk in COVID-19

Altered mentation

OR = 1.39



Stroke

OR = 3.1

Healio

Encephalopathy :

In COVID-19 patients, altered sensorium and encephalopathy were not uncommon. The basic pathological change seen in this disease is cerebral edema, with key clinical features being headache, confusion,delirium, loss of consciousness, seizure, and coma.
COVID-19 patients with encephalopathy were, by large,older male patients with cardiovascular comorbidities and severe infection with systematic inflammation and multi-organ dysfunction. Early identification of COVID-19 patients with altered sensorium is critical, as underlying potential reversible causes, including impending respiratory failure, require timely intervention . The pathophysiology behind the cerebral dysfunction is hypothesized to be in part inflammatory-mediated .This is supported by the fact that the encephalopathic Italian patient had a dramatic response to high-dose steroids

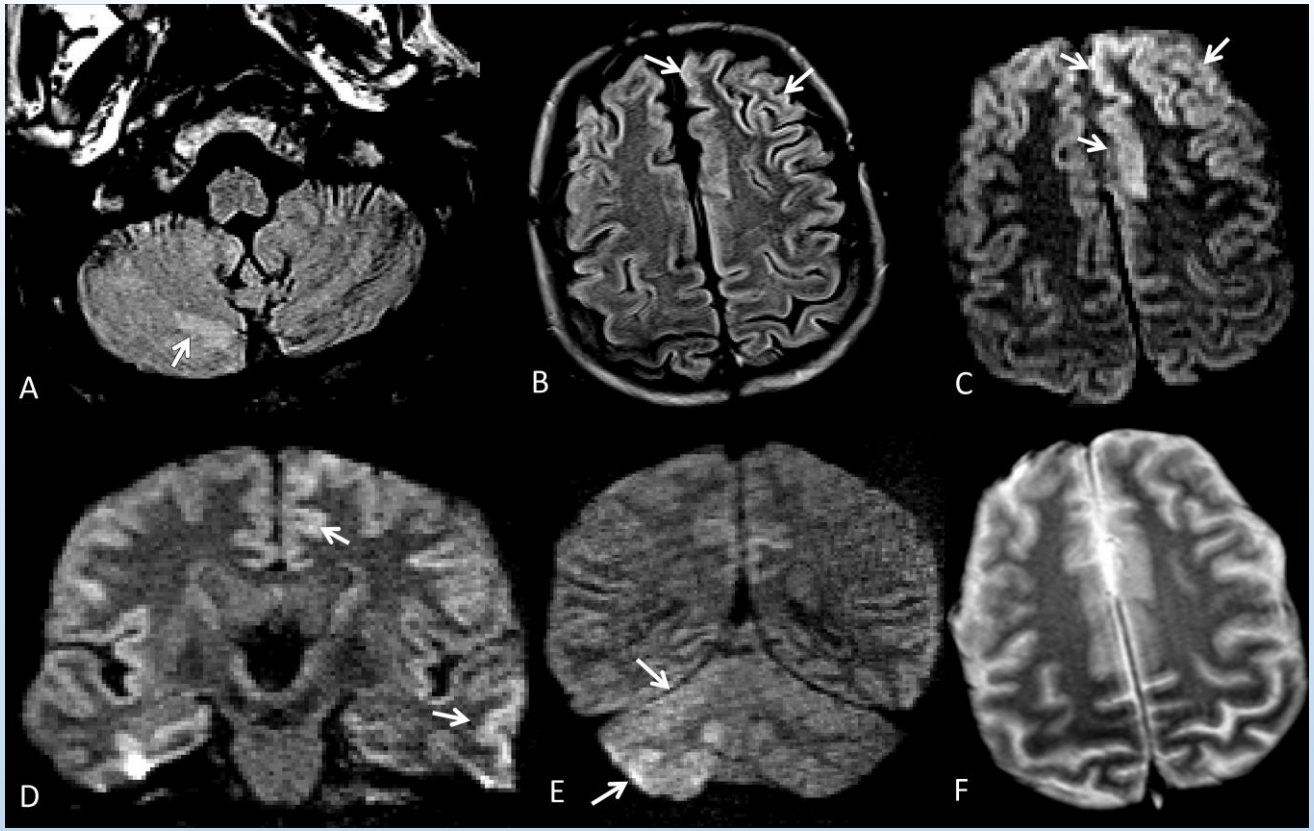


Figure 2: Images of acute encephalopathy in a 60-year-old-man without history of seizures who presented with convulsion. *A, B*, Fluid-attenuated inversion-recovery images show multifocal areas of hyperintensity in the right cerebellum (arrow in *A*), left anterior cingular cortex, and superior frontal gyrus (arrows in *B*). *C–E*, Diffusion-weighted images show restricted diffusion in the left anterior cingulate cortex and superior frontal gyrus (arrows in *C*), superior frontal and middle temporal gyrus (arrows in *D*), and right cerebellum (arrows in *E*), consistent with cerebellar diaschisis. *F*, MRI scan obtained with gradient-echo sequence shows no hemosiderin deposits.

Mahammedi A. Published Online: May 21, 2020
https://doi.org/10.1148/radiol.2020201933

Encephalomyelitis:

It is still unknown how COVID-19 causes encephalomyelitis.It is thought that once viral particles gain entry into the milieu of the neuronal tissue, their interaction with the ACE2 receptors in neurons could initiate a cycle of viral budding accompanied by neuronal damage. In other cases, it may cause an acute inflammatory demyelination resulting in ADEM, which was described in one COVID-19 case , and previously in MERS-CoV .

COVID-19 is also thought to cause acute hemorrhagic encephalitis through the mechanism of a cytokine storm. Acute hemorrhagic leukoencephalitis is a rare demyelinating disorder that is usually fatal; ICU care, use of high-dose corticosteroid therapy, immunoglobulins, plasma exchange, and dehydrating agents have led to survival in only some patients . This has been seen in one COVID-19 case thus far.

Three neuro-immunological entities related toCOVID-19 infection surfaced in systematic review : acute transverse myelitis, GBS and its variants, and Bell’s palsy .

The time course of the disease is alike what is known for other viruses known to cause the above in that the symptoms of respiratory or gastrointestinal infection usually precede that of the neuro-immunological phenomena. This suggests that the underlying mechanism of such neuro-immunological phenomena in COVID-19 patients is likely to be grounded by the hypothesis of molecular mimicry, where mimicry between microbial and nerve antigens is thought to be a major driving force behind the development of the disorder .

Neuromuscular (Nerve and Muscle):

Muscle involvement in the form of muscle tiredness, soreness and pain which is due to the inflammatory response in muscles or direct muscle damage by the virus. In severe cases, muscle protein myoglobin is released in the blood leading to kidney failure.

Peripheral nervous system involvement can present as Gullian Bare Syndrome (GBS), a rapidly progressive limb weakness which is a polyradiculopathy (multiple nerve bundle involvement). GBS like illness develops 7 (range 7-24) days after the onset of respiratory symptoms. Facial palsy, a weakness of the one side of the face with an inability to close the eye of the affected site of varying degrees has been reported as COVID-19 manifestation especially when associated with fever, cough, etc.

Psychiatric

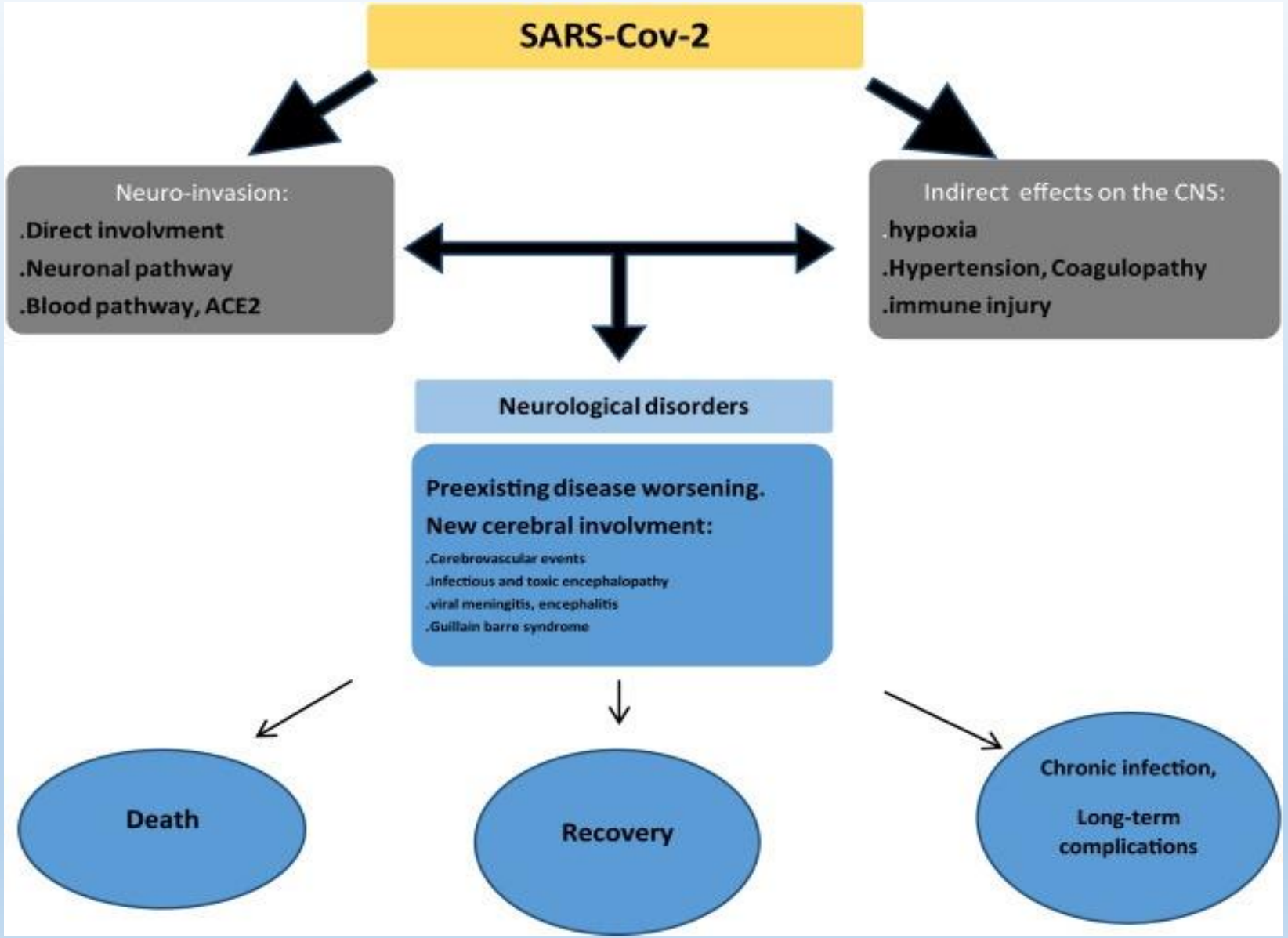
- China - 48% of COVID-19 patients manifested psychological distress during early admission
- Social stigma, "labeled"
- Survivors of critical illness >30% depression, >32% anxiety, and 20% PTSD 1 year follow up
- Family, community distress + support

COVID-19 Handbook, Zhejiang China
Barrett and Brown 2008
[illegible] SMA et al. 2019
James M. Smith et al. 2020

Cerebrovascular symptoms:

Swelling or inflammation of the brain with raised pressure in CSF (fluid in the brain) due to immune response to COVID-19 can present as confusion, abnormal behaviour, and seizures. Though this manifestation is not that commonly seen; but when encountered can be severe and leads to morbidity if not treated early.

The COVID-19 pandemic has overwhelmed health care systems all over the world and more so in countries like Iran since its emergence in December 2019. Despite, its most characteristic manifestations involve lungs, patients with COVID-19 have also shown neurological manifestations which have led to more mortality and morbidity. How it causes neurological involvement by direct involvement of medullary centers in the brain, due to inflammatory reaction remains unclear. However, identification of neurological manifestations is a step forwards in better understanding the virus and thus treating the patients affected by the pandemic.


SARS-Cov-2
Neuro-invasion:
.Direct involvment
.Neuronal pathway
.Blood pathway, ACE2
Indirect effects on the CNS:
.hypoxia
.Hypertension, Coagulopathy
.immune injury
Neurological disorders
Preexisting disease worsening.
New cerebral involvment:
.Cerebrovascular events
.Infectious and toxic encephalopathy
.viral meningitis, encephalitis
.Guillain barre syndrome
Death
Recovery
Chronic infection,
Long-term complications

Conclusion:

While COVID-19 typically presents as a self-limiting respiratory disease, it has been reported in up to 20% of patients to progress to severe illness with multi-organ involvement. The neurological manifestations of COVID-19 are not uncommon, but our study found most resolve with treatment of the underlying infection.

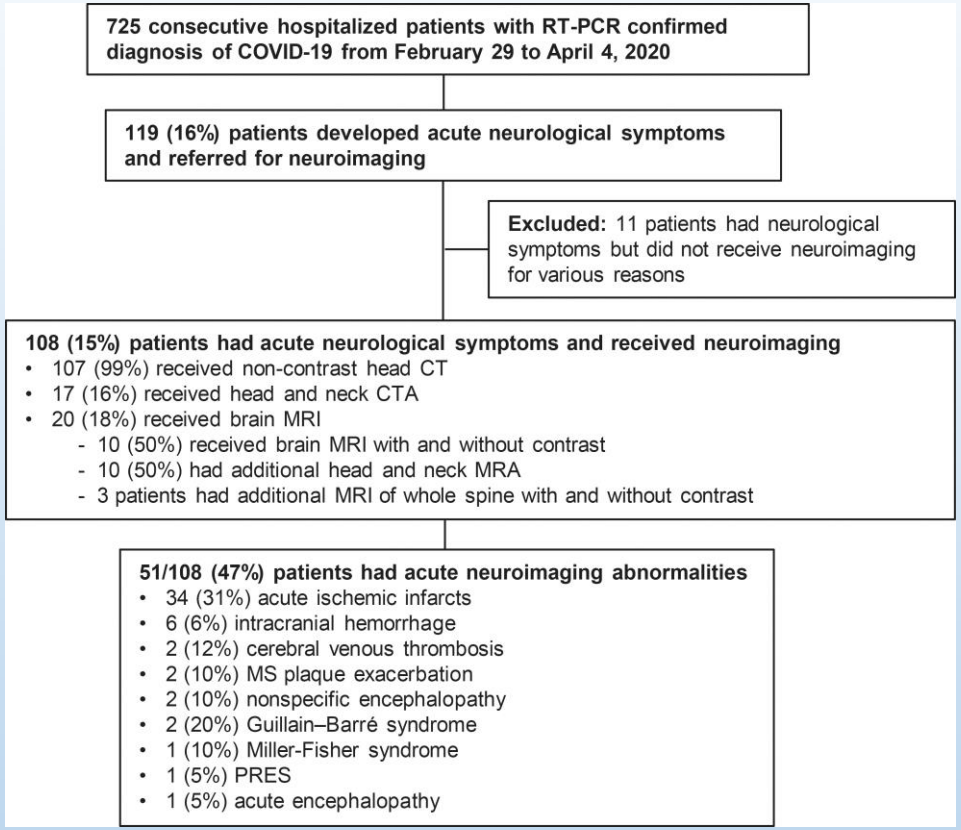


Figure 1: Study flowchart. COVID-19 = coronavirus disease 2019, CTA = CT angiography, MRA = MR angiography, MS = multiple sclerosis, PRES = posterior reversible encephalopathy syndrome, RT-PCR = real-time reverse-transcriptase polymerase chain reaction.

Mahammedi A. Published Online: May 21, 2020
https://doi.org/10.1148/radiol.2020201933


CORONAVIRUS

Table 2: Characteristics of Hospitalized Patients with COVID-19

Characteristic	Value
Sex	
M	69 (64)
F	39 (36)
Age	
Mean (y)*	69 ± 15
<50 y	11 (10)
≥50 y	97 (90)
Median (y)†	71 (60.5–79)
Past medical history	
Hypertension	55 (51)
Diabetes	30 (28)
Coronary artery disease	25 (23)
Cerebrovascular disease	15 (14)
Malignancy	13 (12)
Multiple sclerosis	1 (1)
HIV	1 (1)
Behçet disease	1 (1)
Hemoglobinopathy	1 (1)
Neurologic signs	
Altered mental status	64 (59)
Ischemic stroke	34 (31)
Headache	13 (12)
Myalgias	13 (12)
Seizure	10 (9)
Dizziness	4 (4)
Neuralgia	3 (3)
Ataxia	2 (2)
Hyposmia	2 (2)

Note.—Except where indicated, data are numbers of patients (n = 108), with percentages in parentheses. COVID-19 = coronavirus disease 2019, HIV = human immunodeficiency virus.


COVID-19

data from 37 articles: twelve retrospective studies, two prospective studies, and the rest case reports/series. The most commonly reported neurological manifestations of COVID-19 were myalgia, headache, altered sensorium, hyposmia, and hypogeusia. Uncommonly, COVID-19 can also present with central nervous system manifestations such as ischemic stroke, intracerebral hemorrhage, encephalo-myelitis, and acute myelitis, peripheral nervous manifestations such as Guillain-Barré syndrome and Bell’s palsy, and skeletal muscle manifestations such as rhabdomyolysis.

Table 1 Characteristics of studies included in our systematic review

SN	Study	Type of publication	Country	Source	Neurological manifestation
1	Mao 2020 [5]	Retrospective study	China	JAMA Neurology	Total patients: 214 Any: 78 (36.44%) CNS: 53 (24.76%) • Dizziness: 36 (16.82%) • Headache: 28 (13.08%) • Impaired consciousness: 16 (7.4%) • Acute cerebrovascular disease: 6 (2.8%) • Ataxia: 1 (0.5%) • Epilepsy: 1 (0.5%) PNS: 19 • Hypoguesia: 12 (5.6%) • Hyposmia: 11 (5.14%) • Neuralgia: 5 (2.33%) Muscle injury: 23 (10.74%)
2	Li 2020 [7]	Retrospective study	China	SSRN (preprint)	Total patients: 224 • Acute ischemic stroke: 11 (5%) • Cerebral venous sinus thrombosis: 1 (0.5%) • Intracerebral hemorrhage: 1 (0.5%)
3	Toscano 2020 [8]	Case-report/ series	Italy	The New England Journal of Medicine	Guillain-Barré syndrome
4	Zhao Hua 2020 [9]	Case-report/ series	China	The Lancet Neurology	Guillain-Barré syndrome
5	Gutiérrez-ortiz 2020 [10]	Case-report/ series	Spain	Neurology	Miller Fisher syndrome and polyneuritis cranialis
6	Poyiadji 2020 [11]	Case-report/ series	USA	Radiology	Encephalitis
7	Huaxia 2020 [12]	Newspaper article	China	Xinhua News	Encephalitis
8	Zhai 2020 [13]	Case-report/ series	China	Research square (preprint)	Ischemic stroke
9	Sharifi-Razavi 2020 [14]	Case-report/ series	Iran	New Microbes and New Infections	Intra-cerebral hemorrhage
10	Filatov 2020 [15]	Case-report/ series	USA	Cureus	Encephalopathy
11	Zhao Kang 2020 [16]	Case-report/ series	China	medRxiv (preprint)	Acute myelitis
12	Karimi 2020 [17]	Case-report/ series	Iran	Iran Red Crescent Medical Journal	Encephalopathy
13	Chen Tao 2020 [18]	Retrospective	China	BMJ	Total: 274 patients

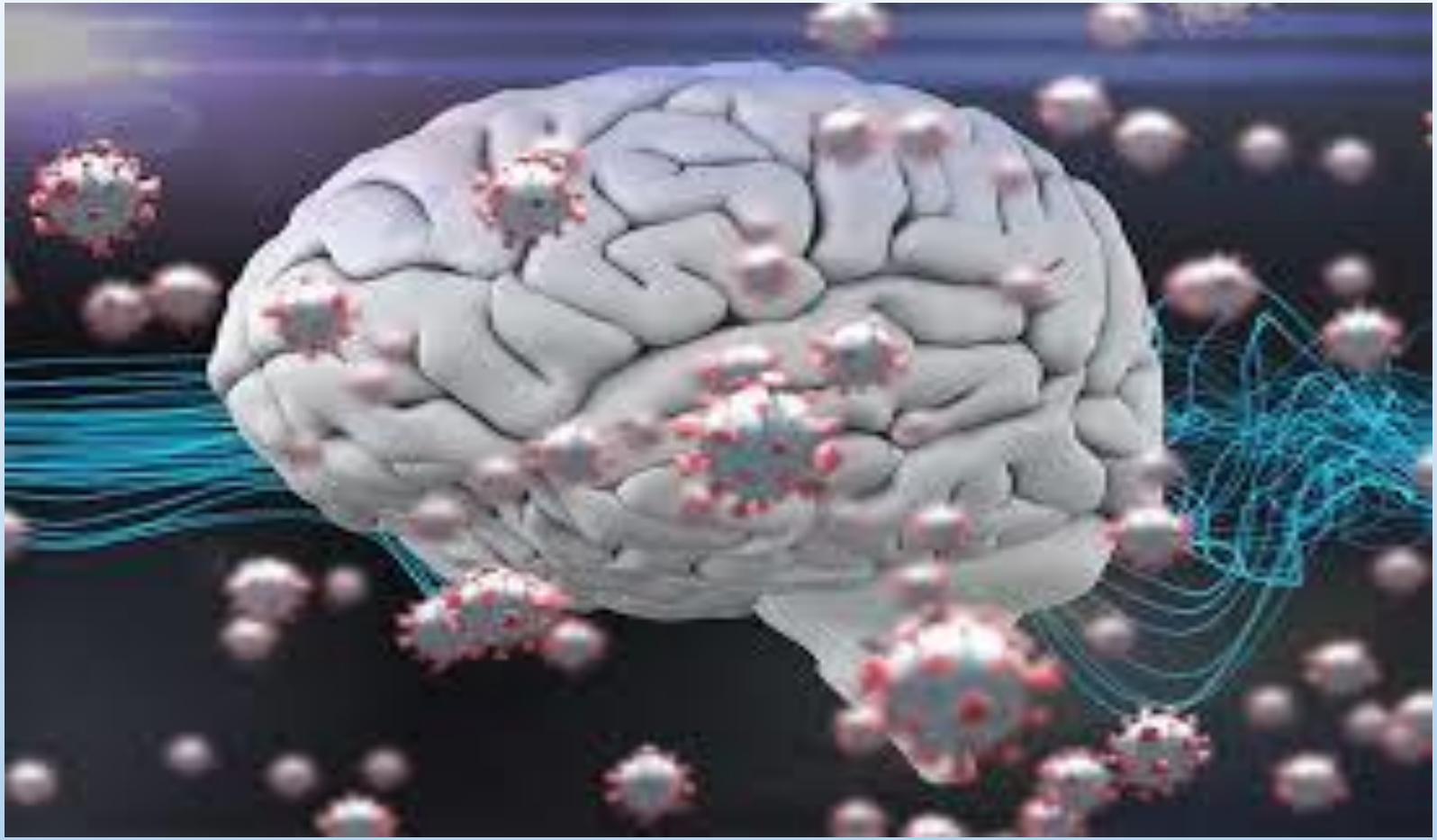
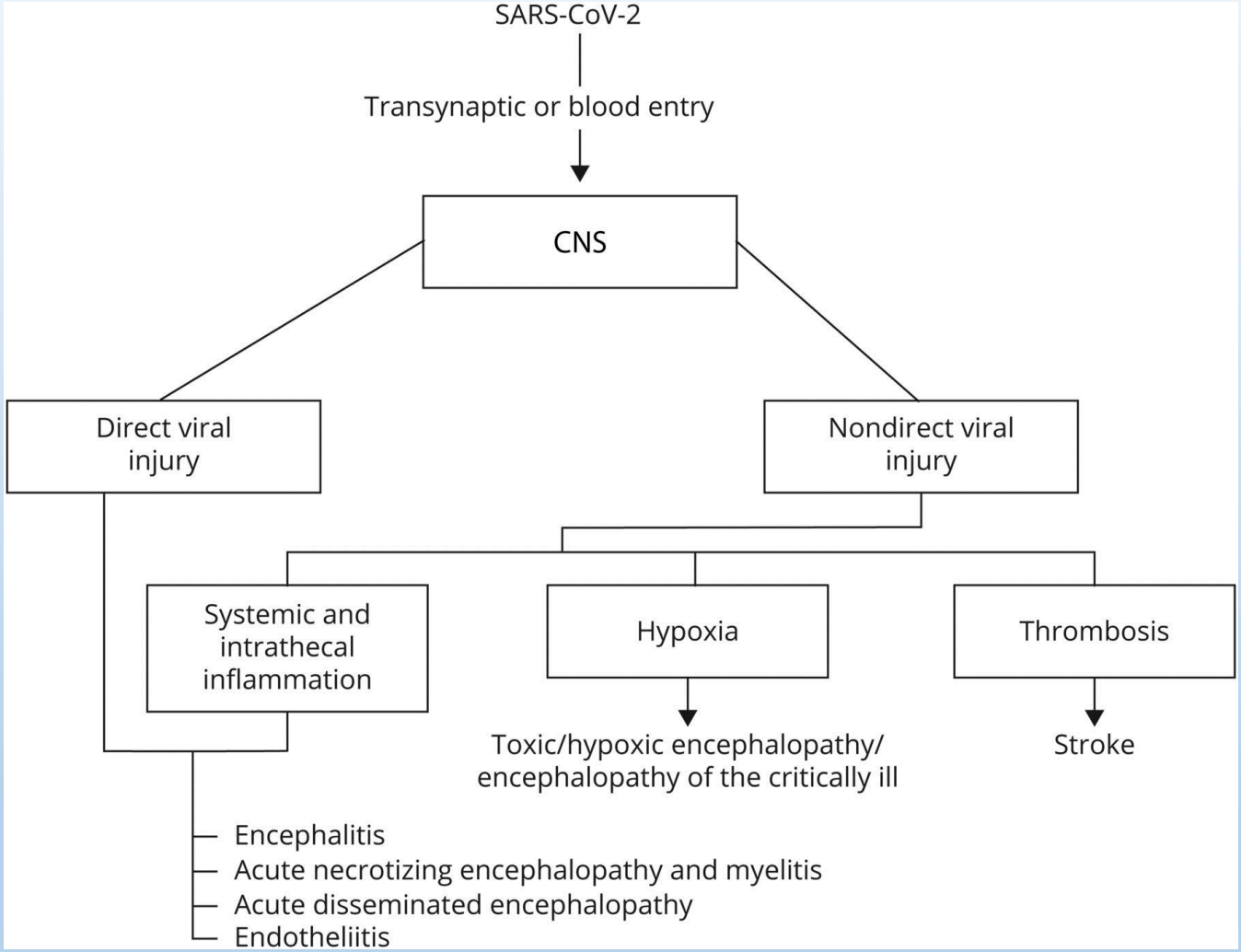


Figure Proposed CNS entry routes, mechanisms and their respective associated clinical pictures



Marta Bodro et al. Neurol Neuroimmunol Neuroinflamm 2021;8:e923

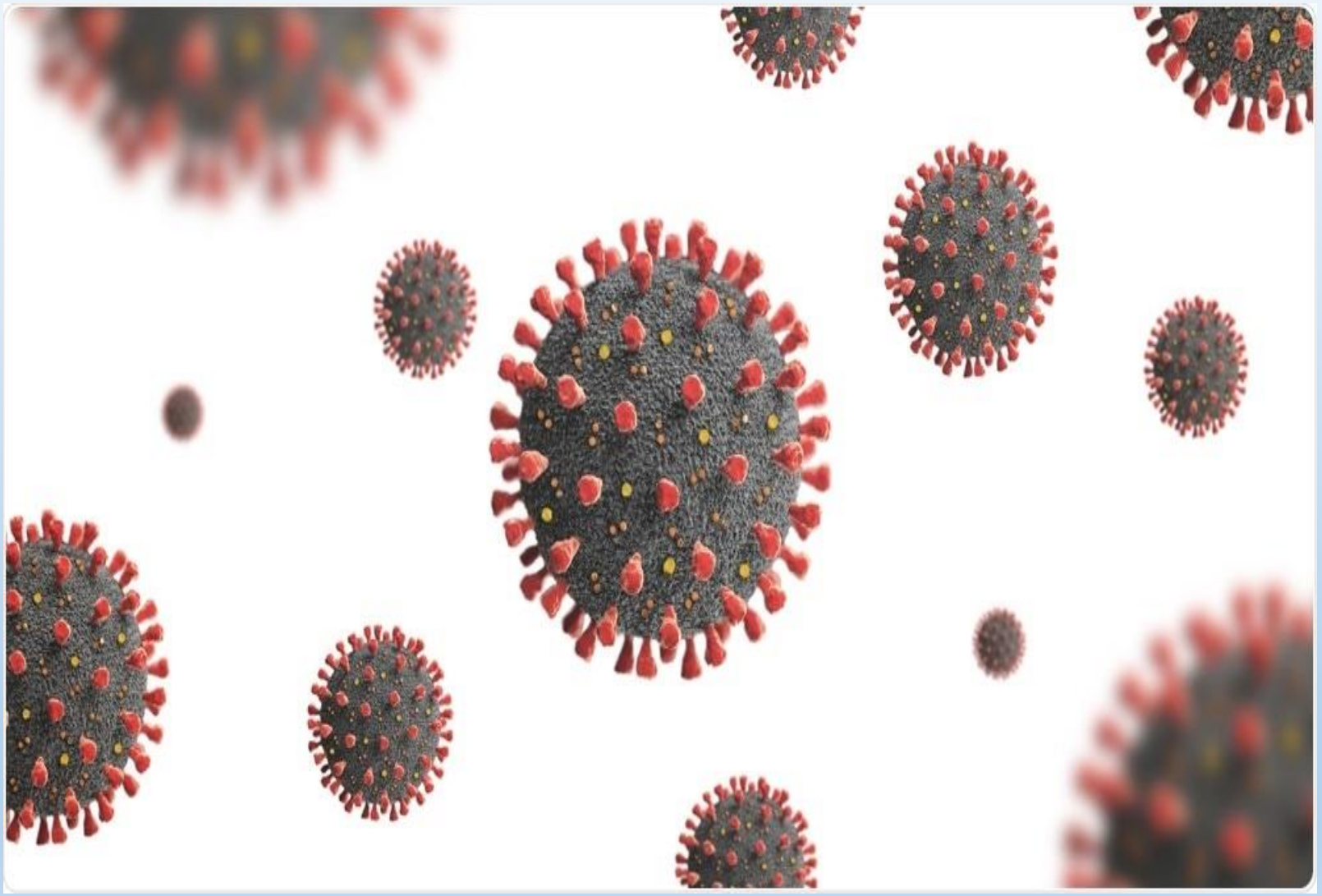


Table 1. Clinical Characteristics of Patients With COVID-19

Characteristic	No. (%) Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	*P* value[a]
Age, mean (SD), y	52.7 (15.5)	58.2 (15.0)	48.9 (14.7)	
Age, y				
<50	90 (42.1)	24 (27.3)	66 (52.4)	<.001
≥50	124 (57.9)	64 (72.7)	60 (47.6)	
Sex				
Female	127 (59.3)	44 (50.0)	83 (65.9)	.02
Male	87 (40.7)	44 (50.0)	43 (34.1)	
Comorbidities				
Any	83 (38.8)	42 (47.7)	41 (32.5)	.03
Hypertension	51 (23.8)	32 (36.4)	19 (15.1)	<.001
Diabetes	30 (14.0)	15 (17.0)	15 (11.9)	.29
Cardiac or cerebrovascular disease	15 (7.0)	7 (8.0)	8 (6.3)	.65
Malignancy	13 (6.1)	5 (5.7)	8 (6.3)	.84
Chronic kidney disease	6 (2.8)	2 (2.3)	4 (3.2)	.69
Typical symptoms				
Fever	132 (61.7)	40 (45.5)	92 (73.0)	<.001
Cough	107 (50.0)	30 (34.1)	77 (61.1)	<.001
Anorexia	68 (31.8)	21 (23.9)	47 (37.3)	.04
Diarrhea	41 (19.2)	13 (14.8)	28 (22.2)	.17
Throat pain	31 (14.5)	10 (11.4)	21 (16.7)	.28
Abdominal pain	10 (4.7)	6 (6.8)	4 (3.2)	.21
Nervous system symptoms				
Any	78 (36.4)	40 (45.5)	38 (30.2)	.02
CNS	53 (24.8)	27 (30.7)	26 (20.6)	.09
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	.42
Headache	28 (13.1)	15 (17.0)	13 (10.3)	.15
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	.03
Ataxia	1 (0.5)	1 (1.1)	0	NA
Seizure	1 (0.5)	1 (1.1)	0	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	.69
Impairment				
Taste	12 (5.6)	3 (3.4)	9 (7.1)	.24
Smell	11 (5.1)	3 (3.4)	8 (6.3)	.34
Vision	3 (1.4)	2 (2.3)	1 (0.8)	.37
Nerve pain	5 (2.3)	4 (4.5)	1 (0.8)	.07
Skeletal muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<.001
Onset of symptoms to hospital admission, median (range), d				
CNS				
Dizziness	1 (1-30)	1 (1-30)	1 (1-14)	NA
Headache	1 (1-14)	1 (1-3)	3 (1-14)	NA
Impaired consciousness	8 (1-25)	10 (1-25)	1 (1-3)	NA
Acute cerebrovascular disease	9 (1-18)	10 (1-18)	1 (1)	NA
Ataxia	2 (2)	2 (2)	NA	NA
Seizure	2 (2)	2 (2)	NA	NA
PNS				
Impairment				
Taste	2 (1-5)	3 (1-3)	2 (1-5)	NA
Smell	2 (1-5)	1 (1-4)	2 (1-5)	NA
Vision	2 (1-3)	3 (2-3)	1 (1)	NA
Nerve pain	1 (1-1)	1 (1-1)	1 (1)	NA
Skeletal muscle injury	1 (1-11)	1 (1-11)	1 (1-6)	NA

Abbreviations: CNS, central nervous system; COVID-19, coronavirus disease 2019; NA, not applicable; PNS, peripheral nervous system.

[a] *P* values indicate differences between patients with severe and nonsevere infection, and *P* less than .05 was considered statistically significant.

References	Country	Type of study	Total number of patients	Three most common manifestations	Neurological manifestations
Zhu *et al.* 2020[69]	China	Meta-analysis	38 studies involving 3062 COVID-19 patients	Fever (80.4%), fatigue (46%), cough (63.1%) and expectoration (41.8%)	Muscle soreness (33%) and headache (15.4%)
Fu *et al.* 2020[70]	China	Meta-analysis	43 studies involving 3600 patients	Fever (83.3%), cough (60.3%), and fatigue (38.0%)	Headache (11.3%)
Cao *et al.* 2020[71]	China	Meta-analysis	31 articles and 46959 patients	Fever (87.3%), cough (58.1%), dyspnea (38.3%)	Muscle soreness or fatigue (35.5%) and headache (9.4%)
Rodriguez-Morales *et al.* 2020[72]	Latin America	Systematic literature review with meta-analysis	656 patients from 27 articles	Fever (88.7%), cough (57.6%) and dyspnea (45.6%)	Headache (8%)


COVID-19
THANK YOU