Pain in Covid 19

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Definition

- **Coronavirus disease 2019** (**COVID-19**) is a contagious **respiratory and vascular** disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

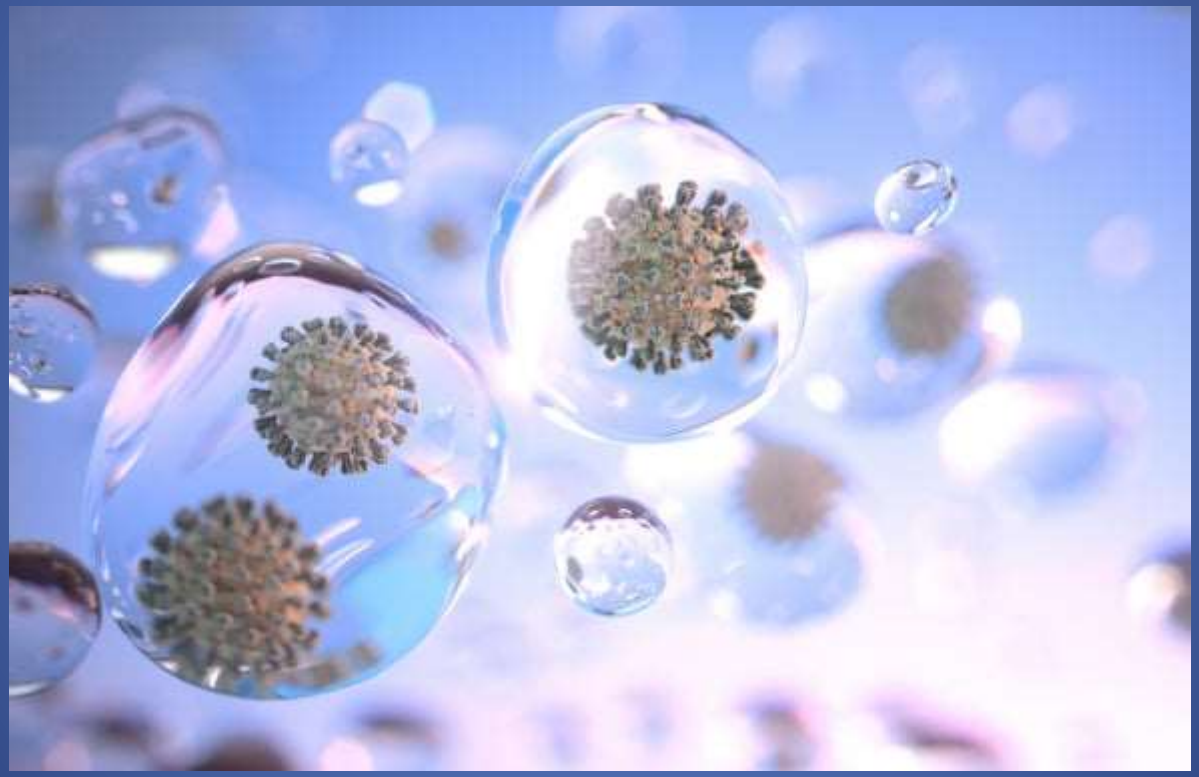
- The first case was identified in Wuhan, China in December 2019, though evidence suggests that the virus may have already been actively spreading months earlier in places such as Italy

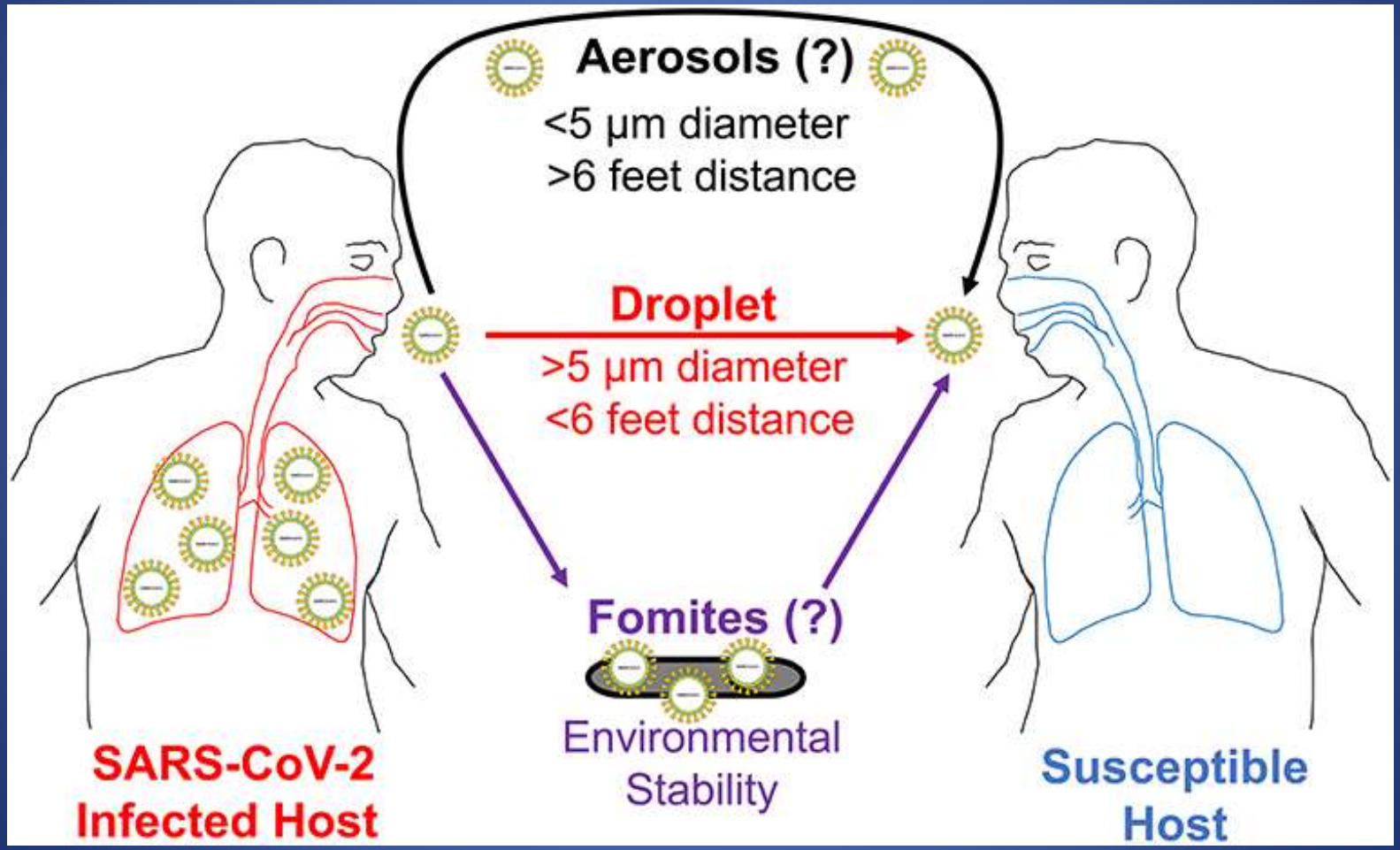
- Symptoms begin one to fourteen days after exposure to the virus.
- While most people have mild symptoms, some people develop acute respiratory distress syndrome (ARDS).
- ARDS can be precipitated by cytokine storms, multi-organ failure, septic shock, and blood clots.

Spread

- COVID-19 spreads via, saliva and other bodily fluids and excretions.
- These fluids can form small **droplets and aerosols**, which can spread as an infected person **breathes, coughs, sneezes, or speaks.**

The virus may also spread via **contaminated surfaces and direct contact.**




Aerosols (?)
<5 μm diameter
>6 feet distance
Droplet
>5 μm diameter
<6 feet distance
Fomites (?)
Environmental
Stability
SARS-CoV-2
Infected Host
Susceptible
Host

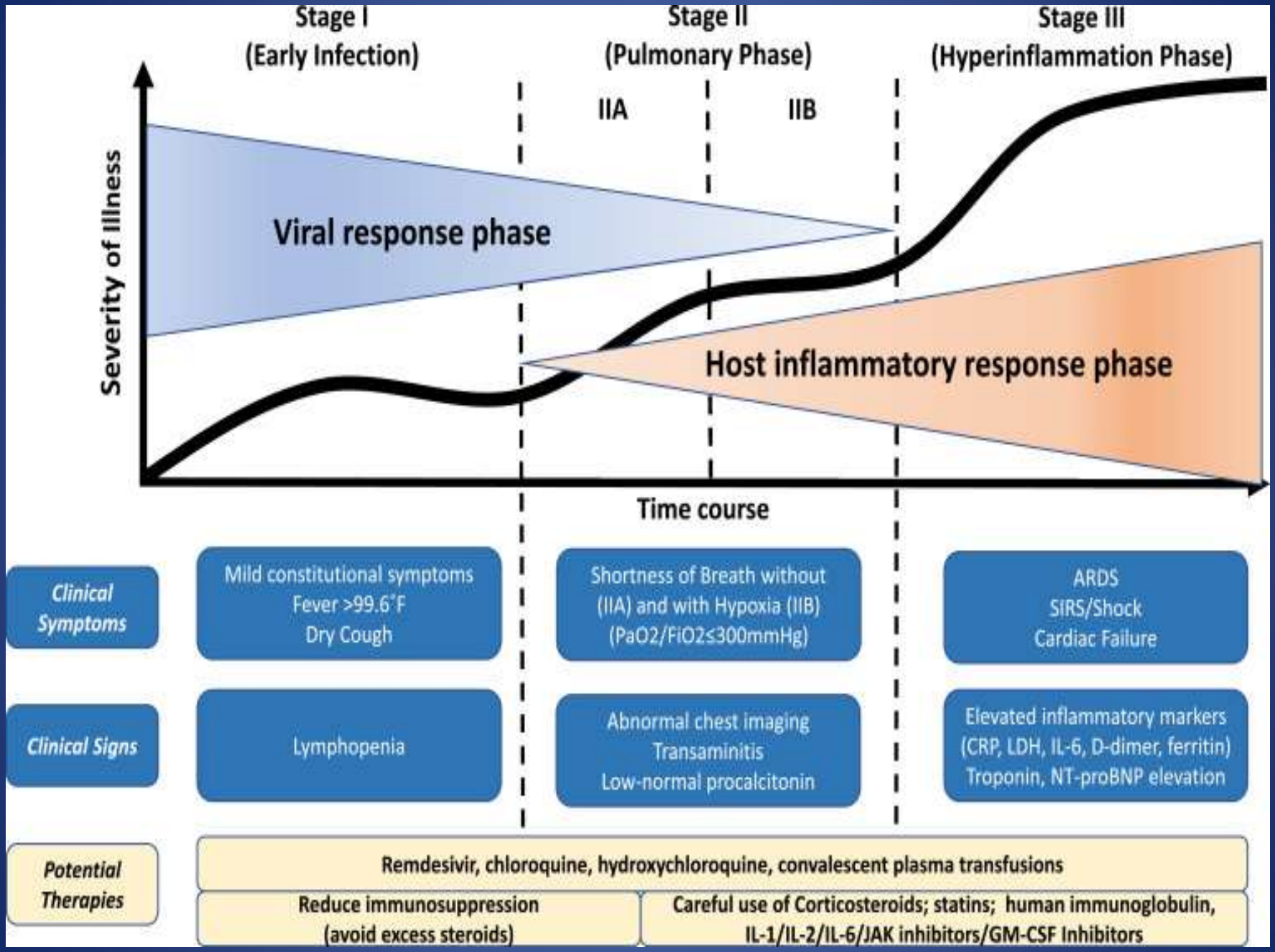
Covid 19 around the world (2021/01/07)

Covid 19 (2021/01/07)

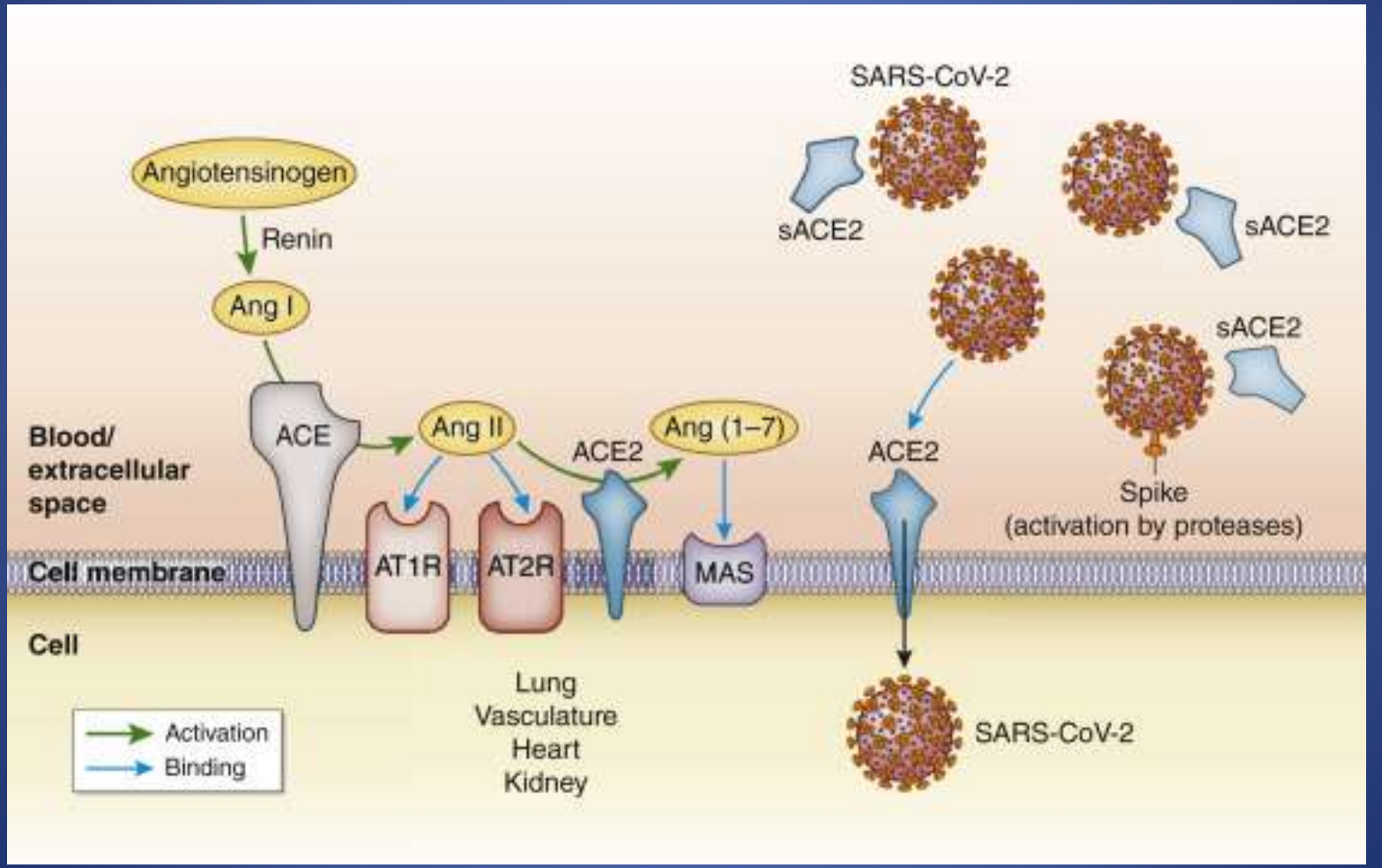
#	Country, Other	Total Cases	New Cases	Total Deaths	New Deaths	Total Recovered	Active Cases
1	USA	21,868,561	+10,945	370,114	+124	13,026,143	8,47
2	India	10,405,097	+9,159	150,470	+98	10,026,751	22
3	Brazil	7,874,539		199,043		7,036,530	63
4	Russia	3,332,142	+23,541	60,457	+506	2,709,452	56
5	UK	2,836,801		77,346		1,345,824	1,41
6	France	2,705,618		66,565		198,756	2,44
7	Turkey	2,283,931		22,070		2,164,040	9
8	Italy	2,201,945		76,877		1,556,356	56

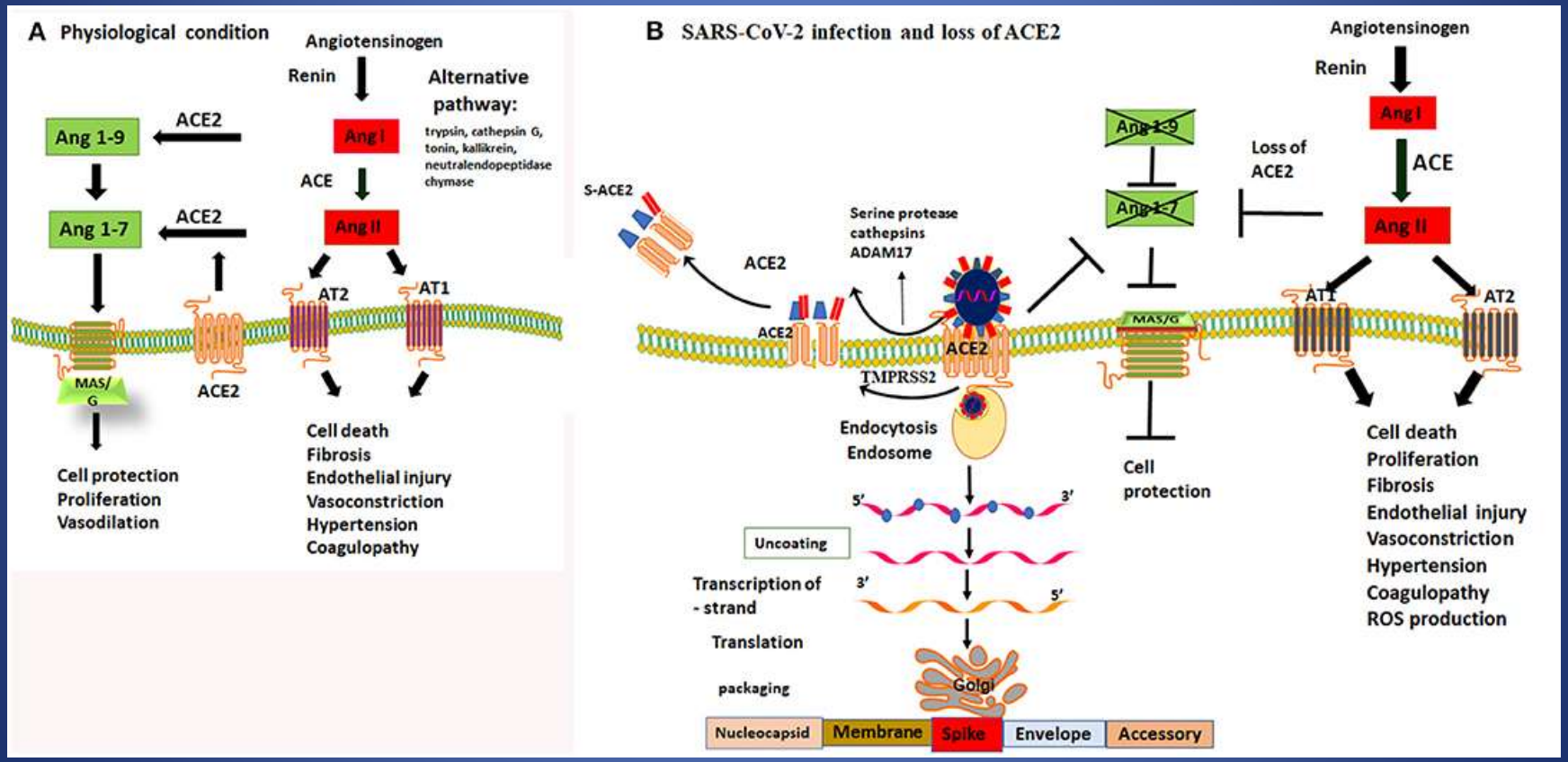
Covid 19 in iran (2021/01/07)

COVID 19 COURSE OF ILLNESS


Stage I
(Early Infection)
Stage II
(Pulmonary Phase)
IIA
IIB
Stage III
(Hyperinflammation Phase)
Severity of Illness
Viral response phase
Host inflammatory response phase
Time course
Clinical Symptoms
Mild constitutional symptoms
Fever >99.6˚F
Dry Cough
Shortness of Breath without (IIA) and with Hypoxia (IIB) (PaO2/FiO2≤300mmHg)
ARDS
SIRS/Shock
Cardiac Failure
Clinical Signs
Lymphopenia
Abnormal chest imaging
Transaminitis
Low-normal procalcitonin
Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
Troponin, NT-proBNP elevation
Potential Therapies
Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions
Reduce immunosuppression (avoid excess steroids)
Careful use of Corticosteroids; statins; human immunoglobulin, IL-1/IL-2/IL-6/JAK inhibitors/GM-CSF Inhibitors

PATHOPHYSIOLOGY OF COVID 19


SARS-CoV-2
sACE2
sACE2
sACE2
Angiotensinogen
Renin
Ang I
ACE
Ang II
ACE2
Ang (1–7)
ACE2
Spike
(activation by proteases)
Blood/
extracellular
space
Cell membrane
AT1R
AT2R
MAS
Cell
Lung
Vasculature
Heart
Kidney
SARS-CoV-2
Activation
Binding


A Physiological condition
Angiotensinogen
Renin
Alternative pathway:
trypsin, cathepsin G, tonin, kallikrein, neutralendopeptidase chymase
Ang 1-9
ACE2
Ang I
ACE
Ang 1-7
ACE2
Ang II
AT2
AT1
MAS/G
ACE2
Cell protection
Proliferation
Vasodilation
Cell death
Fibrosis
Endothelial injury
Vasoconstriction
Hypertension
Coagulopathy
B SARS-CoV-2 infection and loss of ACE2
Angiotensinogen
Renin
Ang I
ACE
Ang 1-9
Loss of ACE2
Ang 1-7
Ang II
S-ACE2
ACE2
Serine protease cathepsins ADAM17
AT1
AT2
MAS/G
ACE2
ACE2
TMPRSS2
Endocytosis
Endosome
Cell protection
Cell death
Proliferation
Fibrosis
Endothelial injury
Vasoconstriction
Hypertension
Coagulopathy
ROS production
5′
3′
Uncoating
Transcription of - strand
3′
5′
Translation
packaging
Golgi
Nucleocapsid
Membrane
Spike
Envelope
Accessory

COVID 19 DIAGNOSIS

Common COVID-19 Diagnostic Methods: RNA

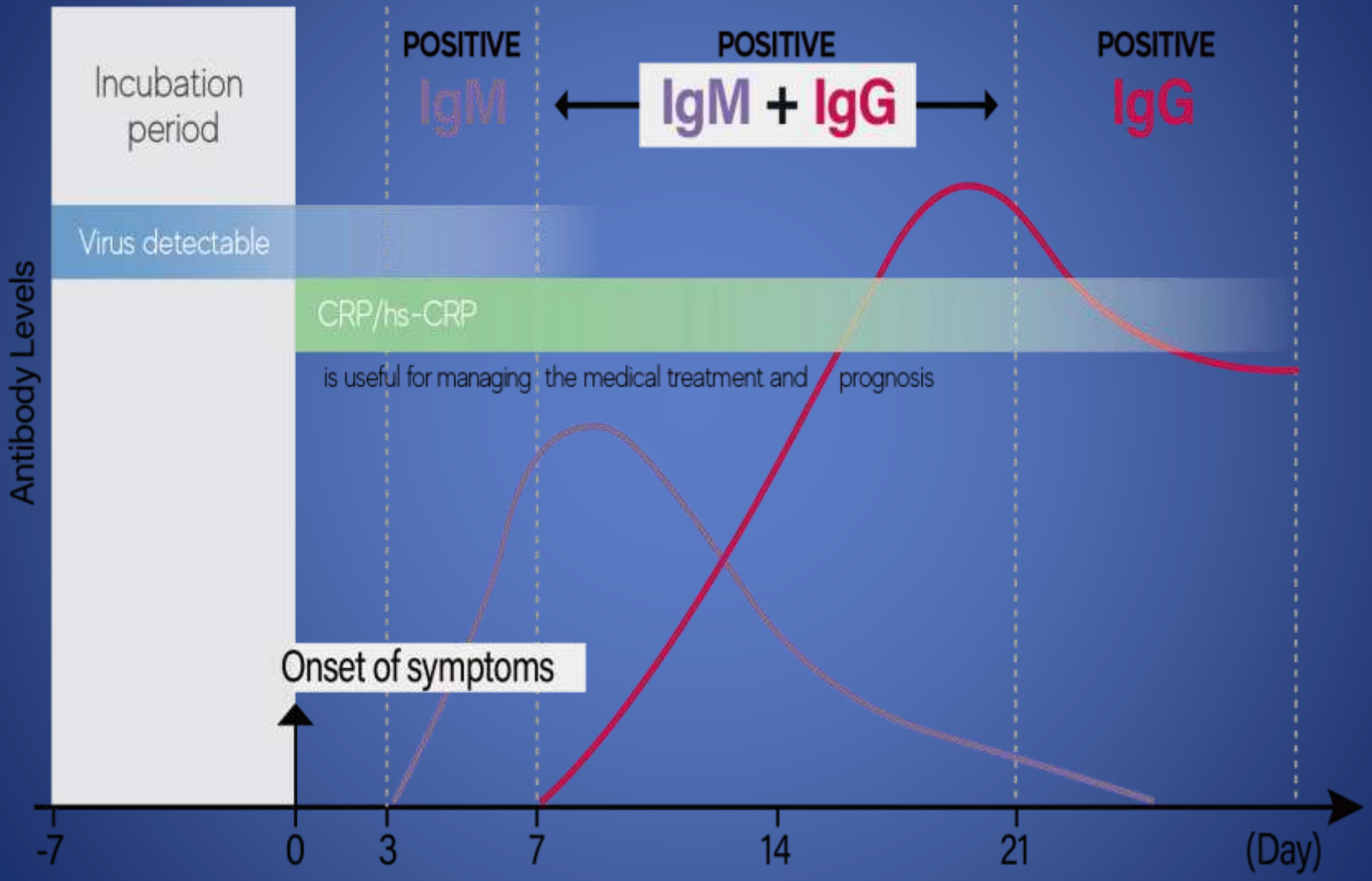
Viral Nucleic Acid Assays	
Typically indicate	▪ Current infection
Specimen sources	▪ Upper (eg, nasopharyngeal swabs or washes, oropharyngeal swabs, nasal aspirates) or lower (eg, sputum, bronchoalveolar lavage fluid, tracheal aspirates) respiratory tract
Considerations	▪ Primary method for COVID-19 diagnosis with multiple RT-PCR kits available ▪ False negatives may result from improper sampling or handling, low viral load, or viral mutations ▪ SARS-CoV-2 RNA undetectable by ~ Day 14 following onset of illness in some cases/samples

Udugama. ACS Nano. 2020;14:3822. Lee. Front Immunol. 2020;11:879.

Common COVID-19 Diagnostic Methods: Antibodies

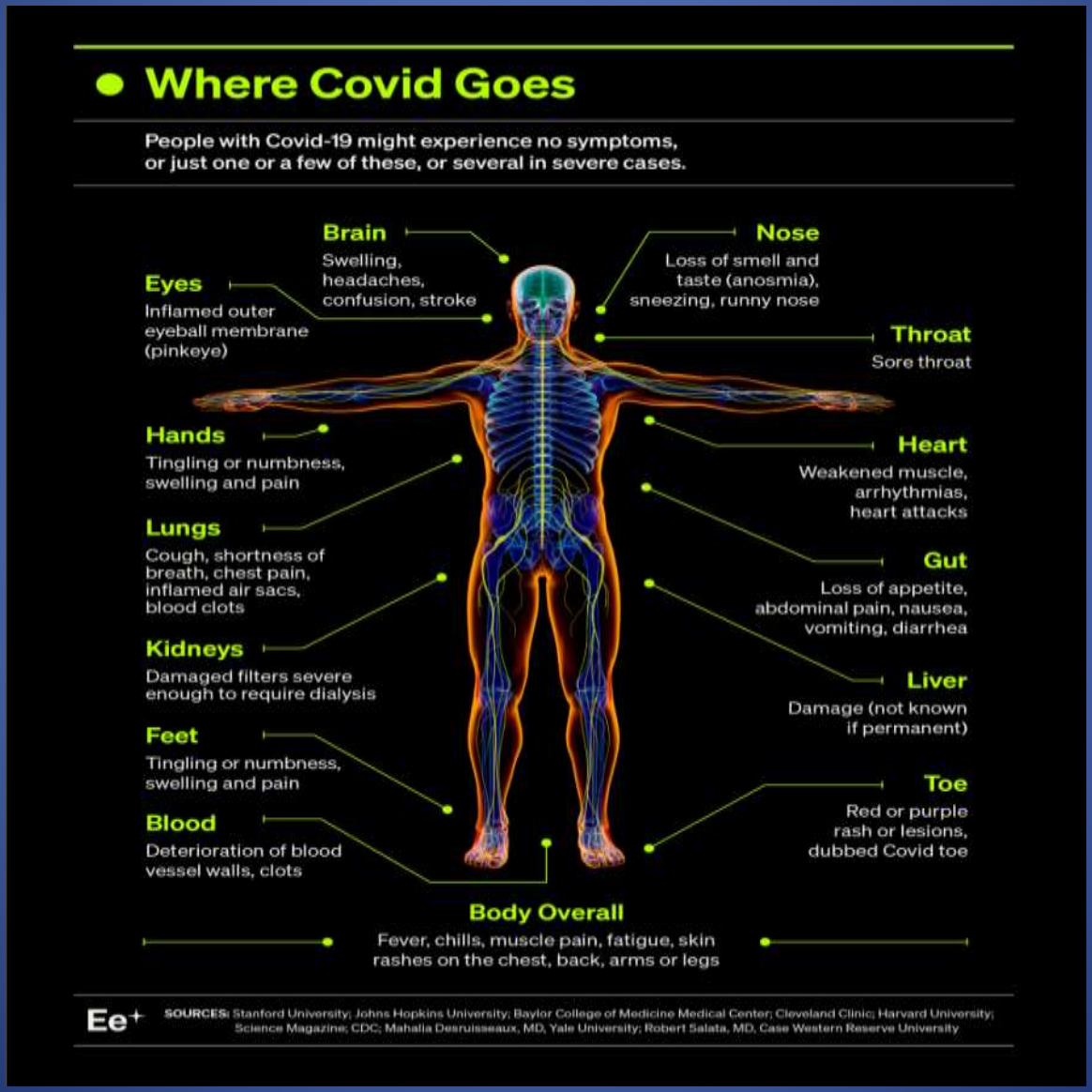
Updated

Serologic Assays	
Typically indicate	▪ Past infection, but may have some utility in diagnosis of current infection among those presenting late or when RT-PCR negative/unavailable
Specimen sources	▪ Most often blood serum or plasma, but may include saliva, sputum, or other biological fluids
Considerations	▪ Provides a delayed but wider window of time for detection ▪ May be useful for COVID-19 surveillance and identification of convalescent plasma donors ▪ **False negatives**: Low sensitivity in first wk after symptoms with subsequent rises during second/third wks and scant data thereafter; unclear if low-level antibody detectable in cases of mild/asymptomatic disease ▪ **False positives**: Due to cross-reactivity ▪ Uncertain if positive read = immune protection if re-exposed


Incubation period
POSITIVE
IgM
POSITIVE
IgM + IgG
POSITIVE
IgG
Virus detectable
CRP/hs-CRP
is useful for managing the medical treatment and prognosis
Antibody Levels
Onset of symptoms
-7
0
3
7
14
21
(Day)

COURSE AND SYMPTOMS OF COVID 19

From head to toe



Common symptoms:

Fever: 83–99%

Loss of Appetite: 40–84%

Fatigue: 44–70%

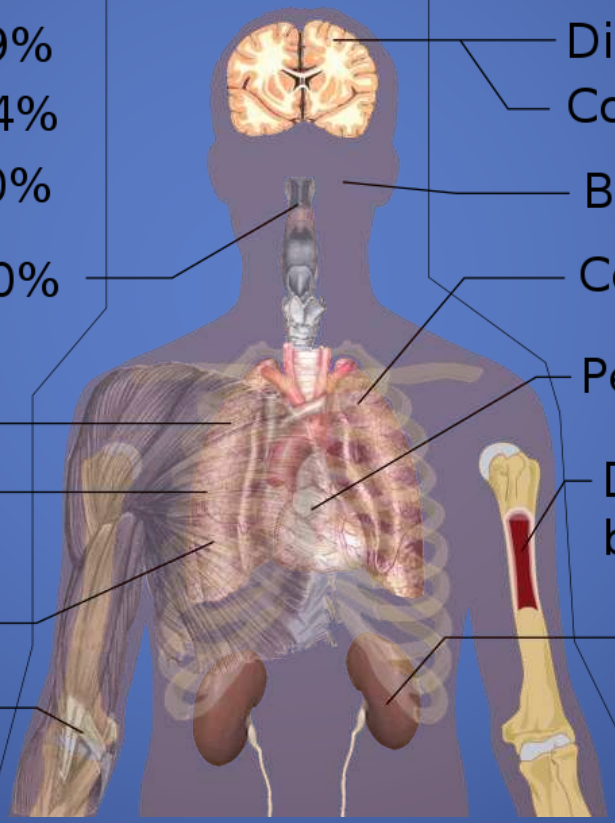
Loss of smell: 15 to 30%

Shortness of breath: 31–40%

Cough: 59–82%

Coughing up sputum: 28–33%

Muscle aches and pain: 11–35%



In severe disease:

Difficulty waking

Confusion

Bluish face or lips

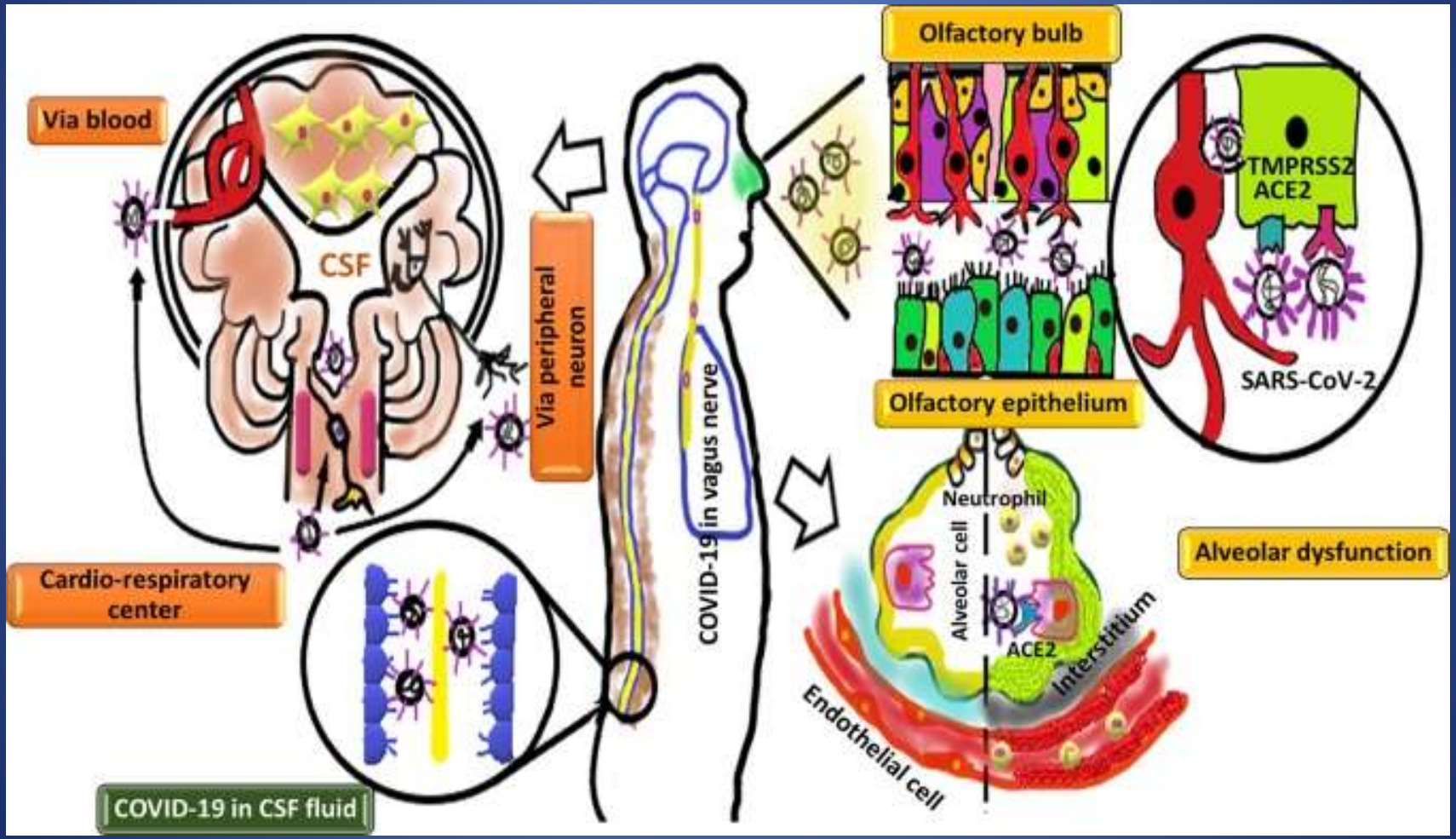
Coughing up blood

Persistent chest pain

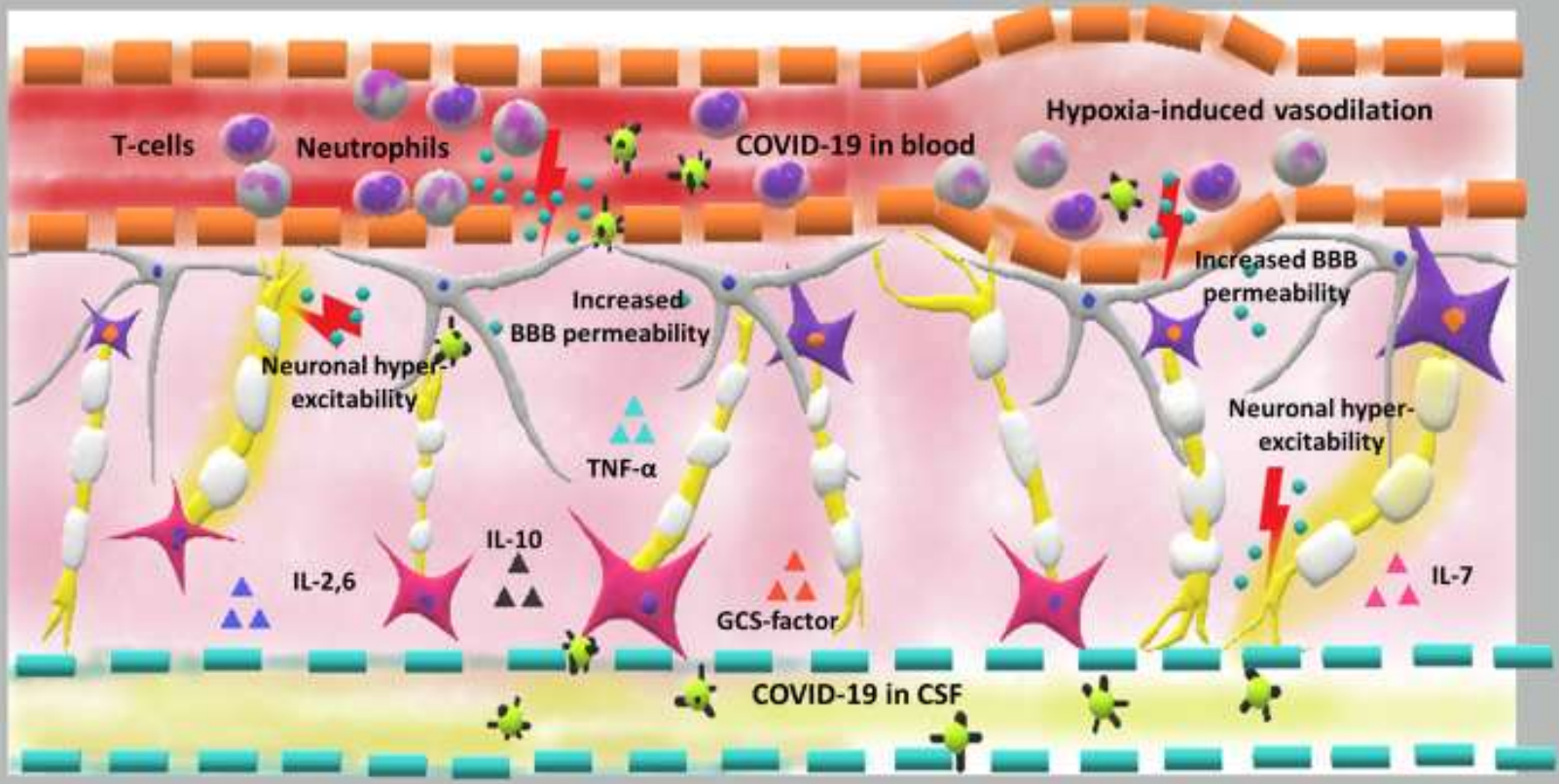
Decreased white blood cells

Kidney failure

High fever


Olfactory bulb
Via blood
CSF
Via peripheral neuron
COVID-19 in vagus nerve
TMPRSS2
ACE2
SARS-CoV-2
Olfactory epithelium
Neutrophil
Alveolar cell
Alveolar dysfunction
Cardio-respiratory center
ACE2
Interstitium
Endothelial cell
COVID-19 in CSF fluid

SARS COV 2 in nervous system



3 coarses of covid 19

- **Regular acute pattern**
- **Irregular acute form**
- **Post covid 19 chronic syndrome**

Regular Acute Pattern
Six distinct 'types' of COVID-19 identified

1. (‘flu-like’ with no fever): Headache, loss of smell, muscle pains, cough, sore throat, chest pain, no fever.
2. (‘flu-like’ with fever): Headache, loss of smell, cough, sore throat, hoarseness, fever, loss of appetite.
3. (gastrointestinal): Headache, loss of smell, loss of appetite, diarrhea, sore throat, chest pain, no cough.
4. (severe level one, fatigue): Headache, loss of smell, cough, fever, hoarseness, chest pain, fatigue.
5. (severe level two, confusion): Headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain.
6. (severe level three, abdominal and respiratory): Headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain, shortness of breath, diarrhea, abdominal pain.

Irregular acute form (without other symptoms)

- Low Back pain
- Arthralgia /Arthritis
- Myalgia
- Eye pain
- Leg pain
- Headache
- Chest pain
- Weakness
- Loss of smell

PAIN IN COVID 19

Pain in Covid 19

- Pain is one of the variables affecting health status that brings the patient to a hospital and helps the physician to early diagnosis of the disease.
- Considering, that the **Covid 19 is a newfound illness**, the presence of pain may not be taken seriously or might be mistaken to be originating due to other illnesses.
- Therefore, identifying clinical symptoms in this disease is very important and needs to be investigated and documented.

Pain prevalence in Covid 19

- The prevalence of
- **Myalgia** in 28 analyzed articles was 18%
- **Headache** prevalence in 21 articles was equal 10%
- **Sore throat** with analyze of 16 articles was 12% .

PATHOPHYSIOLOGY OF PAIN IN COVID 19

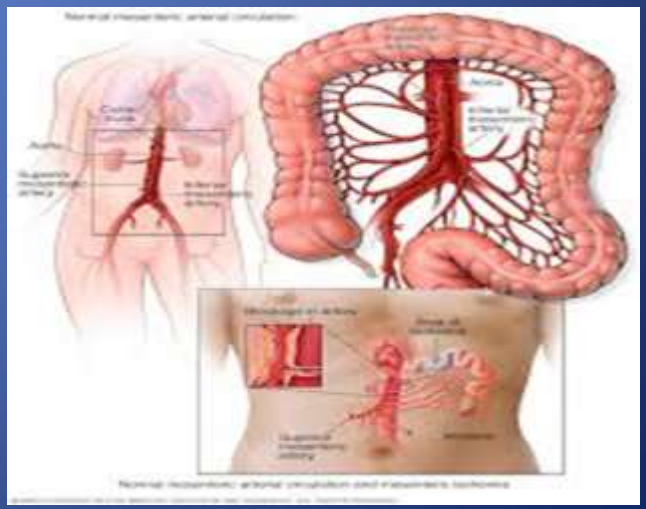
Pathophysiology of pain in covid 19

- **Nociceptive pain due to inflamation**

- A pain stimulus can be in the form of tissue inflammation which will cause the release of inflammatory mediators such as histamine, prostaglandin E2, and leukotriene which will stimulate nociceptors, and can also be in the form of heat, stretching, and others which also stimulate nociceptors.

- **Nociceptive visceral pain :**

1. Gastroenthritis due to viral infection
2. Ischemic pain (mesentric ischemia)



Pathophysiology of pain in covid 19

- Acute pain presents as **arthralgia or arthritis** that commonly occurs in viral infection.
- **Viral pathogen could** :

1. Directly invade the joints by lytic process
2. Induce immune systems to react by immune complex formation
3. And also inflammatory cytokines

Pathophysiology of pain in covid 19

- In COVID-19, more than one-third of patients experience different neurological symptoms, which may involve:
- **the central nervous system** (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and epilepsy),
- **the peripheral nervous system** (taste impairment, smell impairment, vision impairment, and neuralgia)
- **skeletal muscular damage**

Pathophysiology of pain in covid 19

- **Sheraton et al**. hypothesized that

- **CNS symptoms may occur due to the inflammatory mechanisms**
- **But PNS symptoms are due to immune-mediated processes,**

(but more research is needed to explain SARS-CoV-2 related neuropathy.)

Pathophysiology of pain in covid 19

- **Su et al.** suggest that
- central pain could be induced through the ACE2-positive cells in the human spinal dorsal horn via the decrease of functional ACE2 (Angiotensin-converting enzyme 2), which then results in the accumulation of Ang. II (Angiotensin II) and the decrease of Ang (1–7)

Pathophysiology of pain in covid 19

- **Helms et al**. showed that patients with COVID-19 had neurological symptoms such as
- perfusion abnormalities
- Confusion
- Agitation
- Ischemic stroke.

Pathophysiology of pain in covid 19

- The pain induced by COVID-19 infection could result from the effect of spinal ACE2 on pain sensation and the direct or indirect tissue damage
- **Studies shows :**
- **ACE 1/AngII/AT1 receptor pathway** facilitated pain transmission in the spinal dorsal horn
- While **ACE 2/Ang (1-7)/Mas receptor** pathway might alleviate pain through the inhibition of p38 mitogen-activated protein kinase phosphorilation

(yamagata etal 2020)

-

- **So it causes neuropathic pain :**
- SARS-COV 2 might infect the ACE 2 positive cells in spinal dorsal horn ,the decrease of functional ACE2 then sesults in the accumulation of Ang II and decrease of Ang (1-7), consequently, SARS-COV2 infection in the spinal cord could induce pain

- In addition to spinal dorsal horn, SARS-COV2 also **attacks directly ACE 2** positive cells in other tissues, such as GI, kidney and heart, leading to damage to this tissues.(nociceptive pain).
- Beside the direct attack, SARS-COV2 may cause **cytokine storm**, involving IL6,IL10 and TNF, that induces damage in tissuse ind triggering pain(indirect Attack)

(Chen et al, 2020)

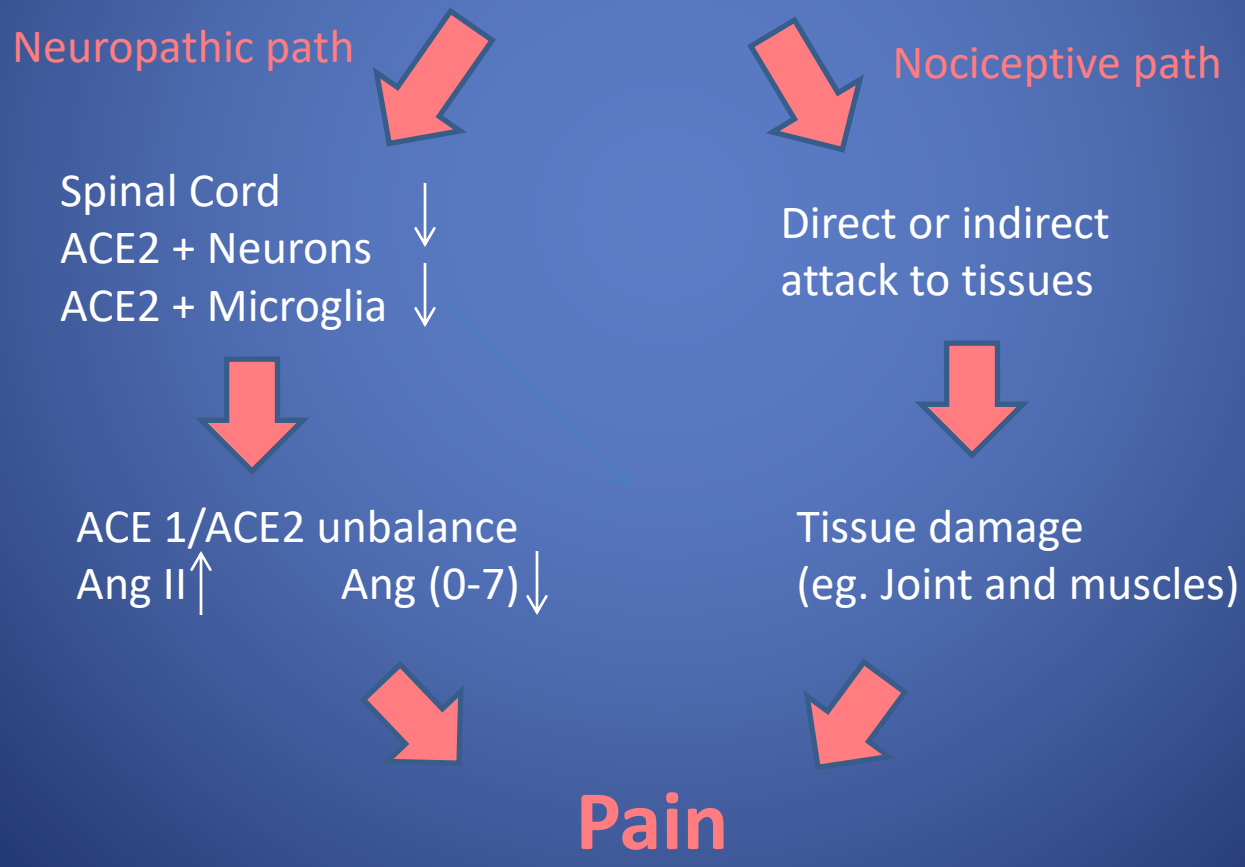
Pathophysiology of pain in covid 19

- One of the most common causes of pain in COVID-19 infection is the associated **muscle pain**.
- Multiple studies have shown that **myalgia** is one of the most common symptoms at onset, seen in nearly 36% of patients.
- Myalgia during viral infection is most commonly mediated by Interleukin-6 (IL-6), whose upregulation causes muscle and joint pain.
- It is believed that myalgia in COVID-19 patients might reflect the generalized inflammation and cytokine response.
- As SARS-CoV-2 induces a strong inflammatory response, elevated cytokine levels (IL-6, IL-10, and TNF α) are present, especially in patients with a moderate or severe disease course.

Pathophysiology of pain in covid 19

- It is believed that **invasion of virus in the muscle and joint**, inducing inflammatory response **may cause pain**.
- The increasing numbers of inflammatory mediators also involve in this pathogenesis and could damage the muscle.
- The COVID-19 patients often experience arthralgia, or general weakness caused by the impact of the virus itself
- SARS-COV-2 can affect **directly or indirectly to the tissue damage** including joint and muscle resulting pain in infected patients.

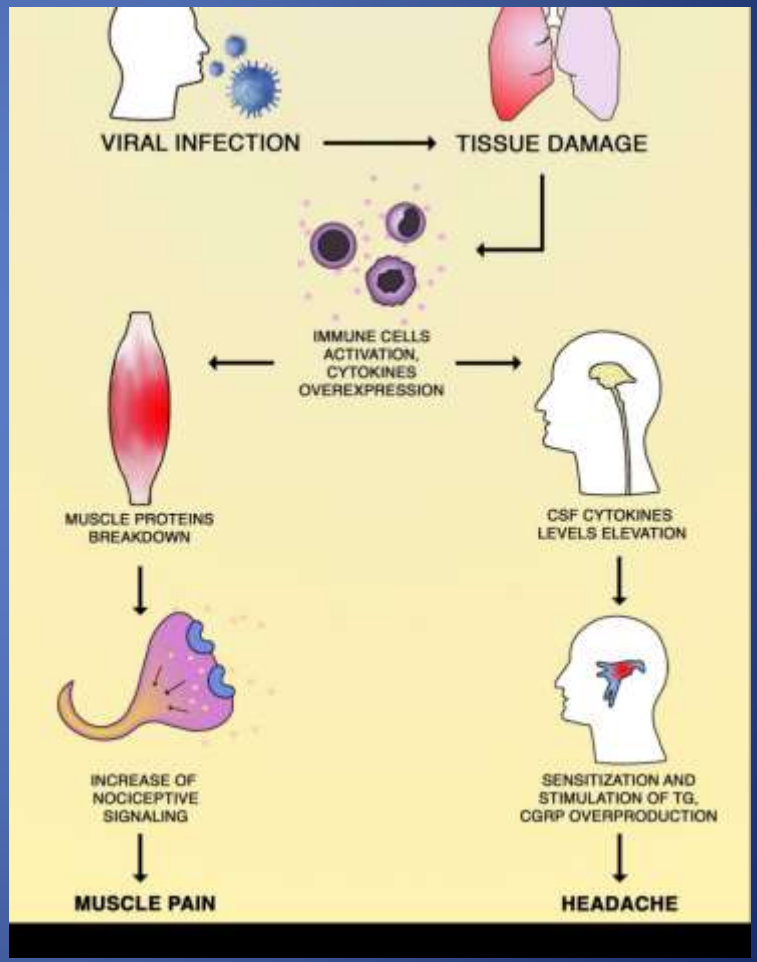
SARS-COV 2



(Su et al 2020)

Pathophysiology of pain in covid 19

- Putative mechanisms of myalgia and headache during viral infection. The specific mechanism of headache during infection remains unclear.
- The assumed pathomechanisms involve the **overexpression of proinflammatory cytokines, such as TNF-α and PGE2, in the cerebrospinal fluid (CSF),** which **sensitize and stimulate trigeminal ganglia (TG)** neurons to produce calcitonin gene related peptide (CGRP).
- CGRP has a crucial role in the pathogenesis of migraine, influencing arteries' dilatation and possibly to direct a nociceptive transmission.
- The **myalgia** during viral infection is believed to be the effect of proinflammatory cytokines influence on muscle tissue.
- TNF-α is responsible for the intensified breakdown of muscle proteins and PGE2 could increase the nociceptive signaling.



Headache in covid 19

- the **most common neurological symptom is headache**, often accompanied by high fever, moreover headache can occasionally be seen alone as the **first sign or even the sole sign** of the disease.
- A recent meta-analysis reported that the prevalence of headache was **10.9%** with a high level of heterogeneity

Headache in covid 19

- Headache in covid is **acute onset**, and or **worsening previous chronic headache**.
- The underlying mechanisms of headache related to COVID-19 are not clear at this early moment.
- A **direct invasion of trigeminal nerve endings** in the nasal or oral cavity by the virus seems one of the most reasonable mechanisms underlying headache according to our results showing the close relation between headache and anosmia/ageusia.

Headache in covid 19

- Headache in relation with a systemic viral infection, (without signs of meningo-encephalitis) is described in the International Classification of Headache Disorders.
- Headache was triggered more frequently by stress and social isolation in patients without COVID-19 whereas patients diagnosed with COVID-19 reported also infection itself and the drugs as triggers of headache.

Headache charachteristic

- Charachteristic of viral headache is **diffuse pain of moderate/severe intensity**, commonly with fever
- **long-lasting bilateral headaches over 48– 72 h**
- **headaches resistant to analgesics**
- The quality of headache is **pulsating and pressing** characters in COVID-19 patients.
- pulsating type was more pronounced in patients with previous headaches.
- **photophobia** was more frequently experienced by infected participants than those without COVID-19
- **Osmophobia** was more frequently seen in the group with COVID- 19, which may also be related to the olfactory dysfunction.

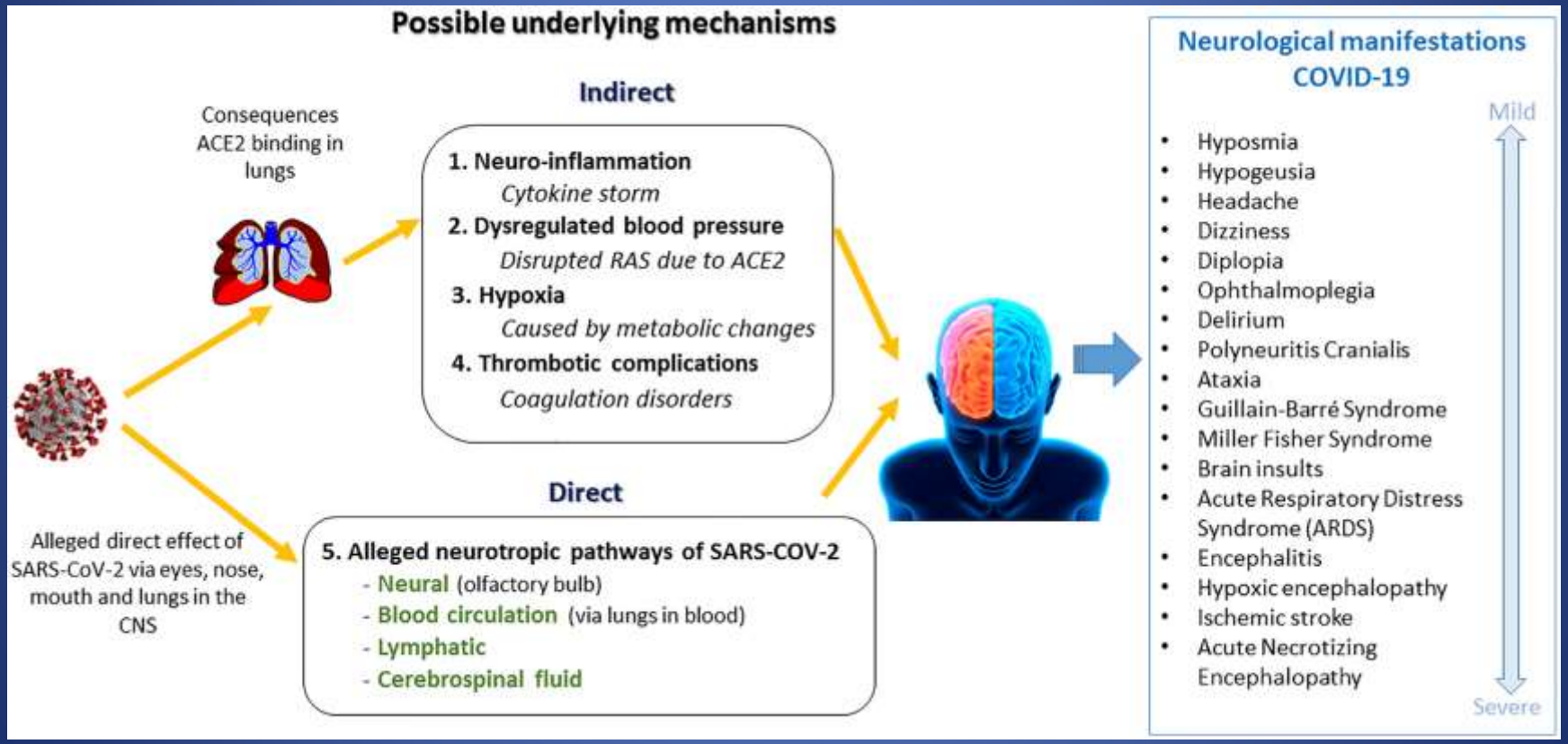
Male gender

bilateral, long-lasting

and

resistance to analgesics were more frequently seen in people with covid 19

Pathophysiology of neurological manifestation of Covid 19



PAIN ASSESSMENT DURING COVID-19

- The golden standard for the assessment of pain are tools based on patient self-assessment, e.g., visual analogue scale (VAS) or numerical assessment scale (NRS), which assume patient–physician cooperation

Pain assessment in ICU

- **Pain in ICU** patients can be divided into four categories:

1. acute pain associated with the disease
2. continuous pain/discomfort associated with ICU treatment
3. intermittent procedural pain
4. chronic pain present before admission to the ICU

Pain assessment in ICU is important

- Why ?
- Under-treatment of pain, especially when using neuromuscular blocking agents, prone positioning or extracorporeal membrane oxygenation (ECMO) may trigger :
- Delirium
- Heart failure
- Other organ dysfunctions
- Persistent neuropathies

ICU Assessment Scales

- SO :
- in patients who are unable to self-report pain, behavioral pain assessment scales should be used, namely the Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT)

The CPOT scale was designed for the critical detection of **pain in sick patients** and includes **four** behavioral categories: facial expressions, body movements, muscle tone, susceptibility with a fan (for intubated patients) or verbalization (for extubated patients). Each category is scored on a 0–2 scale (0–8 points in total)

Appendix 2: Critical-Care Pain Observation Tool (CPOT)

Indicator		Description	Score
Facial expression	Relaxed, neutral	No muscle tension observed	0
	Tense	Presence of frowning, orbit tightening, levator contraction, or any other change (e.g., opening eyes or tearing during nociceptive procedures	1
	Grimacing	All previous facial movements plus eyelid tightly closed	2
Body movements	Absence of movements or normal position	Does not move at all or normal position (movements not aimed toward the pain site)	0
	Protection	Slow, cautious movements, touching, or rubbing the pain site, seeking attention through movements	1
	Restlessness	Pulling tube, attempting to sit up, moving limbs, not following commands, trying to climb out of bed	2
Compliance with the ventilator (intubated patient)	Tolerating ventilator or movement	Alarms not activated, easy ventilation	0
or	Coughing but tolerating	Coughing, alarms may be activated	1
Vocalization (nonintubated patient)	Fighting ventilator	Asynchrony: blocking ventilation, alarms frequently activated	2
	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Muscle tension	Relaxed	No resistance to passive movements	0
Evaluation by passive flexion and extension of upper limbs (in rest or when patient is being turned)	Tense, rigid	resistance to passive movements	1
	Very tense or rigid	Strong resistance to passive movements, inability to complete them	2
Total			-/8

BPS was developed by Payen et al. to assess pain in mechanically ventilated unconscious patients. The scale is based on three types (ranges) of behavior: facial expressions, upper limb movements and ventilation compatibility

Appendix 1: Behavioral Pain Scale (BPS) Tool

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing with movement	2
	Fighting ventilator	3
	Unable to control ventilation	4

COVID 19 PAIN TREATMENT

Pain Treatment in Covid 19

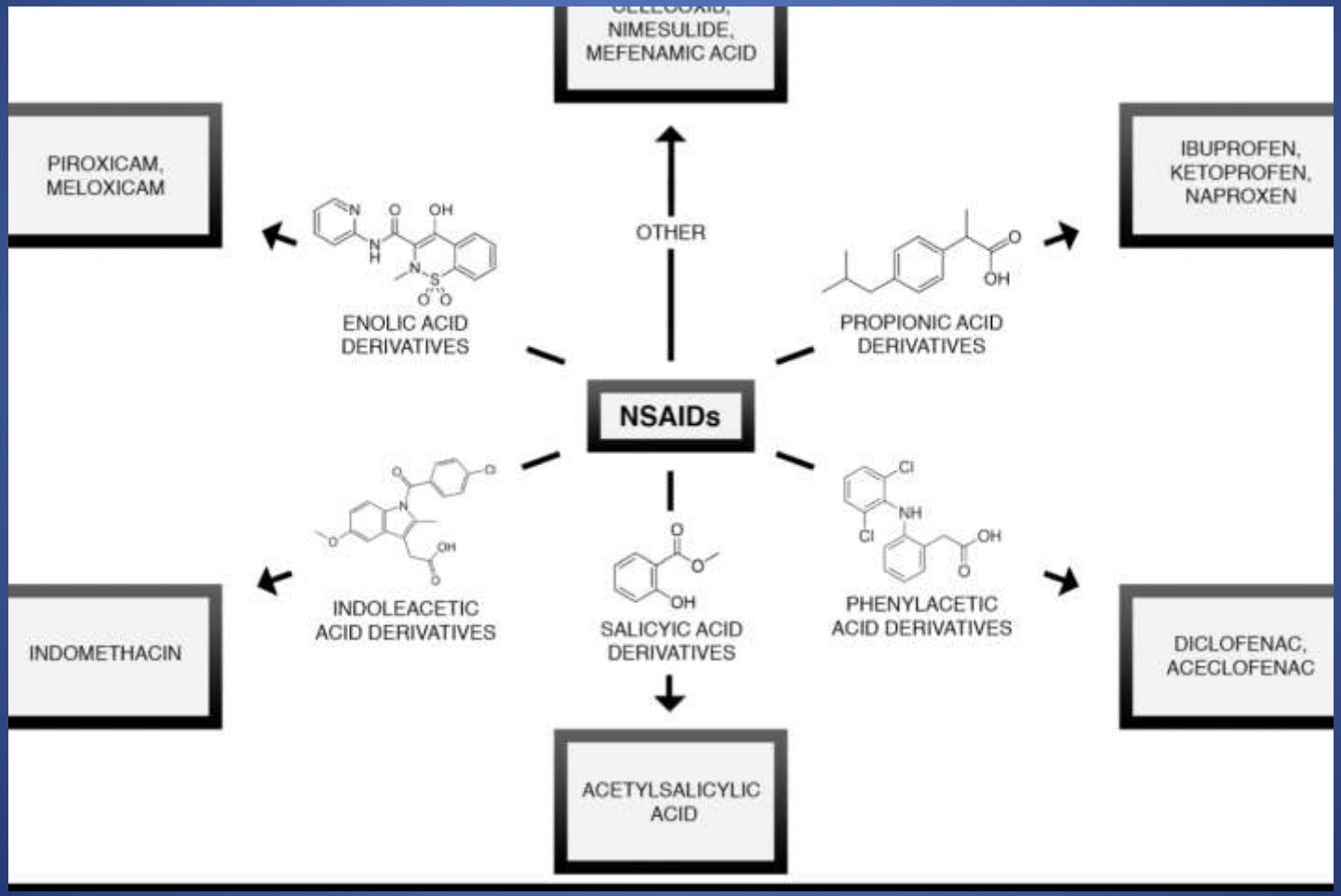
There are currently **no clinical trials or specific guidelines** regarding the topic of pain management in COVID-19 patients

NSAIDS

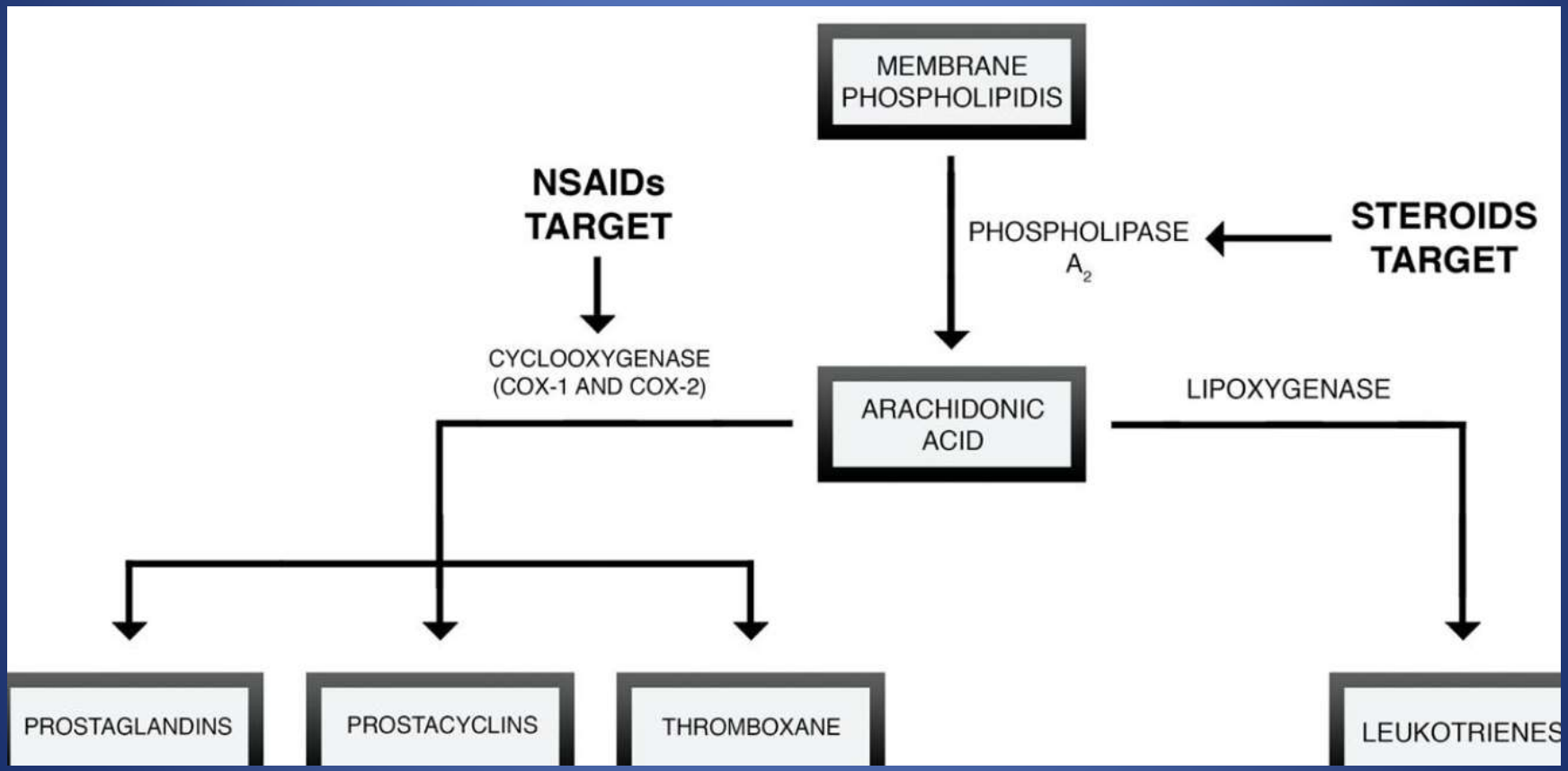
NSAIDS

- The most **widely used** drugs worldwide
- Easy **accessibility and efficacy**

NSAIDS


NIMESULIDE,
MEFENAMIC ACID
PIROXICAM,
MELOXICAM
IBUPROFEN,
KETOPROFEN,
NAPROXEN
OTHER
ENOLIC ACID
DERIVATIVES
PROPIONIC ACID
DERIVATIVES
NSAIDs
INDOLEACETIC
ACID DERIVATIVES
SALICYIC ACID
DERIVATIVES
PHENYLACETIC
ACID DERIVATIVES
INDOMETHACIN
DICLOFENAC,
ACECLOFENAC
ACETYLSALICYLIC
ACID

NSAIDs influence the **arachidonic acid** cascade and **prostaglandins biosynthesis** through the **inhibition of cyclooxygenase (COX)**



- Recently, concerns about the possible higher frequency of adverse effects and exacerbation of symptoms of viral respiratory tract infections, such as COVID-19, in patients treated with NSAIDs have been raised

- However, according to the WHO (as of 19th of April 2020), there is no evidence for the aforementioned hypothesis .

Ibuprofen

- The controversies regarding the safety of ibuprofen in COVID-19 have emerged after a report to public media was made by a French infectious disease specialist, who observed the decompensation and development of severe symptoms in an early stage of infection in four children after administration of ibuprofen.
- The report was firstly confirmed by the French Minister of Health and the WHO.
- However, having reviewed the available data, **the WHO published their recommendations, underlining no evidence of COVID-19 patient decompensation after the usage of NSAIDs .**
- **Concern surrounded a possible increased expression of the ACE – 2 receptor which is the target for cell penetration of SARS COV 2 by Ibuprofen**

- Nonetheless, the previous study by Kotsiou et al. reported that pre-hospital usage of NSAIDs in the treatment of symptoms of community-acquired pneumonia is connected with the exacerbation of pneumonia, prolonged hospitalization, and more severe pleural effusions .

- Several studies suggest that this effect should be considered in COVID-19 treatment

- In conclusion, no study to date has reported higher mortality of COVID-19 patients treated with ibuprofen.
- Despite this, in doubtful cases, **paracetamol or metamizole** should be used instead of ibuprofen, especially in over the counter (OTC) usage

Paracetamol

- There are, some cases where the use of paracetamol might not be beneficial, due to its pharmacokinetic properties.
- As paracetamol is metabolized mainly by two **cytochrome P450 isoenzymes** (CYP1A2 and CYP2E1) cytokine storm associated with viral infection can potentially disrupt the metabolic functioning of cytochrome P450

Metamizole (Dipyrone)

- metamizole does not interact with therapeutic agents, commonly used in SARS-CoV-2 therapy .
- Moreover, it affects SARS-CoV-2 main protease (Mpro), **curbing its transcription and replication**.
- However, the role of metamizole in infection symptoms control is questionable because of its association with **agranulocytosis** (the adverse effect that could lead to a sudden worsening of COVID-19 patient condition).

Naproxen

- **Naproxen is similar to ibuprofen** but long acting
- **There is a hypotheses** : naproxen **binding competed with NP** association with **viral RNA** and impeded the NP self-association process which **strongly reduced viral trascription/replication**
- So naproxen may have the **potential to present antiviral properties against SARS-COV2**
- Recent clinical trials shown that the combination of clarithromicin, naproxen and oseltamivir reduced hospitalization in H3N2 flu

- Overall, both the EMA (European Medicines Agency) and the WHO do not recommend altering or discontinuing NSAID therapy in patients using them in chronic treatment, with suspected or diagnosed SARS-CoV-2 infection.

- It is also worth remembering that NSAIDs could interfere with the inhibition of platelet COX-1 by aspirin. The number of patients using acetylsalicylic acidin the anti-platelet dosing range is still increasing and any influence on their therapy could result in an increased risk of cardiovascular events.

- NSAIDs administration, lead to around 12% of deaths amongst COVID-19 patients

OPIOIDS

- Yamamoto et al. verified the effects of **oxycodone** intravenous administration. It was found to reduce dyspnea in almost 70% of patients, without causing any significant adverse effects
- **Fentanyl**, in comparison with oxycodone and morphine, significantly reduced brain oxygen supply. Similar to other opioids, its use was associated with not only decreases in respiratory rate, mediated by receptor agonism, but also reduced tidal volume.

- Another property of opioids is the induction of immunosuppression
- The suppression of immunity after **fentanyl** administration is dose dependent
- With regards to a **decrease** in NK cells' activity and the concentration of proinflammatory cytokines, a change in Il-1 and Il-6 are the most notable characteristics

- multiple dissertations suggest that **oxycodone** has a higher safety profile than morphine or fentanyl.
- Hernandez et al. suggest that oxycodone immunosuppressing effect subsides sooner (after around 6 h) than after morphine administration

- Wiese et al. have found that the immunosuppressing attributes of opioids influence the frequency of infections at the viral infection episode
- And opioids may be effective in **cytokine storm** by immunosuppression

- **Tramadol** and **buprenorphine** seem to be a clinically superior choice. Neither of them has immunosuppressive properties, so, in theory, they do not prolong viral shedding.
- In addition, buprenorphine is safe in multiorgan failure and has a ceiling effect for respiratory depression

CORTICOSTEROIDS

- **Steroids** are efficacious in decreasing the extent of immunopathological damage.
- the **side effects** indivertibly associated with their long-term use dissuaded physicians from prolonged therapy, fearing the rebound effect of the infection, and consequentially the development of adverse effects, such as acute respiratory distress syndrome.

- So it is important when using steroids during Covid 19 course ?
- Dexamethasone was successful in alleviating inflammatory response
- animal studies involving swine infected with CoV provided further evidence that one or two doses of corticosteroid during the acute phase of the infection can successfully ameliorate the early inflammatory response; however, their prolonged use might promote replication of the virus

NEUROPATHIC PAIN TREATMENT

- Peripheral nervous system involvement, including painful neuropathies, was reported in many patients with SARS-CoV-2 infection
- This may be a consequence of either viral invasion of the peripheral nerves (neurotropism) or prolonged immobility during severe illness, or both
- **Gabapentin and pregabalin** are calcium channel 2-ligands commonly used in the treatment neuropathic pain
- Currently, there are no clinical trials exploring this topic

- calcium channel ligands reduce respiratory drive; therefore, combined therapy with opioids might be potentially hazardous and the use of duloxetine in such cases ought to be thoroughly considered

POST COVID 19 SYNDROME

- Despite passing months after the first case of COVID-19, scientists are facing **long-term complications.**

- This disease can cause :
- Heart failure
- Neurological diseases, such as **stroke**
- Lung disease.

- These symptoms reflect the **post-viral syndrome associated with COVID-19 .**

- Moreover :
- Difficulty in reading
- Insomnia
- General myalgia
- Dry skin
- Increased anxiety
- Fatigue and brain fog, which may be related to cytokines that cross the blood-brain-barrier (BBB) and affect the brain.

- **myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)** reffer to patients thay are experiencing long-term adverse effects of symptoms ME/CFS, such as persistent fatigue, diffuse myalgia, depression, and non restorative sleep

- According to post-mortem findings in COVID-19 cases, the olfactory pathway is the way, by which the virus can cross the BBB and enter the hypothalamus.
- The perivascular space along the olfactory nerves that can pass the cribriform plate into the nasal mucosa is an important pathway involved in brain lymphatic drainage.
- Thus, the anosmia observed in some COVID-19 patients may be related to the effects of coronavirus affecting this pathway.
- Moreover, the virus disturbs lymphatic drainage from the microglia in the brain.

- Production of cytokines in nervous system can cause post-viral symptoms
- Because pro-inflammatory cytokines cross the BBB in circum-ventricular organs, like the hypothalamus, resulting in autonomic impairment that is presented as a high fever

A study in italy shows

- The patients who were discharged from the hospital were assessed :
- 12.6% had no symptoms of COVID-19
- 32% had one or two symptoms
- 55% had three or more.
- Also, 53% had fatigue, 43% dyspnea, 27% joint pain, and 21% chest pain. According to this study, 87.4% had persistence of at least one symptom, especially fatigue and dyspnea