

# **COVID-19 infekció. Szövődmények. Patomechanizmus**

Belgyógyászati Szakvizsga Előkészítő Tanfolyam

2021.05.17-Június 11.

Pécs

On-line tanfolyam

## **SARS-CoV2 fertőzés (COVID-19): Bevezető**

-A koronavírus betegség-19 (COVID-19) az új típusú koronavírus (SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, korábbi nevén 2019-nCoV) által okozott fertőző megbetegedés, melyet először a kínai Hupej tartományban található Vuhanban észleltek.

-A WHO felé **2019 december 31-én** jelentették.

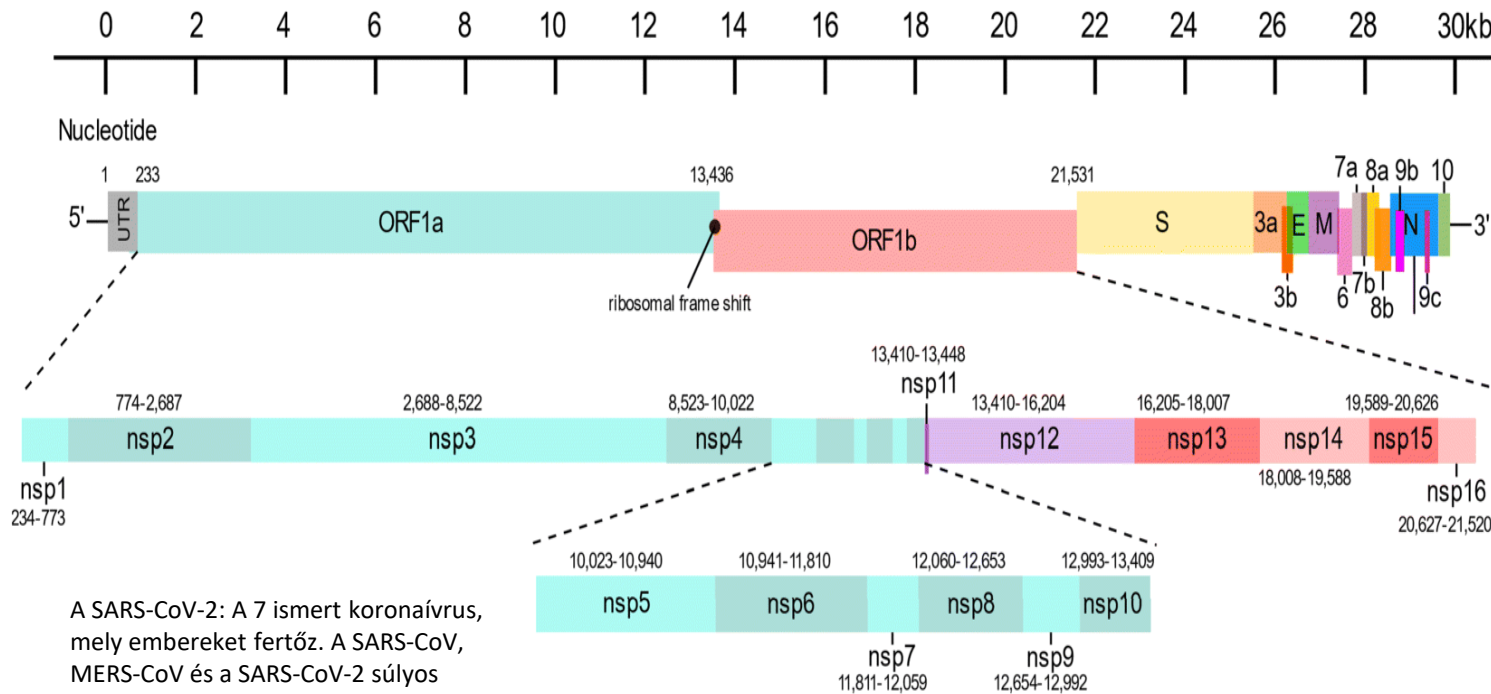
-**2020 január 30-án** a WHO a COVID-19 **járványt** nemzetközi egészségügyi veszélyhelyzetté nyilvánította.

-**2020 március 11-én** a WHO a COVID-19-et **globális pandémiának** minősítette, melyhez hasonlóra utoljára a 2009-es H1N1 influenza járvány kapcsán került sor.

# A humán koronavírusok genomjai és hasonlóságai

**A**

SARS CoV-2 ~29,813 bases



A SARS-CoV-2: A 7 ismert koronaírvus, mely embereket fertőz. A SARS-CoV, MERS-CoV és a SARS-CoV-2 súlyos betegséget tud előidézni, míg a HKU1, NL63, OC43 és 229E csak enyhe tüneteket okoznak.

**B**



**C**

Percent identity matrix – full genome

1: SARS-CoV-2	100.00	86.85	81.25	81.58	79.34	78.40	80.09	96.75
2: SARS-CoV	86.85	100.00	78.31	77.09	75.59	74.81	76.30	86.56
3: MERS-CoV	81.25	78.31	100.00	79.39	77.76	77.06	78.20	80.81
4: HKU1	81.58	77.09	79.39	100.00	83.89	79.68	83.86	80.40
5: OC43	79.34	75.59	77.76	83.89	100.00	77.50	77.97	78.27
6: 229E	78.40	74.81	77.06	79.68	77.50	100.00	82.86	77.58
7: NL63	80.09	76.30	78.20	83.86	77.97	82.86	100.00	79.03
8: RaTG13	96.75	86.56	80.81	80.40	78.27	77.58	79.03	100.00

# COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

2021. 06.02. 20:26 GMT

Cases: 172,202,809

Deaths: 3,696,969

Recovered: 154,843,373

Doses given

1,980,000,000  
+34,400,000

Fully vaccinated

737,000,000  
+5,040,000

% of population fully vaccinated

5.6%  
+0.1%

Hungary: 804,987

Deaths: 29,774

Recovered: 705,378

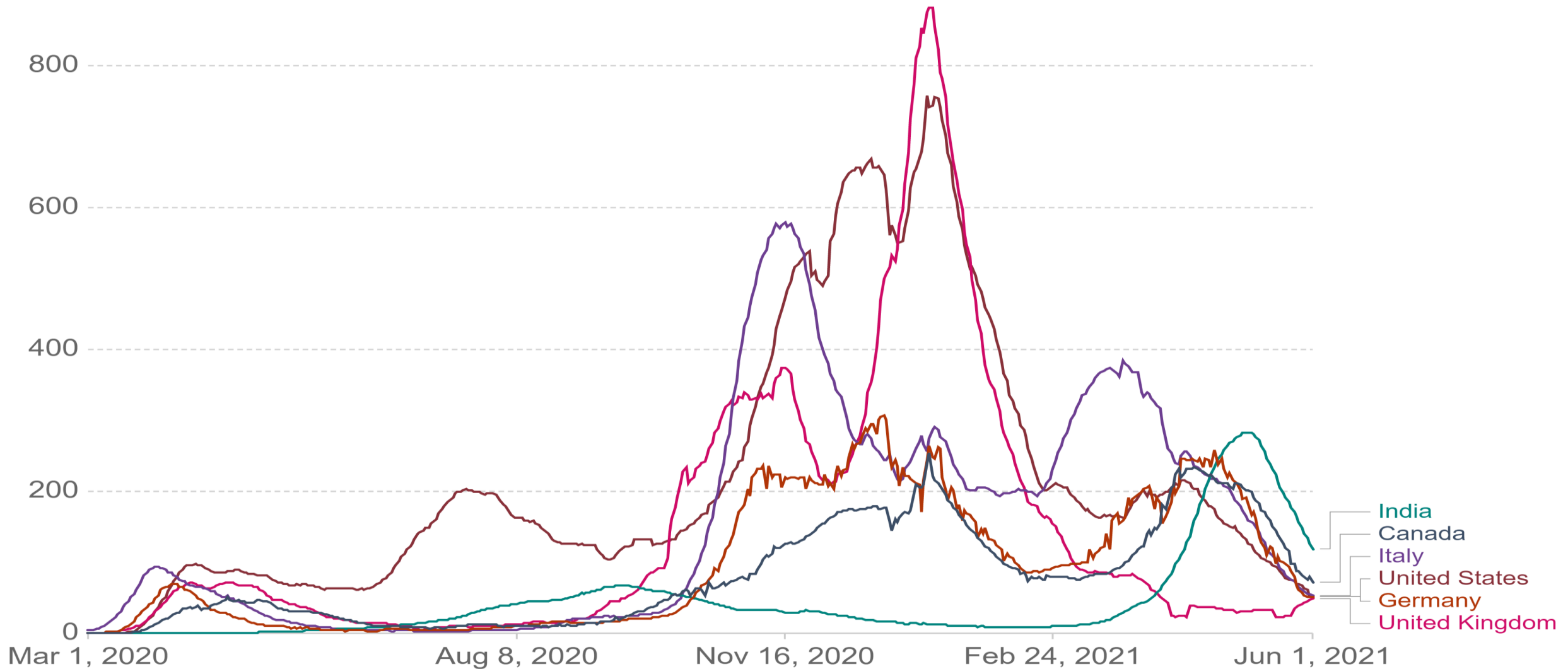
Doses given  
8.9M

Fully vaccinated  
3.69 M

% of population fully vaccinated  
37.8%

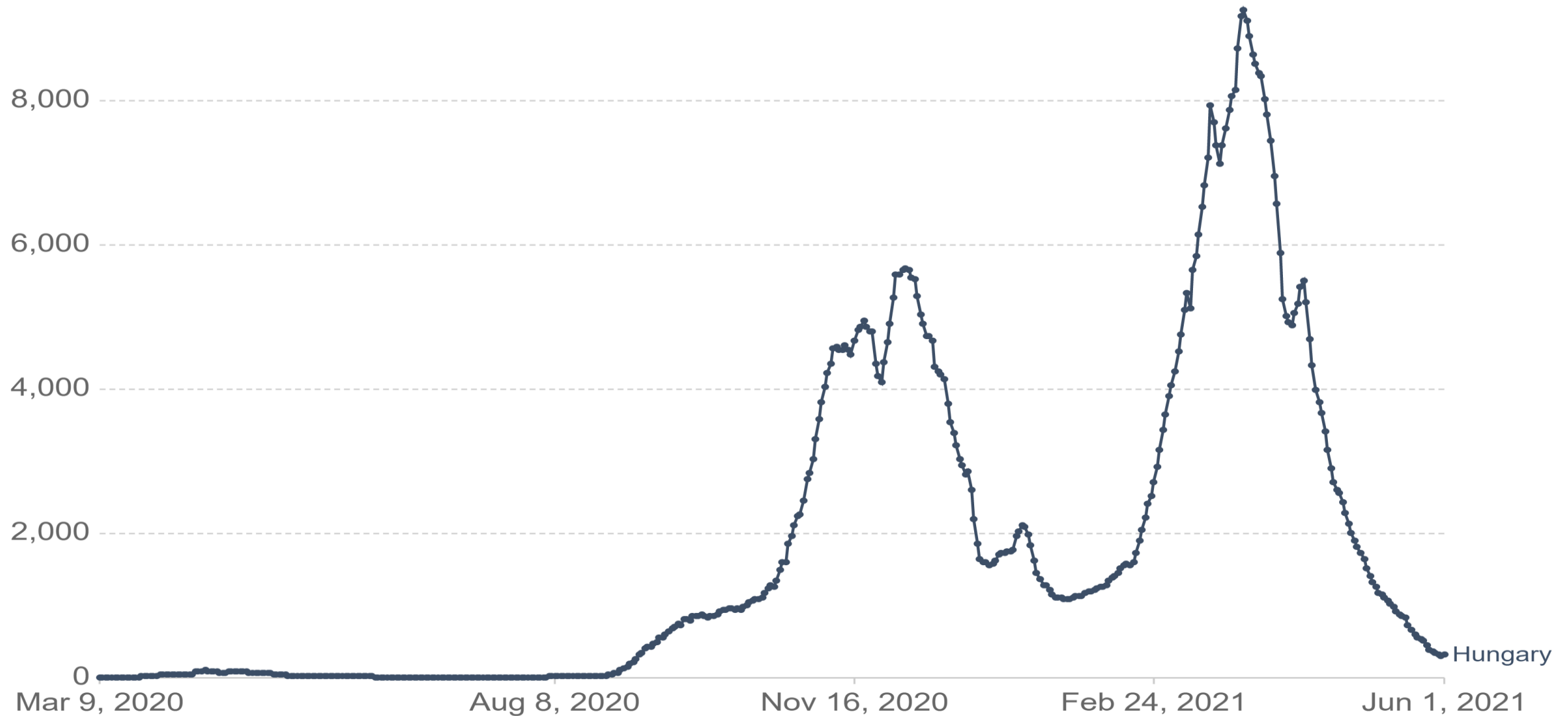
# Daily new confirmed COVID-19 cases per million people

Shown is the rolling 7-day average. The number of confirmed cases is lower than the number of actual cases; the main reason for that is limited testing.



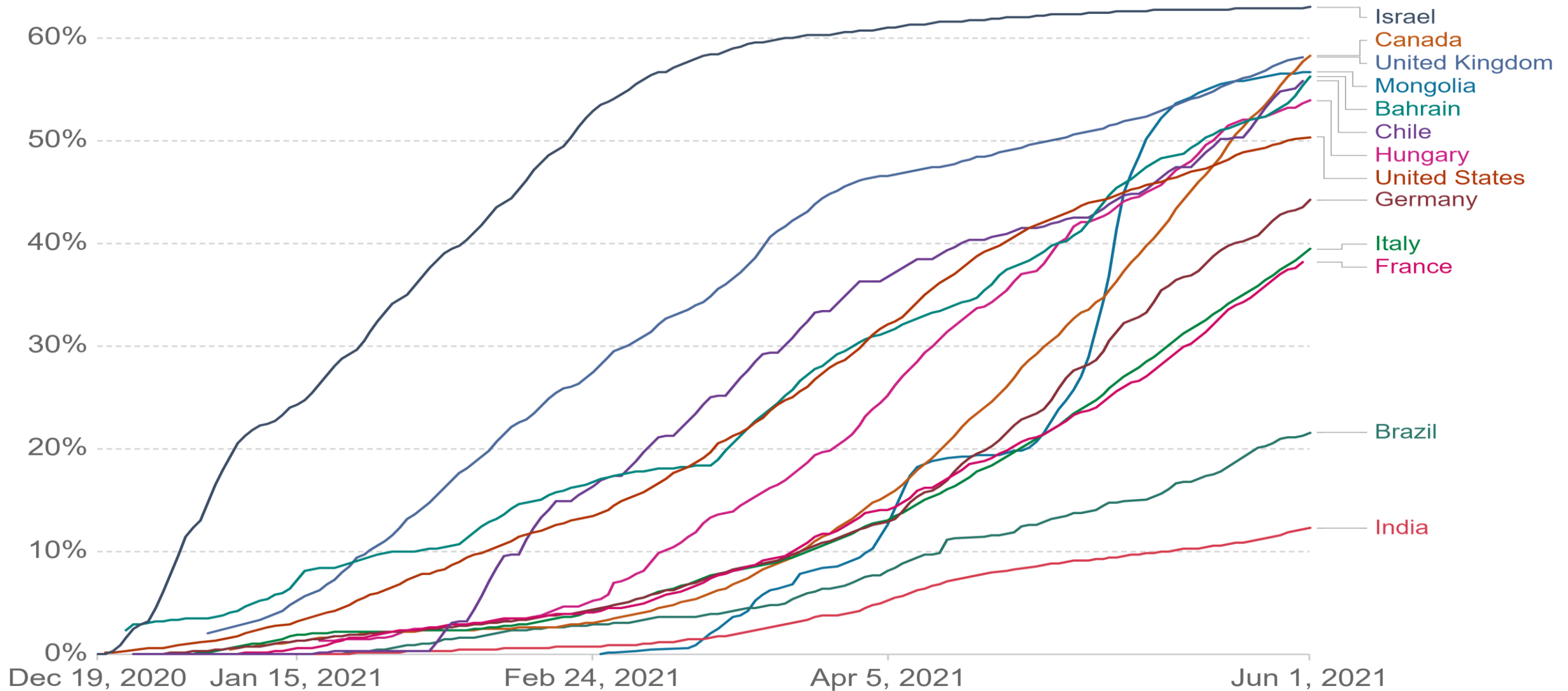
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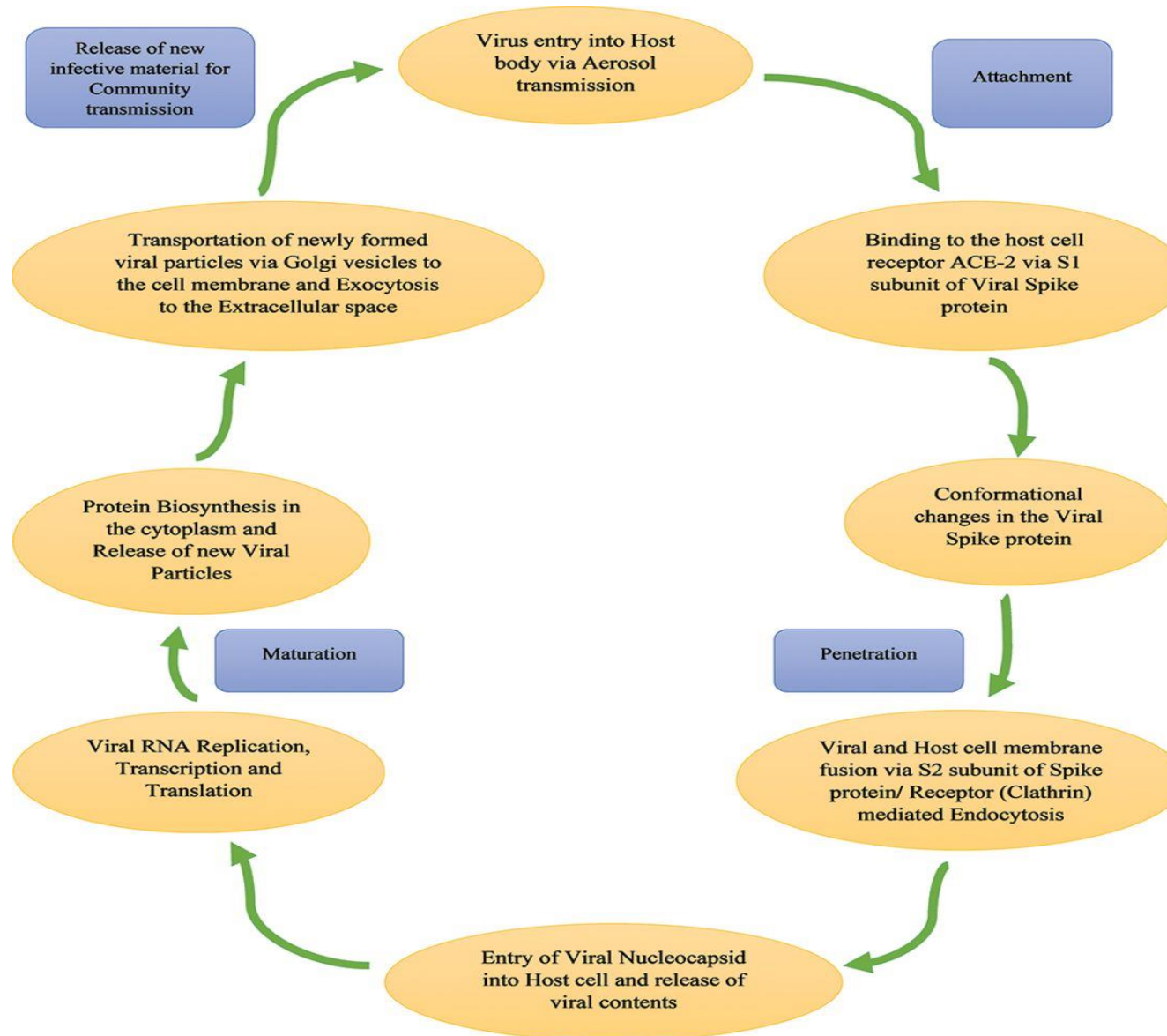


# Share of people who received at least one dose of COVID-19 vaccine

Share of the total population that received at least one vaccine dose. This may not equal the share that are fully vaccinated if the vaccine requires two doses.

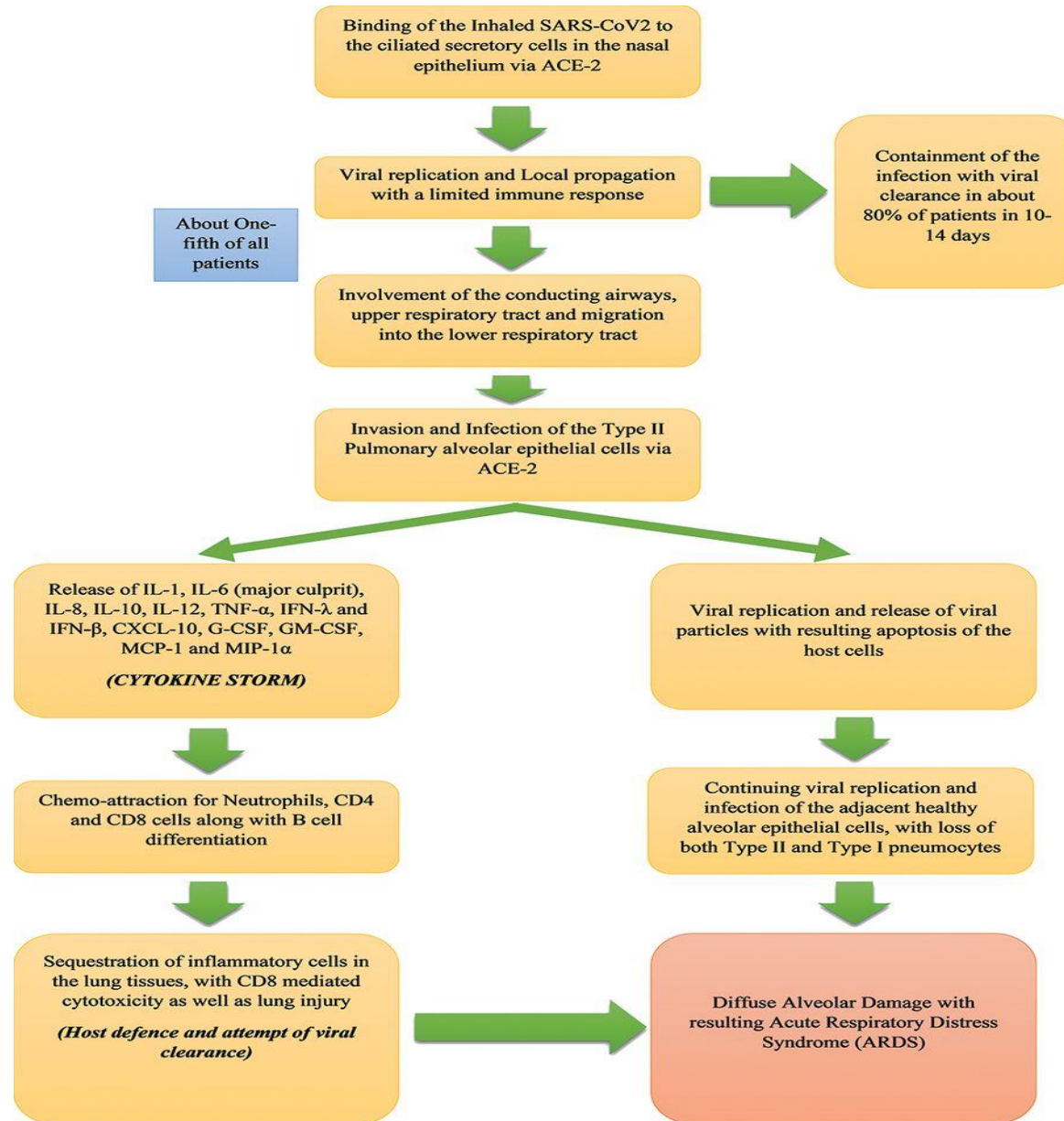


# A súlyos akut légzési szindróma SARS-CoV-2 élelciklusa





# A COVID-19 kórélettana



## A COVID-19 betegség klinikai spektruma

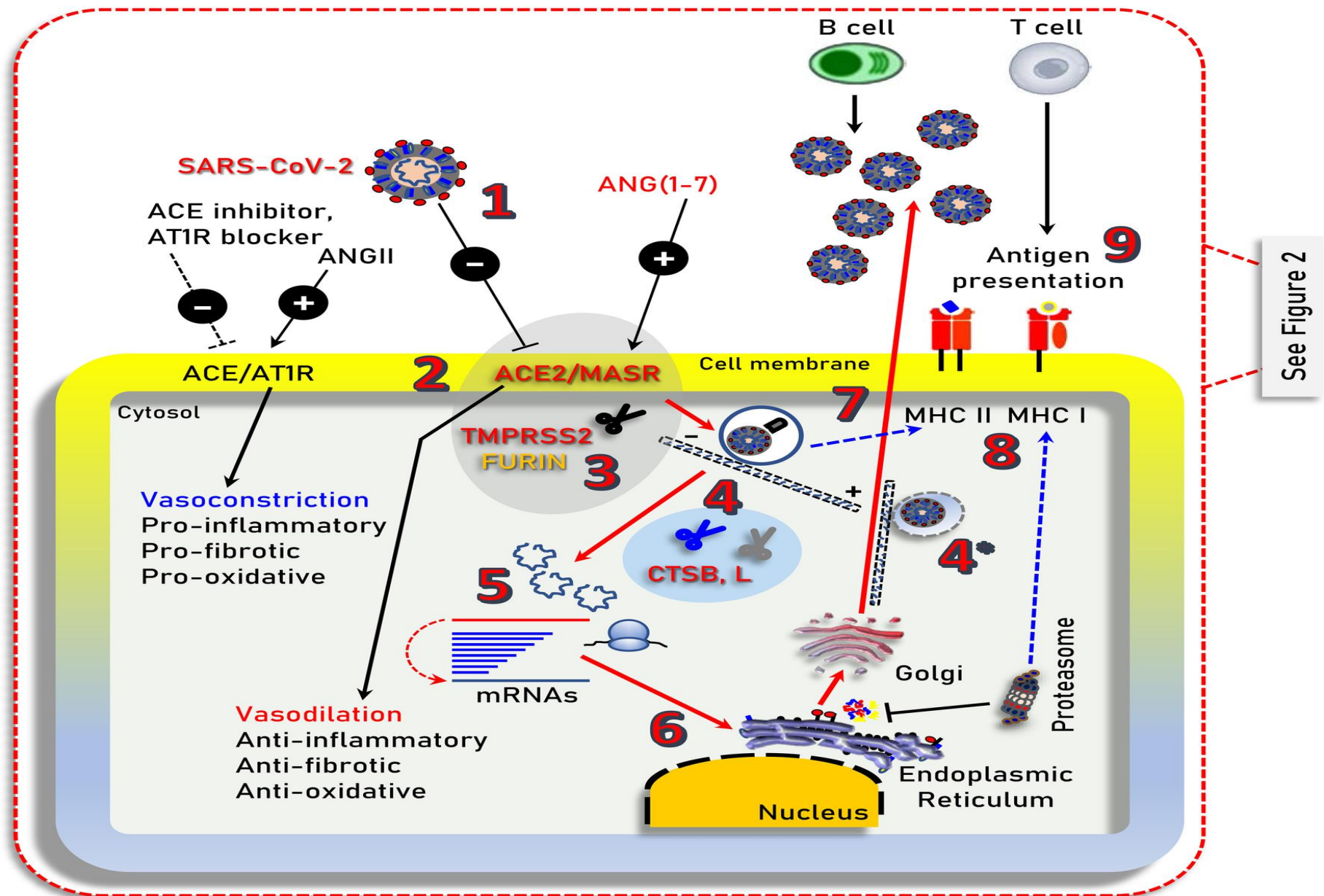
Severity of disease	Presentation
Asymptomatic	<ul style="list-style-type: none"><li>•No clinical symptoms</li><li>•Positive nasal swab test</li><li>•Normal chest X-ray</li></ul>
Mild illness	<ul style="list-style-type: none"><li>•Fever, sore throat, dry cough, malaise and body aches or</li><li>•Nausea, vomiting, abdominal pain, loose stools</li></ul>
Moderate illness	<ul style="list-style-type: none"><li>•Symptoms of pneumonia (persistent fever and cough) without hypoxemia</li><li>•Significant lesions on high-resolution CT chest</li></ul>
Severe illness	<ul style="list-style-type: none"><li>•Pneumonia with hypoxemia (<math>\text{SpO}_2 &lt; 92\%</math>)</li></ul>
Critical state	<ul style="list-style-type: none"><li>•Acute respiratory distress syndrome, along with shock, coagulation defects, encephalopathy, heart failure and acute kidney injury</li></ul>

## A COVID-19-ben szenvedő betegeknel észlelt szövődmények

Frequency	Complication
Commonly seen	<ul style="list-style-type: none"><li>•Acute respiratory distress syndrome</li><li>•Acute respiratory failure</li><li>•Sepsis</li><li>•DIC</li><li>•Acute liver and kidney injury</li><li>•VTE (PE)</li></ul>
Rare	<ul style="list-style-type: none"><li>•Rhabdomyolysis</li><li>•Multisystem inflammatory syndrome</li><li>•Aspergillosis</li><li>•Pancreatitis</li><li>•AIHA</li><li>•Neurological complications</li></ul>

# A fő sejtszignál tengelyek és replikációban részt vevő sejt-komponensek illusztrációja

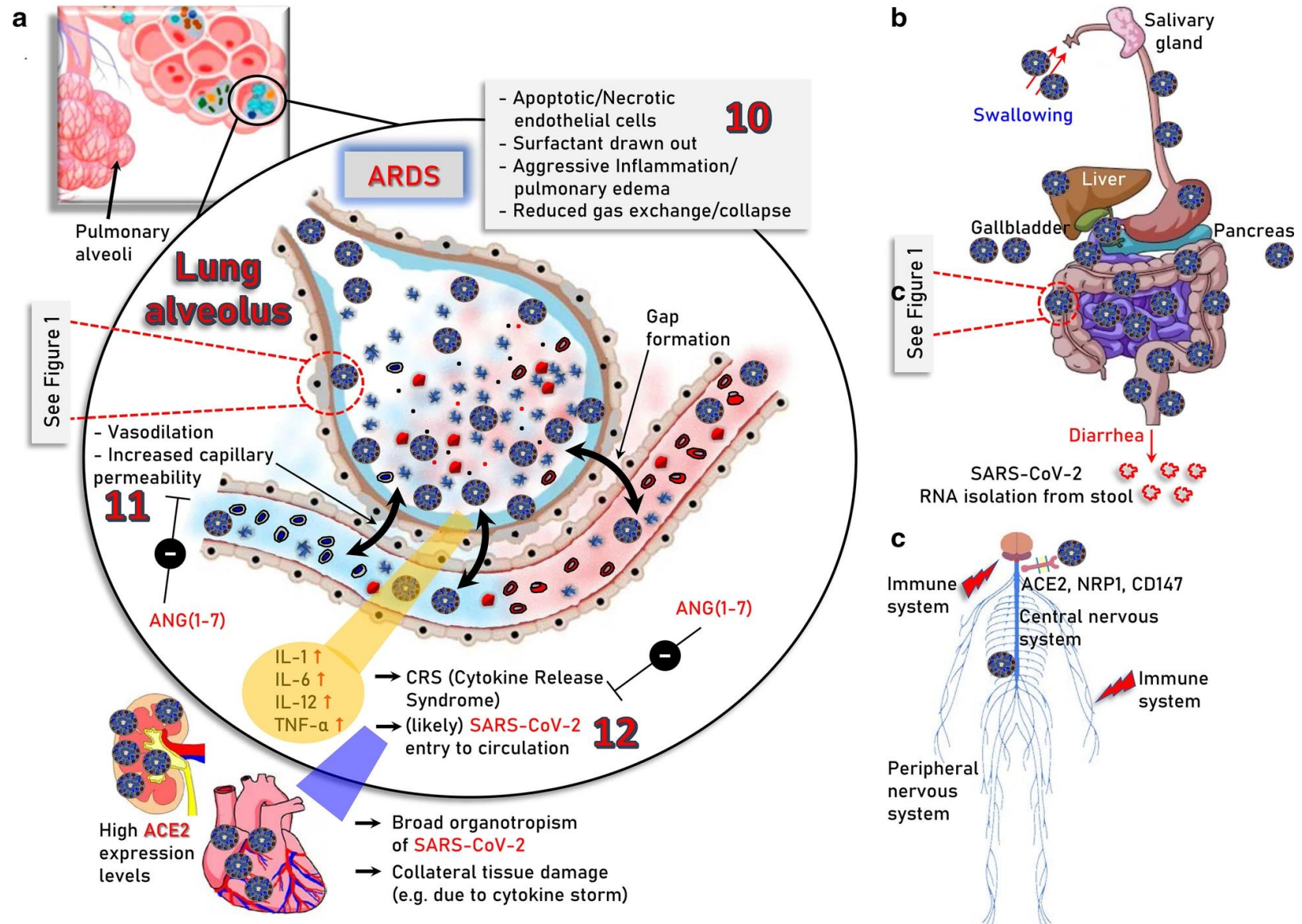
1. SARS-CoV-2 (extracellular); 2. binding to ACE2; 3. TMPRSS2 (or Furin) priming; 4. clathrin-mediated endocytosis (entry to early and acidic late - microtubule bound-endosomes) - 4\* denotes endosomal compartments during exocytosis; 5, 6. uncoating, genomic RNA release and viral-protein synthesis in free and endoplasmic reticulum-attached ribosomes; 7. vesicle-mediated exocytosis; 8. antigen presentation by endocytic compartments (MHC II) and proteasomes (MHC I); 9. immune cell attraction and development of immunity or elimination of infected cells.



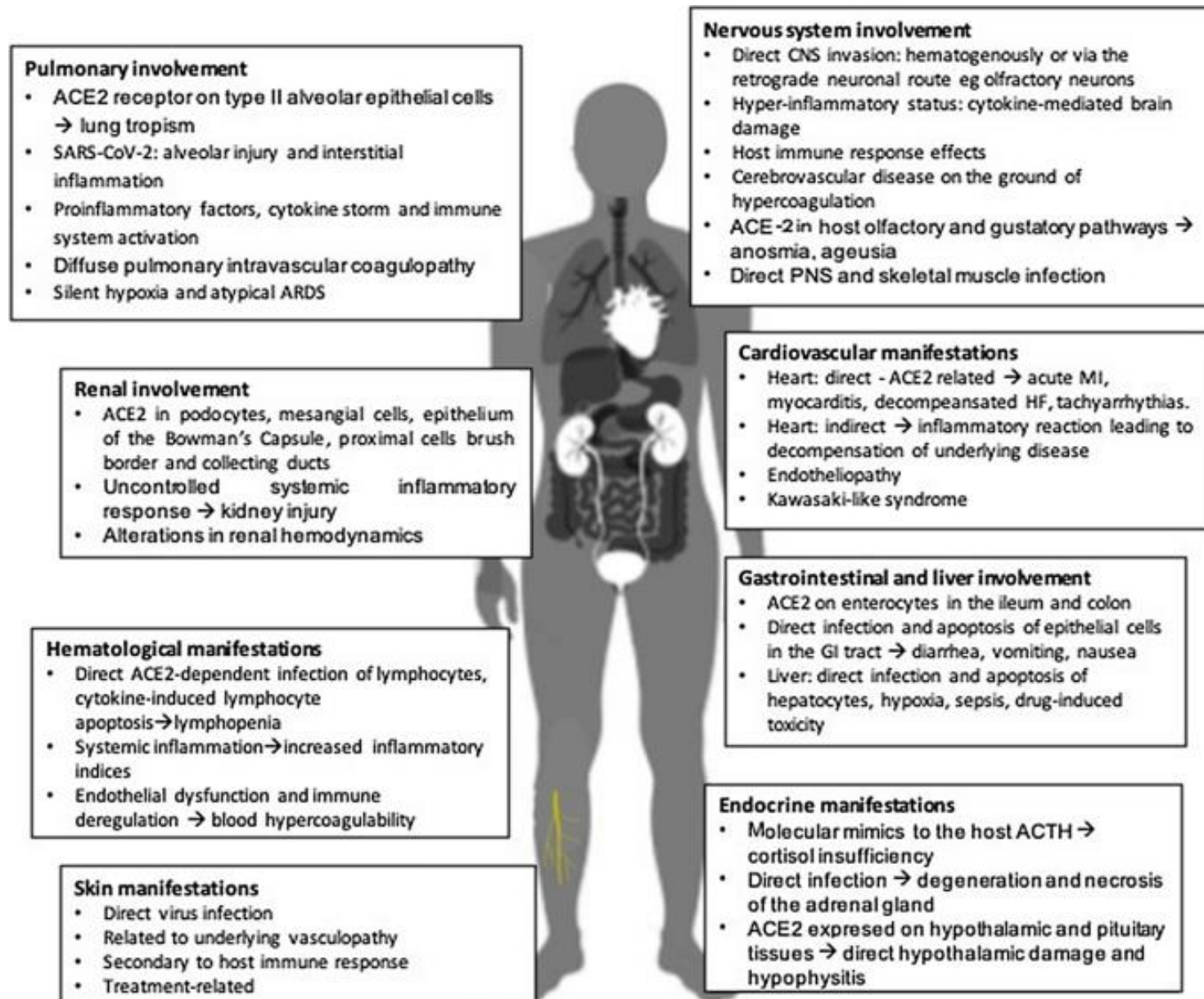


# Major súlyos COVID-19 patológiák és fertőzési utak

**a** The modules involved in, **10.** acute phase of SARS-CoV-2 infection in the lung (ARDS); **11.** vasodilation, increased capillary permeability, apoptosis/necrosis of endothelial cells as well as **12.** ARDS-induced “cytokine storm” and likely virus entry to the circulation which may then cause systemic failure due to broad organotropism in tissues expressing high levels of ACE2 (e.g., heart and kidneys) or the “cytokine storm”-related excessive inflammation, are indicated. **b** Sites of potentially SARS-CoV-2 infected organs in the alimentary tract of the digestive system and in accessory organs i.e., salivary glands, liver, gallbladder, and pancreas. ACE2 is expressed in relatively high levels in duodenum, small and large intestines, rectum, as well as in gallbladder. Thus, following the consumption of contaminated food the virus likely reaches the stomach passively; the reported adverse effects in other accessory organs like liver or pancreas are probably the result of excessive inflammation during severe COVID-19. **c** Central (brain, spinal cord) and peripheral nervous system as an infection route of SARS-CoV-2; ACE2, neuropilin-1 (NRP1) and CD147 that reportedly potentiate virus infectivity into the central nervous system are shown.

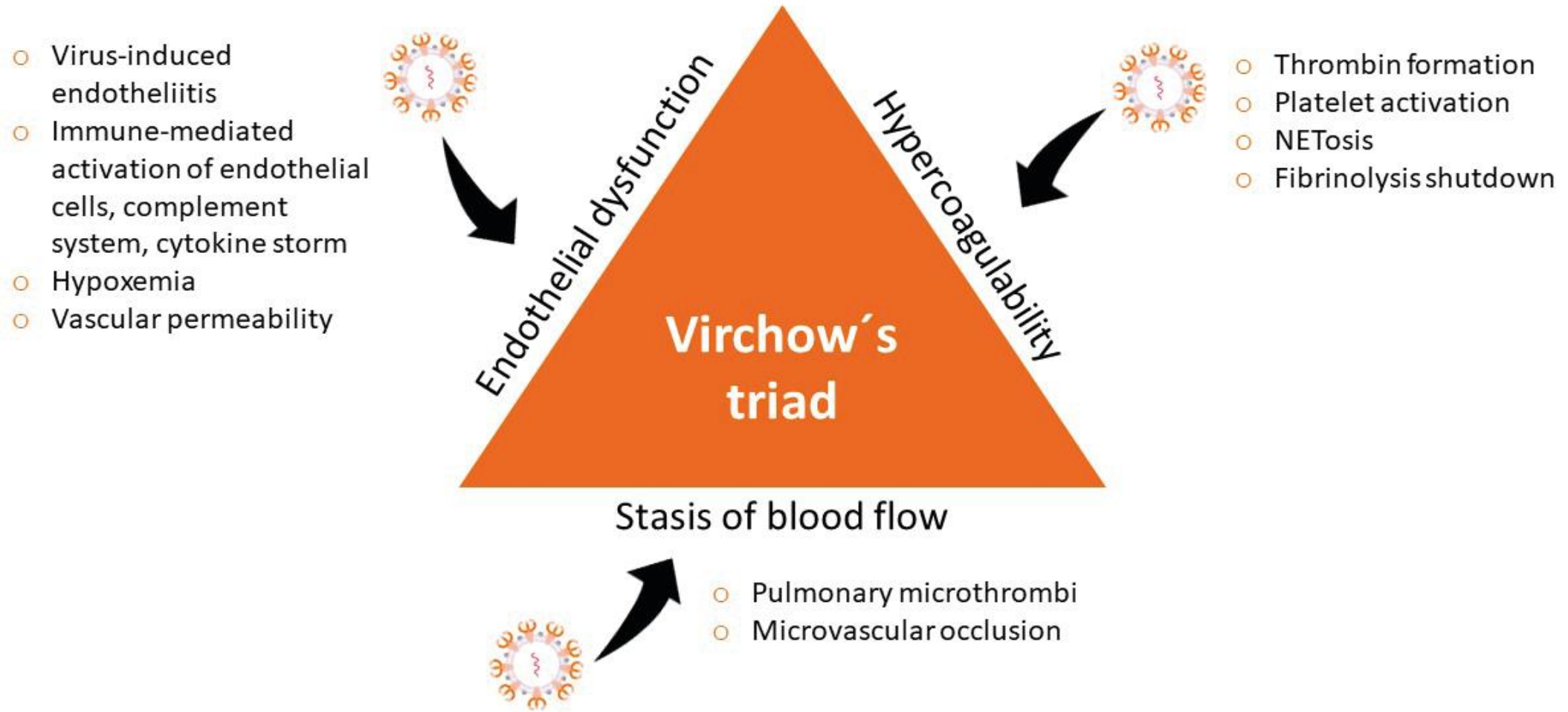


# A COVID-19 fertőzés szisztémás megnyilvánulásainak és patofiziológiájának sematikus áttekintése



# A SARS-CoV-2 fertőzés hatása Virchow trombózis triádjára

## Impact on Virchow's triad in COVID-19 associated coagulopathy

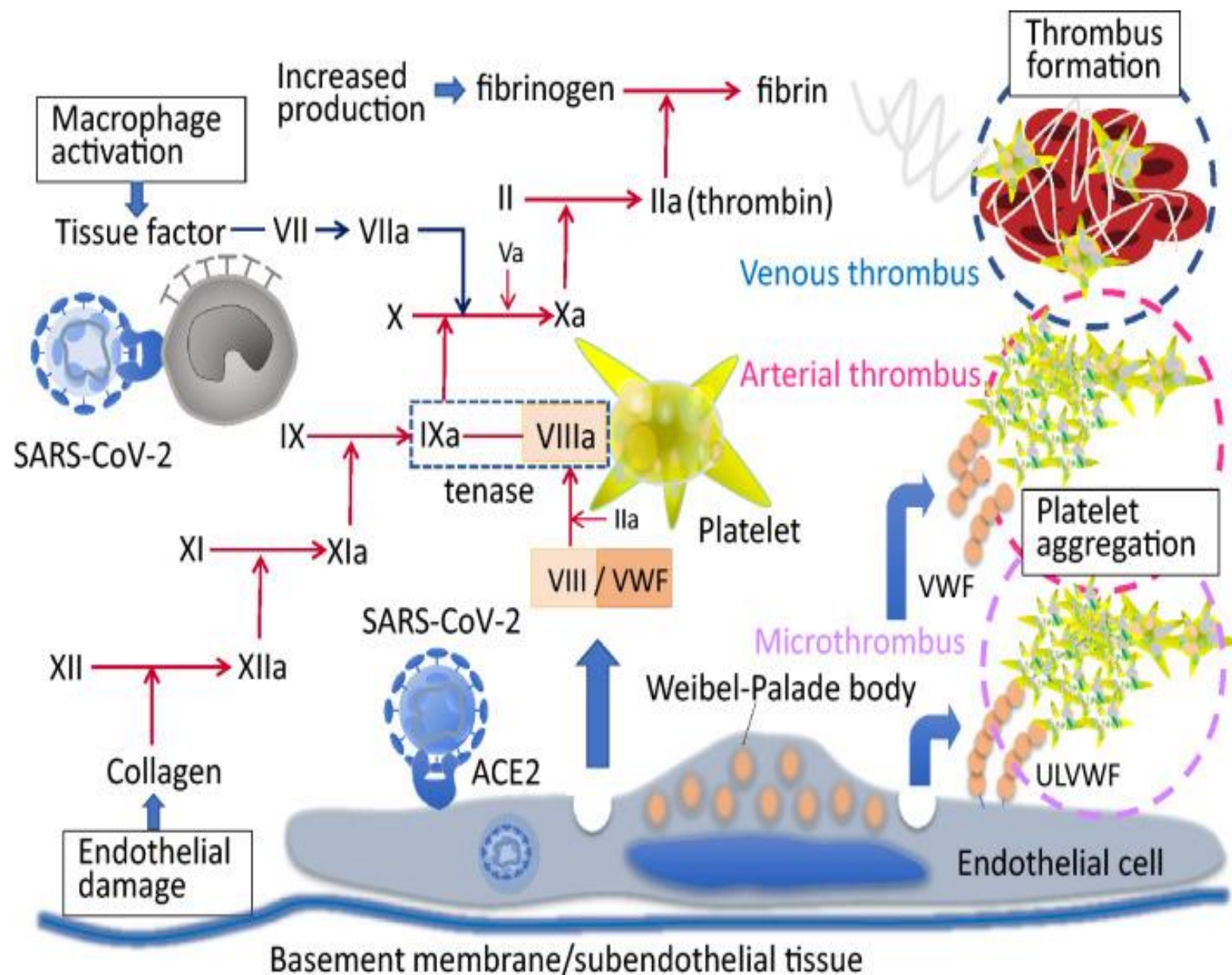




## Az alvadékképződés mechanizmusai COVID-19 fertőzésben

### SARS-CoV-2

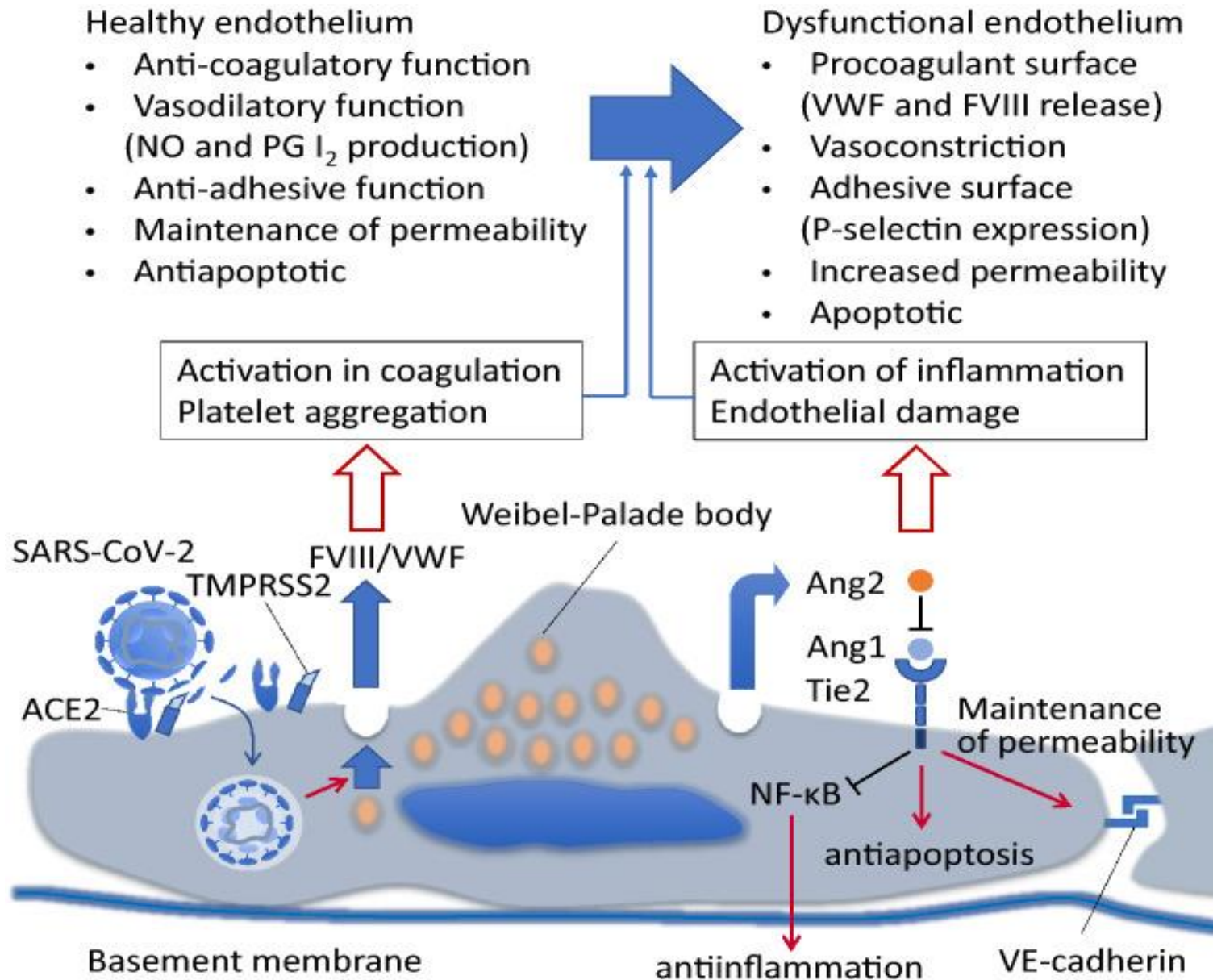
infects monocyte/macrophage and vascular endothelial cell. The activated macrophage and endothelial damage are the two-wheels of the vicious cycle of the thrombus formation. The infected monocyte/macrophage expresses tissue factor on the surface and initiates coagulation cascades. The infected endothelial cell release FVIII & VWF from Weibel–Palade body and accelerates coagulation. Released VWF stimulates platelet aggregation and ULVWF activates platelet adhesion on the endothelial cell. These multi-factorial prothrombotic changes result in arterial, venous, and microvascular thrombosis





## Az endoteliális sejt funkcionális változása angiopoietin útvonalokon keresztül

Angiopoietin (Ang)-1 binds to Tie2 receptor and promotes variable actions including an anti-inflammatory through inhibiting the NF $\kappa$ B signaling, apoptosis, and maintain vascular permeability by through the regulating cytoskeletal architecture and VE-cadherin. Severe acute respiratory syndrome (SARS)-CoV-2 infection stimulates endothelial cells to release stored Ang2 from Weibel Palade bodies into the circulation. Ang2 competitively antagonizes Ang1/Tie2 signaling, thus turns the anticoagulant, and anti-inflammatory features of endothelial cells to the opposite ways.



## Trombózis a COVID-19-ben

- A fertőző betegségek járhatnak fokozott thrombosis rizikóval, a COVID-19-ben látott prothrombotikus állapot más betegségekhez képest szokatlanul sok thrombotikus szövődménnyel jár együtt.
- Az elhunyt COVID-19 betegek kb. 70%-ában az ISTH kritériumoknak megfelelő DIC volt jelen.
- A más légúti fertőzések talaján kialakuló pneumoniával összevetve kb. 10-szer magasabb a VTE előfordulása a COVID-19 betegekben.
- A thromboemboliás események magas incidenciája a COVID-19 betegekben – amik egyúttal sokszor halálos kimenetelűek is- a COVID-19 asszociált coagulopathia diagnosztikájának és kezelésének fontosságára hívja fel a figyelmet.

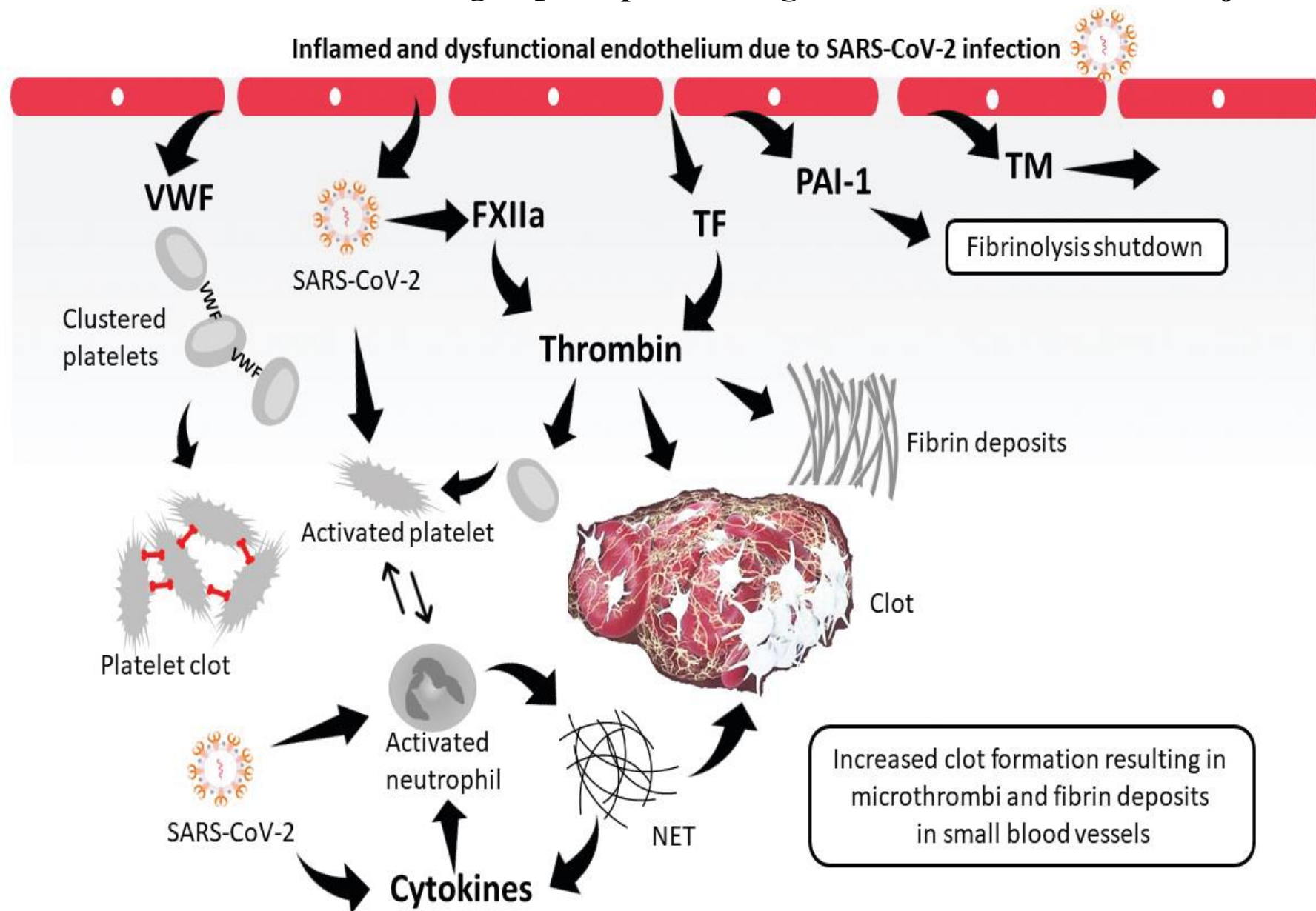
# A COVID-19 thromboticus szövődményei

- VTE, CVK-asszociált thrombosis, acut myocardialis infarctus, végtag ischaemia, cerebrovascularis történés.
- Az egyik vizsgálatban az ITO-ra került kritikus állapotú betegek körében a thromboticus szövődmények összesített előfordulása 31% volt (kummulativ incidencia 49%).
- A COVID-19-ben szenvedő betegek körében a VTE előfordulása kb. 20%-a, az ischaemiás stroke előfordulása kb. 3%.
- A VTE gyakorisága az ATE-hoz (AMI, ischaemiás stroke, systemás arterialis embolizáció) képest magasabb (27% vs 3,7 %).
- A VTE-k közül a PE előfordulása a legmagasabb, ami feltehetően a tüdő erek *in situ* bekövetkező thrombosisából alakul ki.
- A SARS-CoV-2 hematológiai hatásaira, szövődményeire fokozott figyelmet fordítanak az egyre súlyosabb manifesztációk és magas mortalitás miatt.

# COVID-19 és coagulopáthia

- A COVID-19 fertőzéssel járó **fokozott thrombotikus** kockázat a vírus által okozott **direkt endothel** és **microvascularis** károsodás következménye lehet, melyet gyulladás és citokinek felszabadulása követ, tovább fokozva a **hypercoagulabilitást**.
- A **C5b-C9 komplement faktorok** COVID-19 betegekben **megnövekedett** szintje súlyos károsodásokat okoz. Ez azt sugallja, hogy a komplement aktiváció lehet az endothel károsodás és a thrombosisok fő mediátora a betegekben.
- A renin-angiotensin-aldosteron rendszer (RAAS) egyensúlya felborul, az angiotenzin II szintje az angiotenzin I-hez képest megnő, gyulladásához és oxidatív stresszhez vezet, ami **endothel diszfunkciót** okoz, és tovább fokozza a betegben a thrombosis rizikót.

## A COVID-19 asszociált koagulopátia patofiziológiai mechanizmusainak sémája



## Jelentősen megváltozott koagulációs laboratóriumi paraméterek és indikációik COVID-19 fertőzésben

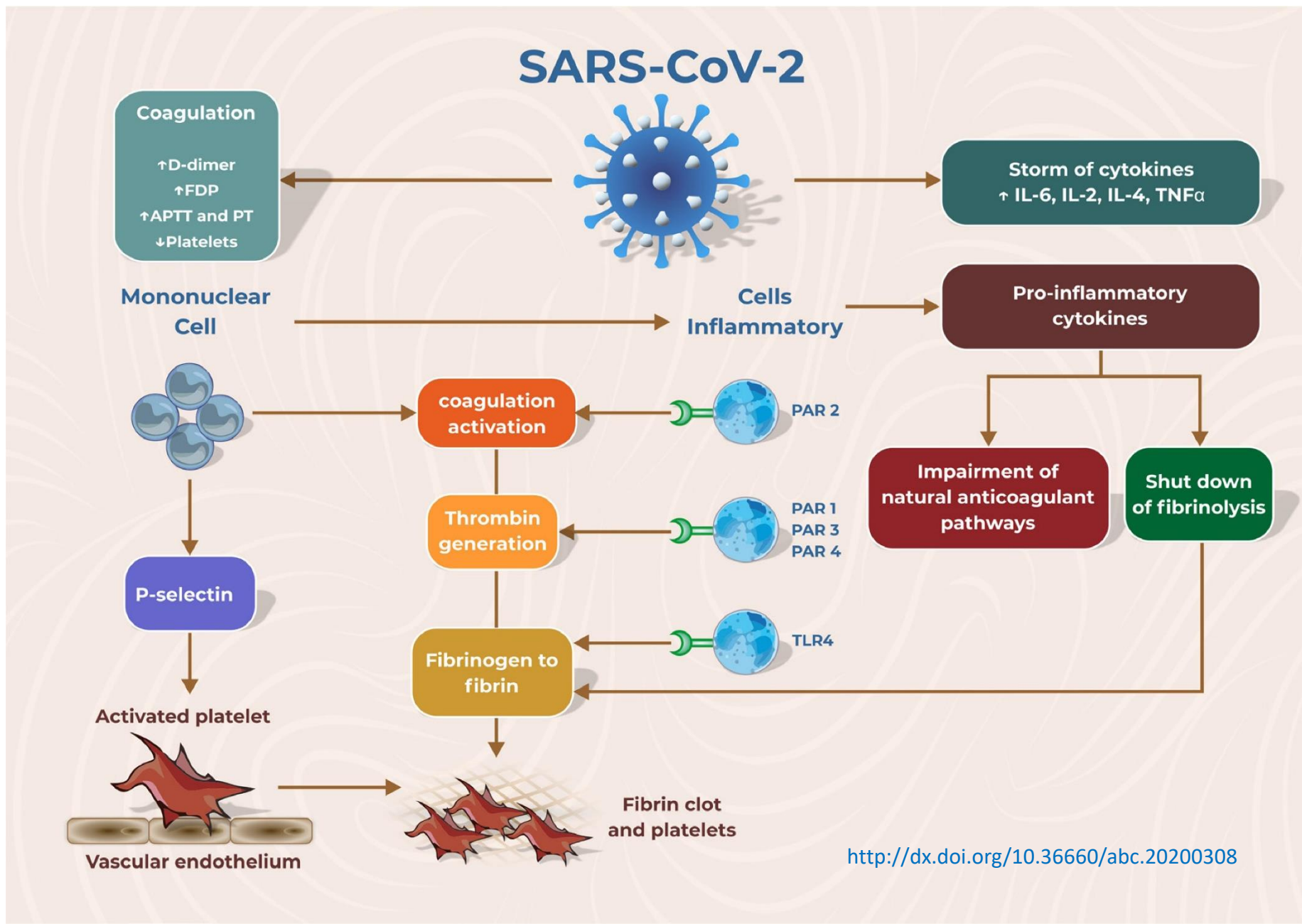
Laboratory Coagulation Parameter	Change in COVID-19	Indication
D-dimer	↑↑	Increased clot formation
Prothrombin time	↑	Unbalanced extrinsic coagulation
Fibrinogen	↑ (acute phase) ↓ (DIC phase)	Inflammation DIC
Platelet count	↓/↑	Increased platelet consumption
Von Willebrand Factor (VWF)	↑↑	Endothelial dysfunction and platelet activation
Coagulation Factor VIII	↑↑	Thrombotic risk
Plasminogen Activator Inhibitor-1 (PAI-1)	↑↑	Endothelial dysfunction/fibrinolysis shutdown
Prothrombin fragment 1+2	↑↑	Increased clot formation
Soluble thrombomodulin	↑↑	Endothelial dysfunction/decreased anticoagulant activity of endothelium



## A SIC, DIC, TMA és CAHA megkülönböztető laboratóriumi eltérsei

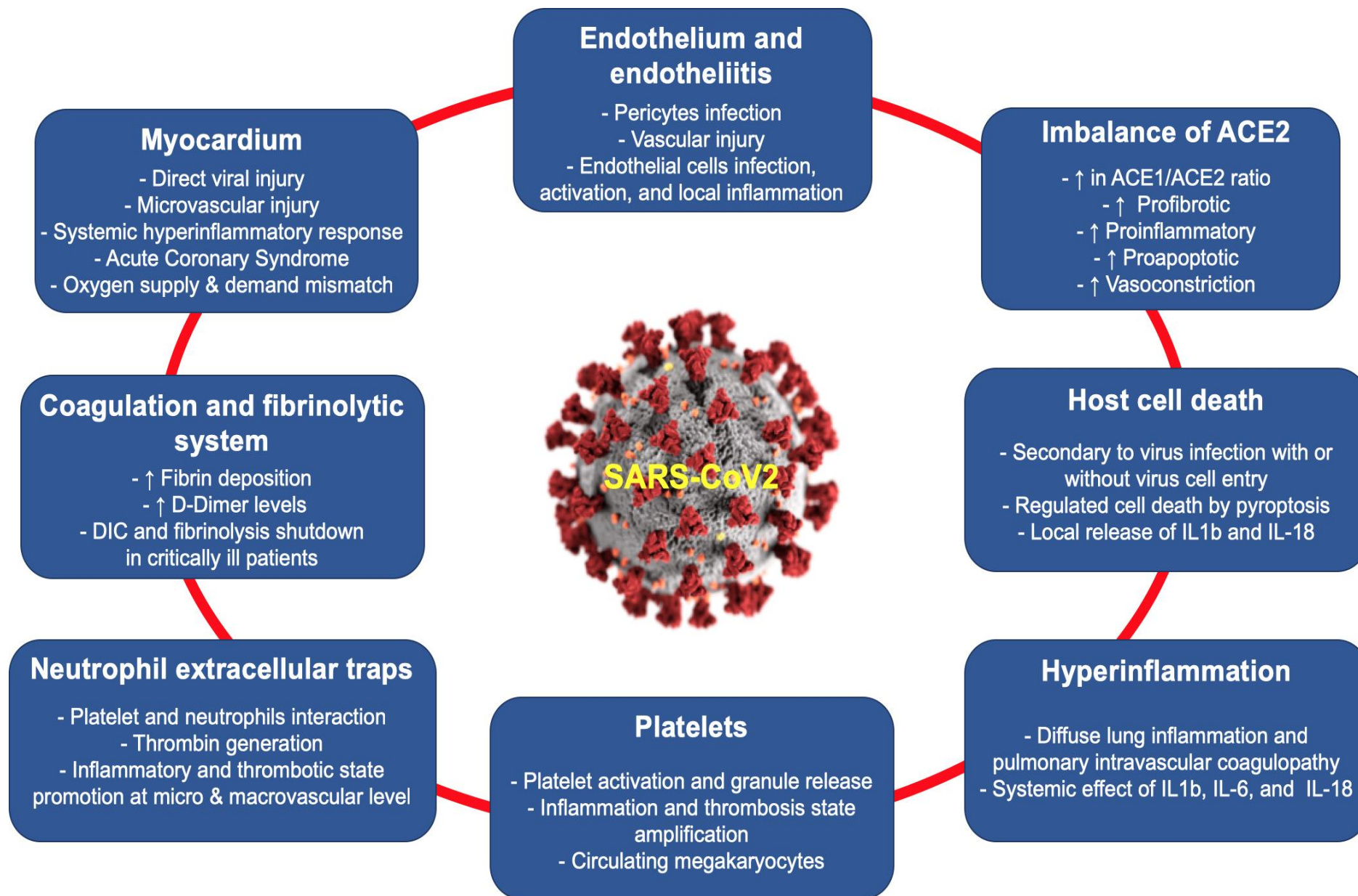
Paraméter	SIC	DIC	Microangiopathy	CAHA <sup>3</sup>
Prothrombin idő	↑	↑ ↑	↔	↑ ↑
Aktivált parciális thromboplastin idő	↑ ↑	↑ ↑ ↔ ↑	↔	↑
Fibrinogen	↓	↓	↔	↑ ↑
Fibrin(ogen) degradációs termékek	↑	↑ ↑	↔	↑ ↑
D-dimer	↑	↑ ↔	↔	↑ ↑ or ↑ +
Thrombocyta szám	↓	↓↓	↓	↑ or ↔
Peripheriás vérkenet + +	+	+	++	+
von Willebrand factor	↑	↑ ↑	↔	↑ ↑
ADAMTS13	↔	↔	↓	↔
Antithrombin	↓	↓	↓	↑
Anticardiolipin antitestek	↔	↔	↔	+
Protein C	↓	↓	↔	+
Protein S	↓	↓	NA	↓
VIII-as factor	↑	↑	NA	↑
Plasminogen	↓	↓	NA	↑

# SARS-CoV-2 és trombo-gyulladás

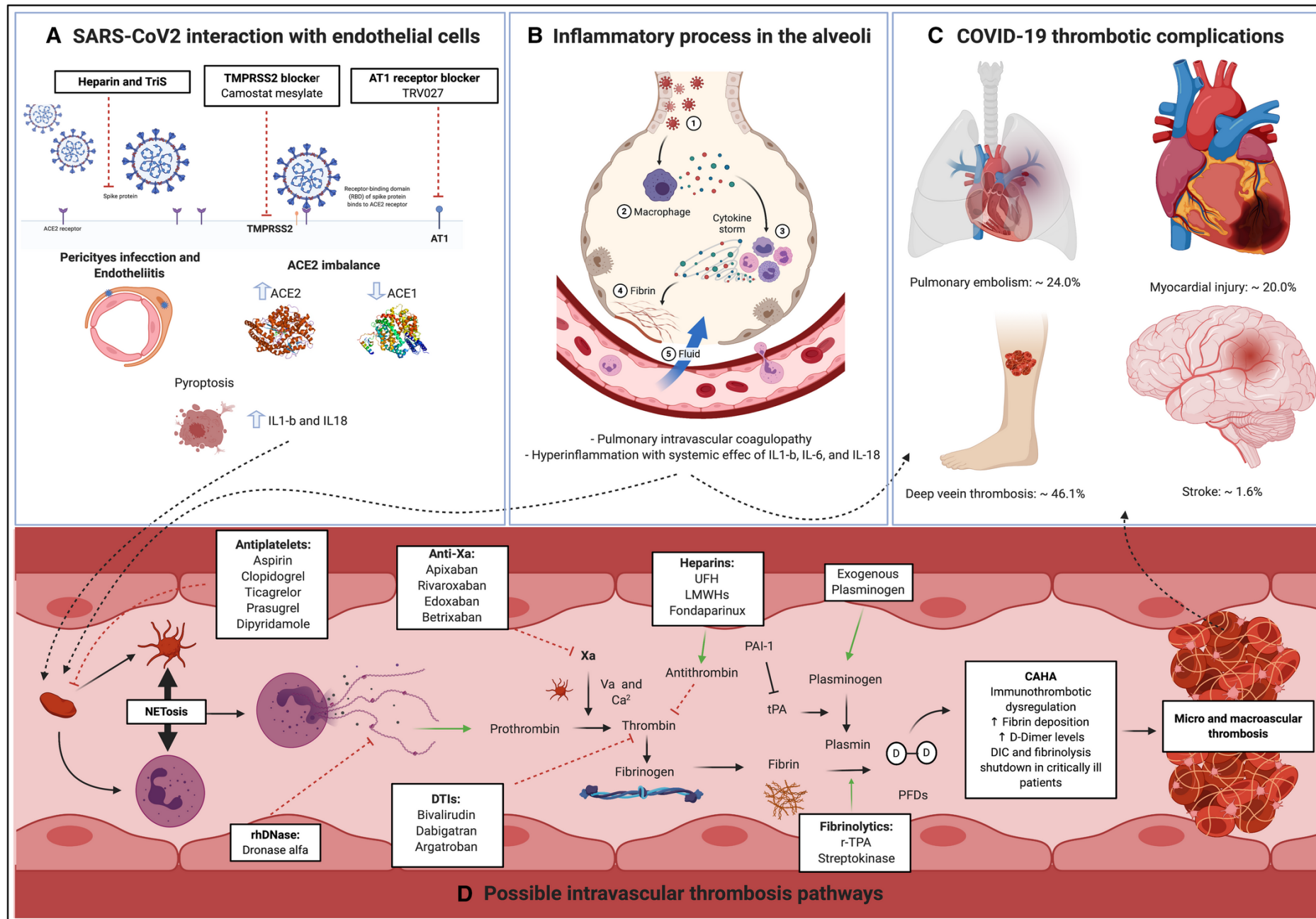




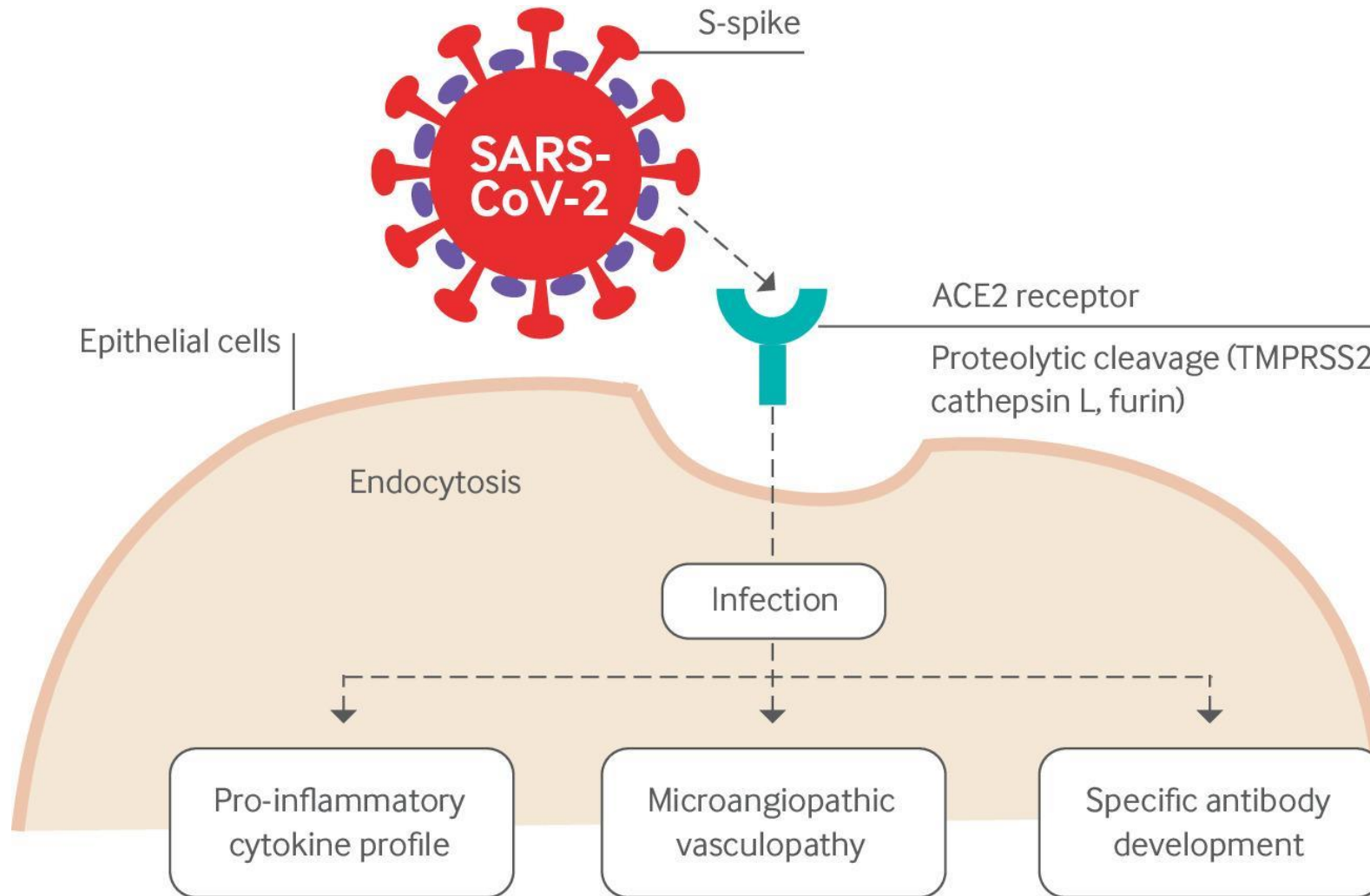
# A COVID-19 fertőzés hatásai CV és koagulációs rendszerre



# A COVID-19 betegség patofiziológiája és COVID-19 asszociált trombózis és koagulopátia

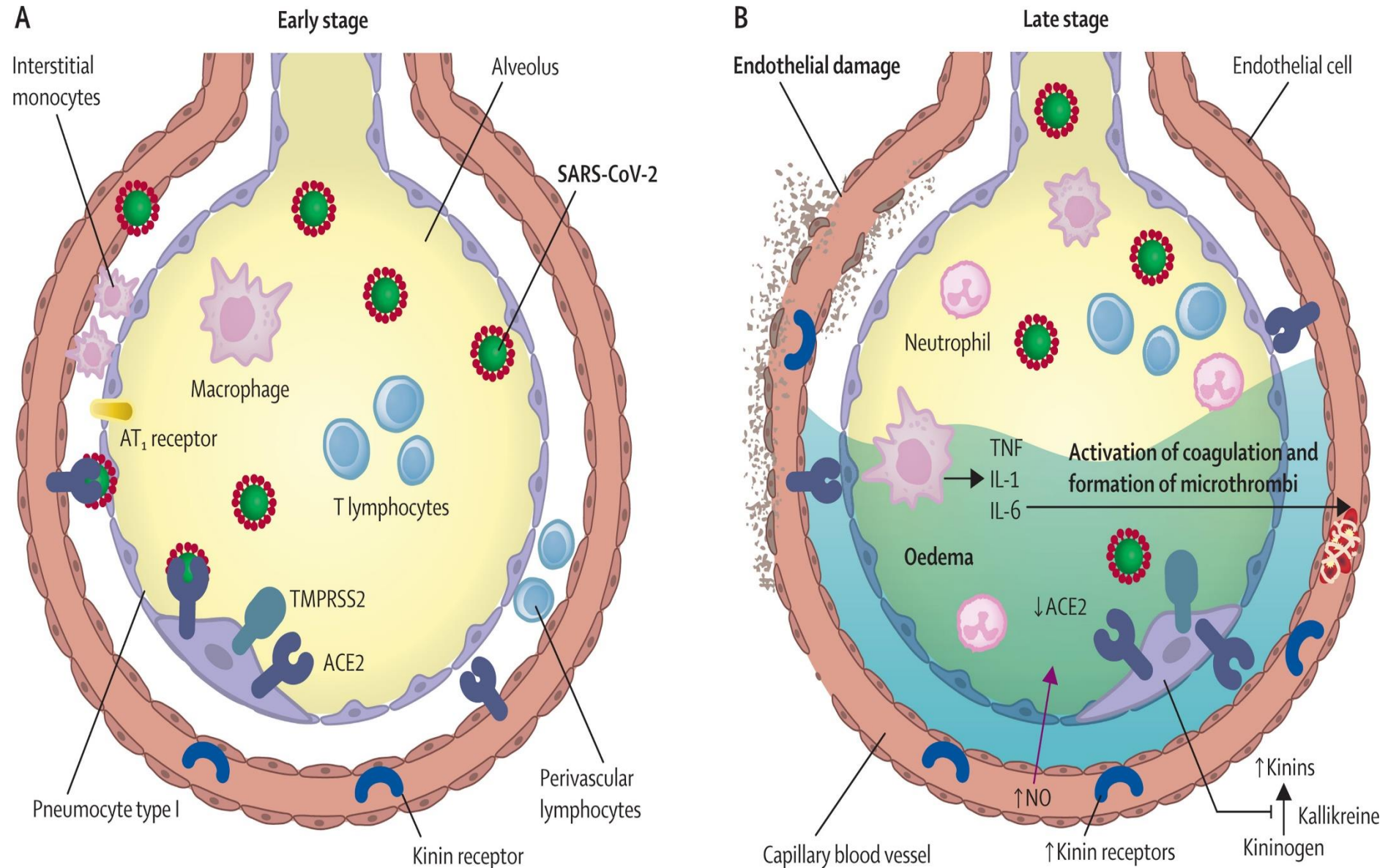


**SARS-CoV-2 S spike protein binds to the ACE2 receptor, which leads to proteolytic cleavage by TMPRSS2, cathepsin L, and furin in the epithelial cell of the respiratory tract**





# Inflammatory mechanisms, alveolar epithelial and endothelial damage, and coagulopathy in COVID-19



# Endothelial Cell Damage and Thrombo-inflammation

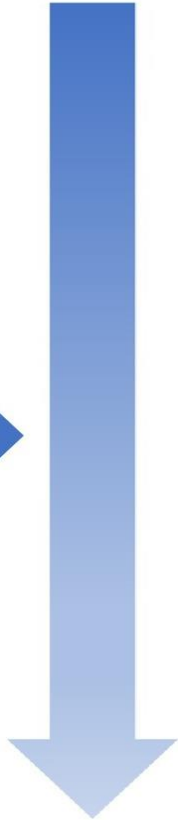
- Direct invasion of endothelial cells by SARS-CoV-2 infection and indirect generation of inflammation and prothrombotic conditions in vasculopathy both contribute to the pathophysiological mechanisms of COVID-19.
- Both venous and arterial endothelia are reported to express ACE2.
- VWF, a circulating blood coagulation glycoprotein associated with endothelial dysfunction, is significantly elevated in COVID-19 patients compared with normal individuals.
- VWF, a carrier of coagulation factor VIII, can trigger platelet aggregation and blood coagulation. Platelet–neutrophil interaction and macrophage activation can further promote proinflammatory responses including cytokine storm and the formation of neutrophil extracellular traps (NETs).
- NETs damage the endothelium and stimulate both extrinsic and intrinsic coagulation pathways, resulting in microthrombus formation and microvascular dysfunction. High levels of NETs were reported in hospitalized patients with COVID-19, and these correlated positively with disease severity.
- Inhibiting NETs may be a therapeutic target to reduce NET-mediated thrombotic tissue damage associated with COVID-19.

# Mechanism of cardiac manifestations in COVID-19

- ACE2 is expressed in the vascular system (endothelial cells, vascular smooth muscle cells, and migratory angiogenic cells) and the heart (cardiofibroblasts, cardiomyocytes, endothelial cells, pericytes, and epicardial adipose cells).
- ACE2 functions as a virus entry receptor by binding to the spike (S) protein of SARS-CoV and SARS-CoV-2. In addition, completion of cell entry requires priming of the S subunit by the cellular serine protease TMPRSS2 (transmembrane protease serine 2) or other proteases (cathepsin L, cathepsin B, factor X, trypsin, elastase, and furin).
- Patients with previous CVD were associated with more severe COVID-19 disease, possibly because they had higher plasma levels of ACE2.
- Compared with the lung, the human heart has higher expression of ACE2 and with much lower content of TMPRSS2. The susceptibility of the heart in SARS-CoV-2 infection was diminished to some extent by a lower proportion of ACE2<sup>+</sup>/TMPRSS2<sup>+</sup> cells. Other S protein priming proteases that are prominently expressed in the human heart, cathepsin L and furin, may increase heart vulnerability to SARS-CoV-2.
- **Dysregulation of RAAS:** ACE2 converts angiotensin II (Ang II) to Ang-(1–7), and the ACE2/Ang-(1–7)/Mas axis combats the adverse impacts of RAAS, which is essential for preserving the physiological and pathophysiological equilibrium of the body.
- Entry of SARS-CoV-2 into cells is assisted by the interaction between S protein and ACE2 extracellular domains, leading to downregulation of surface ACE2 expression. Ang-II/angiotensin 1 receptor (AT1R) activity is then increased at the expense of the ACE2/Ang 1–7/Mas axis, leading to comprehensive negative consequences, including aldosterone secretion, fibrosis, proinflammation, hypertrophy, vasoconstriction, enhanced reactive oxygen species and vascular permeability, cardiac remodeling, gut dysbiosis, and multiple organ dysfunction syndrome (MODS) in COVID-19.

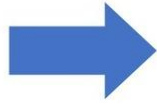
# The clinical cardiovascular manifestations of COVID-19

**Direct effects**



**Indirect effects**

SARS-CoV-2



Direct cardiotoxicity  
Dysregulation of the RAAS  
Endothelial damage and  
thromboinflammation  
Immune dysregulation induced  
cytokine storm  
Demand-supply mismatch



Acute cardiac injury

AMI

Myocarditis

Arrhythmia

Heart failure

VTE/PE

Shock

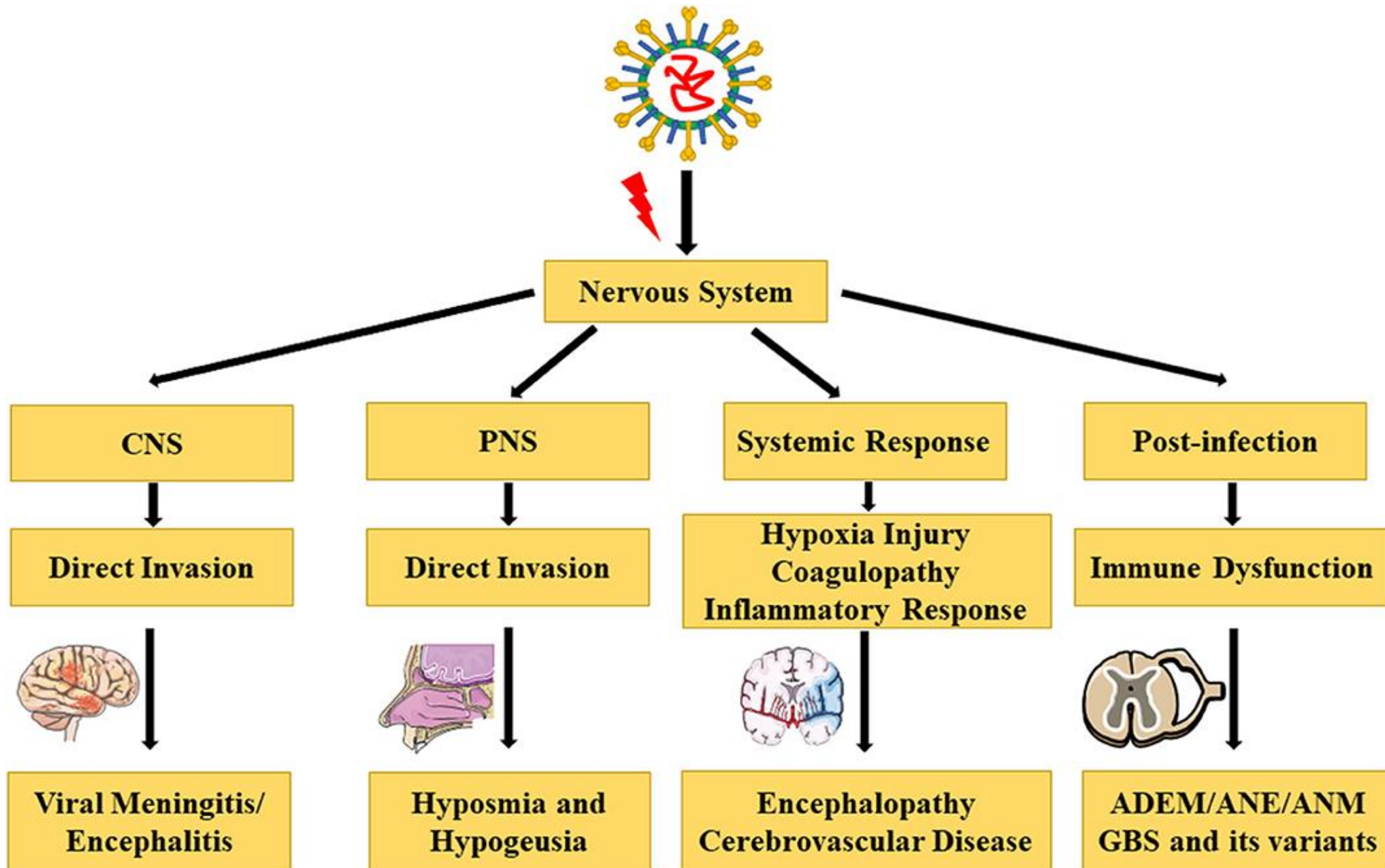
Pathophysiology mechanisms

Cardiovascular manifestations

**Trends in Endocrinology & Metabolism**



# A COVID-19 fertőzés szövődményei és patofiziológiája idegrendszerben



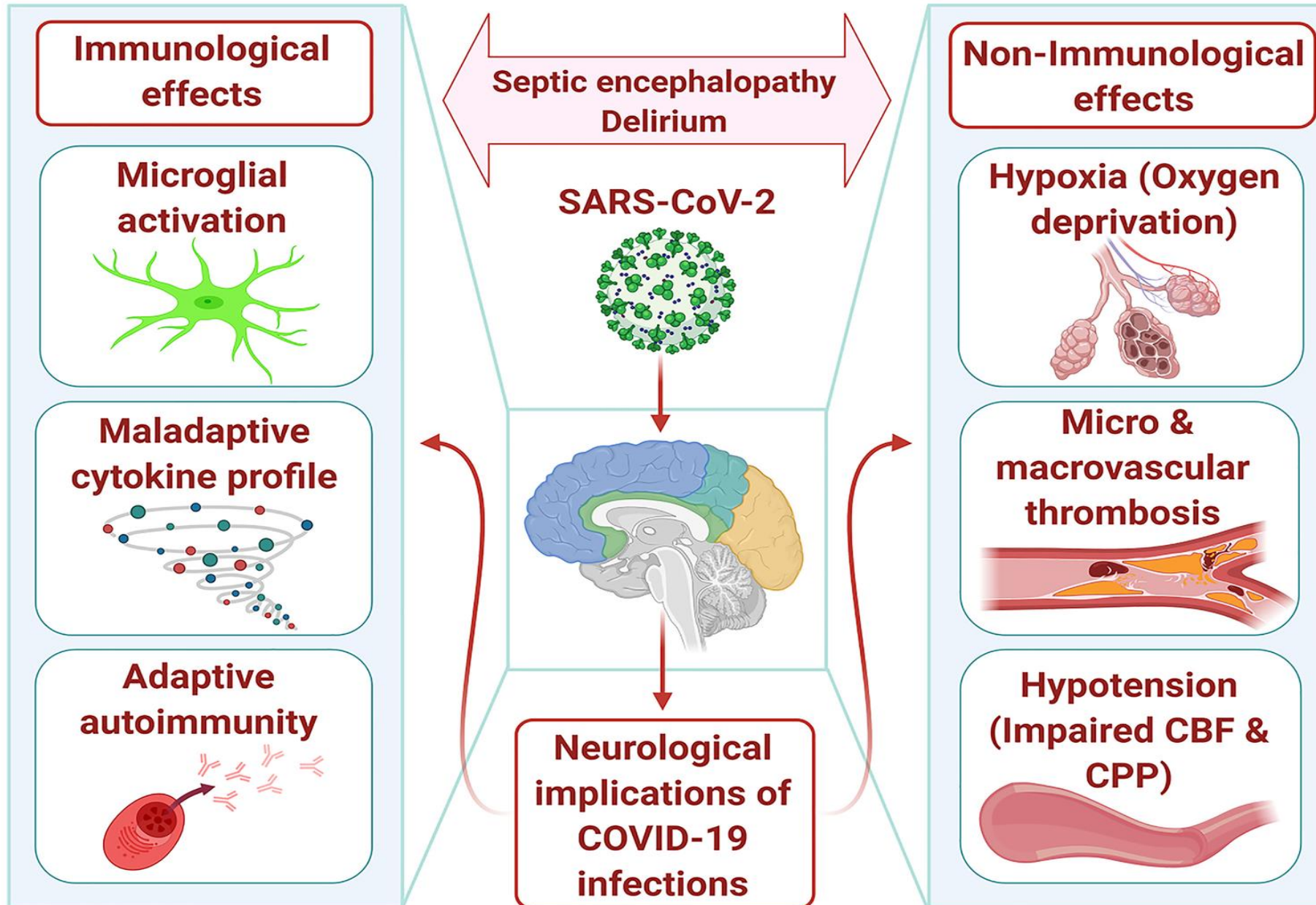


# A COVID-19 okozta szövődmények klinikai megnyilvánulásai és kiegészítő vizsgálati eredményei az idegrendszerben

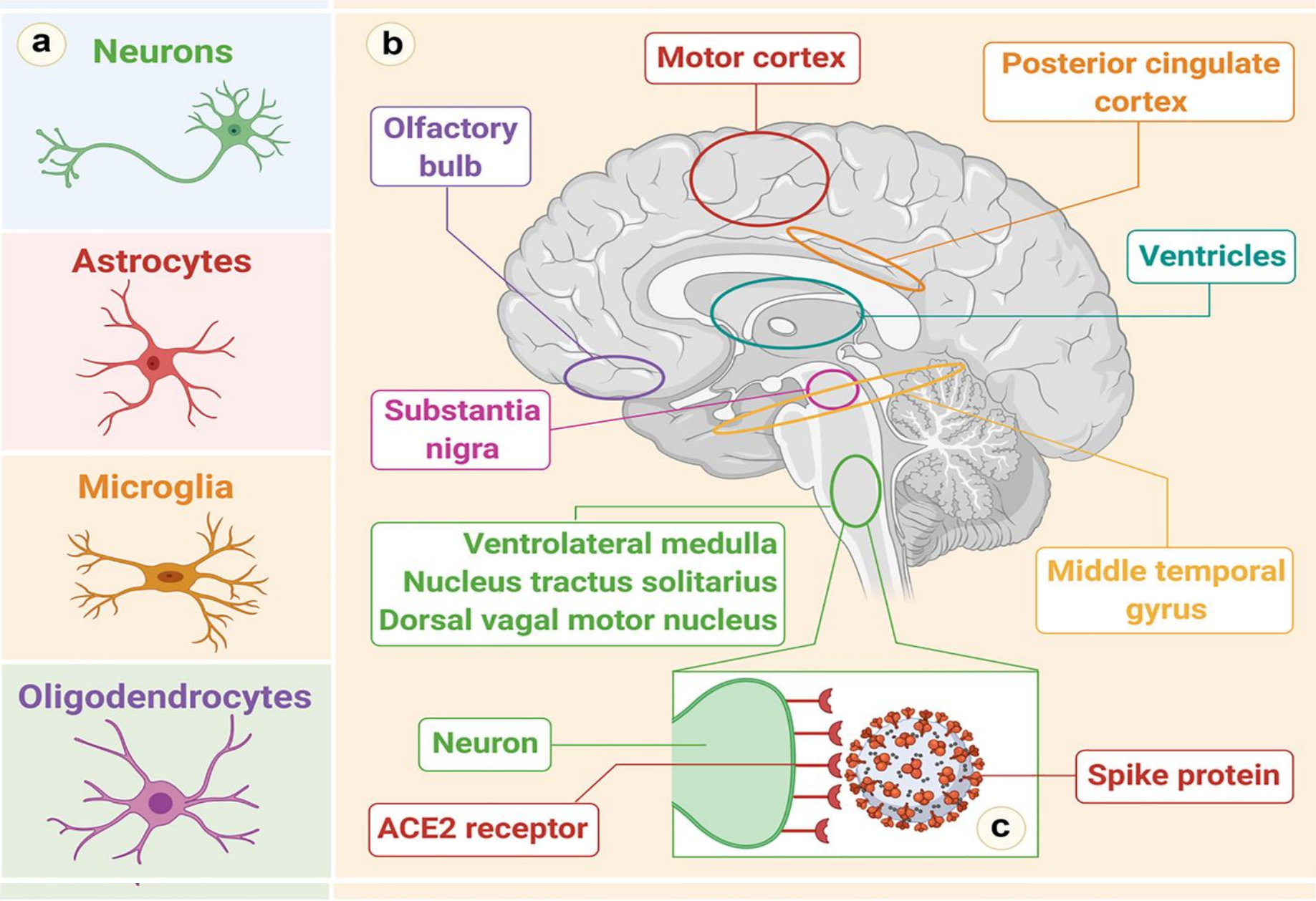
Complication	Clinical manifestations	Auxiliary examination	References
<b>COVID-19-RELATED COMPLICATIONS IN THE NERVOUS SYSTEM</b>			
Viral meningitis/encephalitis	Headache Altered mental status, meningeal irritation signs	CSF: positive PCR assay for SARS-CoV-2 Increased lymphocytes and proteins MRI: FLAIR hyperintensity EEG: slowing	(25–30)
Acute disseminated encephalomyelitis (ADEM)	Multifocal deficits	MRI: FLAIR hyperintensity, multifocal demyelinating lesions Autopsy: ADEM-like appearance in the subcortical white matter	(31–33)
Encephalopathy	Headache, altered mental status	CSF: negative PCR assay for SARS-CoV-2 EEG: diffuse slowing	(34–36)
Acute necrotizing encephalopathy (ANE)	Altered mental status	CT: hypoattenuation MRI: T2 FLAIR hyperintensity with internal hemorrhage	(37)
Cerebrovascular disease	Sensory or motor dysfunction	CT/MRI: ischemic or hemorrhagic change	(38–40)
Epilepsy	Seizures	CSF: negative PCR assay for SARS-CoV-2 EEG: semirhythmic, irregular, high-amplitude delta waves	(41–43)
Acute myelitis	Flaccid paralysis, hypesthesia Urinary and bowel dysfunction	MRI: T2 hyperintensity	(31, 44, 45)
Hyposmia and hypogeusia	Loss of a sense of smell and taste	Questionnaire-based survey Cross-sectional study	(46–49)
Guillain-Barré syndrome (GBS)	Flaccid paralysis	CSF: negative PCR assay for SARS-CoV-2 MRI: enhancement of affected nerve roots EMG: decreased recruitment	(50–53)
Miller Fisher syndrome (MSF)	Ophthalmoplegia, ataxia, and areflexia	MRI: relative enlargement, T2 hyperintensity, and enhancement of the affected CN Anti-GD1b antibody positive	(54, 55)

COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; EEG, electroencephalography; EMG, electromyography.

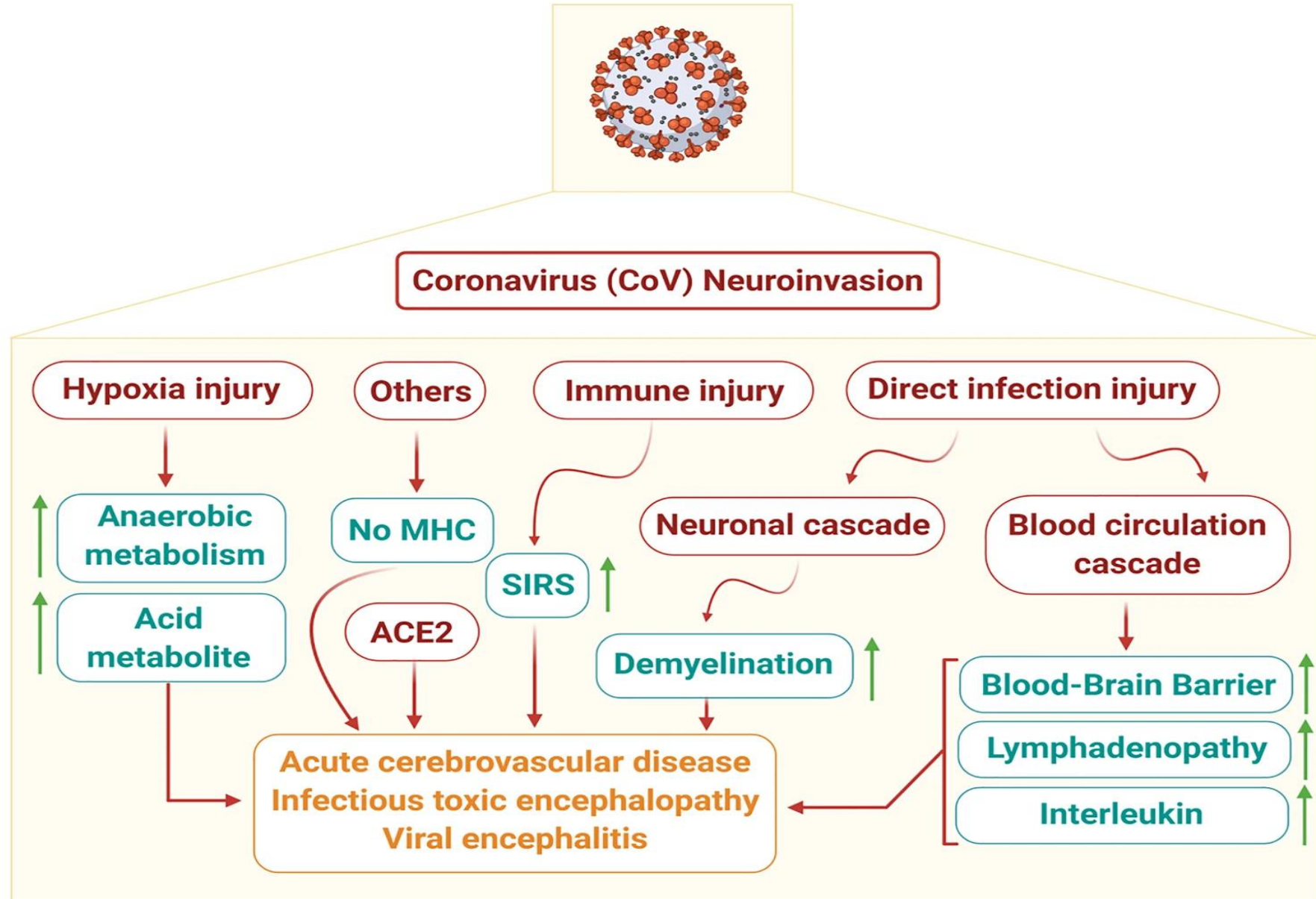
**Schematic representation showing the possible mechanisms underlying neurological consequences of COVID-19**





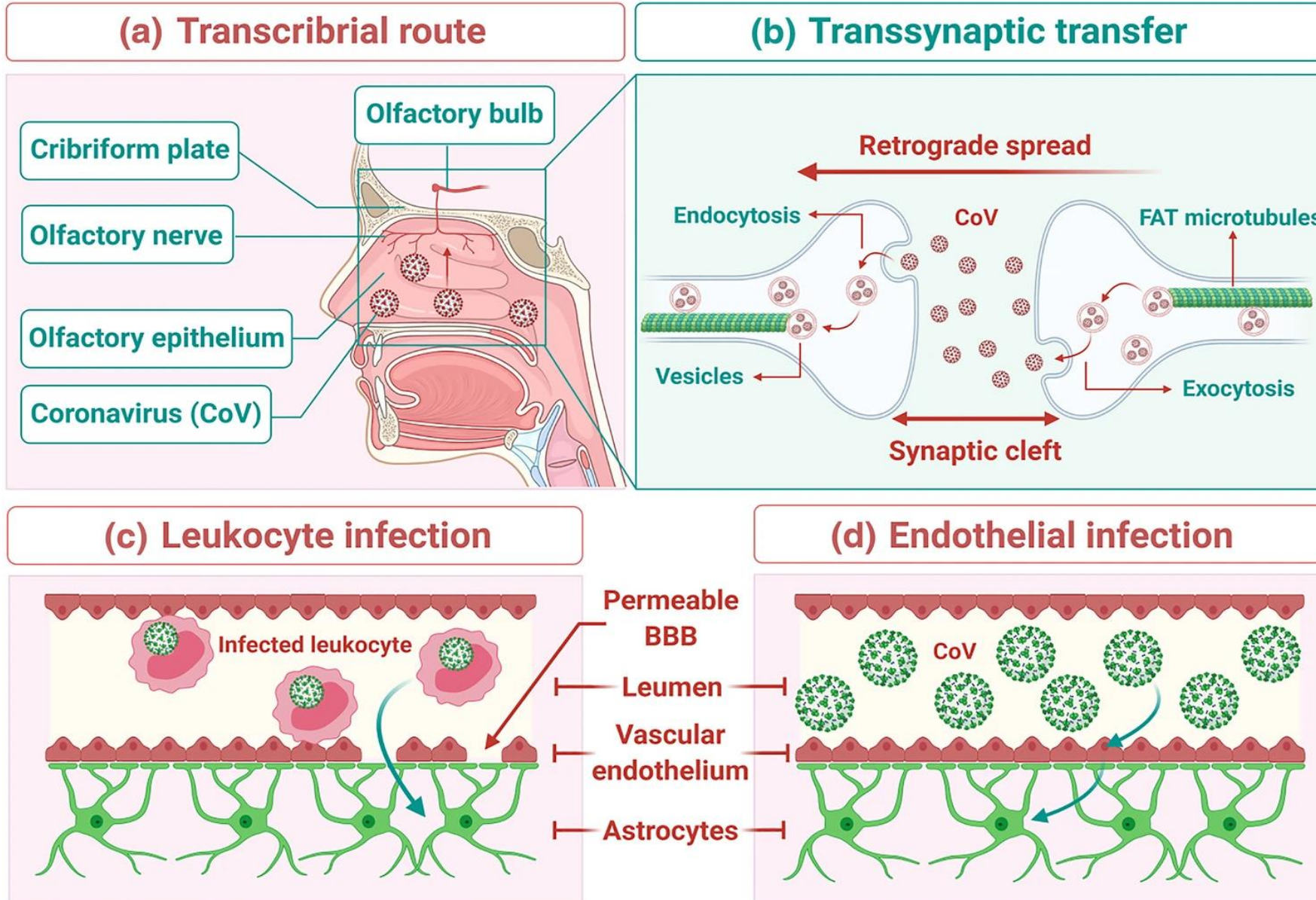


# Schematic representation showing pathomechanisms of nervous system injury caused by coronaviruses



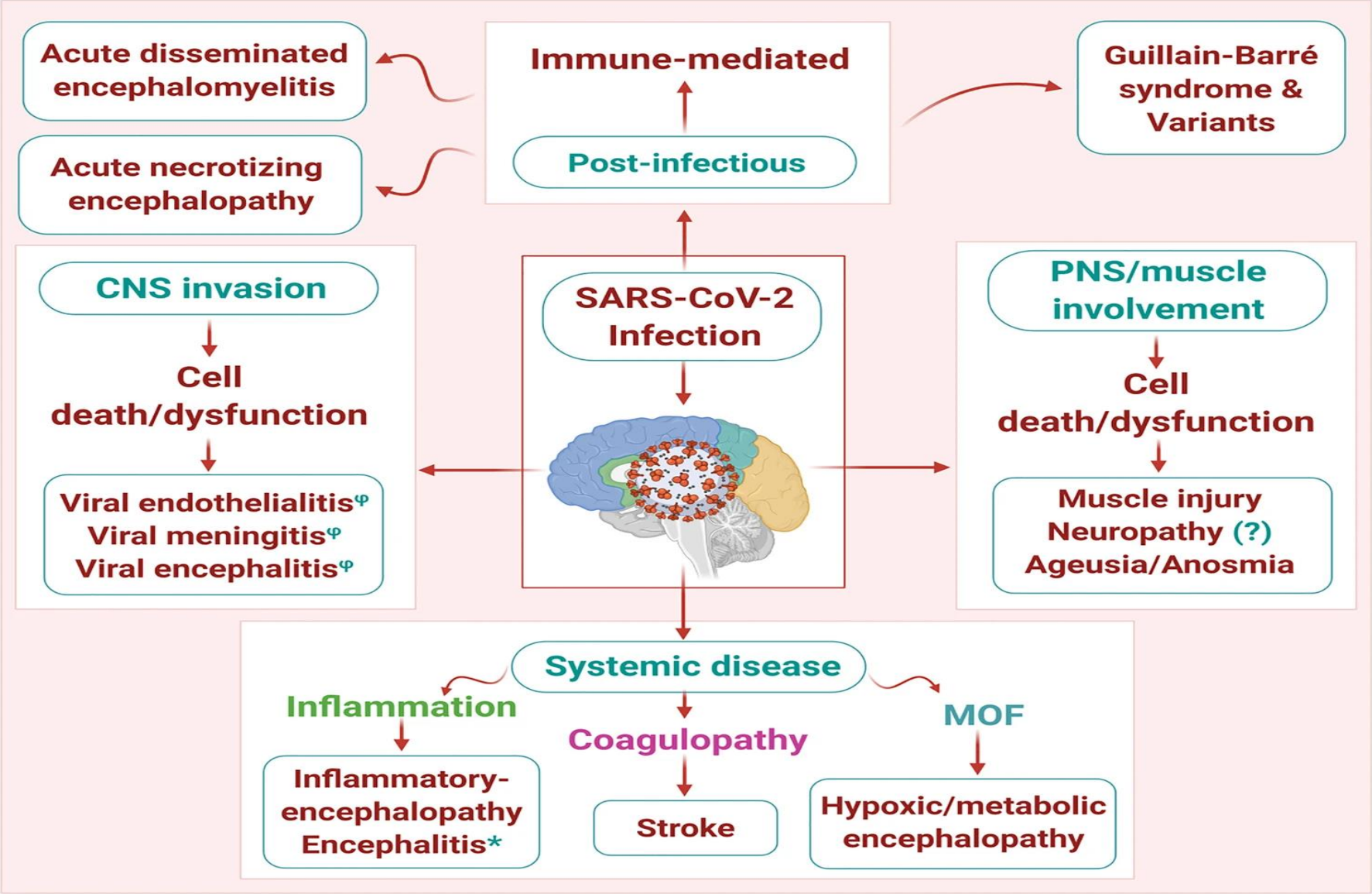


# Pathways of COVID-19 spread in nervous system





Putative mechanisms underlying SARS-CoV-2 neuropathogenesis: Manifestations of systemic disease and as post-infectious, immune-mediated mechanism



# Lehetséges célpontok a COVID-19 éleztveszélyes szövődményeinek enyhítésére

<i>Pre-Phase 1</i>	
- Vaccine (e.g., against the SARS-CoV-2 S protein) <i><b>1</b></i>	
<i>Phase 1 of the disease: Life cycle of the virus (extracellular – early steps of infection)</i>	
- SARS-CoV-2 neutralizing monoclonal antibodies <i><b>1</b></i> (because antibody-dependent enhancement of disease cannot be reliably predicted after either vaccination or treatment with antibodies, the on-going clinical trials for COVID-19 immune interventions should depend on careful analyses for safety in humans; also, preferentially the development of neutralizing antibodies after vaccination should be monitored) – (neutralizing antibodies from Eli Lilly and Regeneron Pharmaceuticals Inc. have received FDA emergency use authorization and GlaxoSmithKline/Vir Biotechnology has moved an anti-SARS-CoV-2 mAb into Phase 3 clinical trials)	
- Soluble ACE2 (decoy for virus) <i><b>2</b></i> (a recent development in this field is the production of engineered human ACE2 with optimum binding to the S protein of SARS-CoV-2)	
- Antibodies or small molecules that target ACE2 <i><b>2</b></i>	
- Treatments that suppress <i>ACE2</i> and/or <i>TMPRSS2</i> genes expression <i><b>2</b></i>	
- TMPRSS2 protease inhibitors <i><b>3</b></i>	
- Inhibitors of membrane fusion and/or clathrin-mediated endocytosis <i><b>4</b></i>	
<i>Phase 1 of the disease: Life cycle of the virus (intracellular)</i>	
- Tubulin polymerization inhibitors <i><b>4,4*,7</b></i>	
- Inhibitors of the endosomal/lysosomal compartments <i><b>4,4*</b></i> (recent studies in non-human primates do not support the use of hydroxychloroquine -either alone or in combination with azithromycin- for the treatment of COVID-19 in humans <a href="#">[158]</a> ; also, chloroquine was not found to inhibit infection of human lung cells with SARS-CoV-2)	
- CTSL/L specific inhibitors <i><b>4</b></i>	
- Small molecule inhibitors of cellular pathways reshaped by SARS-CoV-2 infection (not shown)	
- Inhibitors of the virus’ main protease <i><b>5,6</b></i>	
- Virus’ RNA-dependent RNA polymerase inhibitors <i><b>5,6</b></i>	
- MHC class II/MHC class I antigen presentation enhancement <i><b>8</b></i>	
<i>Phase 2 of the disease: adverse effects of COVID-19</i>	
- ACE inhibitors, AT1R blockers <i><b>10–12</b></i>	
- The ANG(1–7) peptide (or non-peptide analogs) <i><b>10–12</b></i>	
- Antioxidants or radical scavengers <i><b>10–12</b></i>	
- Adjunct immunotherapies (or corticosteroids) to mitigate “cytokine storm” (e.g., inhibition of IL-6 signaling) <i><b>10–12</b></i> (notably, the use of hydrocortisone or dexamethasone showed some beneficial effects on mortality, organ support, days alive and free of mechanical ventilation in patients with severe COVID-19)	
- Anticoagulant medications to alleviate intravascular coagulation (not shown)	
- Additional life-supporting measures (e.g., ventilation or intubation) (not shown)	Trougakos et al. J Biomed Sci (2021) 28:9 <a href="https://doi.org/10.1186/s12929-020-00703-5">https://doi.org/10.1186/s12929-020-00703-5</a>

Kezelések amelyek potenciálisan elnyomhatják a COVID-19 fertőzési ráták és/vagy szövődményeket

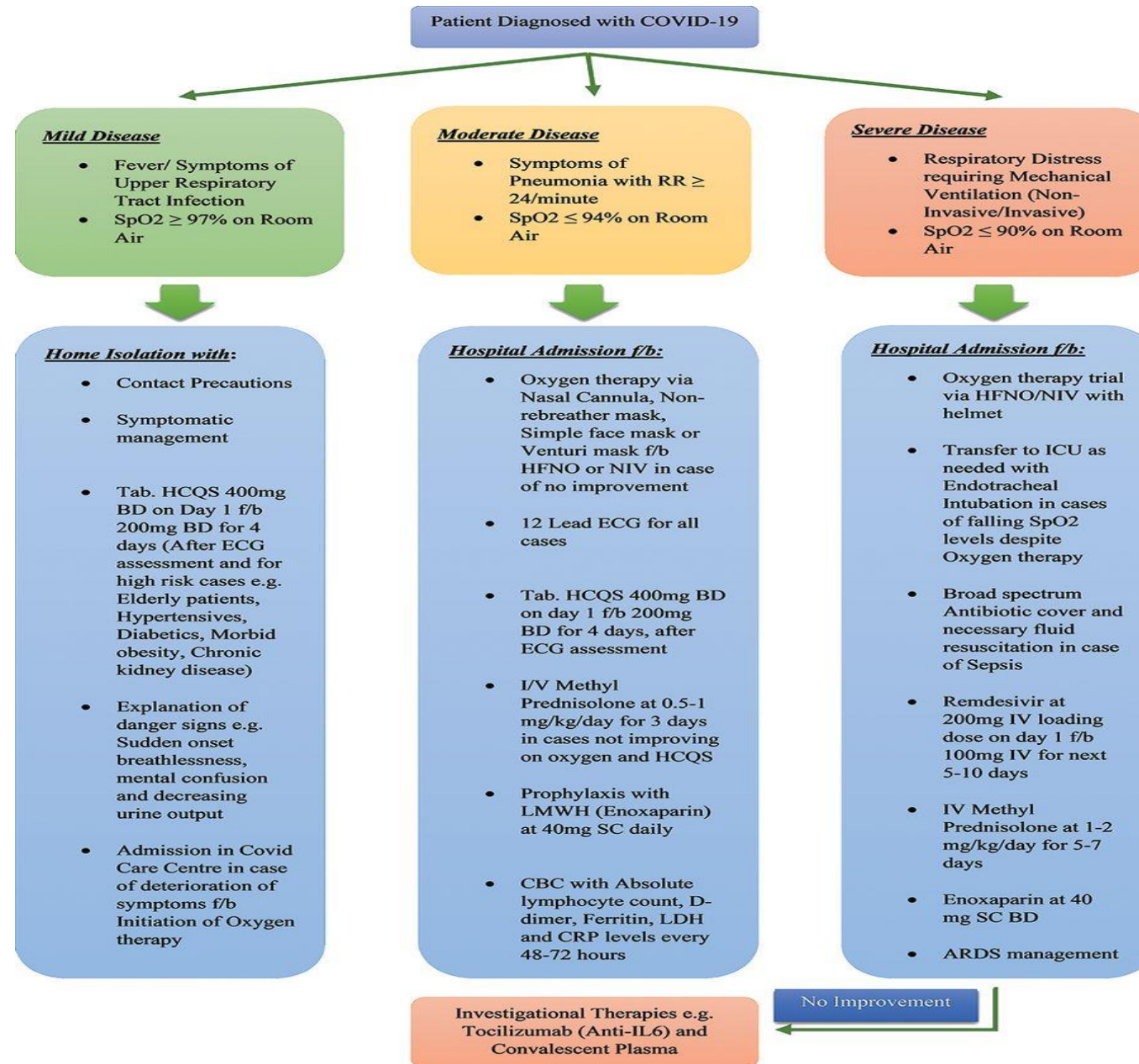
Induction of SARS-CoV-2-specific neutralizing antibodies			
Recombinant Novel Coronavirus Vaccine Gam-COVID-Vac Vaccine	Phase 3 clinical trial (viral two-vector vaccine based on the human adenovirus fused with the S protein of SARS-CoV-2)	Unknown	
Adsorbed COVID-19 (inactivated) Vaccine SARS-CoV-2 Vaccine (Vero cell)	Phase 3 clinical trial (absorbed inactivated SARS-CoV-2)	Unknown	
mRNA-1273 vaccine	Phase 3 clinical trial (mRNA-based vaccine that encodes for a full-length, prefusion stabilized S protein of SARS-CoV-2)	Unknown	
SARS-CoV-2 neutralizing monoclonal antibodies			
COV2-2196, COV2-2130	In vitro and in vivo study (mouse)	Reduce viral burden and level of inflammation in mouse’s lungs	
P2C-1F11, P2B-2F6, P2C-1A3	In vitro (antibodies derived from 8 individuals infected with SARS-CoV-2)	Substantial neutralizing activities against SARS-CoV-2 infection	
CB6	In vivo (specific human antibodies administrated in rhesus macaques)	Prophylactic group: prevention of SARS-CoV-2 infection. Treatment group: reduced SARS-CoV-2 titre	
Soluble angiotensin converting enzyme 2 (ACE2) (decoy for virus)			
GSK2586881	Phase 2 clinical trial (recombinant human ACE2 in ventilated patients with ARDS)	Unknown	
RhACE2 APN01	Ongoing phase 2 clinical trial (recombinant human ACE2)	Unknown	
Antibodies or small molecules that target ACE2			
SSAA09E2	In vitro (small molecule added to 293 T and Vero cells)	Inhibits fusion of the SARS-S envelope with the host cellular membrane	
COV2-2196 COV2-2381	In vivo (monoclonal antibodies administrated in rhesus macaques)	Prophylactic group: prevention of SARS-CoV-2 infection	
TMRPSS2 protease inhibitors			
Camostat mesylate	In vitro (lung cell line)	Blocks SARS-CoV-2 infection of lung cells	
Inhibitors of membrane fusion and/or clathrin-mediated endocytosis			
Ikarugamycin	In vitro (H1299 cells)	Acutely inhibits clathrin-mediated endocytosis (CME)	
Dynasore, Dyngo 4a, Dyngo 6a	In vitro	Inhibit specifically dynamin and clathrin-mediated endocytosis	
Latrunculin b	In vitro	Inhibits Australian bat lyssavirus G-mediated entry into HEK293T cells through actin depolymerization	
SSAA09E3	In vitro (small molecule added to 293 T and Vero cells)	Prevents fusion of the SARS-CoV-2 membrane with the host cellular membrane	
Virus’ RNA-dependent RNA polymerase (RdRp) inhibitors			
Setrobuvir, IDX-184, YAK	In vitro	Bind to RdRp tightly and hence may contradict the polymerase function	
Cathepsin L inhibitors			
SSAA09E1, Oxocarbazate, MDL-28170, K11777, EST	In vitro (293 T cells)	Blocks SARS CoV-2 entry	
Inhibitors of cellular pathways reshaped by SARS-CoV-2 infection			
Cycloheximide	In vitro (human Caco2 cells)	Inhibits translation elongation and SARS-CoV-2 replication	
Emetine	In vitro (human Caco2 cells)	Inhibits the 40S ribosomal protein S14 and SARS-CoV-2 replication	
Pladienolide B	In vitro (human Caco2 cells)	Inhibits splicing factor SF3B117 and SARS-CoV-2 replication	
2-Deoxy-D-glucose	In vitro (human Caco2 cells)	Blocks glycolysis and inhibits SARS-CoV-2 replication	
Ribavirin	In vitro (human Caco2 cells)	Inhibits inosine monophosphate dehydrogenase and SARS-CoV-2 replication	
NMS-873	In vitro (human Caco2 cells)	Inhibits the AAA ATPase p97 and SARS-CoV-2 replication	
ANG(1–7) peptide			
Angiotensin 1–7, TXA127	Ongoing Phase 3 clinical trial	Unknown	Trougakos et al. J Biomed Sci (2021) 28:9 <a href="https://doi.org/10.1186/s12929-020-00703-5">https://doi.org/10.1186/s12929-020-00703-5</a>

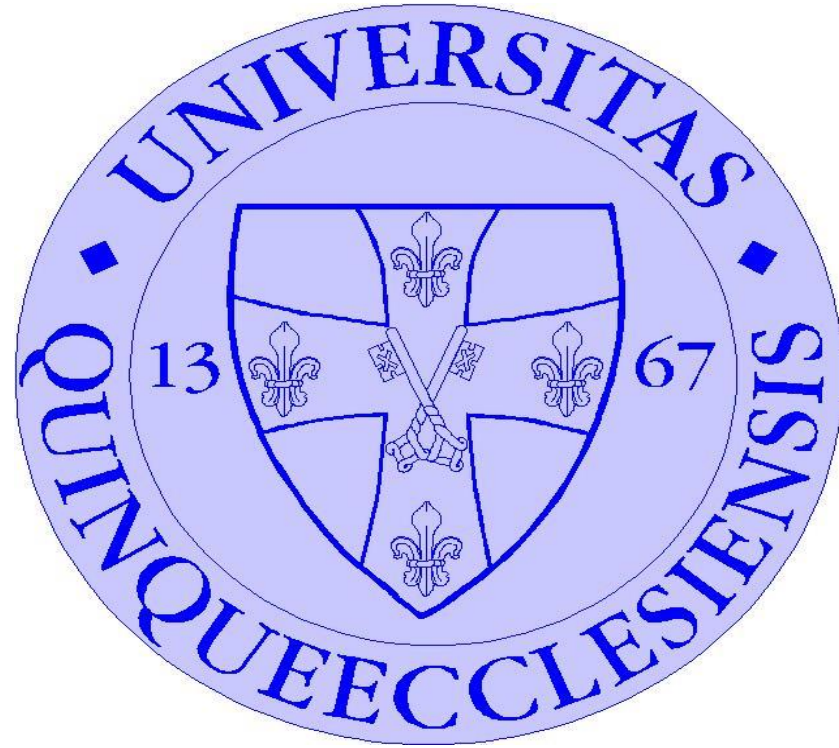
# A COVID-19 kezelési stratégiái

Drug/treatment	Remarks
Oxygen therapy	<ul style="list-style-type: none"> <li>•Nasal cannulas, simple face masks, venture masks or non-rebreather masks for mild cases</li> <li>•HFNO therapy or NIV for moderate cases</li> <li>•Invasive ventilation via endotracheal intubation for severe cases with ARDS</li> </ul>
Antibiotics	<ul style="list-style-type: none"> <li>•Given to prevent/treat secondary bacterial infections</li> <li>•Azithromycin is preferred in view of anti-inflammatory action</li> </ul>
Corticosteroids	<ul style="list-style-type: none"> <li>•I.V methylprednisolone is recommended in moderate-to-severe cases at 1–2 mg/kg/day for 3 days</li> <li>•Recently, dexamethasone has been found to be beneficial in severe cases</li> </ul>
Antiviral drugs	<ul style="list-style-type: none"> <li>•Remdesivir has shown efficacy in moderate cases</li> <li>•Lopinavir/ritonavir have much lower efficacy</li> <li>•Oseltamivir has shown no clear benefit</li> <li>•Recently launched favipiravir shows some efficacy in mild-to-moderate cases</li> </ul>
Immunomodulatory drugs (anti-interleukins and HCQS)	<ul style="list-style-type: none"> <li>•Tocilizumab is a IgG1 monoclonal antibody, directed against the IL-6 receptor which is seen to be beneficial in moderate-to-severe cases of COVID-19</li> <li>•HCQS has shown better efficacy and safety profile as compared to chloroquine</li> </ul>
Plasma exchange	<ul style="list-style-type: none"> <li>•Most beneficial if plasma collected within 2 weeks of patient recovery from disease</li> </ul>
Anticoagulation	<ul style="list-style-type: none"> <li>•Enoxaparin is indicated in moderate-to-severe cases to prevent venous thromboembolism</li> </ul>



# Kezelési protokoll COVID-19 betegeknél





**Köszönöm a megtisztelő figyelmet!**