UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA

Infezione da SARS-CoV-2 come paradigma di infezione sistemica

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Giornate Infettivologiche Sacco

Milano 5 febbraio 2020

COVID-19 and multisystem inflammatory syndrome in children and adolescents

Li Jiang, Kun Tang*, Mike Levin, Omar Irfan, Shaun K Morris, Karen Wilson, Jonathan D Klein, Zulfiqar A Bhutta*

	MIS-C associated with COVID-19	PIMS-TS	MIS-C associated with COVID-19	Complete Kawasaki disease	Incomplete Kawasaki disease	Kawasaki disease shock syndrome
Organisation or publication	WHO[6]	Royal College of Pediatrics and Child Health[39]	US Centers for Disease Control and Prevention[37]	American Heart Association[40]	American Heart Association[40]	Kanegaye et al,[41]
Age	0–19 years	Child (age not specified)	<21 years	Child (age not specified)	Child (age not specified)	Child (age not specified)
Inflammation	Fever and elevated inflammatory markers for 3 days or more	Fever and elevated inflammatory markers	Fever and elevated inflammatory markers	Fever lasting 5 days or more*	Fever lasting 5 days or more*	Fever
Main features	Two of the following: (A) rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet); (B) hypotension or shock; (C) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated troponin or N-terminal pro B-type natriuretic peptide); (D) evidence of coagulopathy (elevated prothrombin time, partial thromboplastin time, and elevated D-dimers); and (E) acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)	Single or multiple organ dysfunction (shock or respiratory, renal, gastrointestinal, or neurological disorder; additional features (appendix 6 pp 3–4)	Clinically severe illness requiring hospitalisation; and multisystem (two or more) organ involvement (cardiac, renal, respiratory, haematological, gastrointestinal, dermatological, or neurological)	Four or more principal clinical features: (A) erythema and cracking of lips, strawberry tongue or oral and pharyngeal mucosa; (B) bilateral bulbar conjunctival injection without exudate; (C) rash; (D) erythema and oedema of the hands and feet in acute phase and periungual desquamation in subacute phase; and (E) cervical lymphadenopathy	Two or three principal clinical features or a positive echocardiogram	Kawasaki disease-like clinical features and any of the following causing initiation of volume expansion, vasoactive agents, or transfer to the intensive care unit: systolic hypotension based on age, or a decrease in systolic blood pressure from baseline by 20% or more, or clinical signs of poor perfusion

Lancet Infect Dis 2020;20:e276-288

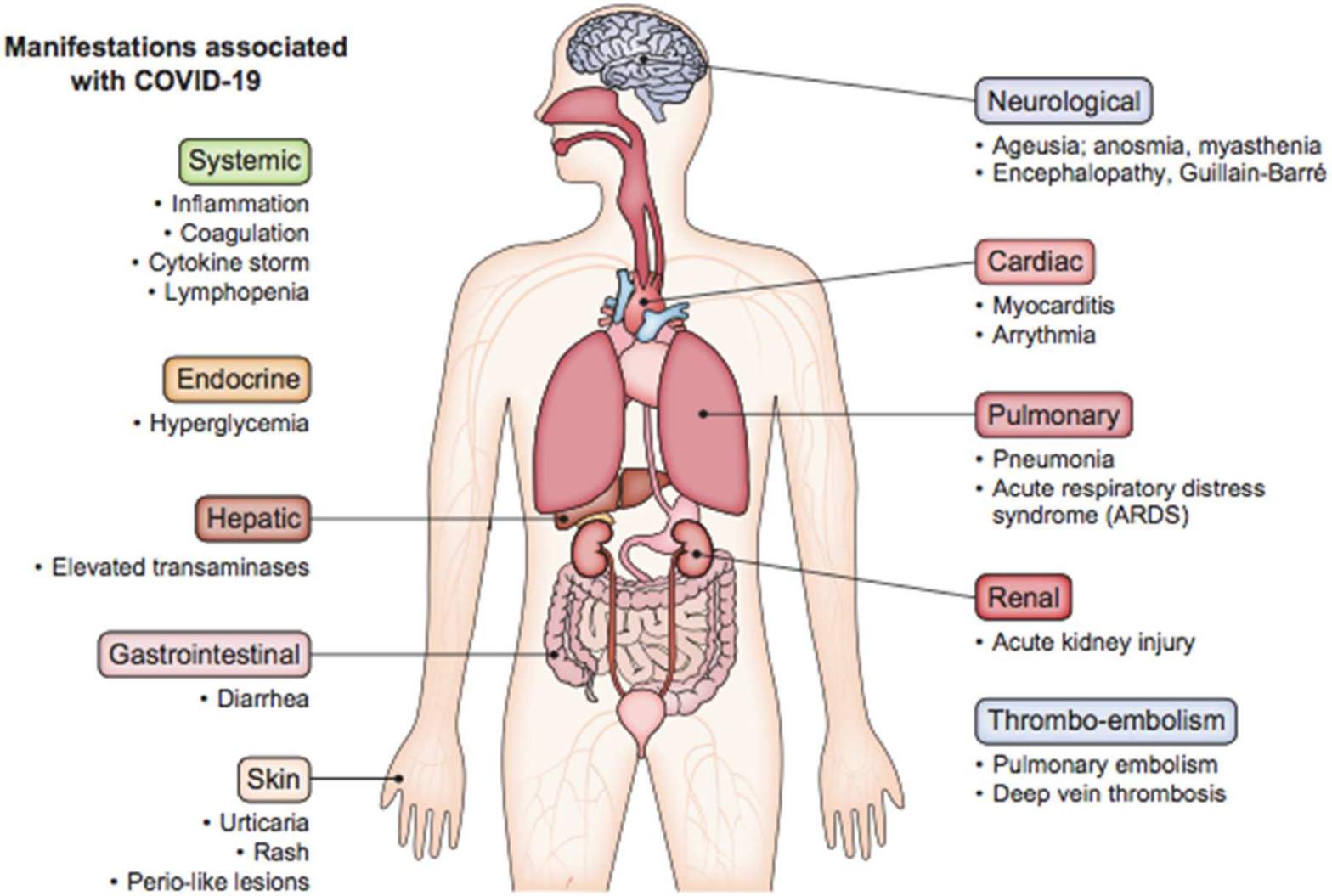

Fig. 3. Systemic manifestations of COVID-19. COVID-19, coronavirus disease 2019.

Clinical Infectious Diseases

CORRESPONDENCE

Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study

Andrea Giacomelli,[1,2] Laura Pezzati,[1,2] Federico Conti,[1,2] Dario Bernacchia,[1,2] Matteo Siano,[1,2] Letizia Oreni,[1] Stefano Rusconi,[1,2] Cristina Gervasoni,[1] Anna Lisa Ridolfo,[1] Giuliano Rizzardini,[3,4] Spinello Antinori,[1,2] and Massimo Galli[1,2]

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Table 1. Characteristics of Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection Assessed for Taste and Olfactory Disorders (N = 59)

Patients	No. (%)
Age, y, median (IQR)	60 (50–74)
Male sex	40 (67.8)
Days from illness onset to hospital admission, median (IQR)	6 (4–10)
Days from illness onset to the interview, median (IQR)	15 (10–21)
Pneumonia at hospital admission	43 (72.8)
Symptoms at hospital admission	
Fever	43 (72.8)
Cough	22 (37.3)
Dyspnea	15 (25.4)
Sore throat	1 (1.7)
Arthralgia	3 (5.1)
Coryza	1 (1.7)
Headache	2 (3.4)
Asthenia	1 (1.7)
Abdominal symptoms	5 (8.5)
No taste or olfactory disorders	39 (66.1)
With olfactory and/or taste disorders	20 (33.9)
Taste disorders only	
Dysgeusia	5 (8.5)
Ageusia	1 (1.7)
Olfactory disorders only	
Hyposmia	3 (5.1)
Anosmia	0 (0)
Mixed taste and olfactory disorders	
Dysgeusia and hyposmia	2 (3.4)
Dysgeusia and anosmia	2 (3.4)
Ageusia and hyposmia	2 (3.4)
Ageusia and anosmia	5 (8.5)

Autopsy series of 68 cases dying before and during the 1918 influenza pandemic peak

Zong-Mei Sheng[a], Daniel S. Chertow[a], Xavier Ambroggio[b], Sherman McCall[c], Ronald M. Przygodzki[d], Robert E. Cunningham[e], Olga A. Maximova[f], John C. Kash[a], David M. Morens[g], and Jeffery K. Taubenberger[a,1]

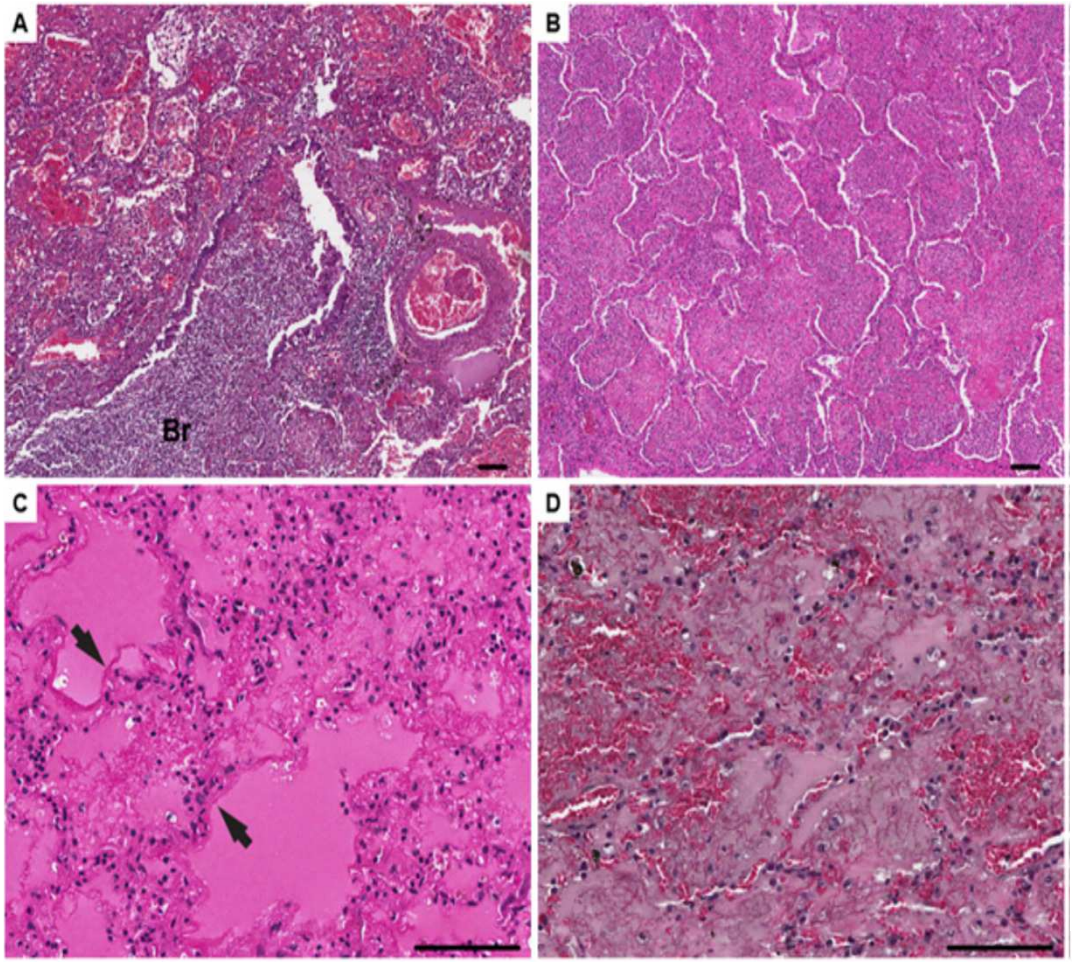

Table 1. Major pulmonary histological diagnoses

Characteristic	No./total no. (%)
Bronchitis	4/4* (100%)
Acute pneumonia	68/68 (100%)
Bronchiolitis	39/68 (57%)
DAD	36/68 (53%)
Acute edema	41/68 (60%)
Acute hemorrhage	27/68 (40%)
Thrombus formation	5/68† (7%)
Pleuritis	10/68 (15%)

*Only 4 of 68 cases had evaluable bronchial tissue.
†One patient with thrombus formation has recently been reported as bearing sickle-cell trait (52).

Postmortem Findings Associated With SARS-CoV-2

Systematic Review and Meta-analysis

Swati Satturwar, MD, Mary Fowkes, MD, PhD,† Carol Farver, MD,‡ Allecia M. Wilson, MD,‡ Albino Eccher, MD,§ Ilaria Girolami, MD,§ Elisabet Pujadas, MD, PhD,† Clare Bryce, MD,† Fadi Salem, MD,† Siraj M. El Jamal, MD,† Alberto Paniz-Mondolfi, MD, PhD,† Bruce Petersen, MD,† Ronald E. Gordon, PhD,† Jason Reidy, MSc,† Filippo Fraggetta, MD,‖ Desiree A. Marshall, MD,¶ and Liron Pantanowitz, MD, MHA‡*

TABLE 5. Key Microscopic Lung Pathology Findings

	COVID-19		SARS-CoV-1			
Histopathology	Total	n (%)	Total	n (%)	Higher Proportion	χ^2
DAD*	157	127 (80.9)	54	54 (100.0)	SARS	12.029
Hyaline membranes	157	126 (80.3)	54	49 (90.7)	SARS	3.122
Inflammatory cells†	157	115 (73.2)	54	45 (83.3)	SARS	2.487
Microthrombi	157	93 (59.2)	54	33 (61.1)	SARS	0.059
Hemorrhage	157	56 (35.7)	54	42 (77.8)	SARS	28.643
Vascular injury‡	157	33 (21.0)	54	26 (48.1)	SARS	14.681
Pulmonary embolism	157	13 (8.3)	54	6 (11.1)	SARS	0.393

Am J Surg Pathol 2021

Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study

Bernadette Schurink, Eva Roos*, Teodora Radonic, Ellis Barbe, Catherine S C Bouman, Hans H de Boer, Godelieve J de Bree, Esther B Bulle, Eleonora M Aronica, Sandrine Florquin, Judith Fronczek, Leo M A Heunks, Menno D de Jong, Lihui Guo, Romy du Long, Rene Lutter, Pam C G Molenaar, E Andra Neefjes-Borst, Hans W M Niessen, Carel J M van Noesel, Joris J T H Roelofs, Eric J Snijder, Eline C Soer, Joanne Verheij, Alexander P J Vlaar, Wim Vos, Nicole N van der Wel, Allard C van der Wal, Paul van der Valk†, Marianna Bugiani†*

Other disease manifestations	
Thromboembolic events	10 (48%)
Deep venous thrombosis	3
Pulmonary embolism (thrombosis)	6
Both	1
Cardiac events	13 (62%)
Arrhythmias	12
Ischaemic events	0
Heart failure	1
Renal failure¶	15 (71%)
KDIGO stage 1	2
KDIGO stage 2	3
KDIGO stage 3	10
Neurological events	10 (48%)
Delirium	5
Cerebrovascular accident (acute stroke)	2
Other‖	3
Necrotising encephalitis	1
Hypoxic encephalopathy	2
Suprainfection (%)	9 (43%)
Aspergillus**	8
Bacterial	1
Viral	0
Autopsy characteristics	
Disease course from symptom onset, days	22 (5–44)
Time from death to autopsy, h	15 (3–88)
Autopsy diagnosis cause of death	
COVID-19 pneumonia	9 (43%)
Pulmonary embolism	2 (10%)
Cerebrovascular accident (acute stroke)	1 (5%)
Multiorgan failure	7 (33%)
Other††	2 (10%)

Lancet Microbe 2020;1: e290-99

Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study

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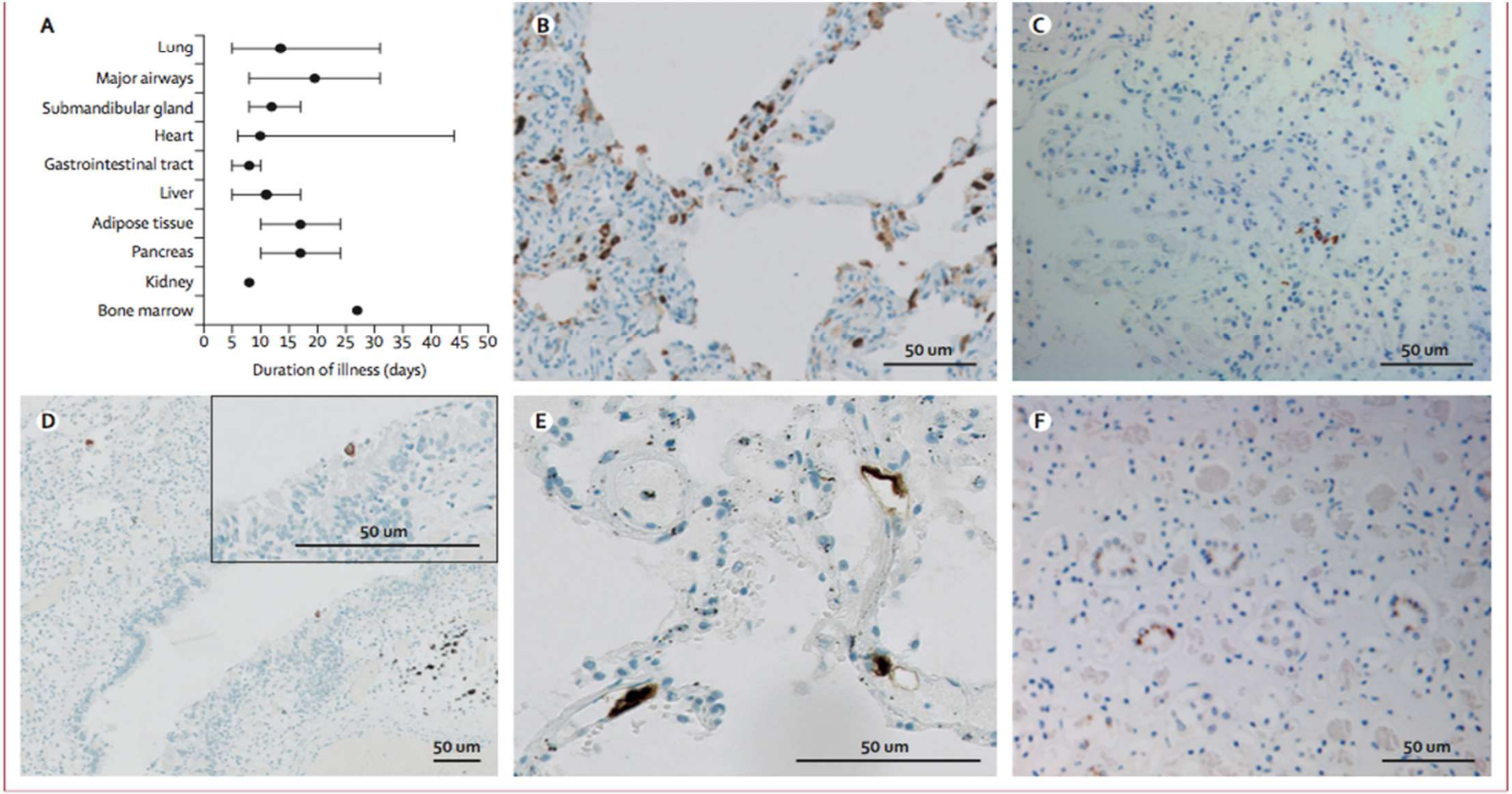
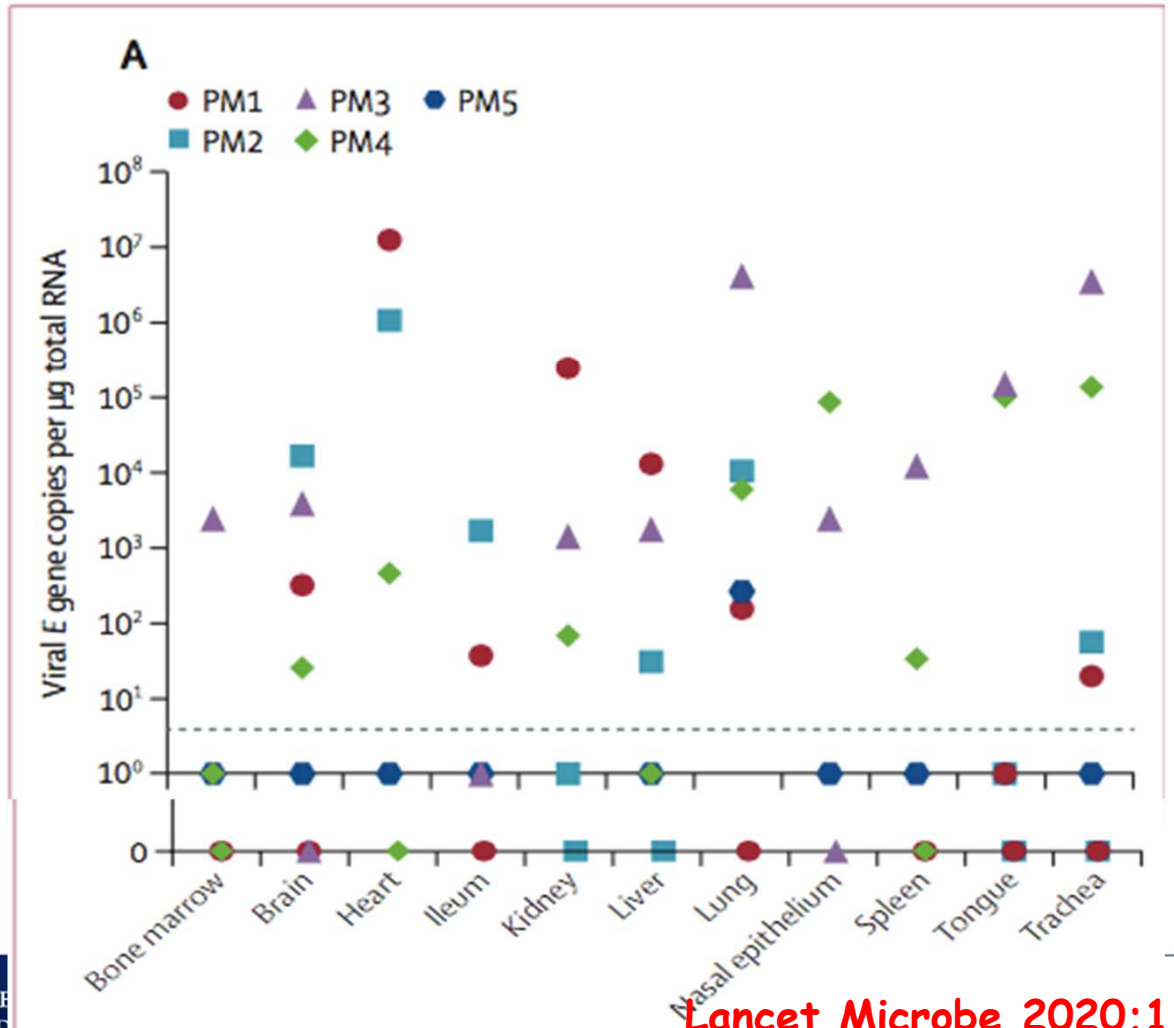


Lancet Microbe 2020;1: e290-99

Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study

Brian Hanley, Kikkeri N Naresh, Candice Roufosse, Andrew G Nicholson, Justin Weir, Graham S Cooke, Mark Thursz, Pinelopi Manousou, Richard Corbett, Robert Goldin, Safa Al-Sarraj, Alireza Abdolrasouli, Olivia C Swann, Laury Baillon, Rebecca Penn, Wendy S Barclay, Patrizia Viola, Michael Osborn



Lancet Microbe 2020;1:e245-53

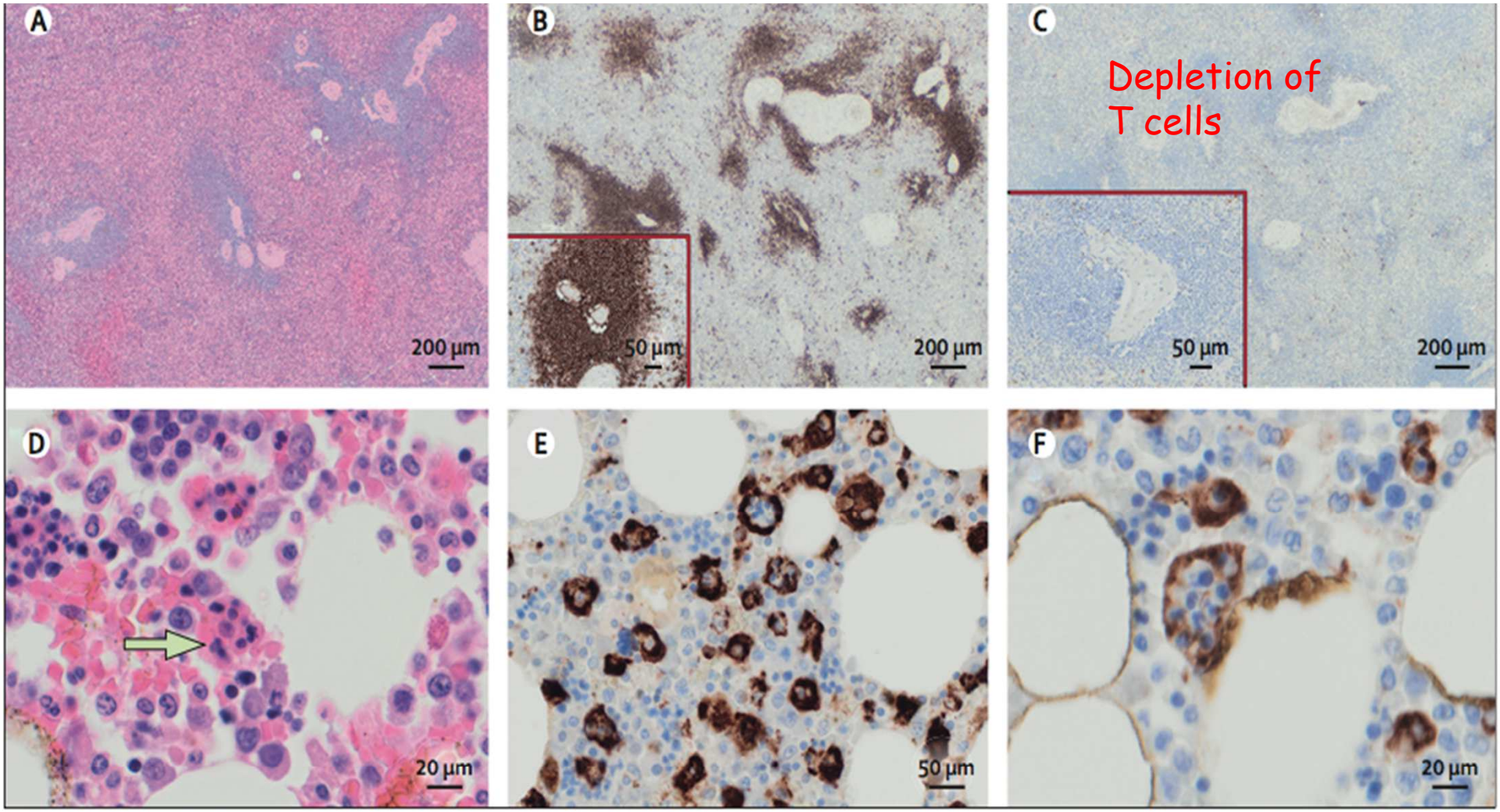


Figure 4: **Pathological findings in haematological organs in patients with COVID-19**

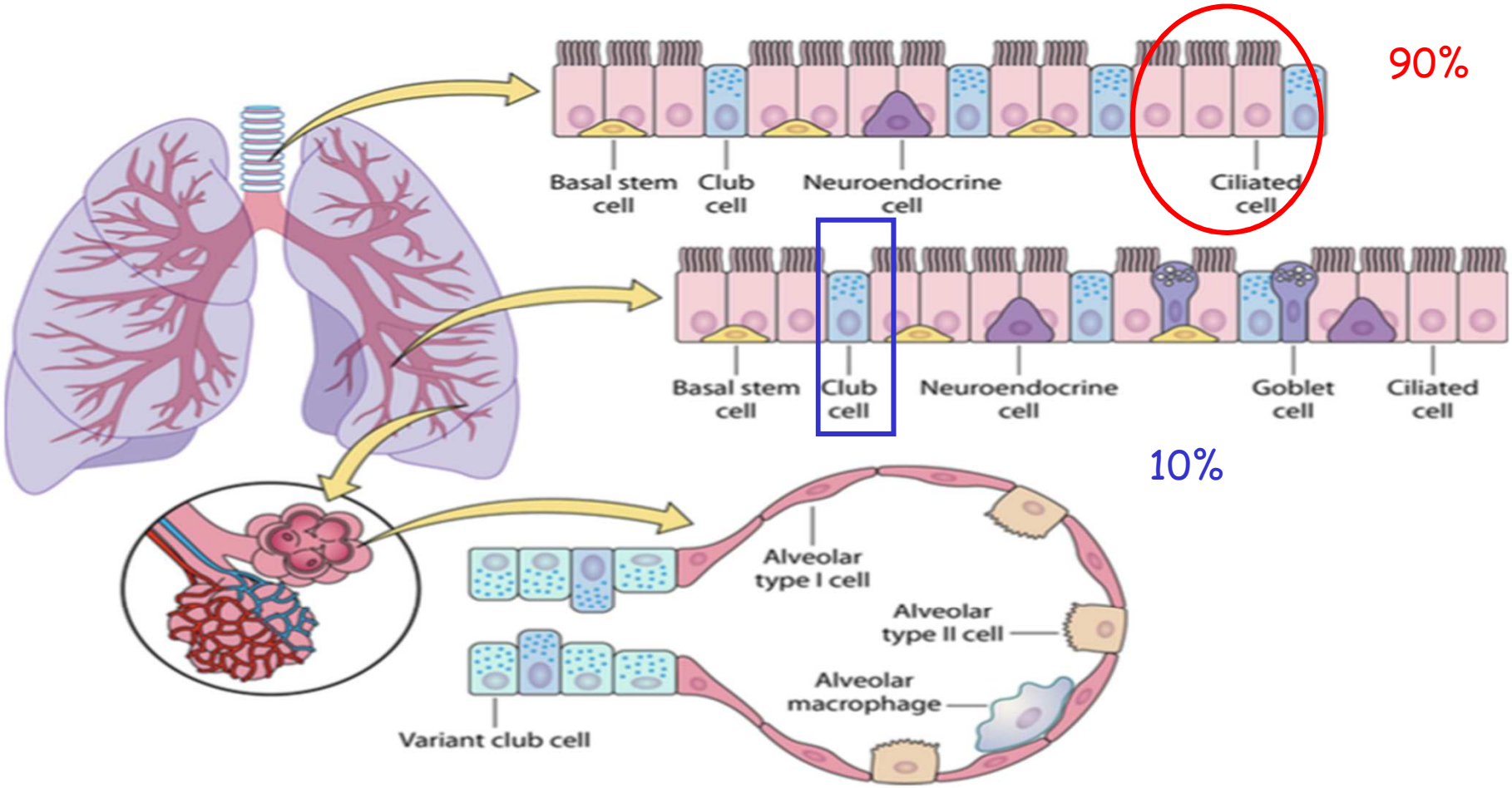
T-cell depletion in the spleen of a 79-year-old woman (PM9) with COVID-19: haematoxylin and eosin staining of the spleen at 10× magnification (A); CD20 staining of spleen indicating presence of B cells (B; 10× magnification), with the insert showing the same region at higher power (20× magnification); and CD3 staining of spleen indicating depletion of T cells (C; 10× magnification), with the insert showing the same region at higher power (20× magnification). Bone marrow phagocytosis in a 97-year-old man (PM8) with COVID-19: haematoxylin and eosin staining of a well preserved bone marrow, with an arrow indicating presence of phagocytosis (D; 40× magnification); and CD68-PGM1 staining of bone marrow indicating presence of phagocytosis (20× [E] and 40× [F] magnification).

Hanley B et al. Lancet Microbe 2020;1:e245-53

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection

environment. In this model, more than 90% of ciliated cells, less than 10% of club cells, and no basal or goblet cells were infected with SARS-CoV-2 (107). Tindle et al. devel-

Aleksandra Synowiec,[a] Artur Szczepański,[a,b] Emilia Barreto-Duran,[a] Laurensius Kevin Lie,[a] Krzysztof Pyrc[a]



Clin Microbiol Rev 2021; 34:e00133-20

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection

Aleksandra Synowiec,[a] Artur Szczepański,[a,b] Emilia Barreto-Duran,[a] Laurensius Kevin Lie,[a] Krzysztof Pyrc[a]

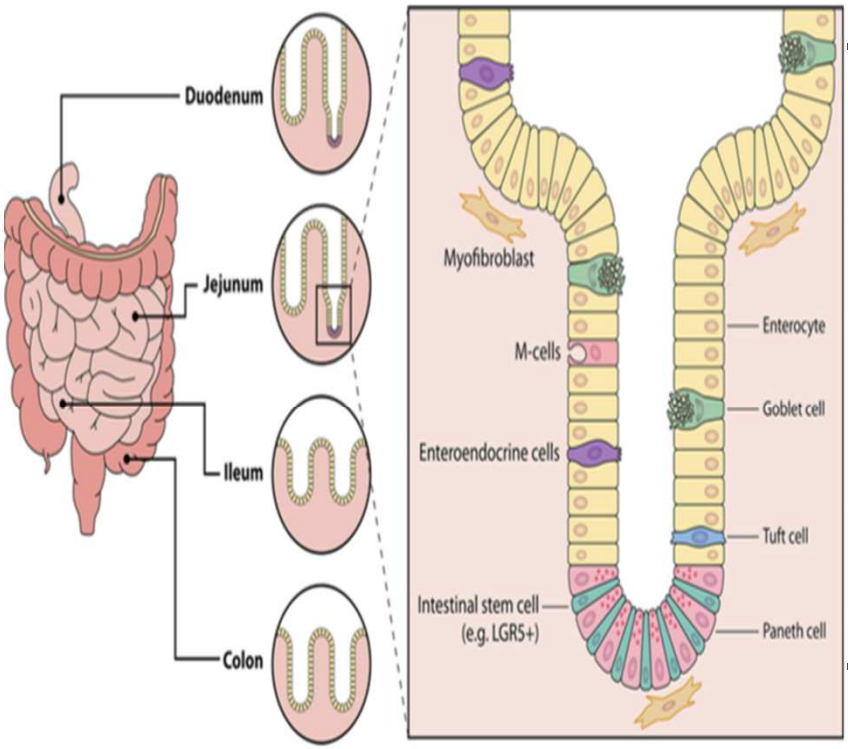


FIG 4 Cell types and their localization in the human intestine.

than that seen in the lungs (139). To be more precise, ACE2 is abundantly expressed in stomach epithelial cells and in enterocytes from the small intestine, including the duodenum, jejunum, and ileum, and it is poorly expressed in colonocytes (140). Unsurprisingly, human colonoids are affected to a lesser extent than organoids deriving from the small intestine (128, 136). Consequently, SARS-CoV and SARS-CoV-2 infect only enterocytes and not goblet cells, EECs, tuft cells, or Paneth cells (123, 136). Mature enterocytes express higher ACE2 levels than immature ones, but the levels of replication are comparable. This may indicate that a low level of ACE2 expression is sufficient for the virus to enter the cell (123, 136) or that there is an additional restriction factor present in mature enterocytes. What is interesting is that ACE2 expression increases during gastric (141) and colorectal (142) cancer development. Increased expression of ACE2 is also observed in patients with inflammatory bowel disease (IBD) (143, 144).

Clin Microbiol Rev 2021; 34:e00133-20

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection

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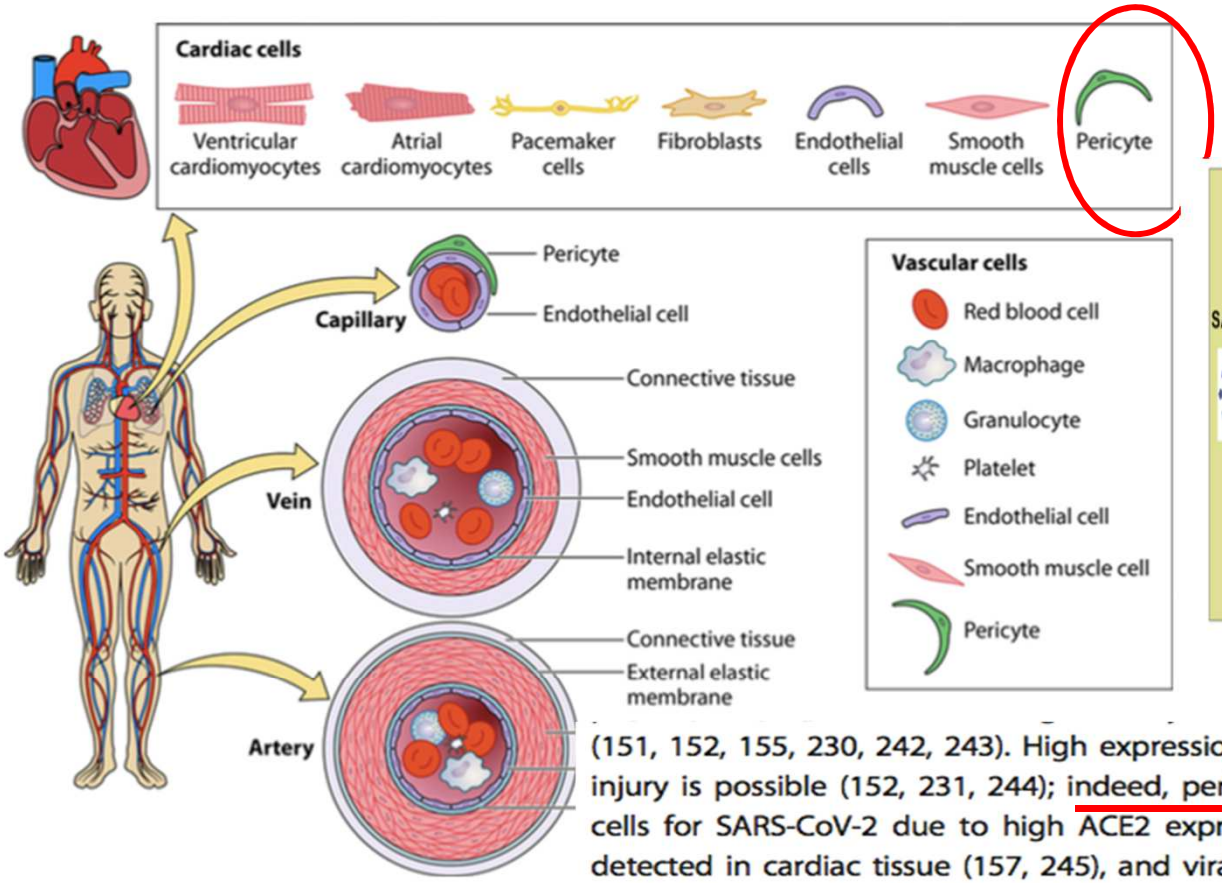
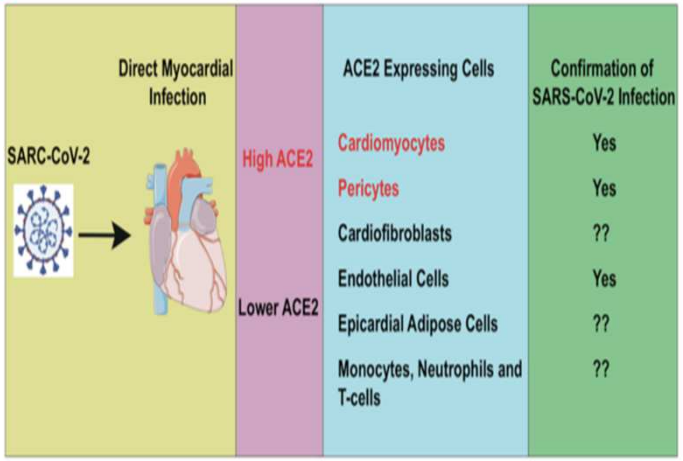




(151, 152, 155, 230, 242, 243). High expression of ACE2 in the heart suggests that direct injury is possible (152, 231, 244); indeed, pericytes are thought to be the target cardiac cells for SARS-CoV-2 due to high ACE2 expression (220, 240). Viral particles have been detected in cardiac tissue (157, 245), and viral replication was shown in human induced

Clin Microbiol Rev 2021; 34:e00133-20

Box 1: Cardiovascular involvement in COVID-19

Clinical Profile:

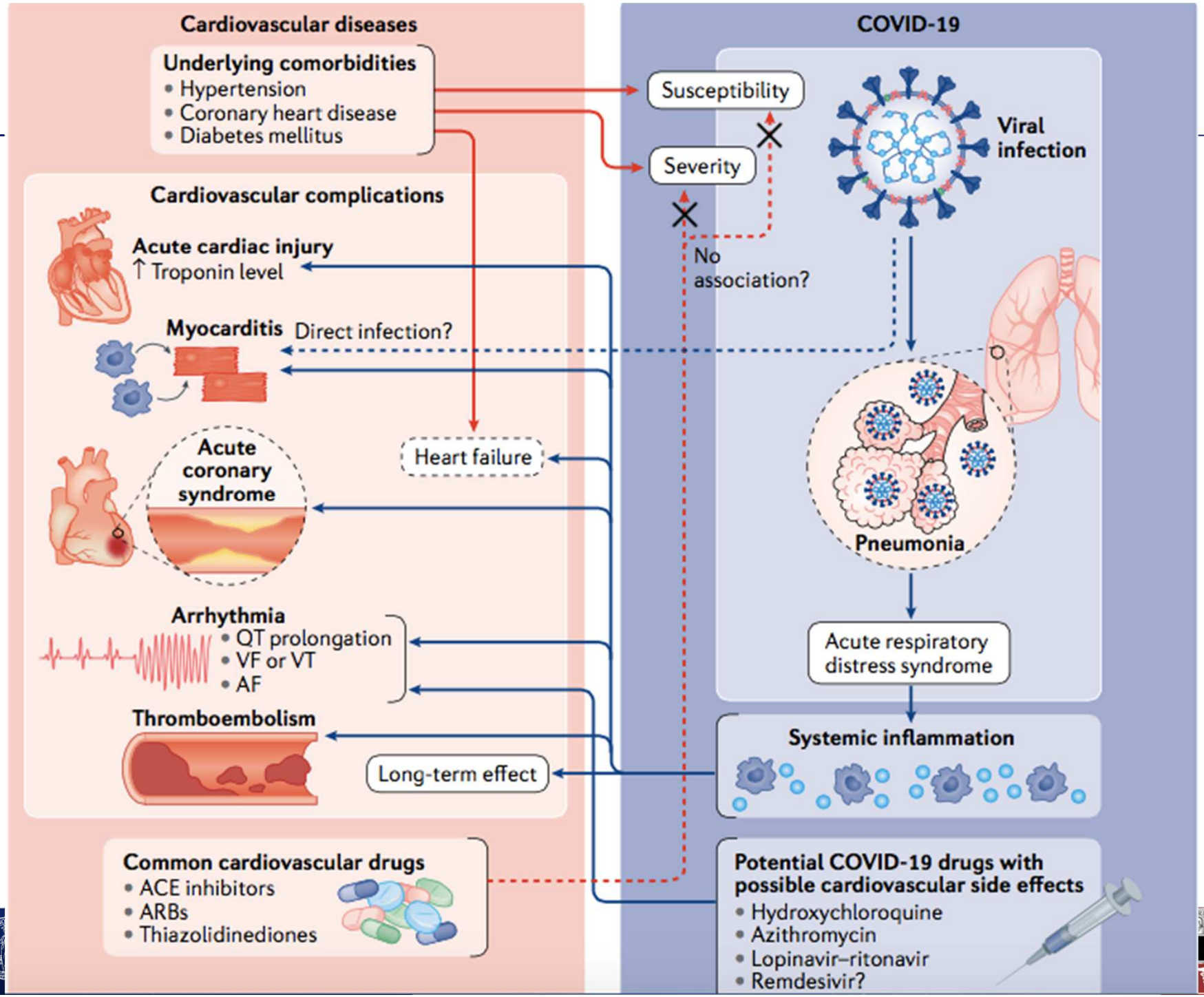
- Myocarditis and myocardial injury (type 1 and 2)
- Arrhythmia
- Acute coronary syndrome
- Acute cor pulmonale
- Cardiomyopathy
- Cardiogenic shock

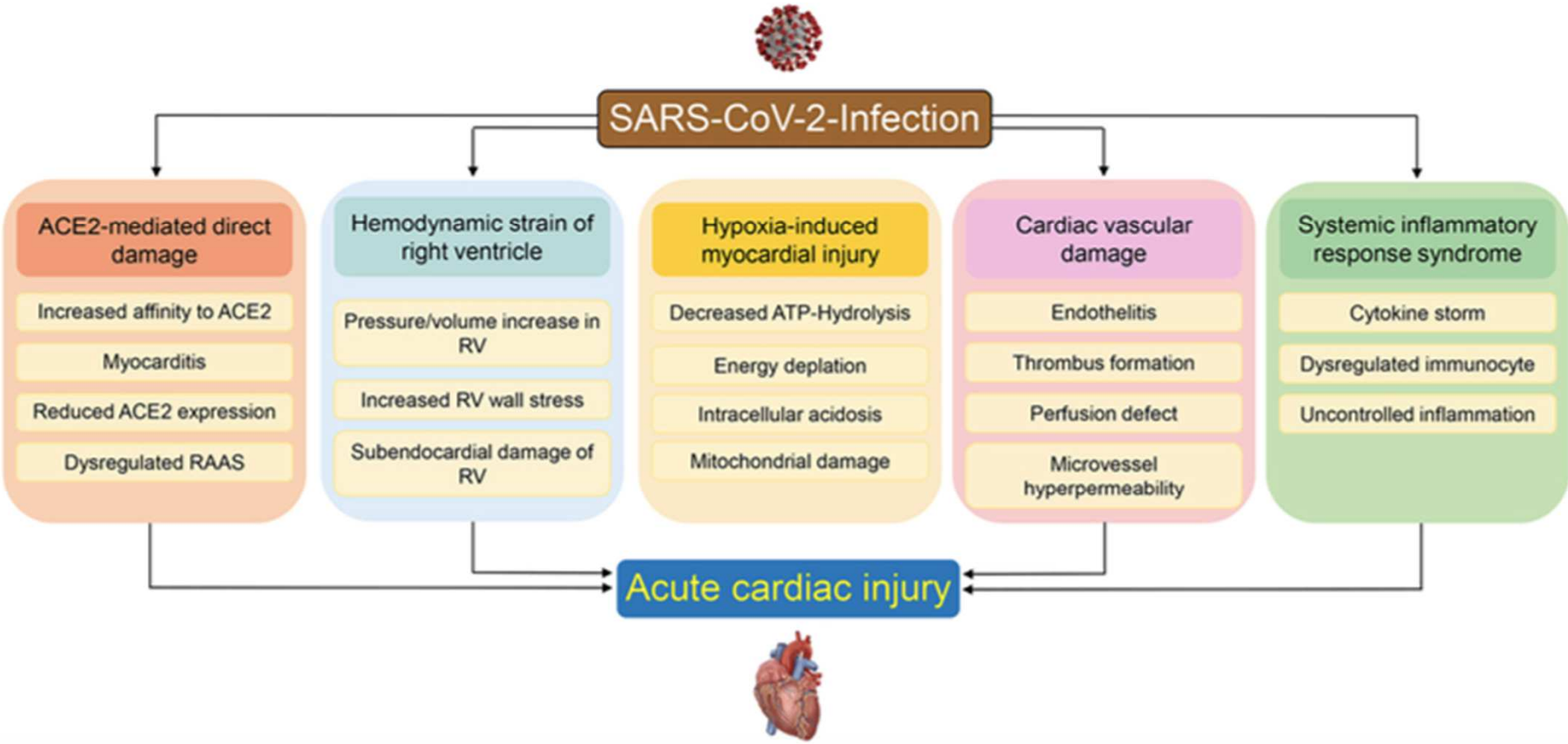
Laboratory markers:

- Elevated cardiac-specific troponin and brain natriuretic peptide
- Abnormal EKG (Prolonged QTc intervals, elevated ST)

Potential mechanism/pathophysiology:

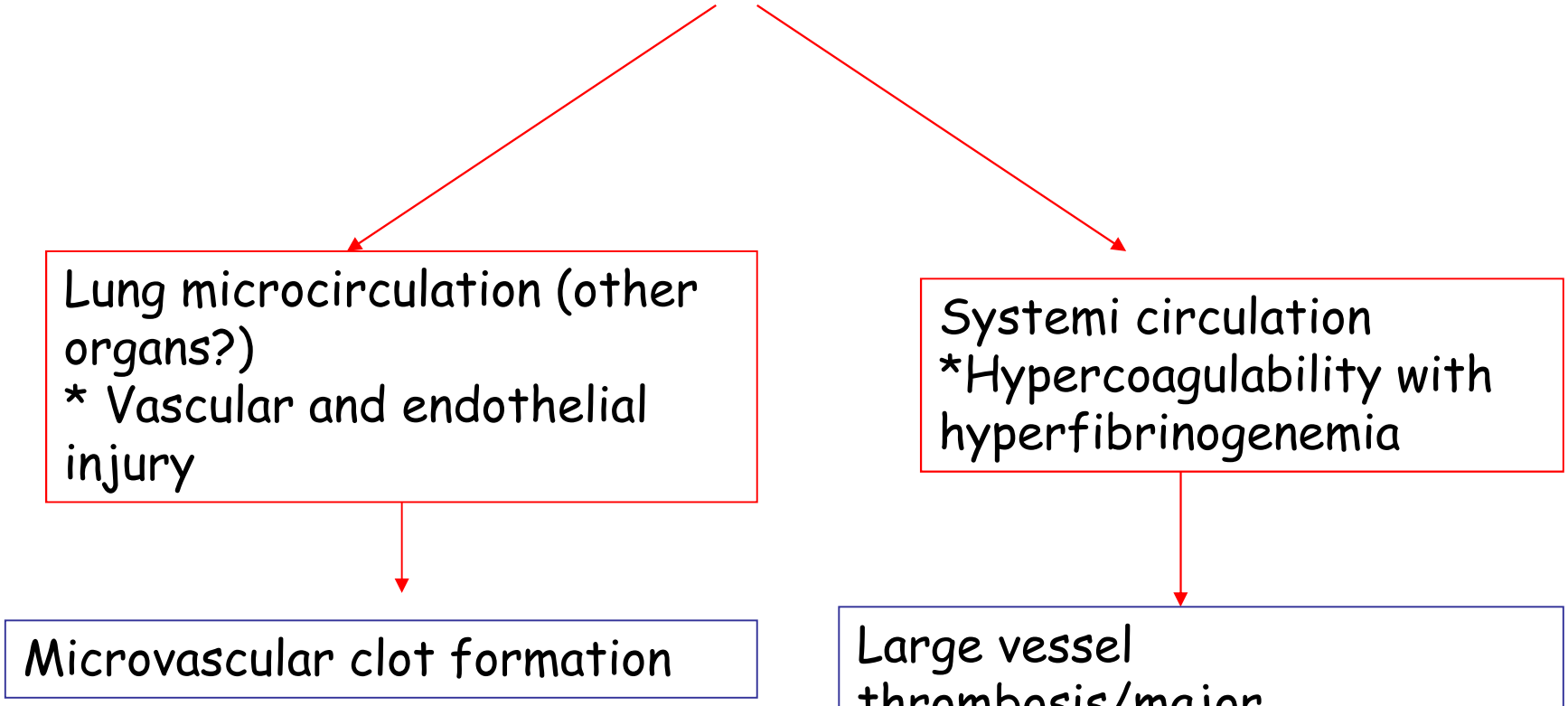
- ACE2 has high expression in cardiovascular tissues that support a direct viral injury
- Systemic inflammation


Cardiovascular diseases
Underlying comorbidities
• Hypertension
• Coronary heart disease
• Diabetes mellitus
Cardiovascular complications
Acute cardiac injury
↑ Troponin level
Myocarditis
Direct infection?
Acute coronary syndrome
Heart failure
Arrhythmia
• QT prolongation
• VF or VT
• AF
Thromboembolism
Long-term effect
Common cardiovascular drugs
• ACE inhibitors
• ARBs
• Thiazolidinediones
COVID-19
Susceptibility
Severity
No association?
Viral infection
Pneumonia
Acute respiratory distress syndrome
Systemic inflammation
Potential COVID-19 drugs with possible cardiovascular side effects
• Hydroxychloroquine
• Azithromycin
• Lopinavir–ritonavir
• Remdesivir?


SARS-CoV-2-Infection
ACE2-mediated direct damage
Increased affinity to ACE2
Myocarditis
Reduced ACE2 expression
Dysregulated RAAS
Hemodynamic strain of right ventricle
Pressure/volume increase in RV
Increased RV wall stress
Subendocardial damage of RV
Hypoxia-induced myocardial injury
Decreased ATP-Hydrolysis
Energy deplation
Intracellular acidosis
Mitochondrial damage
Cardiac vascular damage
Endothelitis
Thrombus formation
Perfusion defect
Microvessel hyperpermeability
Systemic inflammatory response syndrome
Cytokine storm
Dysregulated immunocyte
Uncontrolled inflammation
Acute cardiac injury

Coagulopathy of Coronavirus disease 2019

Two separate pathologic coagulation process



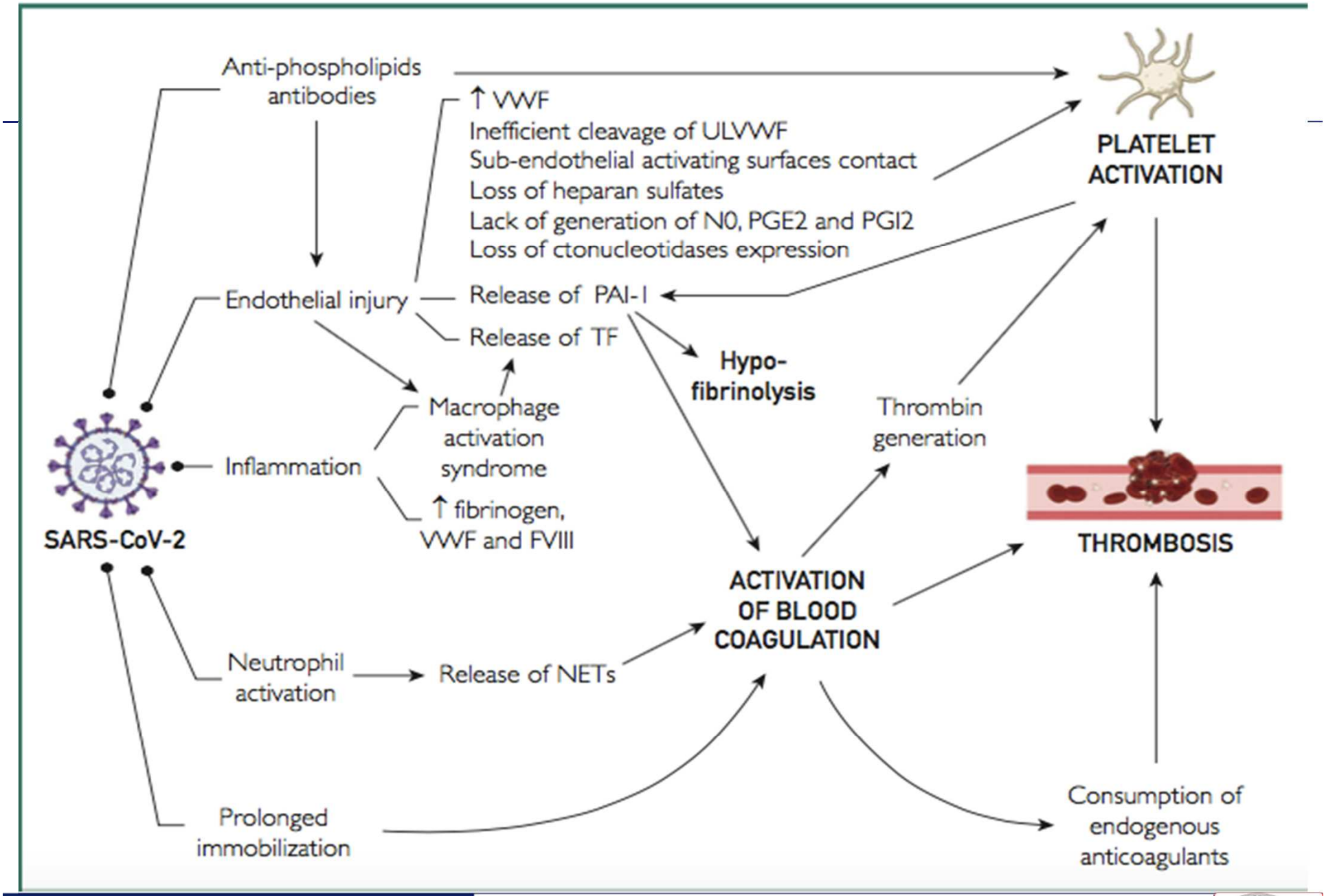
Coagulopathy of Coronavirus disease 2019

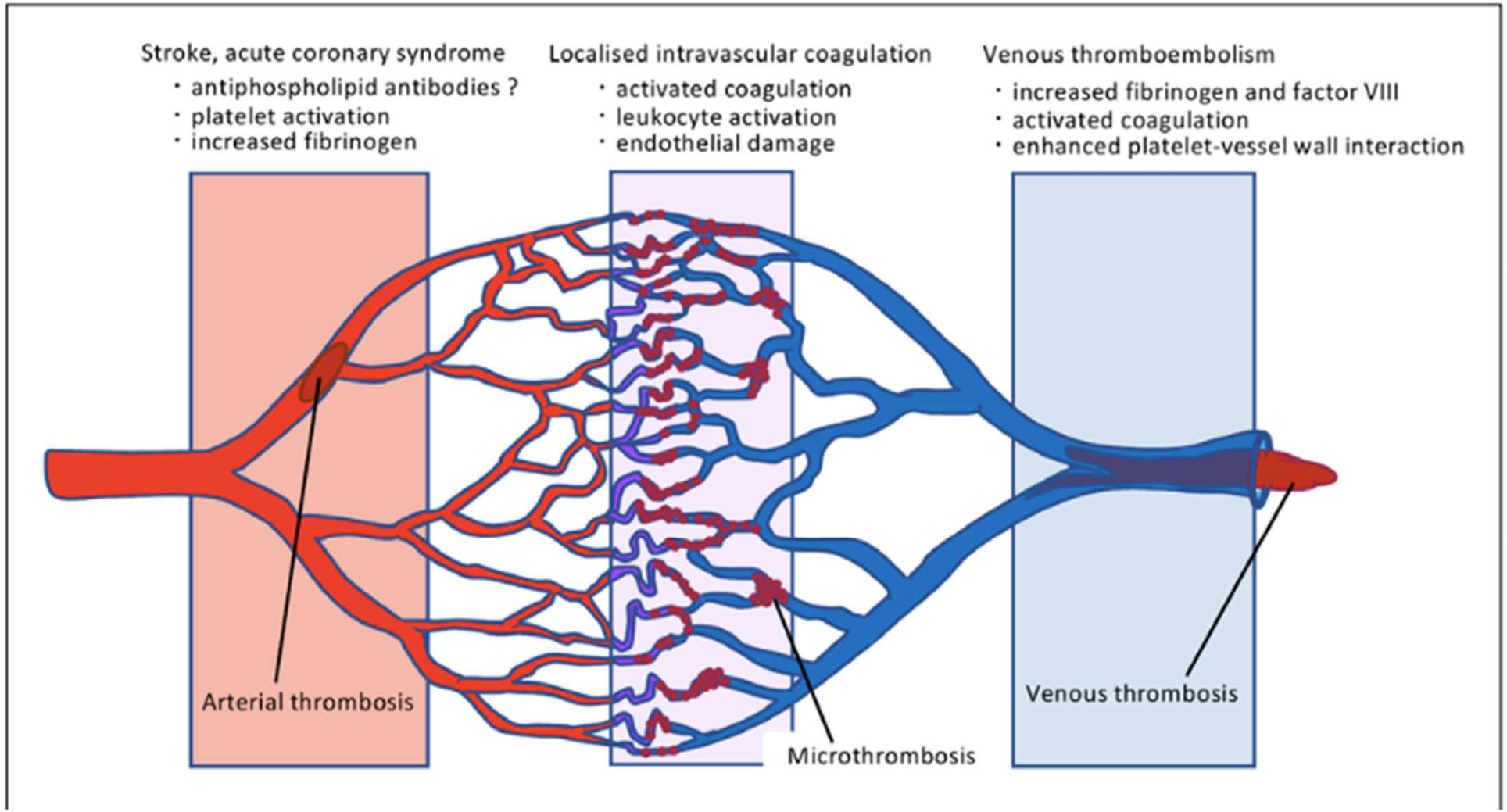
D-dimer increase (46,4%)

Levels > 2.0 mg/L predictive of mortality (Sen 92.3%; Spec 83.3%)

Platelets counts variable

Thrombocytopenia associated with > 5-fold risk of severe disease

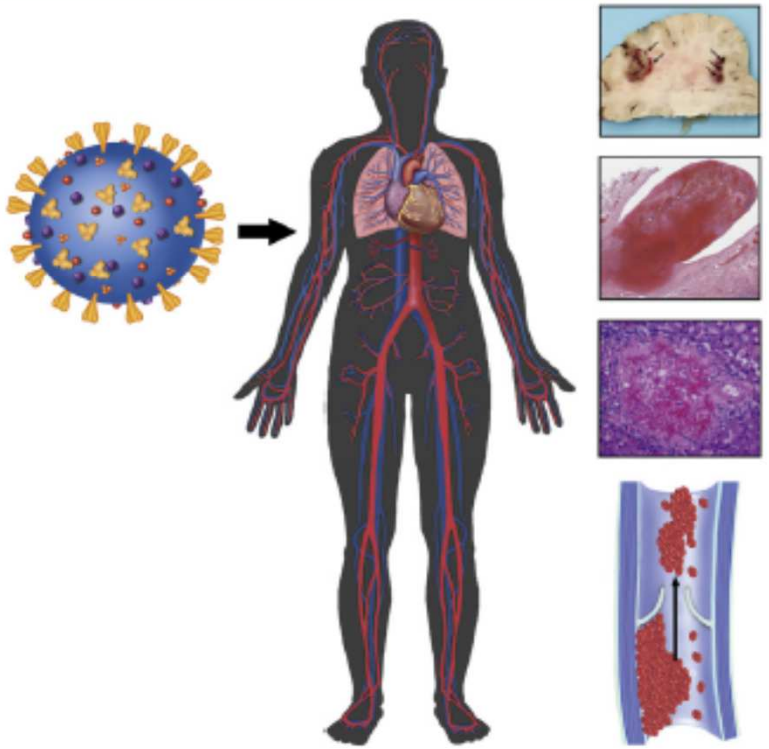

Anti-phospholipids antibodies
↑ VWF
Inefficient cleavage of ULVWF
Sub-endothelial activating surfaces contact
Loss of heparan sulfates
Lack of generation of N0, PGE2 and PGI2
Loss of ctonucleotidases expression
PLATELET ACTIVATION
Endothelial injury
Release of PAI-1
Release of TF
Hypo-fibrinolysis
Thrombin generation
Macrophage activation syndrome
Inflammation
↑ fibrinogen, VWF and FVIII
SARS-CoV-2
THROMBOSIS
ACTIVATION OF BLOOD COAGULATION
Neutrophil activation
Release of NETs
Prolonged immobilization
Consumption of endogenous anticoagulants

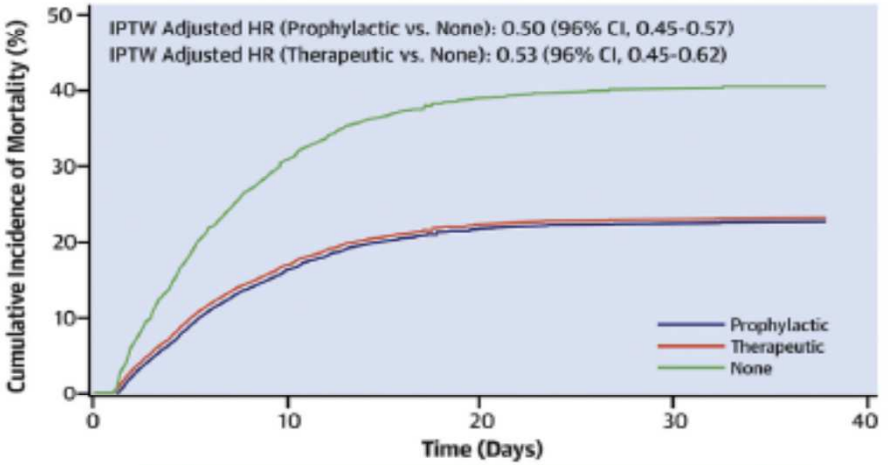

Stroke, acute coronary syndrome
· antiphospholipid antibodies ?
· platelet activation
· increased fibrinogen
Localised intravascular coagulation
· activated coagulation
· leukocyte activation
· endothelial damage
Venous thromboembolism
· increased fibrinogen and factor VIII
· activated coagulation
· enhanced platelet-vessel wall interaction
Arterial thrombosis
Microthrombosis
Venous thrombosis

Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19

CENTRAL ILLUSTRATION In-Hospital Anticoagulation and Outcomes in Coronavirus Disease-2019

Thrombosis in COVID-19





Anticoagulation Associated With Better Outcomes

⬇ Clinical Trial ⬇

Therapeutic vs. Prophylactic LMWH vs. DOAC?

Nadkarni, G.N. et al. J Am Coll Cardiol. 2020;76(16):1815-26.

The clinical spectrum of COVID-19-associated cutaneous manifestations: an Italian multicentre study of 200 adults

TABLE 1. Demographic data and clinical features of 200 patients with COVID-19-associated cutaneous manifestations

Median age at the time of the onset of COVID-19, years (IQR)		57 (40.25-72.25)
Males, n (%)		108 (54)
Females, n (%)		92 (46)
Median latency between cutaneous manifestations and systemic symptoms, days (IQR)*		14 (4-27)
Median duration of cutaneous manifestations, days (IQR)**		12 (8-20)
Cutaneous phenotypes	Urticarial rash, n (%)[§]	19 (10.2)
	Confluent erythematous/maculo-papular/morbilliform rash, n (%)[§]	48 (25.7)
	Papulovesicular exanthem, n (%)[§]	29 (15.5)
	Chilblain-like acral pattern, n (%)[§]	46 (24.6)
	Livedo reticularis-like/racemosa-like pattern, n (%)[§]	4 (2.1)
	Purpuric "vasculitic" pattern, n (%)[§]	13 (6.9)
	Other cutaneous phenotypes, n (%)[§]	28 (15)
	More than one phenotype, n (%)	13 (6.5)

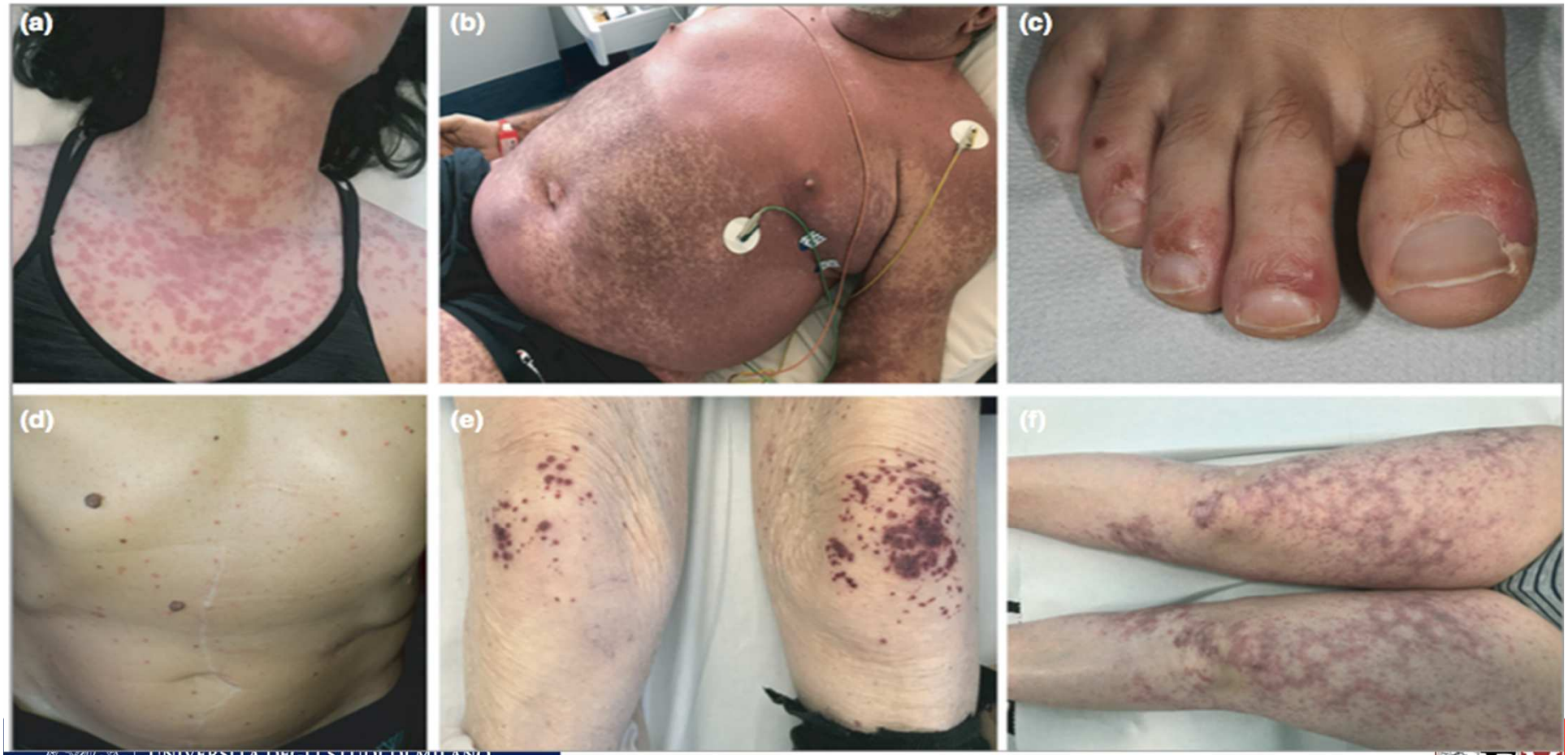
Marzano AV et al J Am Acad Dermatol 2021 Jan 18

REVIEW ARTICLE

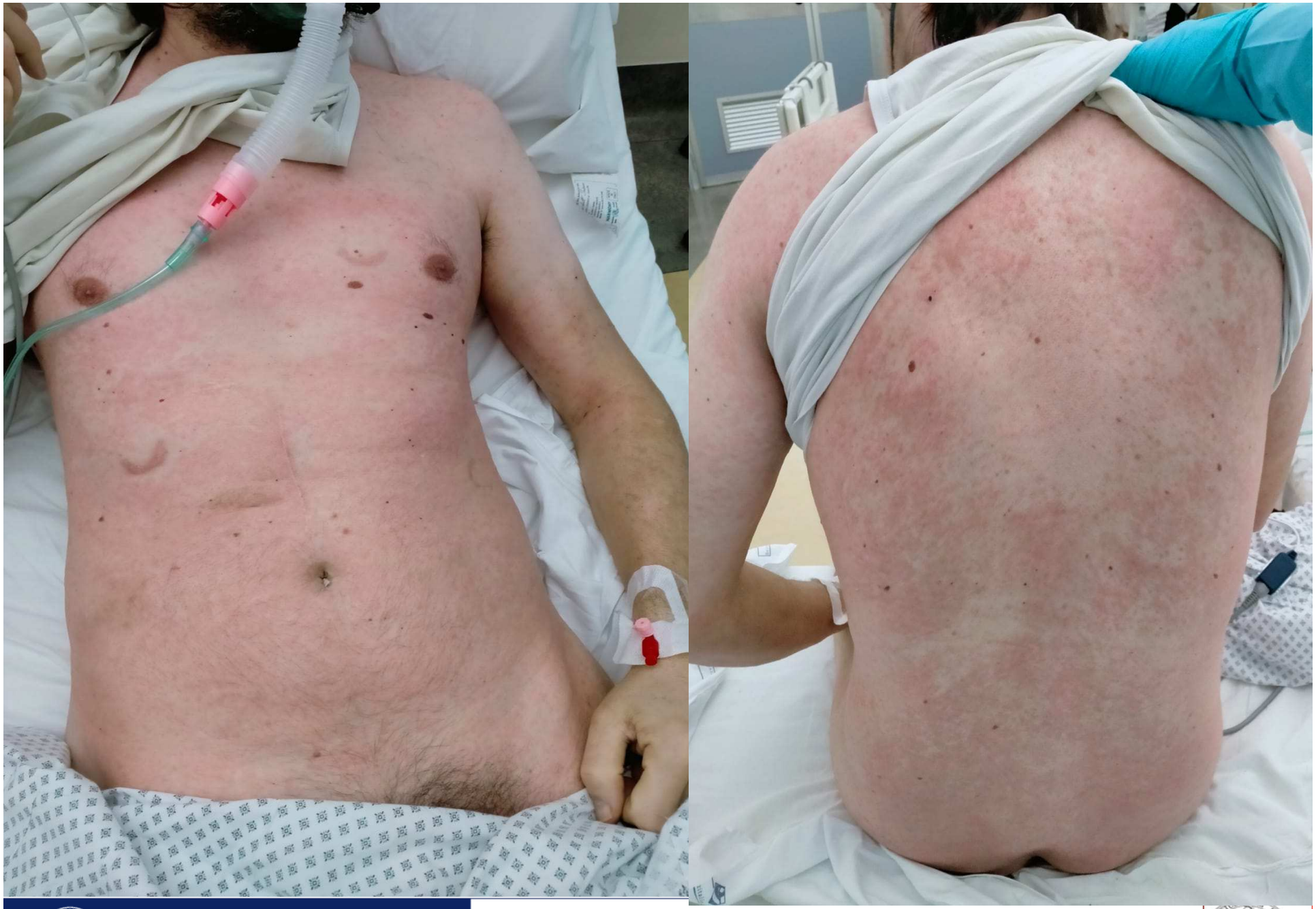
BJD
British Journal of Dermatology

Cutaneous manifestations in patients with COVID-19: a preliminary review of an emerging issue*

A.V. Marzano,[1,2] N. Cassano,[3] G. Genovese,[1,2] C. Moltrasio[1] and G.A. Vena[3]



BJD 2020; 183: 431-42



Courtesy Dr Mario Corbellino

Box 2: Renal involvement in COVID-19

Clinical Profile:

- Acute kidney injury
- Proteinuria
- Hematuria
- Electrolyte imbalances

Laboratory markers:

- Elevated urea, serum creatinine
- Elevated cystatin-C

Potential mechanism/pathophysiology:

- Direct viral injury
- Systemic inflammation
- Alterations in renal hemodynamics

Consideration:

- Assess the urine analysis to rule out the hematuria and proteinuria
- Assess and correct the electrolyte imbalance

Role of serum albumin and proteinuria in patients with SARS-CoV-2 pneumonia

Cinzia Bassoli[1] | Letizia Oreni[2] | Elisabetta Ballone[3] | Antonella Foschi[2] | Andrea Perotti[3] | Annalisa Mainini[2] | Giacomo Casalini[1] | Laura Galimberti[2] | Luca Meroni[2] | Spinello Antinori[1,2] | Laura Milazzo[2]

Results: Serum albumin levels <30 g/L were found in 105/207 (50.7%) patients at hospital admission. Overall, the median albumin value was 29.5 g/L (IQR 25-32.8). A negative association was found between albumin levels and severity of COVID-19 ($P < .0001$) and death ($P = .003$). An inverse correlation was observed between albumin and both C-reactive protein and D-dimer at hospital admission ($r = -.487$ and $r = -.479$, respectively; $P < .0001$). Finally, a positive correlation was found between albumin levels and eGFR ($r = .137$; $P = .049$). Proteinuria was observed in 75% of patients with available data and it did not differ between patients with hypoalbuminemia and those with albumin ≥30 g/L (81% and 67%, respectively; $P = .09$).

Int J Clin Pract. 2020;00:e13946.

Neurological infection with SARS-CoV-2 — the story so far

Tom Solomon

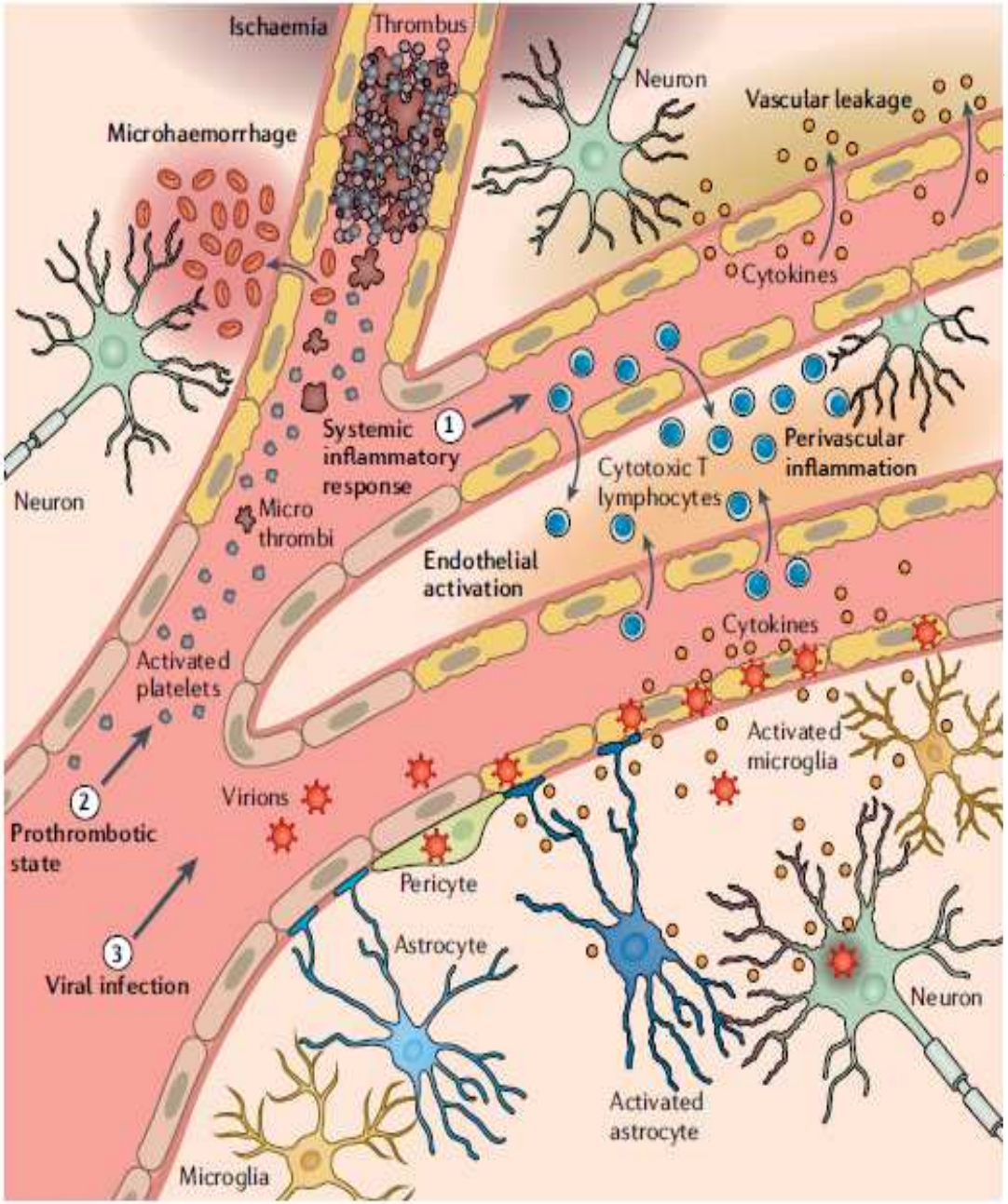


Fig. 1 | **Current understanding of predominant COVID-19 neurological disease mechanisms.** Mechanisms include a systemic inflammatory response (1), a prothrombotic state (2) and direct viral invasion (3).

Key advances

- Anosmia, encephalopathy and stroke are the most common neurological syndromes associated with SARS-CoV-2 infection[1], though many others have been reported.
- Analysis of human biopsy samples suggests that anosmia results predominantly from SARS-CoV-2 infection of non-neuronal cells in the olfactory epithelium and olfactory bulb[2], leading to local inflammation and neuronal malfunction.
- A high proportion of patients admitted to intensive care units with COVID-19 develop delirium, and evidence suggests that this is caused by microvascular and inflammatory mechanisms[3].
- Autopsy data show activation of astrocytes and microglia in COVID-19, particularly in the brainstem, where there is also infiltration of cytotoxic T cells[7,9].
- SARS-CoV-2 can be detected in the brain with PCR and immunohistochemistry, but the evidence to date suggests it is mostly in vascular and immune cells rather than directly infecting neurons[7,9].

JAMA Neurology | Review

Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019
A Review

Adeel S. Zubair, MD; Lindsay S. McAlpine, MD; Tova Gardin, MD, MPP; Shelli Farhadian, MD, PhD; Deena E. Kuruvilla, MD; Serena Spudich, MD

Figure 2. Transsynaptic Viral Spread

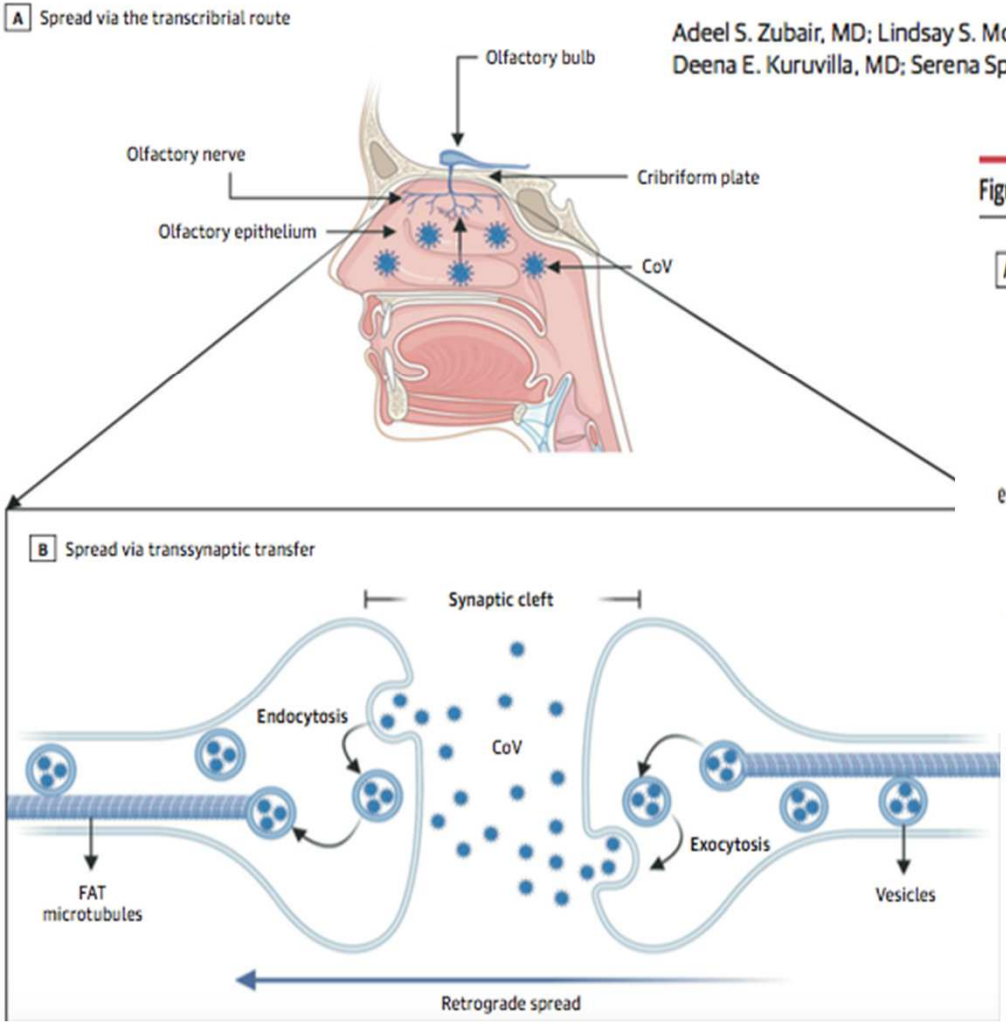


Figure 3. Mechanisms of Spread Across the Blood-Brain Barrier

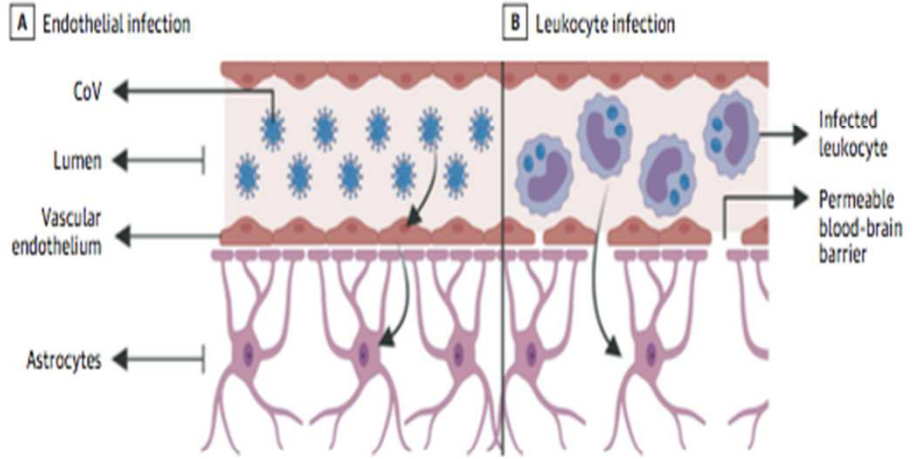
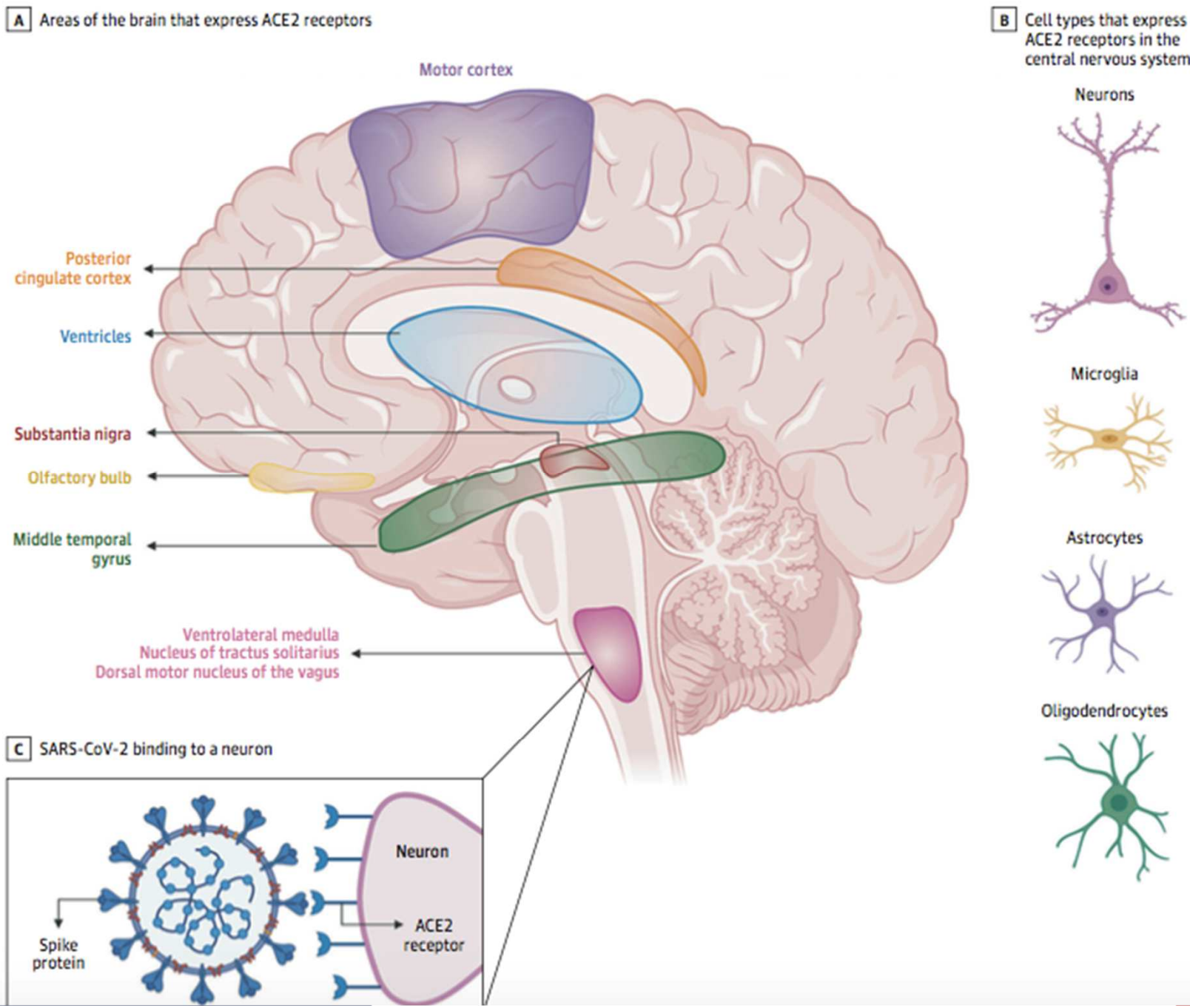


Figure 1. Angiotensin-Converting Enzyme 2 (ACE2) Expression in the Brain



Neurological associations of COVID-19

Mark A Ellul, Laura Benjamin, Bhagteshwar Singh, Suzannah Lant, Benedict Daniel Michael, Ava Easton, Rachel Kneen, Sylviane Defres, Jim Sejvar, Tom Solomon

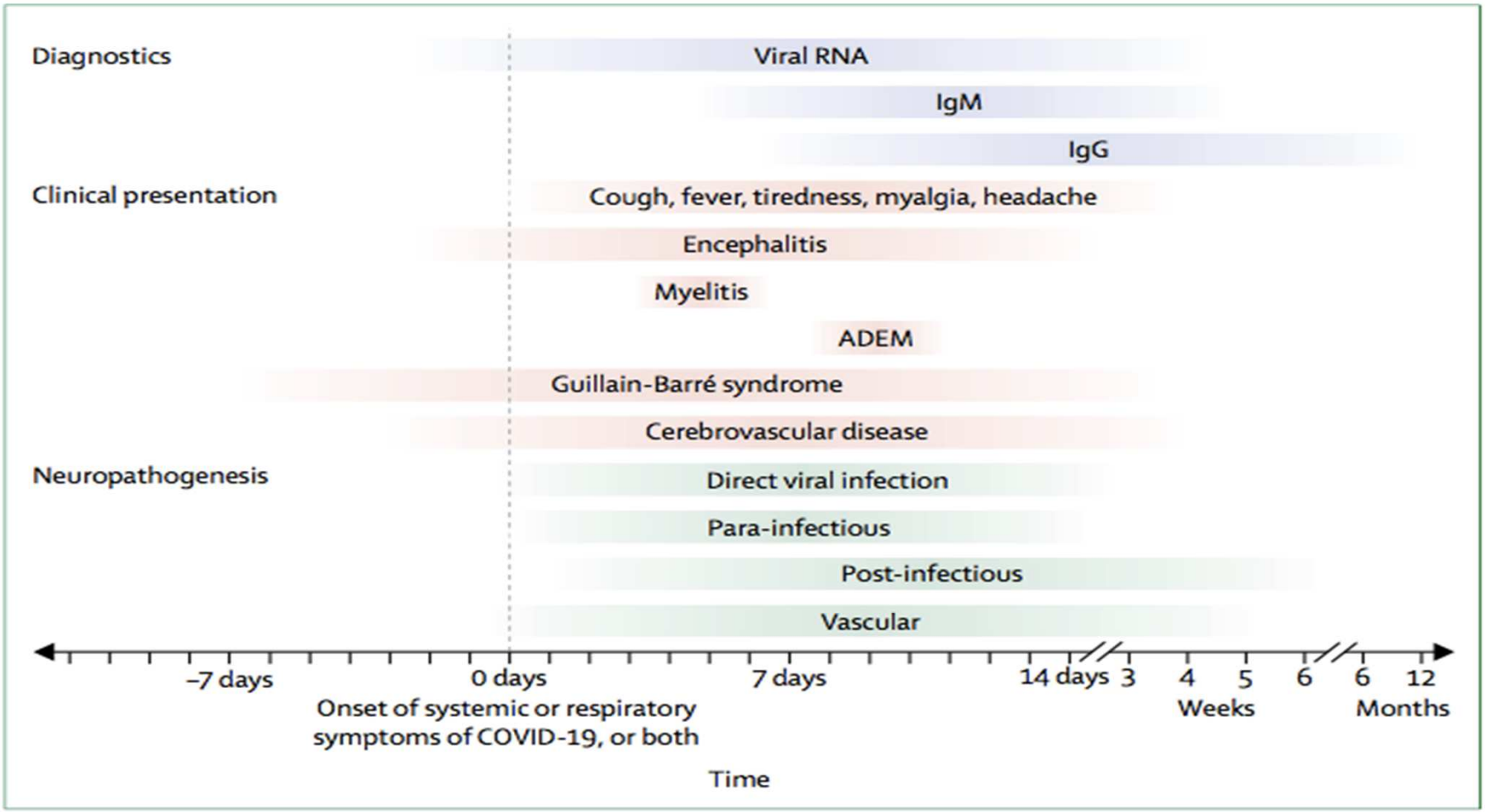


Figure 1: **Approximate timeline for positive diagnostic tests, clinical presentation, and pathogenesis in COVID-19-associated neurological disease**

Neurological manifestations associated with SARS-CoV-2 and other coronaviruses: A narrative review for clinicians

Table 1 – Prevalence and characteristics of neurological manifestations in COVID-19 patients: data from eight cohort studies.

Authors	Mao et al.	Romero-Sanchez et al.	Mahammedi et al.	Guilmot et al.	Agarwal et al.	Varatharaj et al.	Kremer et al.	Paterson et al.	Meppiel et al.
Setting	China, 3 centers	Spain, 2 centers	Italy, 3 centers	Belgium, 3 centers	USA, 1 center	UK-wide surveillance study	France, 11 centers	UK, 1 center	France, 46 centers
COVID-19 patients, total *n* (%)	214 (100)	841 (100)	725 (100)	349 (100)	404 (100)	–	–	–	–
COVID-19 patients with neurological symptoms, *n* (%)	78 (36.4)	483 (57.4)	108 (14.9)	15 (4.3)	295 (73.0)	153	64	43	222
Headache	28 (13.1)	119 (14.1)	13 (1.8)	–	82 (20.3)	–	10	–	24
Dizziness	36 (16.8)	51 (6.1)	4 (0.6)	–	31 (7.7)	–	–	–	5
Altered mental status and/or impaired consciousness	16 (7.5)	165 (19.6)	64 (8.8)	7 (1.5)	86 (21.3)	39	34	–	117
Ataxia	1 (0.5)	–	2 (0.3)	–	20 (5.0)	–	–	–	–
Seizure	1 (0.5)	6 (0.7)	1 (0.1)	2 (0.6)	2 (0.5)	-	2	1	21
Anosmia	12 (5.6)	41 (4.9)	2 (0.3)	2 (0.6)	18 (4.5)	1	1	-	7
Nerve pain	5 (2.3)	–	3 (0.4)	–		–	–	–	–
Dysautonomia	–	21 (2.5)	–	–	1 (0.2)	–	–	–	–
Neuropsychiatric	–	167 (19.8)	–	3 (0.9)		–	–	–	–
Myalgia	23 (10.7)	145 (17.2)	13 (1.8)	–	131 (32.4)	23	–	–	–
Neurological									

Maury A, et al. Rev Neurol 2020, Dec 16

Neurological manifestations associated with SARS-CoV-2 and other coronaviruses: A narrative review for clinicians

Table 1 – Prevalence and characteristics of neurological manifestations in COVID-19 patients: data from eight cohort studies.

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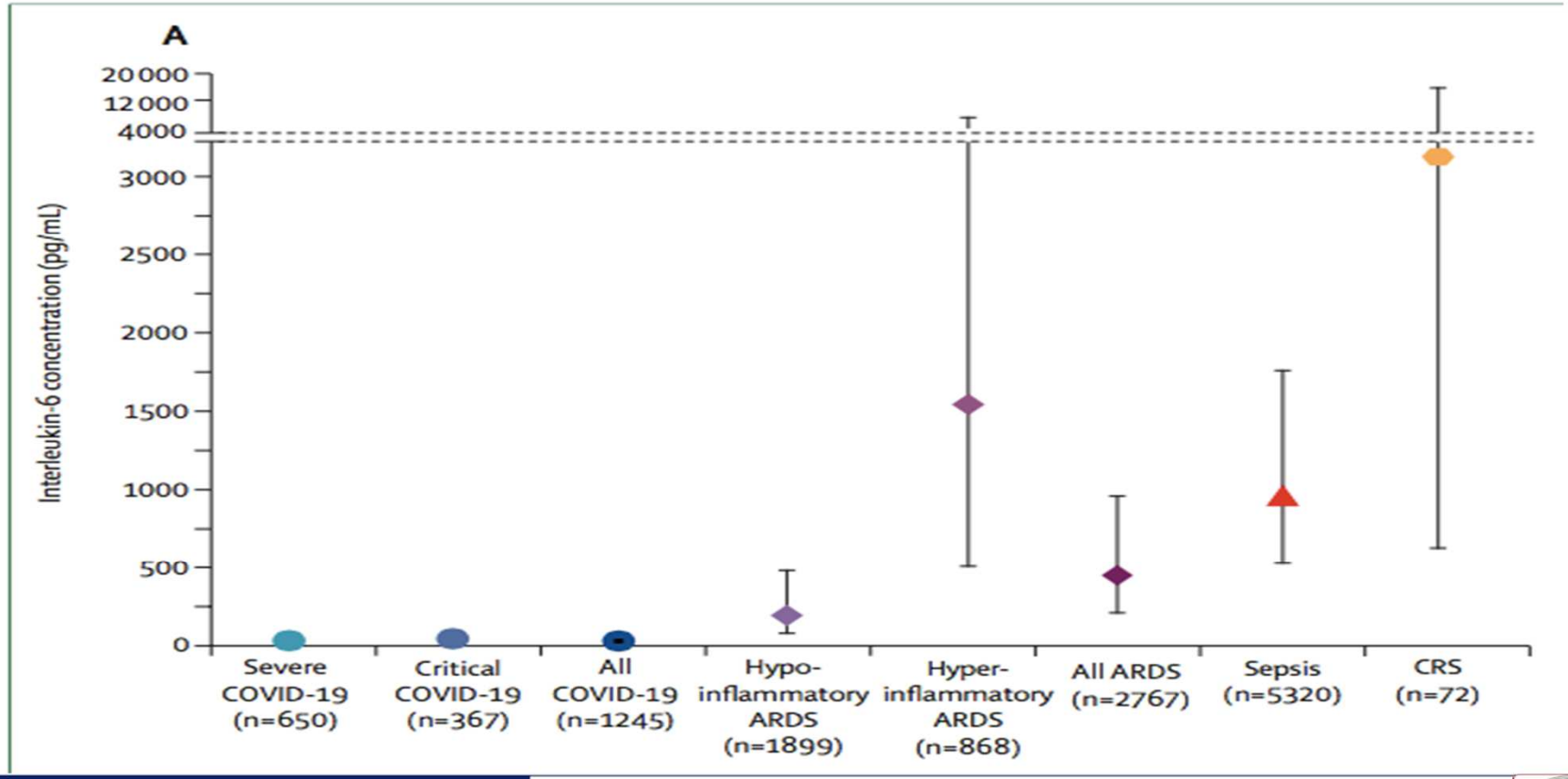
Neurological manifestations, *n* (%)									
Acute cerebrovascular disease	6 (2.8)	14 (1.7)	42 (5.8)	3 (0.9)	3 (0.7)	77	–	–	57
Ischemic stroke	–	11 (1.3)	34 (4.7)	2 (0.6)	2 (0.5)	57	17	8	52
Hemorrhagic stroke	–	–	6 (0.8)	1 (0.3)	1 (0.3)	9	–	–	5
Cerebral Venous Thrombosis	–	–	2 (0.3)	0	0	2	–	–	1
Posterior reversible encephalopathy	–	1 (0.1)	1 (0.1)	0	0	–	–	–	0
Encephalopathy/ encephalitis	–	1 (0.1)	4 (0.6)[a]	10 (2.9)[c]	86 (21.3)	16	19[e]	21[f]	88[g]
Myelitis	–	–	–	–	–	–	–	–	0
Guillain–Barré syndrome and variants	–	1 (0.1)	3 (0.4)[b]	1 (0.3)[d]	0	4	–	7	15[h]
Isolated oculomotor neuropathy	–	–	–	1 (0.3)	0	–	–	1	2

Maury A, et al. Rev Neurol 2020, Dec 16

Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes

Daniel E Leisman, Lukas Ronner*, Rachel Pinotti, Matthew D Taylor, Pratik Sinha, Carolyn S Calfee, Alexandre V Hirayama, Fiore Mastroiani, Cameron J Turtle, Michael O Harhay, Matthieu Legrand, Clifford S Deutschman*



Lancet Respir Med 2020; 8:1233-44

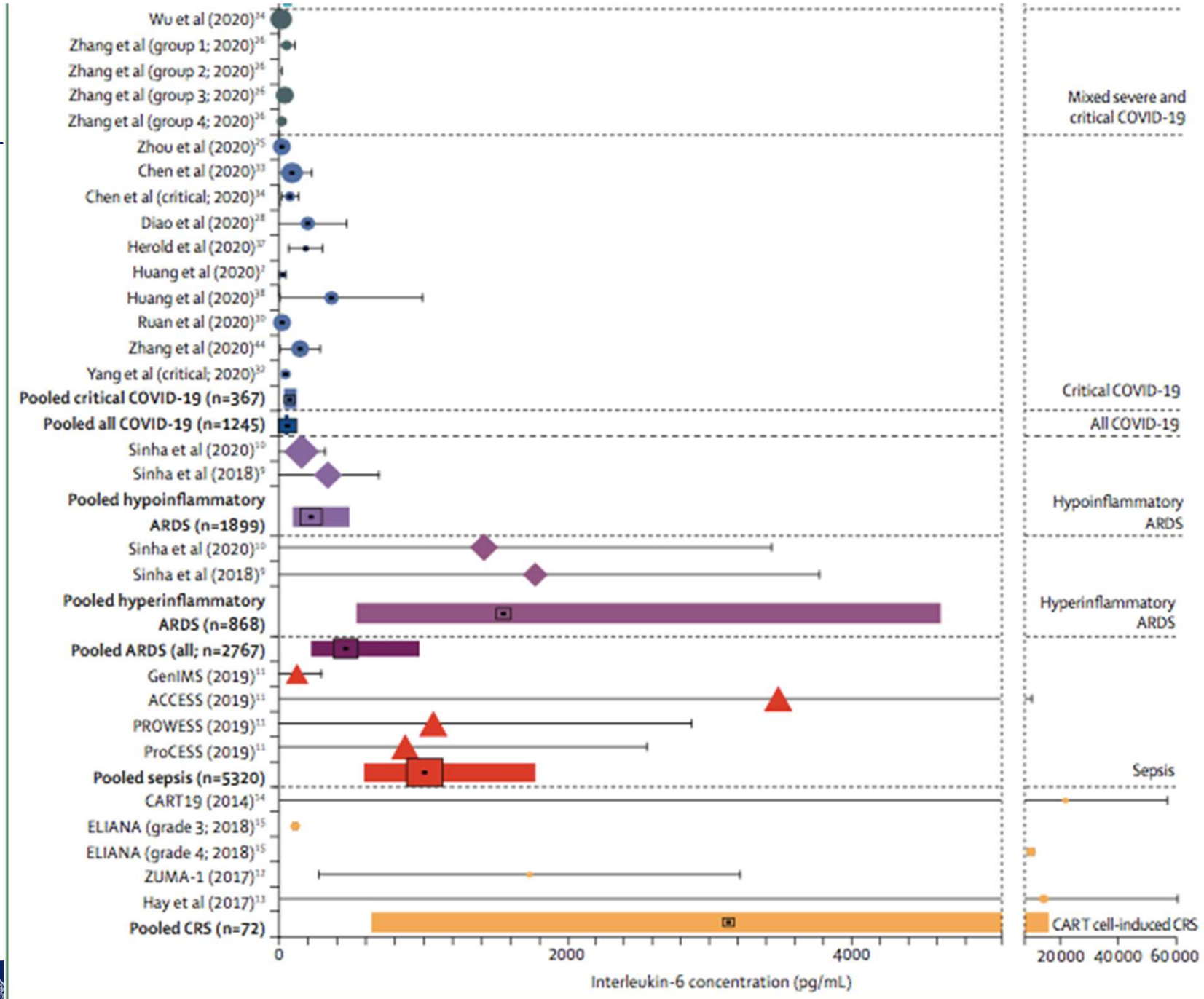
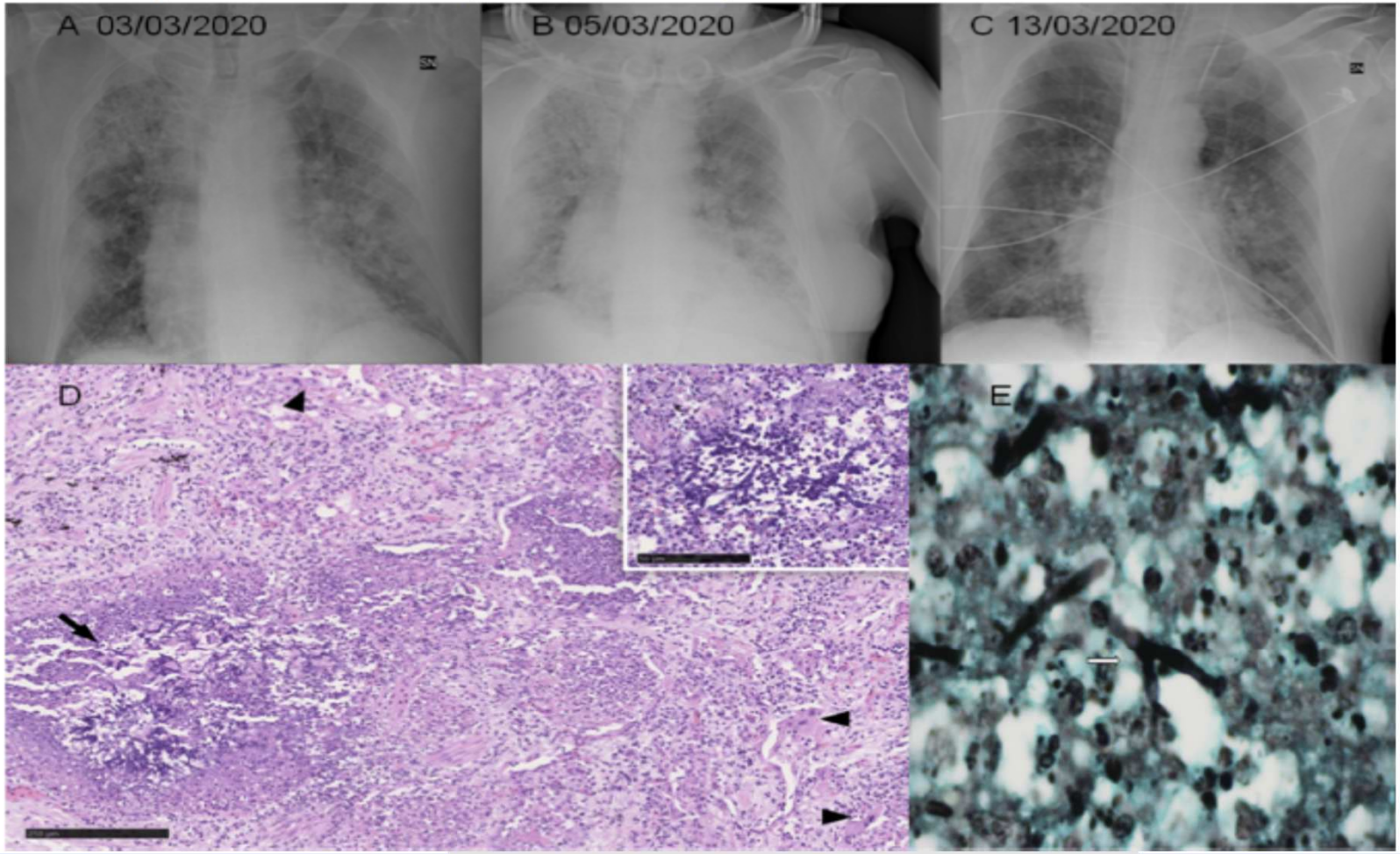


Figure 2: **Interleukin-6 concentrations in patients with COVID-19 versus comparison disorders**

Invasive pulmonary aspergillosis complicating SARS-CoV-2 pneumonia: A diagnostic challenge

Spinello Antinori[a,b,*], Roberto Rech[c], Laura Galimberti[b], Antonio Castelli[c], Elena Angeli[b], Tommaso Fossali[c], Davide Bernasconi[b], Alice Covizzi[a,b], Cecilia Bonazzetti[a,b], Alessandro Torre[b], Luca Carsana[d], Cristina Tonello[d], Pietro Zerbi[a,d], Manuela Nebuloni[a,d]



UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA
Travel Medicine and Infectious Disease
2020;38:101752

EMERGING
INFECTIOUS DISEASES®

COVID-19 associated pulmonary aspergillosis: An analysis of epidemiological and clinical characteristics of 186 international cases from FungiScope® Registry and the literature

Table 1. Characteristics of 186 patients with CAPA.

	n	%
Pathogens *		
A. fumigatus	122	66.0
A. niger	13	7.0
A. flavus	10	5.4
A. terreus	6	3.2
Mortality	97	52.2
Within 6 weeks	89	47.8
Within 12 weeks	93	50.0

CAPA consensus definition (*27*)		
Proven	7	3.8
Probable	82	44.1
Possible	19	10.2
Not classifiable ‡	78	41.9

EMERGING INFECTIOUS DISEASES®

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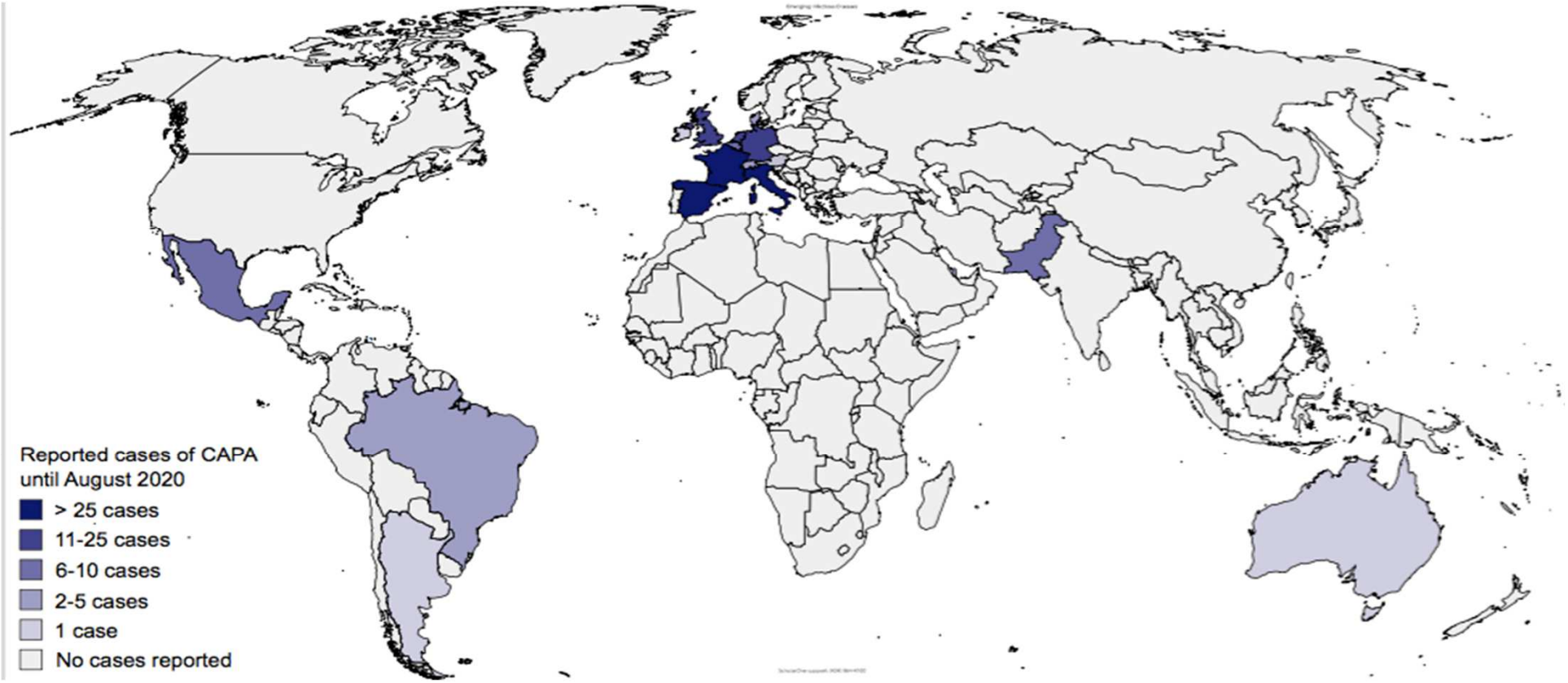


Salmanton-Garcia J et al. FungiScope
ECMM/ISHAM Working Group

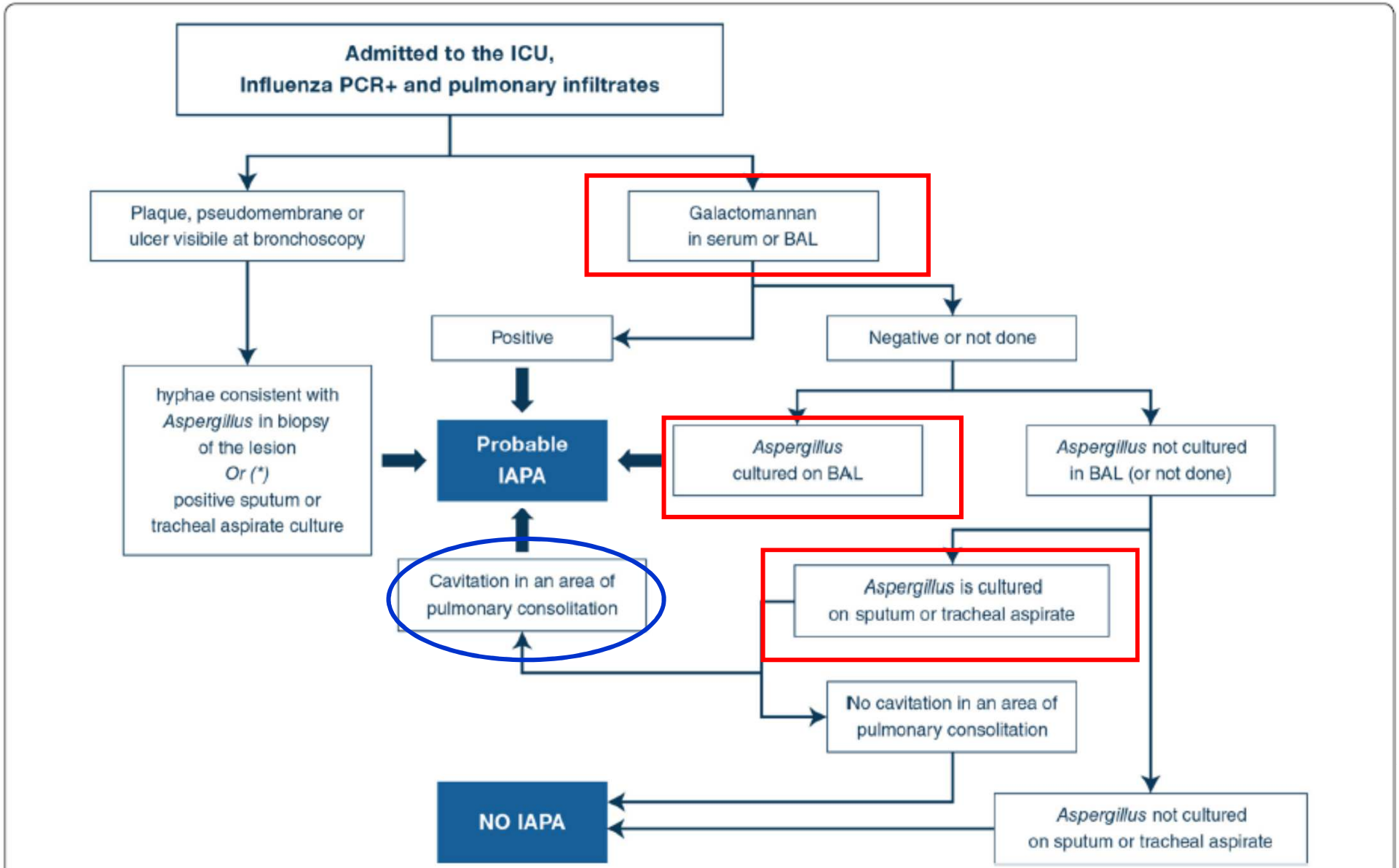


Fig. 1 Flowchart of probable IAPA classification. (*)If hyphae consistent with *Aspergillus* are documented in a biopsy of an airway lesion AND *Aspergillus* is grown from sputum or a tracheal aspirate, the case fulfills the definition of proven IAPA

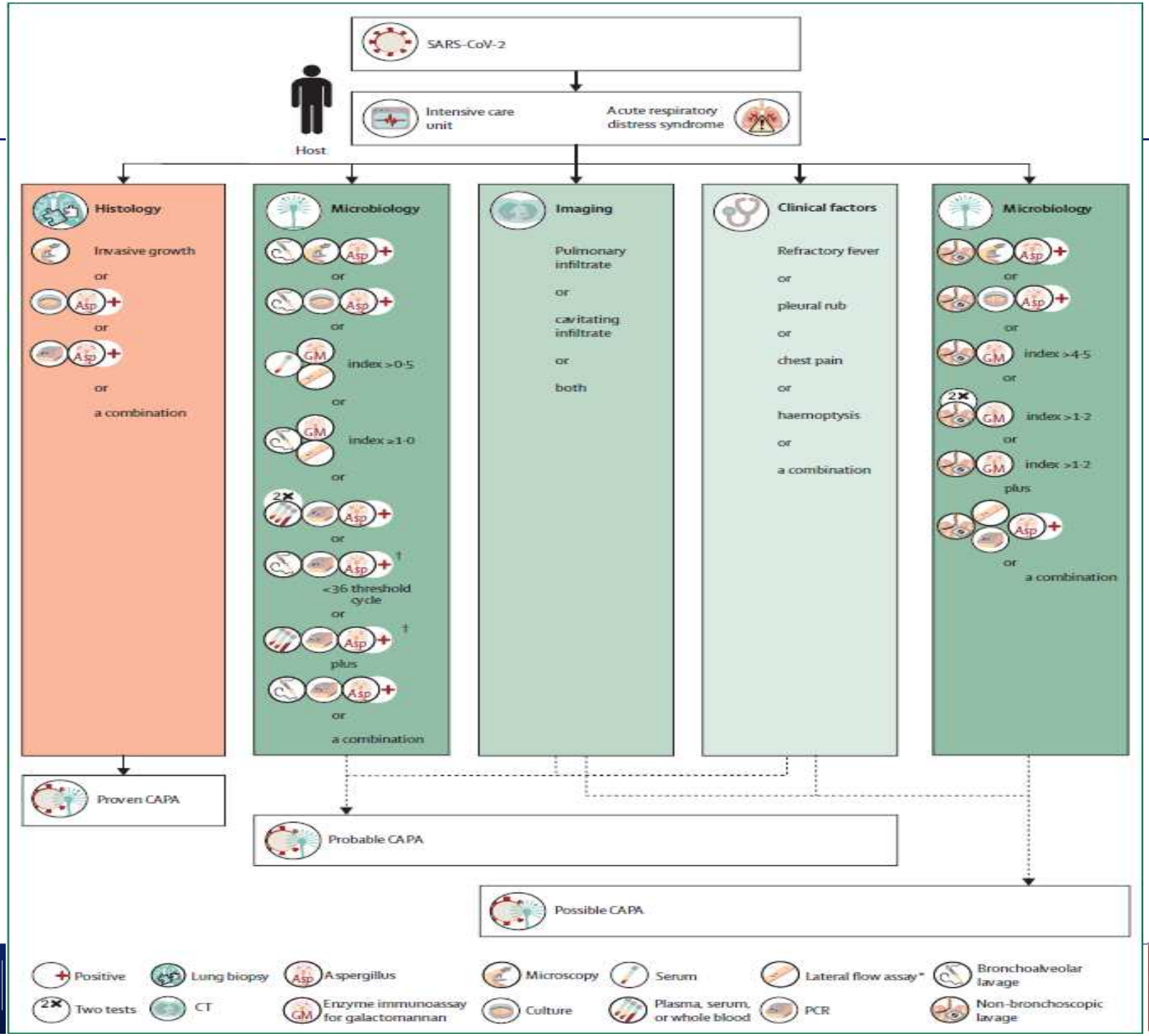
Verweij P, et al Intensive Car Med 2020;46:1524-1535

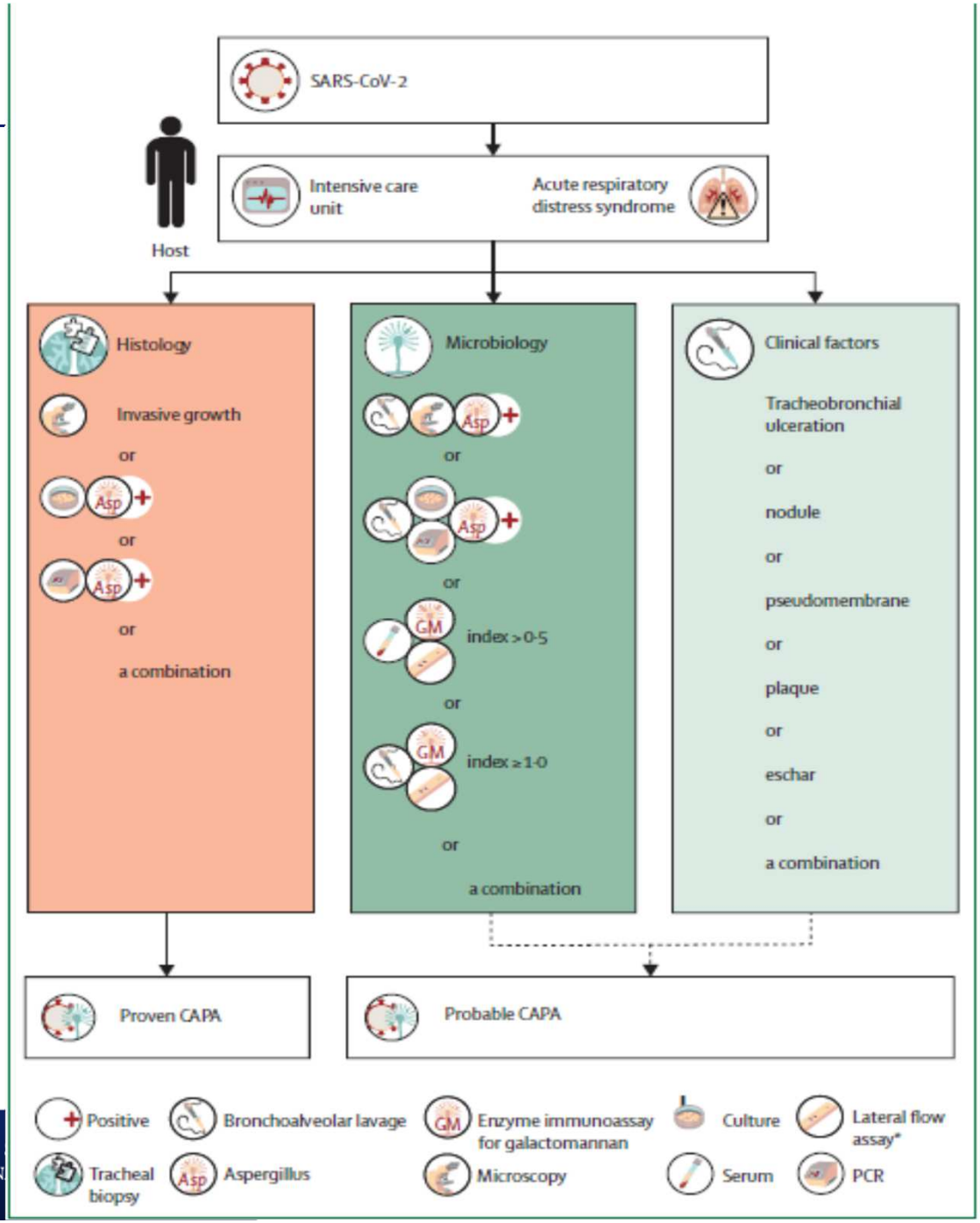
Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance

	Host factors	Clinical factors	Mycological evidence	Comments
(Continued from previous page)				
Proposed case definition for CAPA (adapted from EORTC and MSGERC[3], AspICU[6], and expert case definitions of IAPA[48])				
Tracheobronchitis or other pulmonary form (proven)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	--	At least one of the following: histopathological or direct microscopic detection of fungal hyphae, showing invasive growth with associated tissue damage; or aspergillus recovered by culture or microscopy or histology or PCR obtained by a sterile aspiration or biopsy from a pulmonary site, showing an infectious disease process	--
Tracheobronchitis (probable)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Tracheobronchitis, indicated by tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis	At least one of the following: microscopic detection of fungal elements in bronchoalveolar lavage, indicating a mould; positive bronchoalveolar lavage culture or PCR;† serum galactomannan index >0·5 or serum LFA index >0·5;‡ or bronchoalveolar lavage galactomannan index ≥1·0 or bronchoalveolar lavage LFA index ≥1·0‡	--
Other pulmonary forms (probable)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Pulmonary infiltrate, preferably documented by chest CT, or cavitating infiltrate (not attributed to another cause)	At least one of the following: microscopic detection of fungal elements in bronchoalveolar lavage, indicating a mould; positive bronchoalveolar lavage culture;† serum galactomannan index >0·5 or serum LFA index >0·5;‡ bronchoalveolar lavage galactomannan index ≥1·0 or bronchoalveolar lavage LFA index ≥1·0;‡ two or more positive aspergillus PCR tests in plasma, serum, or whole blood;† a single positive aspergillus PCR in bronchoalveolar lavage fluid (<36 cycles);† or a single positive aspergillus PCR in plasma, serum, or whole blood, and a single positive in bronchoalveolar lavage fluid (any threshold cycle permitted)†	--
Other pulmonary forms (possible)[12]§	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Pulmonary infiltrate, preferably documented by chest CT, or cavitating infiltrate (not attributed to another cause)	At least one of the following: microscopic detection of fungal elements in non-bronchoscopic lavage indicating a mould; positive non-bronchoscopic lavage culture;† single non-bronchoscopic lavage galactomannan index >4·5; non-bronchoscopic lavage galactomannan index >1·2 twice or more; or non-bronchoscopic lavage galactomannan index >1·2 plus another non-bronchoscopic lavage mycology test positive (non-bronchoscopic lavage PCR or LFA)	--

CAPA=COVID-19-associated invasive pulmonary aspergillosis. EORTC= European Organisation for Research and Treatment of Cancer. IAPA=influenza-associated pulmonary aspergillosis. ICU=intensive care unit. IPA=invasive pulmonary aspergillosis. LFA=lateral flow assay. MSGERC=Mycoses Study Group Education and Research Consortium. *Only one of these criteria required for diagnosis. †In case of patients with chronic obstructive pulmonary disease or chronic respiratory disease, the PCR or culture results should be confirmed by galactomannan testing to rule out colonisation or chronic aspergillosis. Galactomannan index should be available; galactomannan-index threshold applies to both enzyme immunoassay and LFA. ‡Visual reader should be used for a primary result and confirmatory galactomannan testing should be sought. §Classification of possible CAPA will most likely be sufficient to initiate antifungal therapy in the clinic but, in line with other consensus statements, it is not recommended for enrolling patients into clinical trials. Possible CAPA could serve as a secondary endpoint in a randomised prophylaxis study. Additional studies are needed to support the specificity of non-bronchoscopic lavage testing. Non-bronchoscopic lavage is considered a blind application of 10–20 mL saline recovered by aspiration via the closed suction system in an intubated patient. Bronchoalveolar lavage and non-bronchoscopic lavage are currently not considered equal for diagnosing CAPA.

Table 2: **Comparison of case definitions for patients with possible, probable, putative, or proven IPA by algorithm or group**


SARS-CoV-2
Host
Intensive care unit
Acute respiratory distress syndrome
Histology
Invasive growth
or
Asp +
or
Asp +
or
a combination
Microbiology
Asp +
or
Asp +
or
GM
index >0·5
or
GM
index >1·0
or
2×
Asp +
or
Asp +
†
<36 threshold cycle
or
Asp +
†
plus
Asp +
or
a combination
Imaging
Pulmonary infiltrate
or
cavitating infiltrate
or
both
Clinical factors
Refractory fever
or
pleural rub
or
chest pain
or
haemoptysis
or
a combination
Microbiology
Asp +
or
Asp +
or
GM
index >4·5
or
2×
GM
index >1·2
or
GM
index >1·2
plus
Asp +
or
a combination
Proven CAPA
Probable CAPA
Possible CAPA
Positive
Two tests
Lung biopsy
CT
Aspergillus
Enzyme immunoassay for galactomannan
Microscopy
Culture
Serum
Plasma, serum, or whole blood
Lateral flow assay*
PCR
Bronchoalveolar lavage
Non-bronchoscopic lavage


SARS-CoV-2
Host
Intensive care unit
Acute respiratory distress syndrome
Histology
Invasive growth
or
Asp
or
Asp
or
a combination
Microbiology
Asp
or
Asp
or
GM
index >0·5
or
GM
index ≥1·0
or
a combination
Clinical factors
Tracheobronchial ulceration
or
nodule
or
pseudomembrane
or
plaque
or
eschar
or
a combination
Proven CAPA
Probable CAPA
Positive
Bronchoalveolar lavage
GM
Enzyme immunoassay for galactomannan
Culture
Lateral flow assay*
Tracheal biopsy
Asp
Aspergillus
Microscopy
Serum
PCR

Edward Hopper: distanziamento sociale

Figure 7. Foreshadowing the Social Distancing of COVID-19
Edward Hopper. *Car Chair*. 1965. Oil on canvas. 40 × 50 in. © 2020 Heirs of Josephine N. Hopper / Licensed by Artists Rights Society (ARS), New York.