UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA

# Inquadramento delle manifestazioni extrapolmonari di SARS-CoV-2


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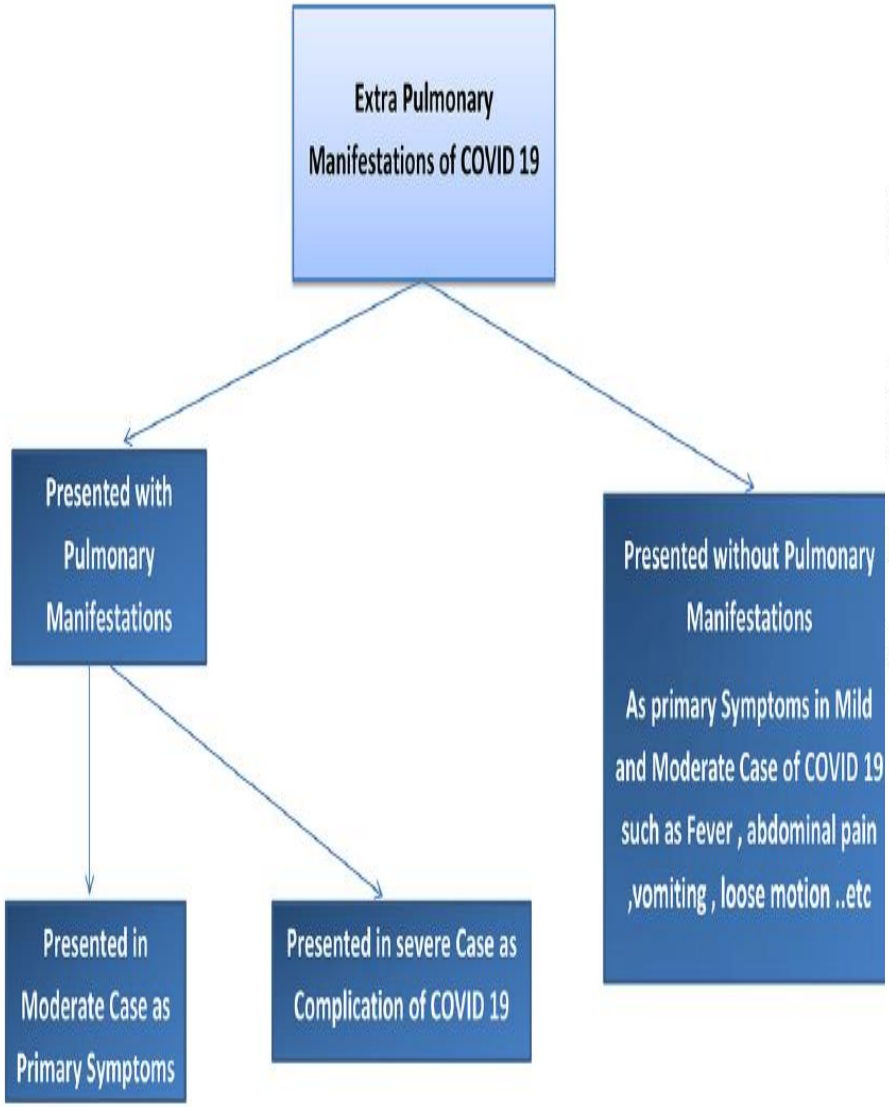
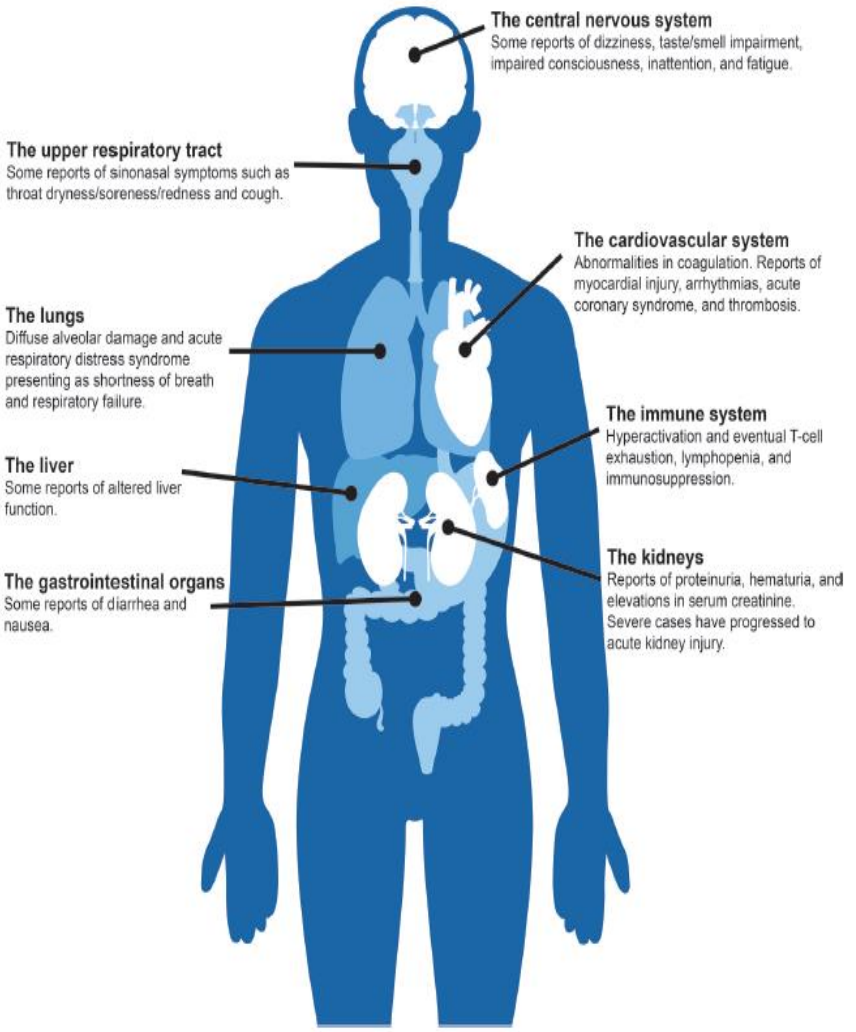
Firenze 11 Gennaio 2022

XIII Workshop Nazionale

Terapia innovative delle epatiti croniche virali e delle infezioni virali

# Clinical patterns of extrapulmonary manifestations of COVID-19





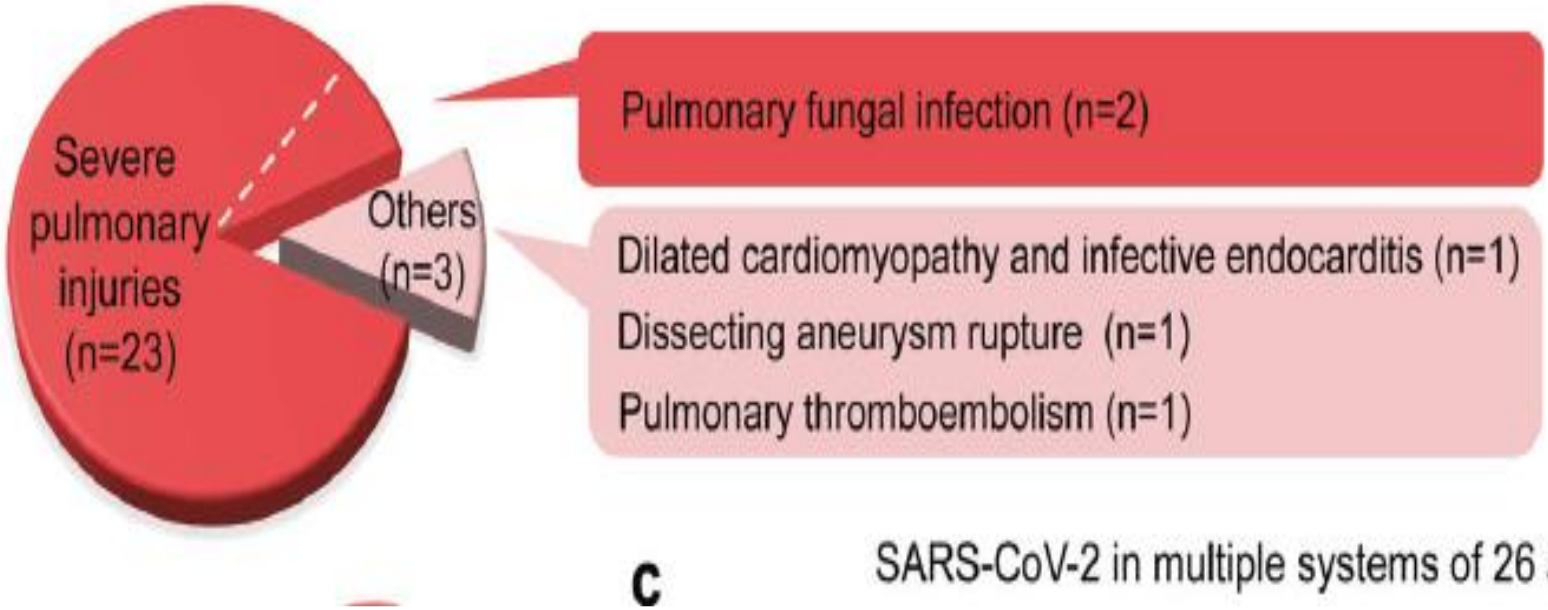

Elrobaa IH et al. Front Public Health 2021;9:711616; Diab AM et al. Can J Physiol Phrmacol 2021;99:577-88.

# A cohort autopsy study defines COVID-19 systemic pathogenesis

Xiao-Hong Yao[1,2], Tao Luo[1,2], Yu Shi[1,2], Zhi-Cheng He[1,2], Rui Tang[1,2], Pei-Pei Zhang[3,4], Jun Cai[5], Xiang-Dong Zhou[6], Dong-Po Jiang[7], Xiao-Chun Fei[4], Xue-Quan Huang[8], Lei Zhao[5], Heng Zhang[4], Hai-Bo Wu[3], Yong Ren[9], Zhen-Hua Liu[10], Hua-Rong Zhang[1,2], Cong Chen[1,2], Wen-Juan Fu[1,2], Heng Li[3], Xin-Yi Xia[11], Rong Chen[12], Yan Wang[1,2], Xin-Dong Liu[1,2], Chang-Lin Yin[13], Ze-Xuan Yan[1,2], Juan Wang[14], Rui Jing[15], Tai-Sheng Li[16], Wei-Qin Li[17], Chao-Fu Wang[4], Yan-Qing Ding[18], Qing Mao[19], Ding-Yu Zhang[12], Shu-Yang Zhang[20], Yi-Fang Ping[1,2] and Xiu-Wu Bian[1,2,3]

Median age 69.8 y

Major death causes for 26 confirmed COVID-19 autopsy cases

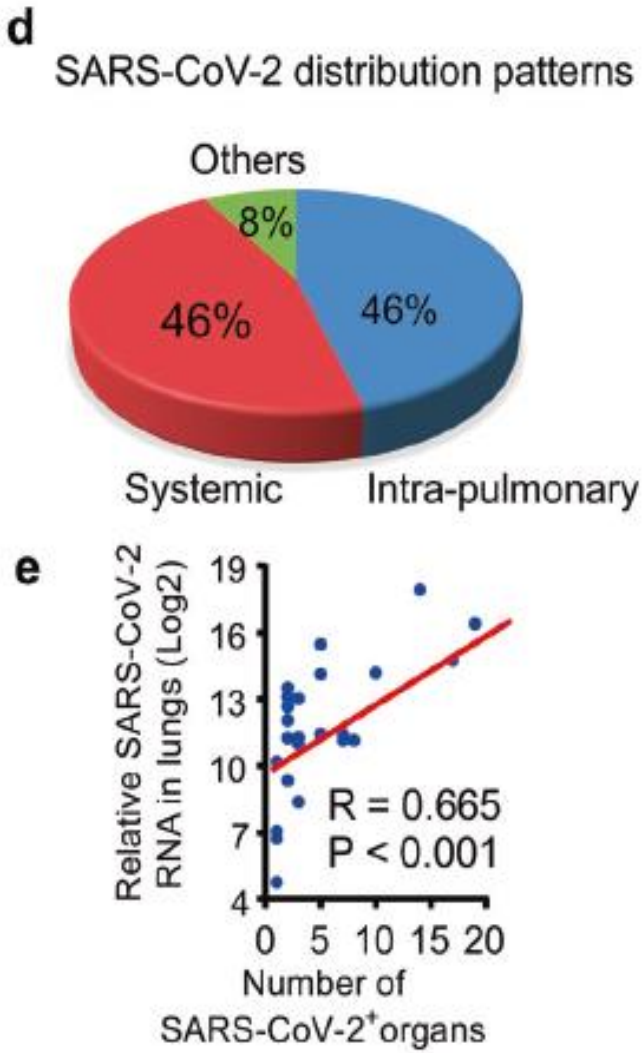



c SARS-CoV-2 in multiple systems of 26 autopsy cases



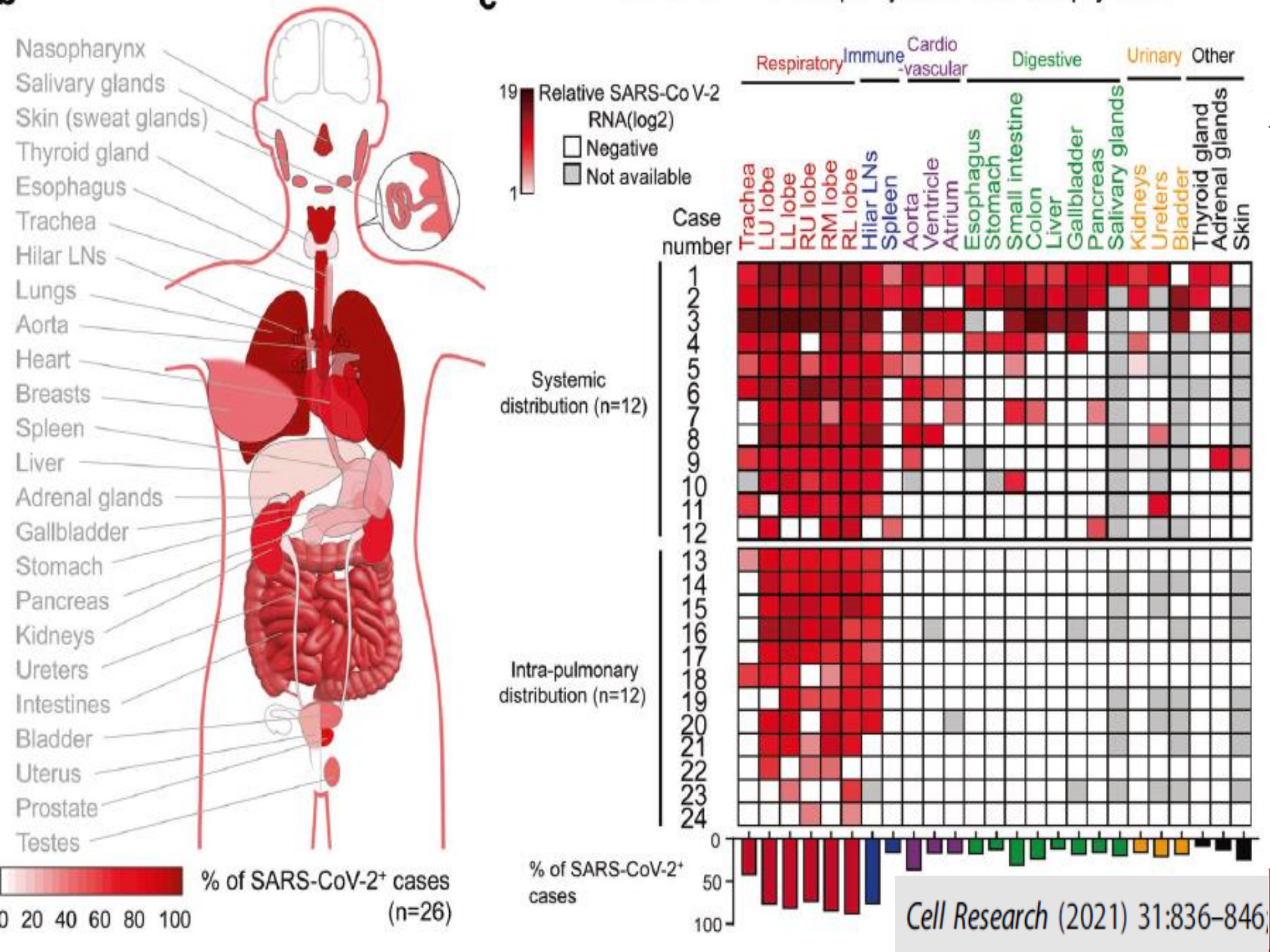
*Cell Research* (2021) 31:836–846

# Comparison of viral infection rate between SARS-CoV-2 and SARS-CoV (literature)



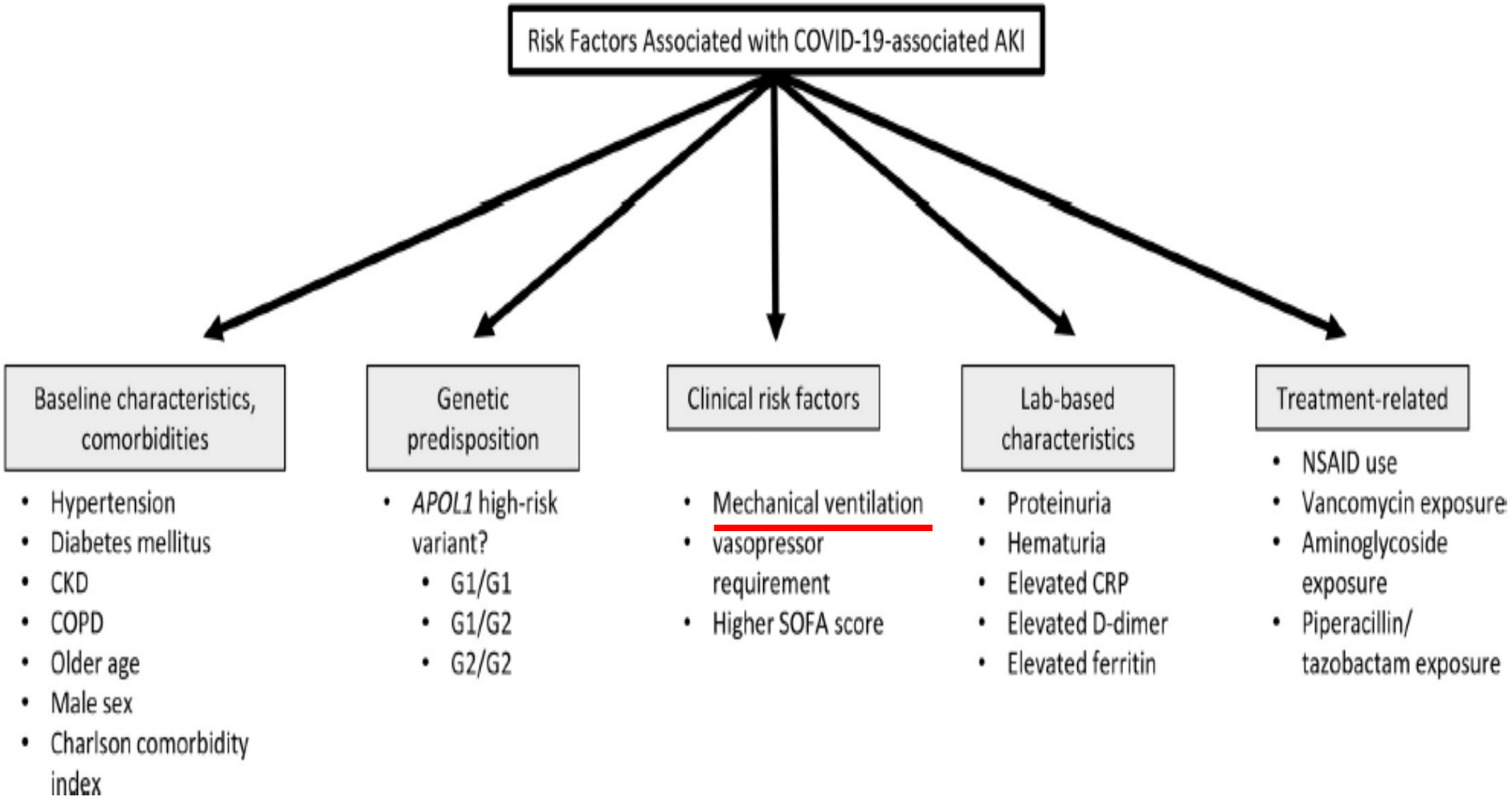



Yao X-H et al. Cell Research 2021




*Cell Research* (2021) 31:836–846

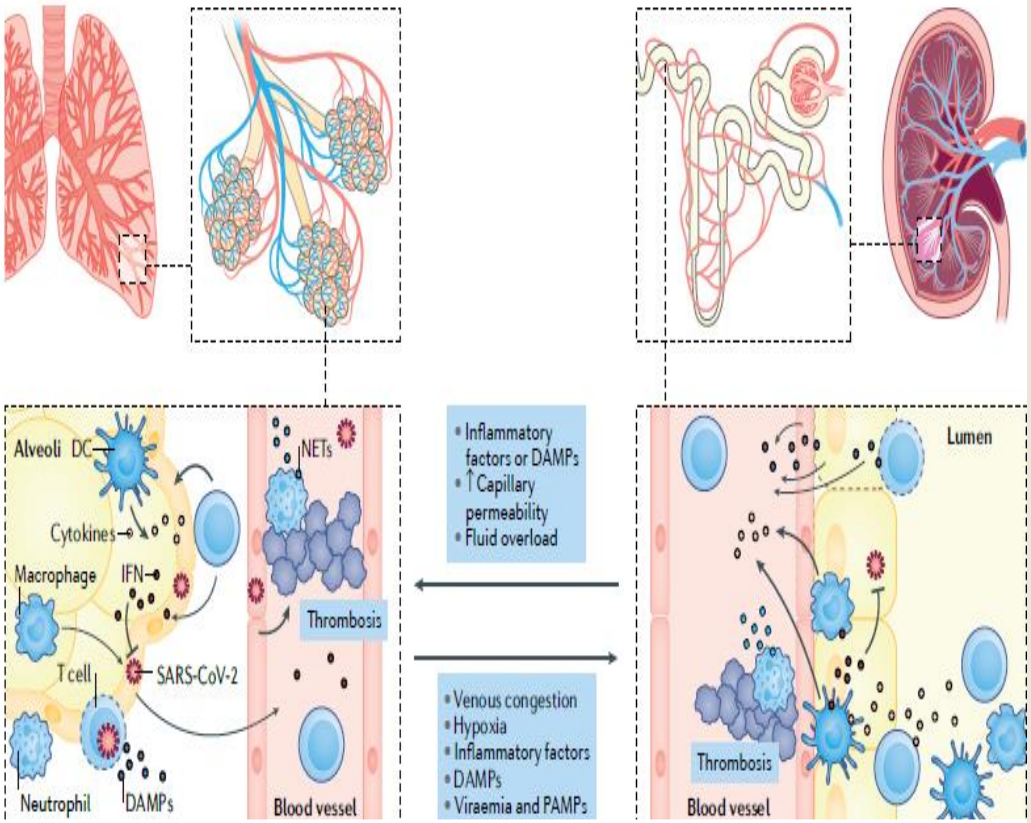
# Risk factors for COVID-19 associated AKI






Menez S & Parikh CR. Am J Physiol Renal Physiol 2021,321:F403-410

# Risk factors for COVID-19 associated AKI




Box 1 | **Factors that may contribute to COVID-19-associated acute kidney injury**

**Acute tubular injury**
- Regional inflammation
- Direct viral infection
- Renal compartment syndrome
- Tissue hypoxia hypoperfusion leading to hypoxaemia, hypotension, hypovolaemia and heart failure
- Nephrotoxic-induced injury (potentially associated with the use of antibiotics (vancomycin, aminoglycosides, colistin) or antivirals (remdesivir, ritonavir))
- Rhabdomyolysis

**Vascular injury**
- Endotheliitis
- Microthrombi
- Thrombotic microangiopathy

**Glomerular injury**
- Collapsing glomerulopathy (potentially caused by interferon-associated podocyte injury)
- Glomerulonephritis

**Interstitial injury**
- Acute interstitial nephritis; infiltration by immune cells
- Interstitial oedema

COVID-19, coronavirus disease 2019.

Legrand M et al. Nature Rev Nephrol 2021; 17: 751-63

# The Prevalence of Acute Kidney Injury in Patients Hospitalized With COVID-19 Infection: A Systematic Review and Meta-analysis

*Samuel A. Silver,* William Beaubien-Souligny,* Prakesh S. Shah, Shai Harel, Daniel Blum, Teruko Kishibe, Alejandro Meraz-Munoz, Ron Wald,† and Ziv Harel†*

**Table 2.** Summary of AKI Events

| Characteristic | AKI | KRT |
|---|---|---|
| No. of studies | 54 | 49 |
| Pooled prevalence (95% CI) | 28% (22%-34%) | 9% (7%-11%) |
| Kidney events in patients admitted to an ICU | | |
| Pooled prevalence (95% CI) | 46% (35%-57%) | 19% (15%-22%) |
| Kidney events in patients admitted to a non-ICU setting | | |
| Pooled prevalence (95% CI) | 12% (6%-19%) | 1% (0%-3%) |

Abbreviations: AKI, acute kidney injury; ICU, intensive care unit; KRT, kidney replacement therapy.

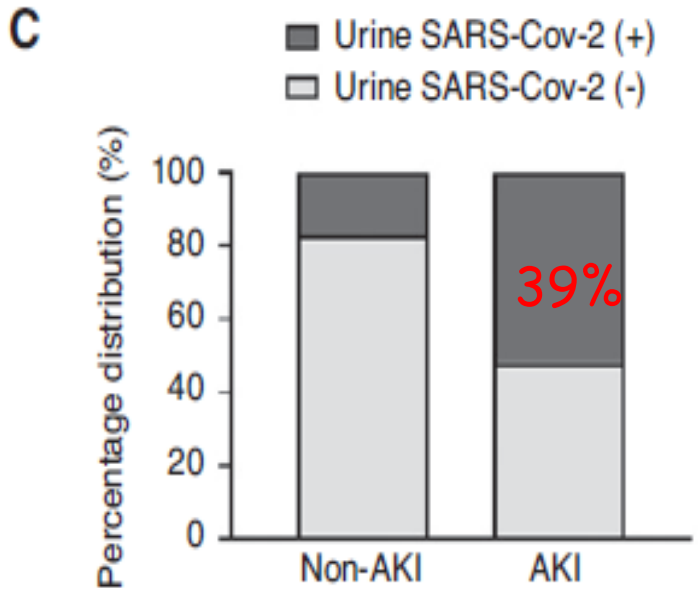
54 studies (30,657 pts) reporting AKI using KDIGO (Kidney Disease: Improving Global Outcomes) stages

AKI complicated the course of 1 in 3 (28%) pts hospitalized with COVID-19



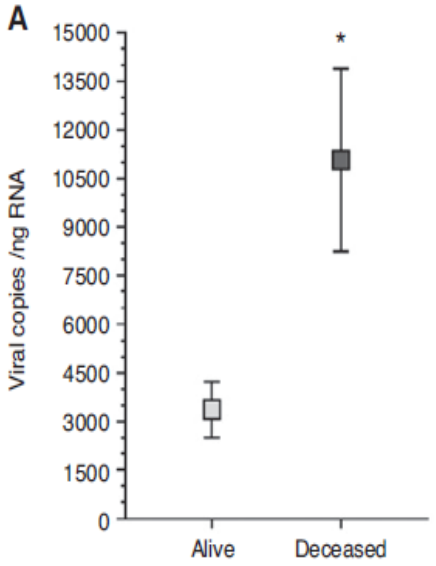
Kidney Med 2021; 3: 83-98

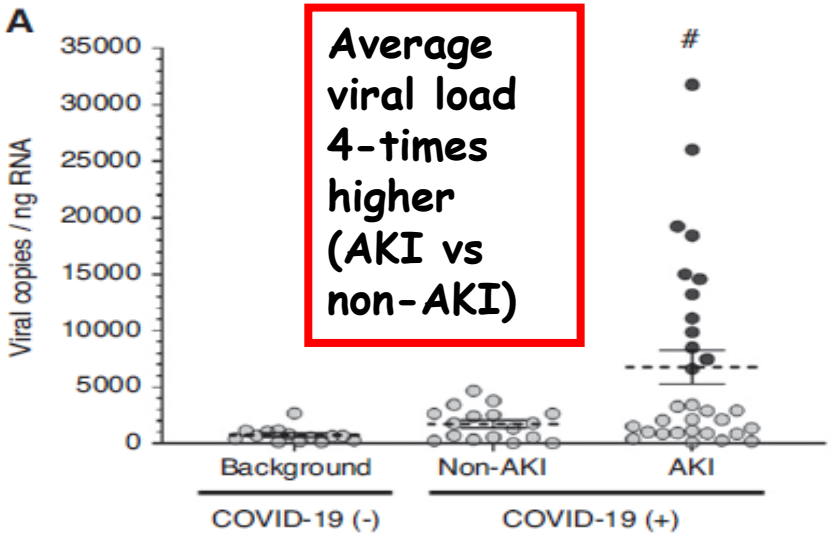
# High SARS-CoV-2 Viral Load in Urine Sediment Correlates with Acute Kidney Injury and Poor COVID-19 Outcome




U-viral load associated with COVID-19 inpatient mortality (p<0.001).

Each increase of 10,000 viral copies/ng RNA associated with a 2.87 fold increased risk of death




**Average viral load 4-times higher (AKI vs non-AKI)**

Caceres PS et al. JASN 2021;32:2517-28

# Acute kidney injury in COVID-19: multicentre prospective analysis of registry data

**1855 admissions**

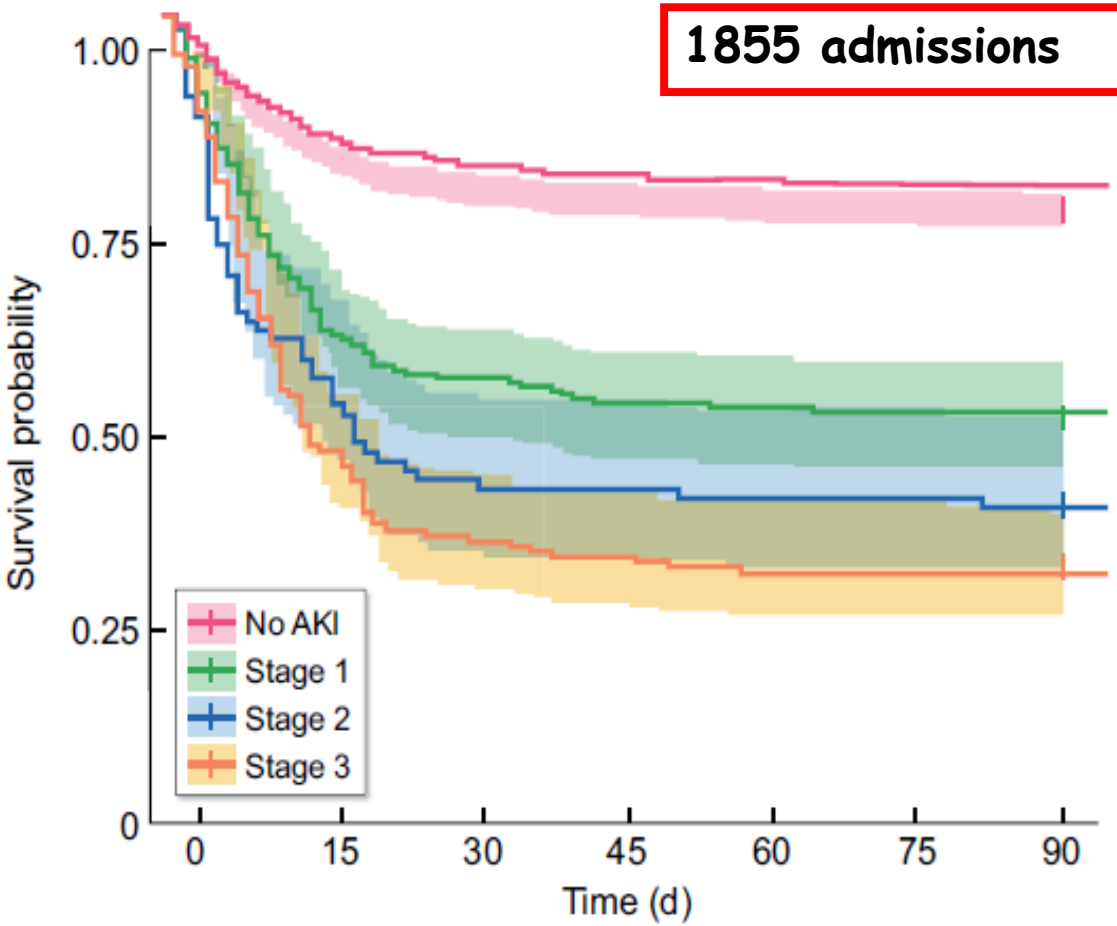
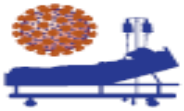



**FIGURE 3:** Kaplan–Meier plot showing survival to 90 days by stage of early AKI.

**Methods**

5 hospitals in London, UK

1st January – 14th May 2020



Cohort study Hospitalized patients with COVID-19

Figure S3). Risk increased with increasing severity of AKI: Stage 1 [HR 1.88 (1.47–2.40), $P < 0.001$], Stage 2 [HR 2.79 (2.06–3.77), $P < 0.001$] and Stage 3 [HR 4.25 (3.37–5.35), $P < 0.001$] (Supplementary data, Figure S3). After inclusion of pre-specified confounders including ethnicity, IMD, smoking history, BMI $\geq 30$ kg/m$^2$, diabetes, HTN and CKD in a multivariable survival analysis, the association between early AKI and death persisted: Stage 1 [HR 1.92 (1.48–2.49), $P < 0.001$], Stage 2 [HR 2.75 (1.97–3.85), $P < 0.001$] and Stage 3 [HR 3.93 (3.04–5.08), $P < 0.001$] (Figures 2 and 3).



Wan YI et al. Clin Kidney J 2021;14:2356-64

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]

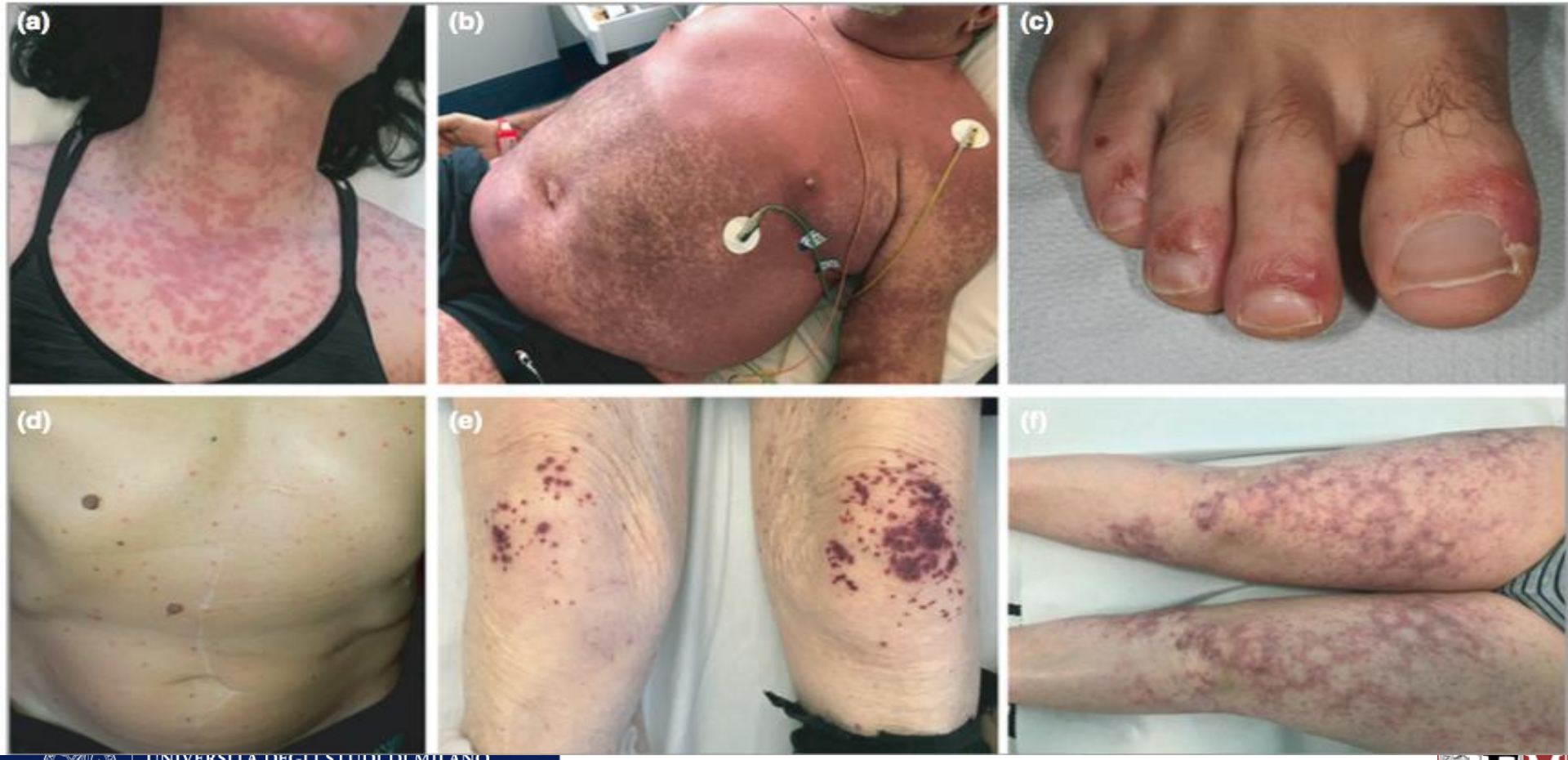
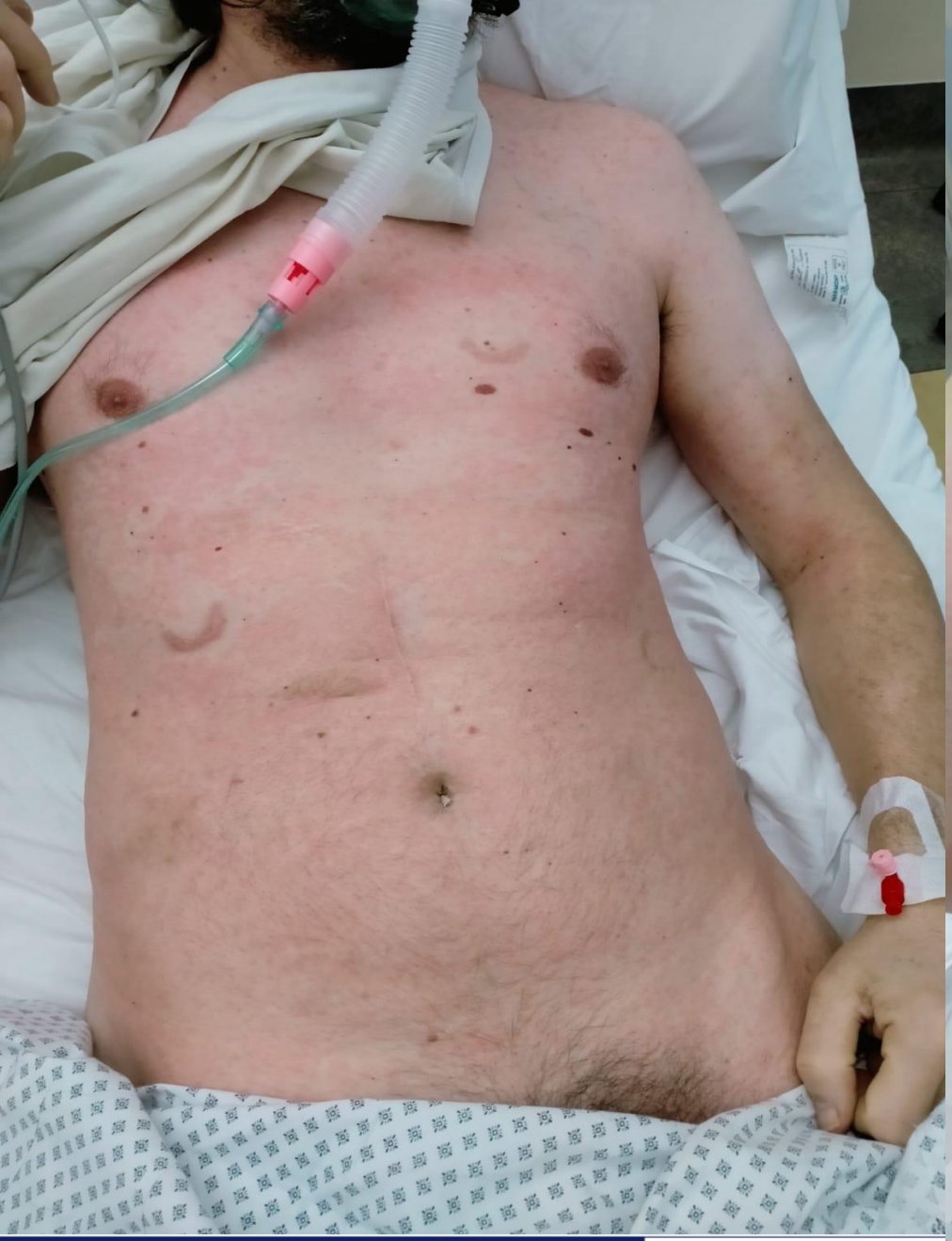


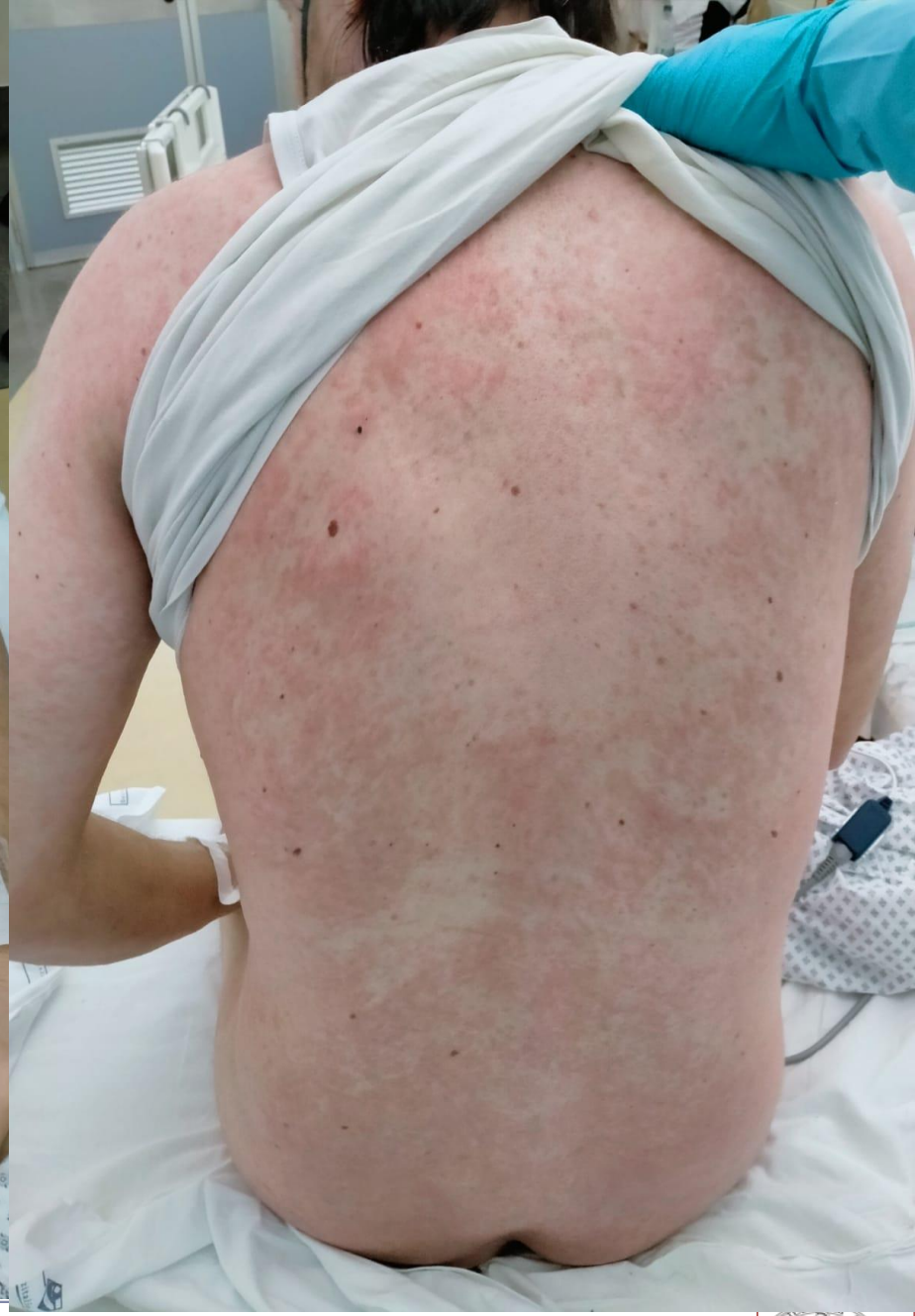
Table 1 Clinical features of COVID-19-associated cutaneous manifestations.

| Cutaneous manifestation | Clinical characteristics | Major site involved | Dermatologic symptoms | §Prevalence[8,18,23] n/s (%) |
|---|---|---|---|---|
| Pseudo-chilblain | Chilblain-like lesions | Feet, hands | Itching, pain | 18/144 (12.5), 100/507 (19.72), 957/460 (48) |
| Vesicular eruption | Vesicles, bullous eruption, varicella-like exanthema and chickenpox-like rash | Trunk | Itching (mild) | 120/957 (12.5), 66/507 (13) |
| Urticarial lesions | Wheals | Trunks, limbs | Itching | 19/144 (13.2), 83/507 (16.37) |
| Maculopapular eruptions | Morbiliform, pityriasis rosea-like eruptions | Trunk | Itching | 218/957 (22.8) |
| Livedo or necrosis | Acral ischemia, necrosis, livedo | Lower limbs | Pain, itching | 35/957 (3.6), 31/507 (6.11), 13/144 (9) |
| Petechiae/purpuric eruption | Petechiae, purpura | Lower limbs | - | 8/507 (1.58%); 5/957 (0.5) |
| Erythema multiforme-like rash | Targetoid lesions | Extremities | - | 9/144 (6.3) |



Sodeifian F et al. Actas Dermo-Sifiliograficas 2021 in press







Courtesy Dr Mario Corbellino

# Differential diagnosis of cutaneous manifestations in COVID-19 patients

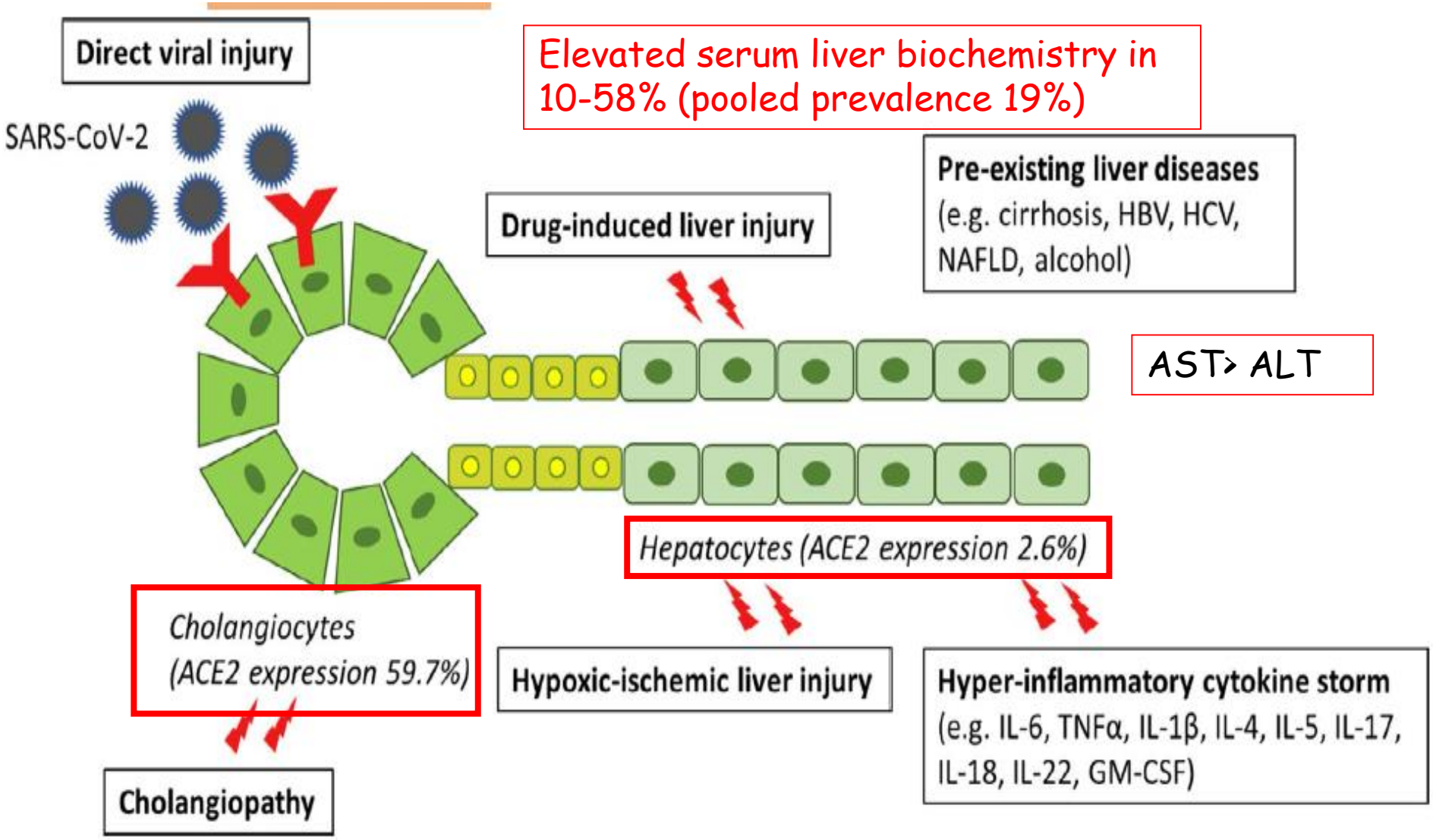
Table 2 Classification of different clinical patterns of cutaneous manifestations and differential diagnosis to be suspected in COVID-19 patients.

| S. No | Cutaneous manifestation | Differential diagnosis |
|---|---|---|
| 1 | Chilblain | Chilblain lupus, perniosis |
| 2 | Vesicular/varicella-like eruption eruption | Pemphigus, Grover disease, varicella |
| 3 | Urticarial rash | Acute idiopathic urticaria, drug-induced urticarial rash |
| 4 | Maculopapular rash | Measles, Epstein-Barr virus infection, drug-induced exanthema |
| 5 | Livedo reticularis | Antiphosholipid syndrome, disseminated intravascular coagulation, deep venous thrombois |
| 6 | Petechiae/purpuric rash | Drug-induced rash, rash associated with virus other than SARS-CoV-2 |
| 7 | Erythema multiform-like rash | Herpes simplex and mycoplasma pneumonia-associated erythema multiforme, Steven-Johnson syndrome |



Sodeifian F et al. Actas Dermo-Sifiliograficas 2021 in press

# Proposed pathogenesis of hepatic manifestations in COVID-19




Ekpanyapong S et al. J Viral Hepatitis 2022;29:4-20

# 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]

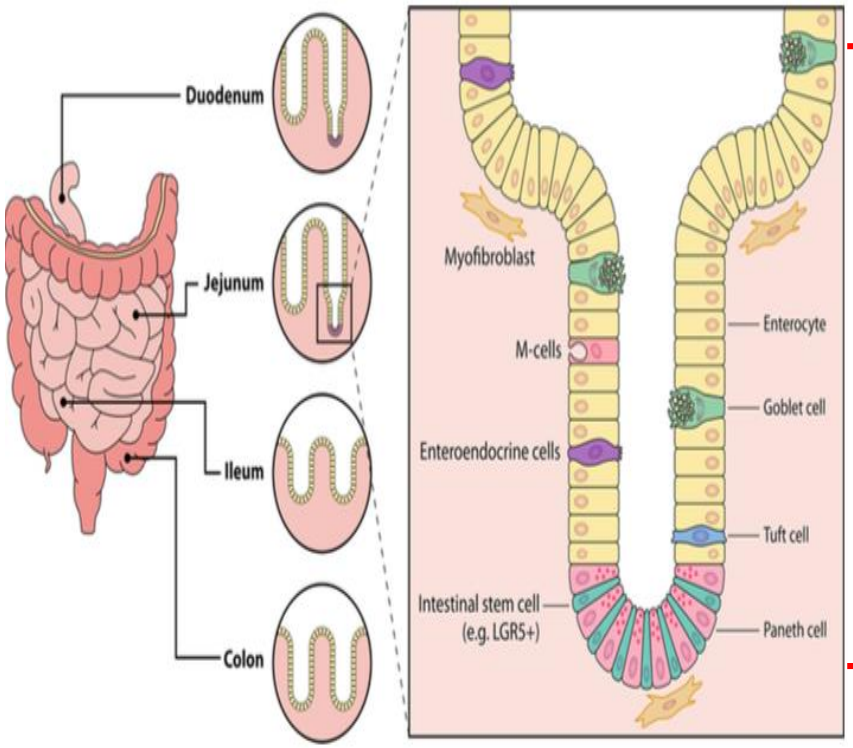



FIG 4 Cell types and their localization in the human intestine.

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

# Unexpectedly High Frequency of Enterococcal Bloodstream Infections in Coronavirus Disease 2019 Patients Admitted to an Italian ICU: An Observational Study

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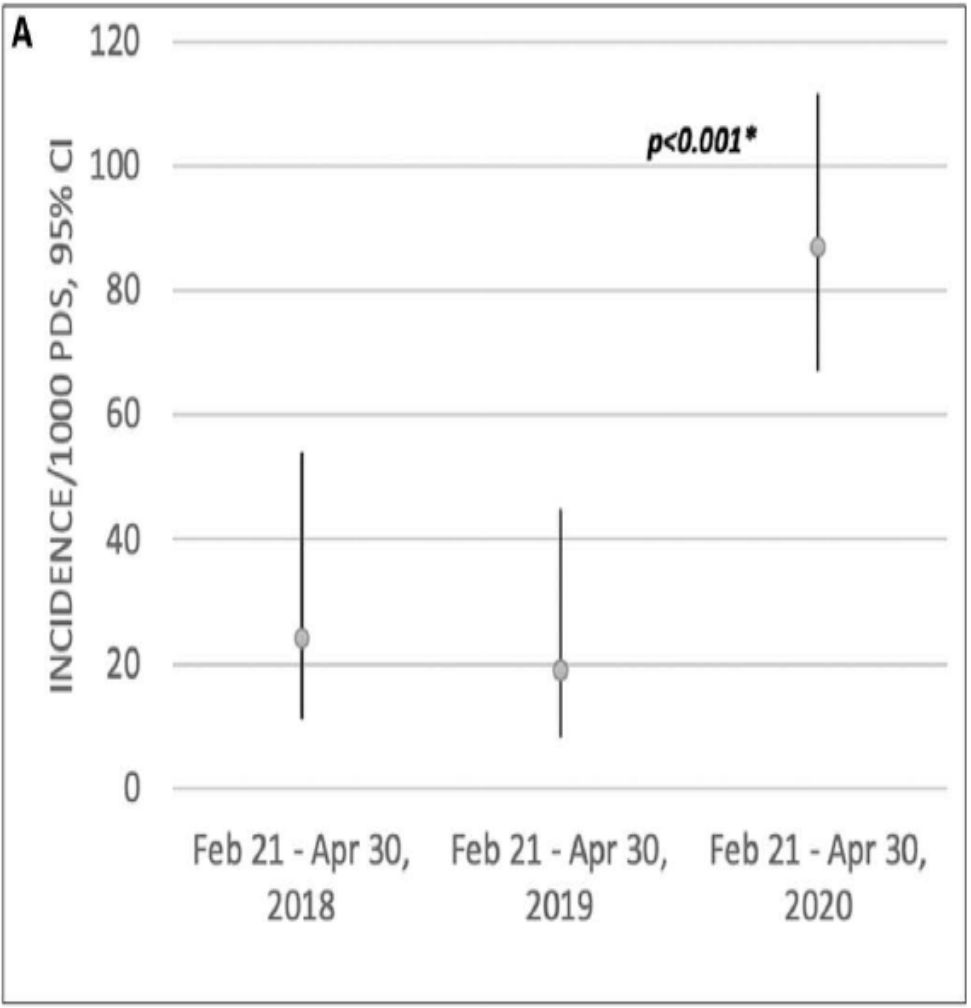
Anna Lisa Ridolfo, MD[1]
Spinello Antinori, MD[1,2]

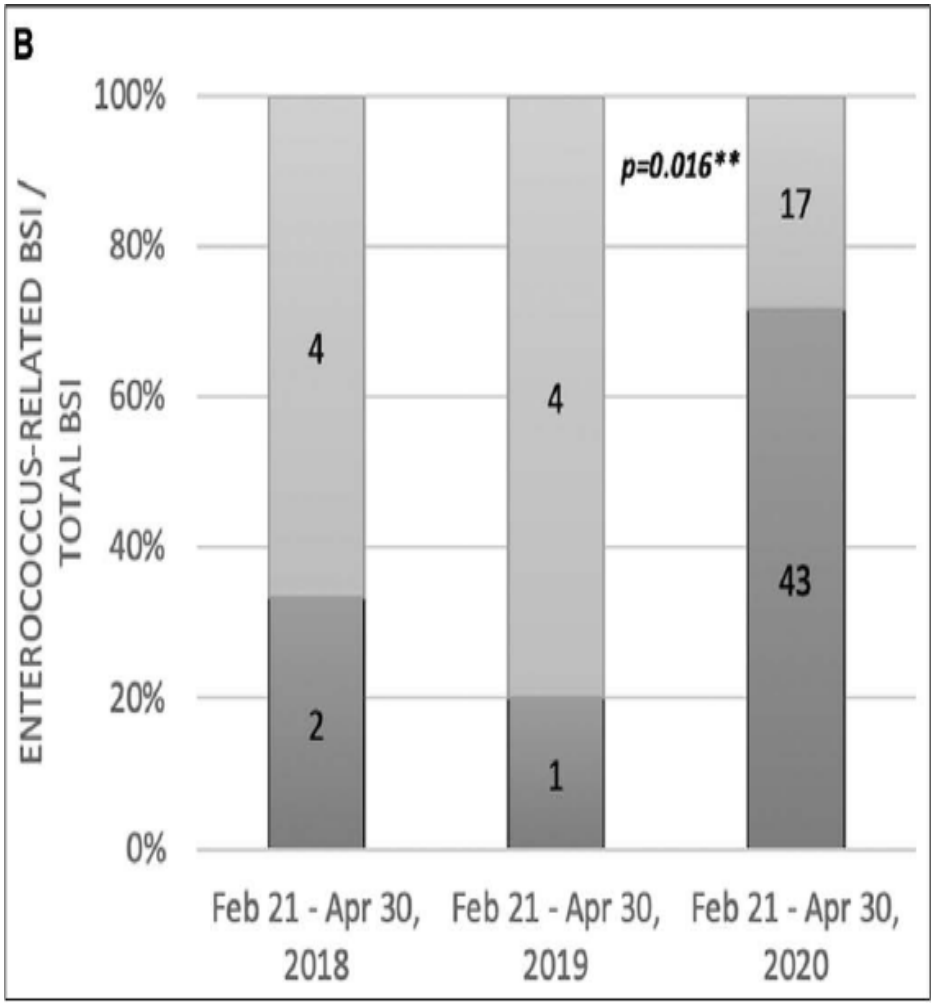
Crit Care Med 2021,49:e31-e40

Characteristics of the Isolates and Types of Bloodstream Infection

| Microorganisms | Isolates ($n = 117$) | Bloodstream Infection Episodes ($n = 93$) | Monomicrobial, $n = 71$ (76.3%) | Polymicrobial, $n = 22$ (23.7%) | Recurrent, $n = 19$ (20.4%) |
|---|---|---|---|---|---|
| Gram-positive, *n* (%) | 85 (72.6) | 74 (79.6) | 52 (73.2) | 22 (100) | 14 (73.7) |
| *Enterococcus* species[b] | 53 (45.3) | 53 (55.8) | 32 (45.1) | 22 (100) | 11 (57.9) |
| Vancomycin-resistant *Enterococcus faecium* | 5 (4.3) | 5 (5.4) | 3 (4.2) | 2 (9.1) | 1 (5.3) |
| *Staphylococcus aureus* | 7 (6) | 7 (7.5) | 3 (4.2) | 4 (18.2) | 2 (10.5) |
| Methicillin-resistant *S. aureus* | 5 (4.3) | 5 (5.4) | 2 (2.8) | 3 (13.6) | 1 (5.3) |
| Coagulase-negative *Staphylococci* | 24 (20.5) | 24 (25.8) | 16 (22.5) | 8 (36.4) | 5 (26.3) |
| *Gemella sanguinis* | 1 (0.8) | 1 (0.8) | 1 (0.8) | 0 (0.0) | 0 (0.0) |
| Gram-negative, *n* (%) | 29 (24.8) | 27 (29.0) | 16 (22.5) | 12 (54.5) | 10 (52.6) |
| Enterobacterales[a] | 19 (16.2) | 19 (20.4) | 10 (14.1) | 9 (40.9) | 5 (26.3) |
| Extended spectrum beta lactamase-positive Enterobacterales | 6 (5.1) | 6 (6.5) | 3 (4.2) | 3 (13.6) | 2 (10.5) |
| Carbapenemase-producing Enterobacterales | 10 (8.5) | 10 (10.8) | 6 (8.5) | 4 (18.2) | 2 (10.5) |
| *Enterobacter* species | 6 (5.1) | 6 (6.5) | 4 (5.6) | 2 (9.1) | 3 (15.8) |
| Cephalosporin-resistant *Enterobacter* | 4 (3.4) | 4 (4.3) | 3 (4.2) | 1 (4.5) | 1 (3.6) |
| *Pseudomonas aeruginosa* | 2 (1.7) | 2 (2.2) | 1 (1.4) | 1 (4.5) | 1 (5.3) |
| MDR *P. aeruginosa* | 1 (0.8) | 1 (1.1) | 1 (1.4) | 0 (0.0) | 1 (5.3) |
| *Stenotrophomonas maltophilia* | 1 (0.8) | 1 (1.1) | 1 (1.4) | 0 (0.0) | 1 (5.3) |
| MDR *S. maltophilia* | 1 (0.8) | 1 (1.1) | 1 (1.4) | 0 (0.0) | 1 (5.3) |
| *Acinetobacter baumannii* | 1 (0.8) | 1 (1.1) | 0 (0.0) | 1 (4.5) | 0 (0.0) |
| Yeasts, *n* (%) | 3 (2.6) | 3 (3.2) | 3 (4.2) | 0 (0.0) | 0 (0.0) |
| *Candida albicans* | 3 (2.6) | 3 (3.2) | 4 (4.2) | 0 (0.0) | 0 (0.0) |

# Unexpectedly High Frequency of Enterococcal Bloodstream Infections in Coronavirus Disease 2019 Patients Admitted to an Italian ICU: An Observational Study






Bonazzetti C et al.Crit Care Med 2021;49:e31-e40

# Unexpectedly High Frequency of Enterococcal Bloodstream Infections in Coronavirus Disease 2019 Patients Admitted to an Italian ICU: An Observational Study

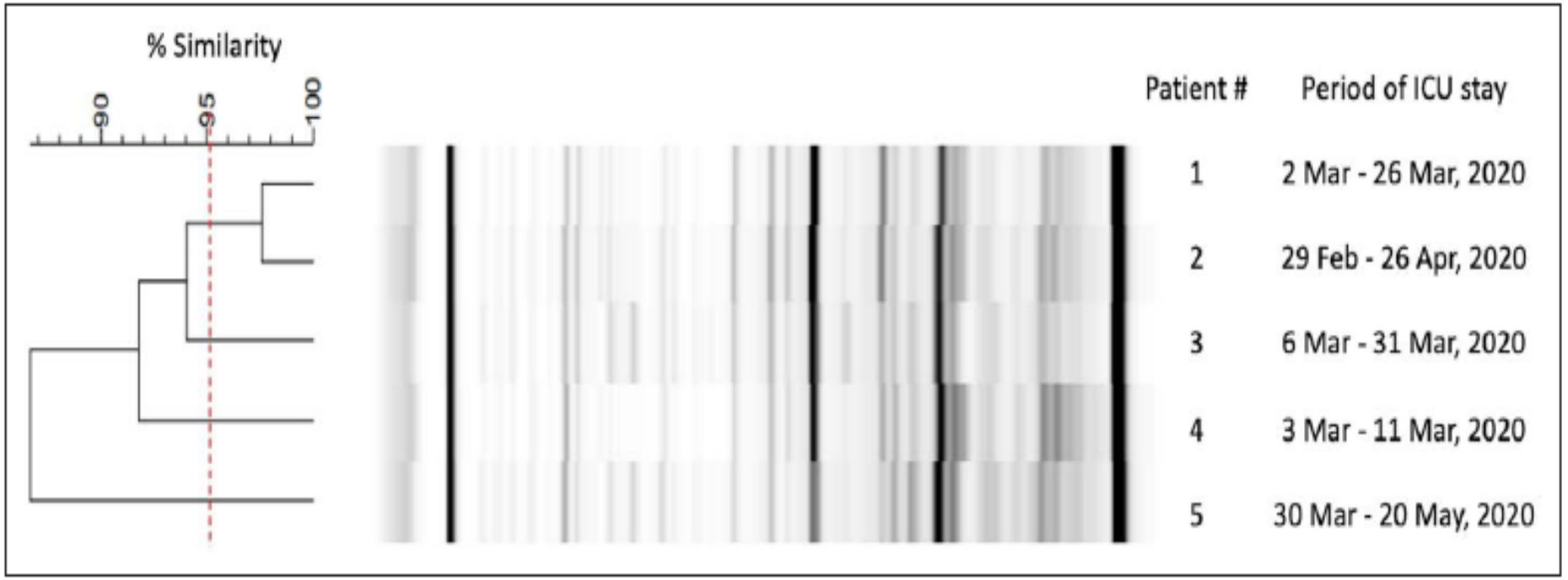



**Figure 3.** Molecular characterization of the five vancomycin-resistant *Enterococcus faecium* strains collected from blood cultures in 2020. The analysis showed a strict genotypic relation between two strains.



Bonazzetti C et al. Crit Care Med 2021;49:e31-e40

**Increased Rates of Secondary Bacterial Infections, Including *Enterococcus* Bacteremia, in Patients Hospitalized with COVID-19**

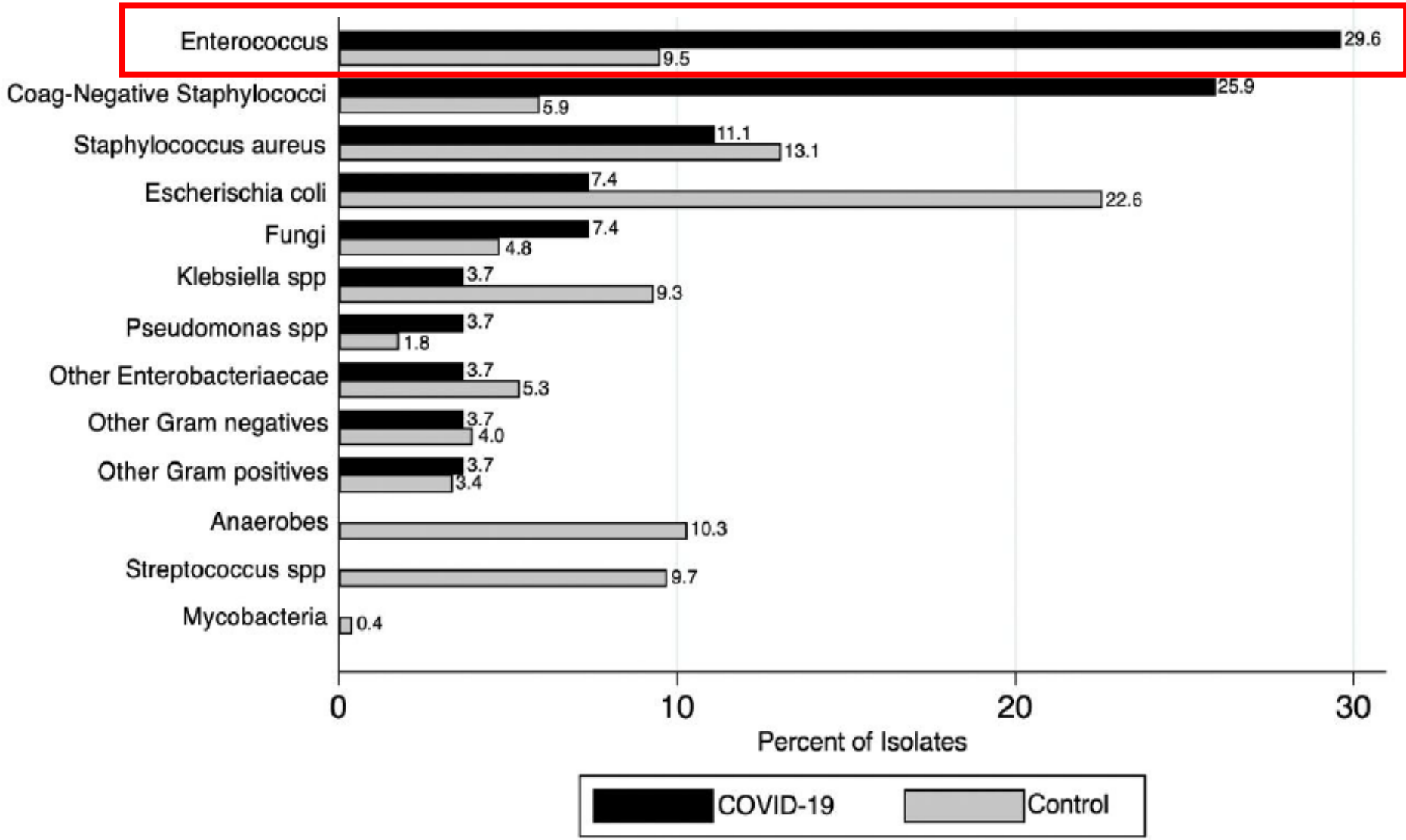
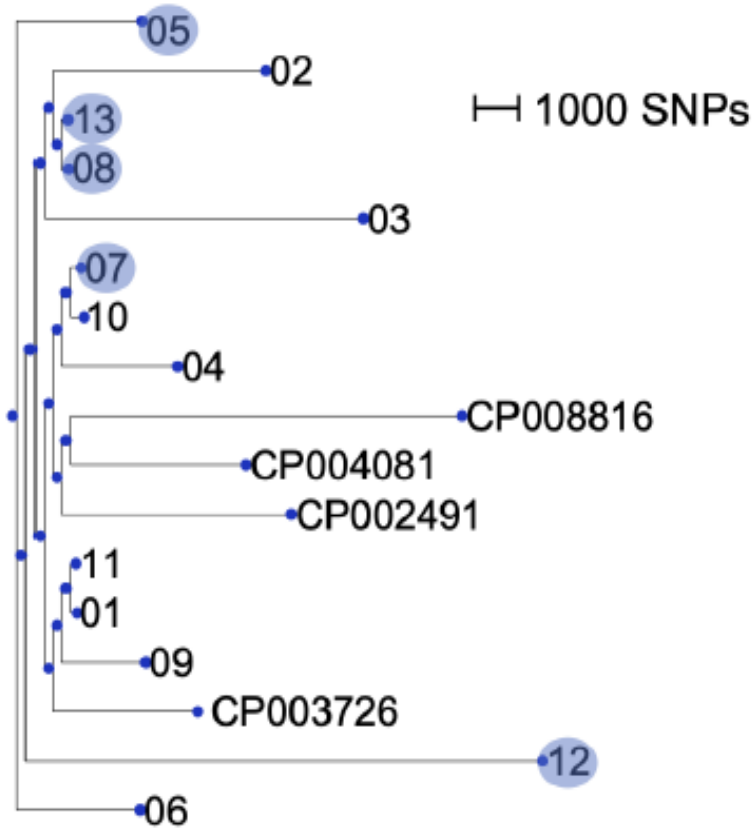



**Figure 1: Organisms isolated from blood culture in patients with COVID-19 patients versus controls.**

De Voe C et al. *Infection Control & Hospital Epidemiology*

**Figure S1.** Whole genome sequencing of E. faecalis blood isolates from a study site ICU demonstrates that the increased rate BSI is not explained by a hospital outbreak. A. Phylogenetic tree demonstrating relatedness of E. faecalis isolates. Shaded isolates are from patients with COVID-19 in the study. Scale bar represents 1000 single nucleotide polymorphisms (SNPs). B. Table demonstrating SNP distances between isolates.

**A**



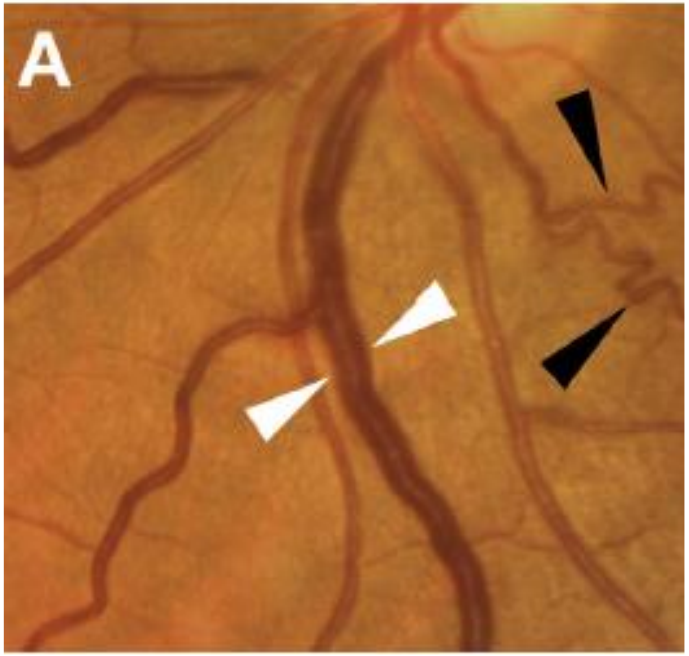

**B**

| | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 01 | 16959 | 16795 | 14719 | 22772 | 22909 | 17918 | 18049 | 2233 | 18064 | 85 | 20354 | 18004 |
| 02 | | 13026 | 16897 | 22802 | 22881 | 18854 | 10537 | 17663 | 18974 | 17023 | 20044 | 10455 |
| 03 | | | 16641 | 22543 | 22649 | 18464 | 14847 | 17380 | 18589 | 16858 | 20044 | 14812 |
| 04 | | | | 23099 | 23244 | 10993 | 18212 | 15699 | 11106 | 14806 | 20252 | 18161 |
| 05 | | | | | 4981 | 22713 | 22592 | 22907 | 22791 | 22842 | 23353 | 22566 |
| 06 | | | | | | 22733 | 22631 | 23010 | 22812 | 22993 | 23435 | 22595 |
| 07 | | | | | | | 18699 | 18212 | 351 | 18002 | 20917 | 18652 |
| 08 | | | | | | | | 18238 | 18845 | 18076 | 20209 | 110 |
| 09 | | | | | | | | | 18349 | 2230 | 20531 | 18188 |
| 10 | | | | | | | | | | 18151 | 21019 | 18794 |
| 11 | | | | | | | | | | | 20403 | 18029 |
| 12 | | | | | | | | | | | | 20171 |

# Retinal findings in patients with COVID-19: Results from the SERPICO-19 study

ScrEening of the Retina in Patients wIth COVID-19

Alessandro Invernizzi[a,b,c,*], Alessandro Torre[d], Salvatore Parrulli[a,b], Federico Zicarelli[a,b], Marco Schiuma[b,d], Valeria Colombo[d], Andrea Giacomelli[b,d], Mario Cigada[b], Laura Milazzo[d], Annalisa Ridolfo[d], Ivano Faggion[d], Laura Cordier[d], Marta Oldani[a], Sara Marini[a], Paolo Villa[e], Giuliano Rizzardini[d], Massimo Galli[b,d], Spinello Antinori[b,d], Giovanni Staurenghi[a,b], Luca Meroni[d]

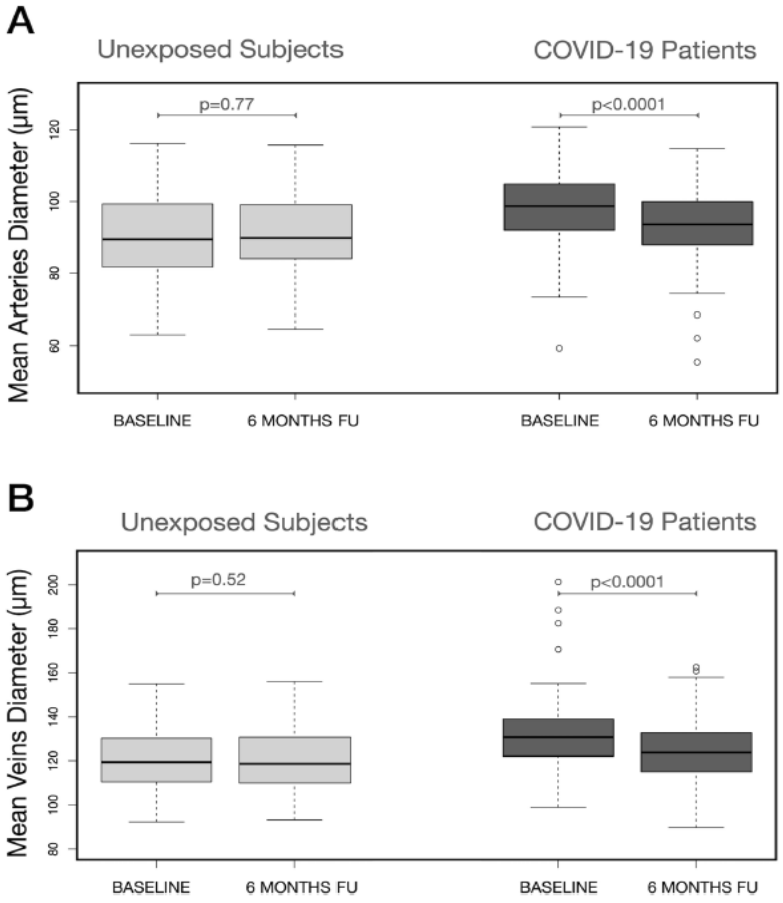


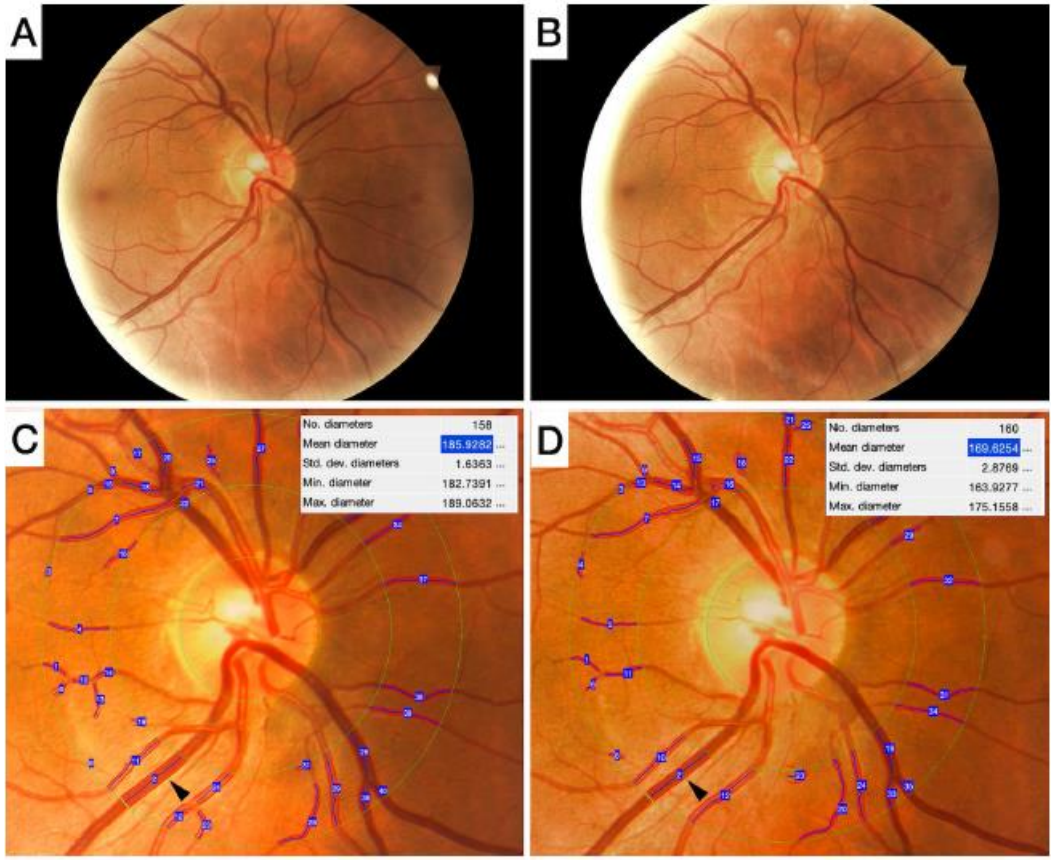

Retinal findings in subjects included in the study.

| | COVID-19 patients ($n$ = 54) | Unexposed subjects ($n$ = 133) | $p$-value[c] |
|---|---|---|---|
| Retinal hemorrhages patients (percentage) | 5 (9·25) | 2 (1·5) | 0·01 |
| Cotton wool spots patients (percentage) | 4 (7·4) | 0 | 0·006 |
| Drusen patients (percentage) | 6 (11·1) | 10 (7·5) | 0·4 |
| Dilated veins[a] patients (percentage) | 15 (27·7) | 4 (3·0) | 0·0001 |
| Tortuous vessels[a] patients (percentage) | 7 (12·9) | 9 (6·7) | 0·24 |
| Mean vein diameter[b] $\mu$m (SD, range) | 138·5 (21·5, 98·5–203) | 123·2 (13·0, 91·1–156·7) | <0·0001 |
| Mean artery diameter[b] $\mu$m (SD, range) | 98·3 (15·3, 71·4–131·8) | 91·9 (11·7, 63·0–119·6) | 0·006 |

# Retinal vessels modifications in acute and post-COVID-19

Alessandro Invernizzi[1,2,3]✉, Marco Schiuma[2,4], Salvatore Parrulli[1], Alessandro Torre[4], Federico Zicarelli[1], Valeria Colombo[4], Sara Marini[1], Elena Villella[1], Alice Bertoni[1], Spinello Antinori[2,4], Giuliano Rizzardini[4], Massimo Galli[2,4], Luca Meroni[4], Andrea Giacomelli[4] & Giovanni Staurenghi[1,2]




UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA

scientific reports 2021;11:19373

# Neurological associations of COVID-19

Lancet Neurol 2020; 19:767-783

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

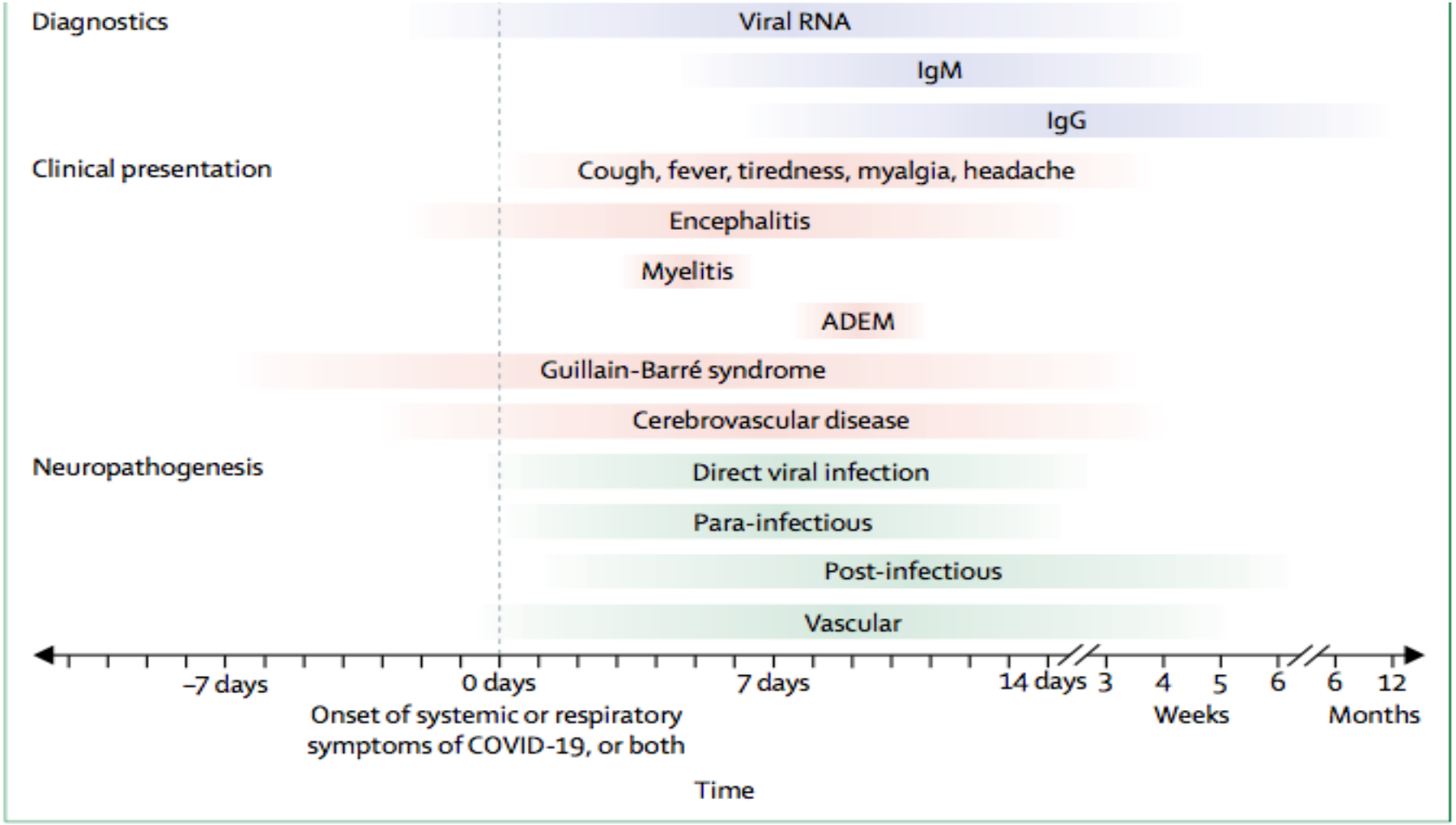



***Figure 1:*** **Approximate timeline for positive diagnostic tests, clinical presentation, and pathogenesis in COVID-19-associated neurological disease**

# Neurological symptoms & manifestations associated with SARS-CoV-2

| Neurological symptoms | Neurological manifestations and complications |
|---|---|
| Gustatory dysfunctions (38.5%) | Stroke (2.3%) |
| Olfactory dysfunctions (hyposmia/anosmia) (35.8%) | Epilepsy and seizures (0.9%) |
| Myalgia (19.3%) | Cerebral venous (sinus) thrombosis (0.3%) |
| Headache (14.7%) | Meningitis, encephalitis, meningoencephalitis |
| Altered mental status (9.4%) [5, 117] | Guillan–Barré syndrome |
| Dizziness (8.77%) | Miller Fisher syndrome/Bickerstaff's encephalitis [118] |
| Nausea and vomiting (4.6%) [51, 119] | Acute myelitis |
| Neuralgia (2.3%) [32, 120] | Posterior reversible encephalopathy syndrome (PRES) |
| Ataxia (0.3%) [121, 122] | Acute hemorrhagic necrotizing encephalopathy [123, 124] |
| Myoclonus [125, 126] | Acute demyelinating encephalomyelitis (ADEM)-like pathology [127, 128] |
| Diplopia [129] | Posthypoxic necrotizing leukoencephalopathy [130] |
| Vision loss [131] | CNS vasculitis [117] |
| Stupor [2] | Acute cerebellitis [132] |
| Meningism [133] | Movement disorders [134] |
| Dysexecutive syndrome [135] | Intensive-care-unit acquired neuropathy [2] |
| Bilateral leg stiffening [136] | Rhabdomyolysis [137] |
| Sustained upward gaze [136] | Critical illness myopathy [138, 139] |
| | Necrotizing autoimmune myositis (NAM) [140] |
| | Acute mesenteric ischemia [141] |



Harapan BN et al. J Neurol 2021;268:3059-71

*Clinical Infectious Diseases*

CORRESPONDENCE

# Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respirator 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]

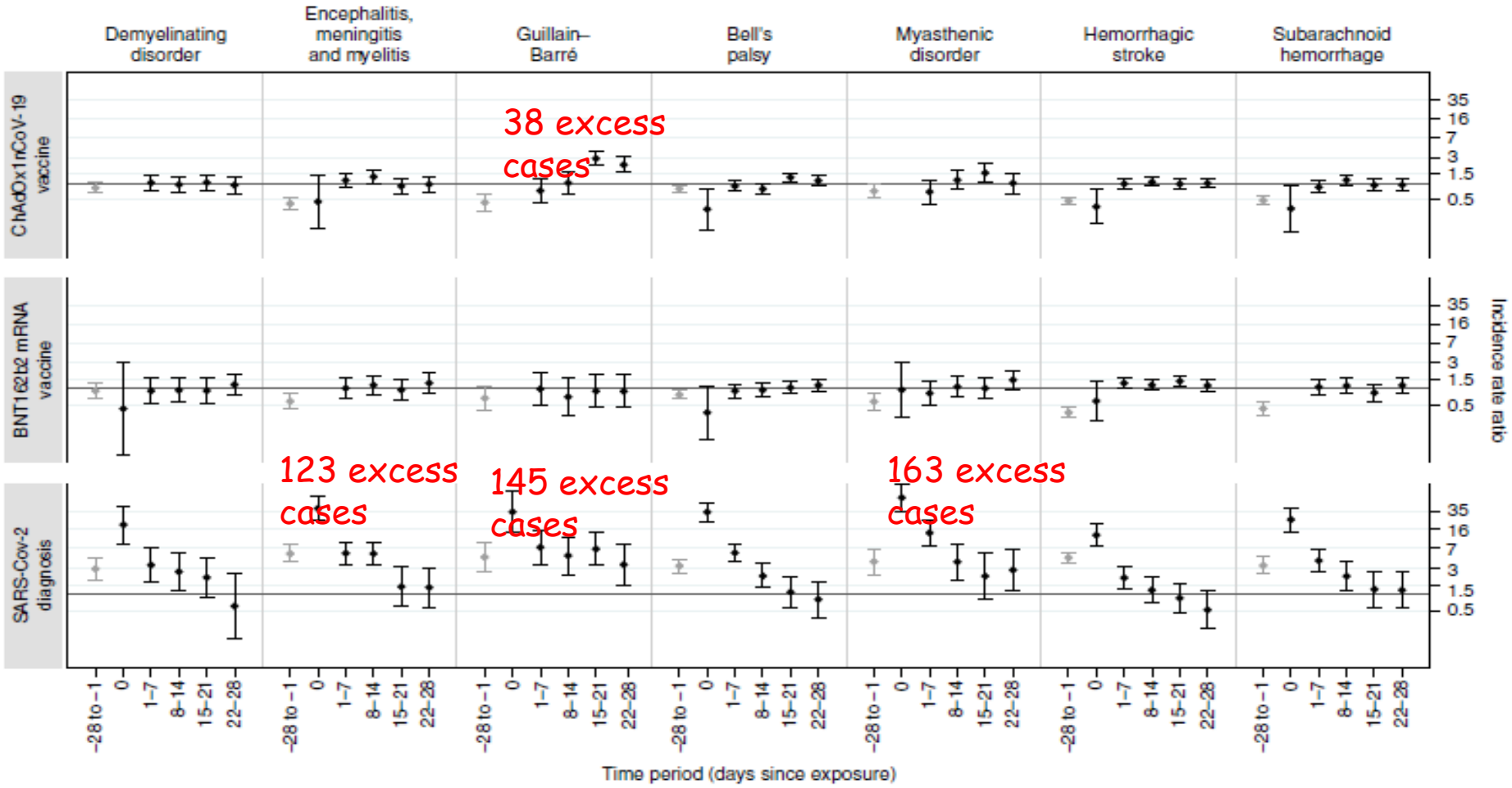
Clin Infect Dis 2020;71:889-90

**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) |

OPEN

# Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection






Patone M et al. Nature Medicine 2021;27:2144-53

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

*Tom Solomon*

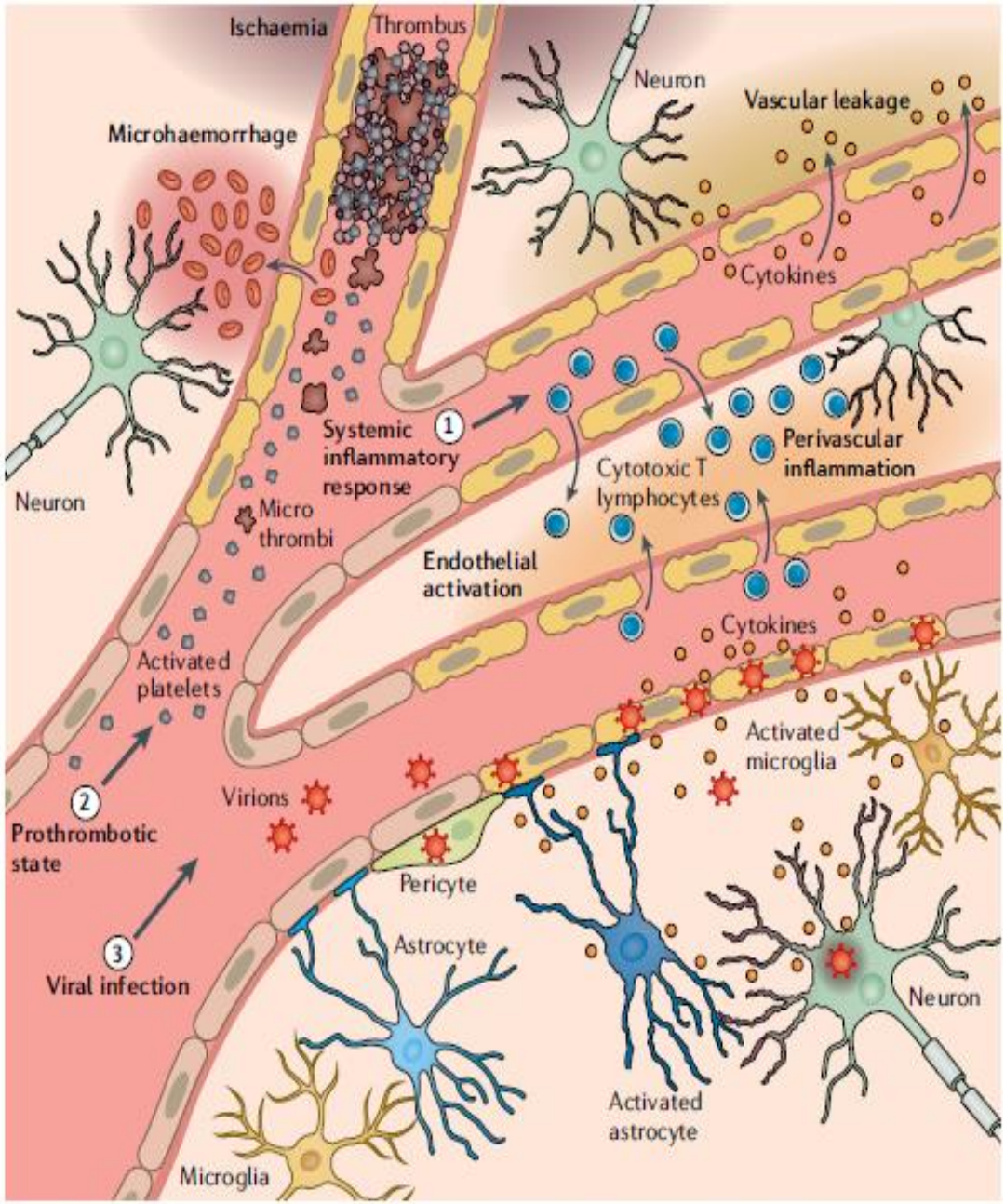


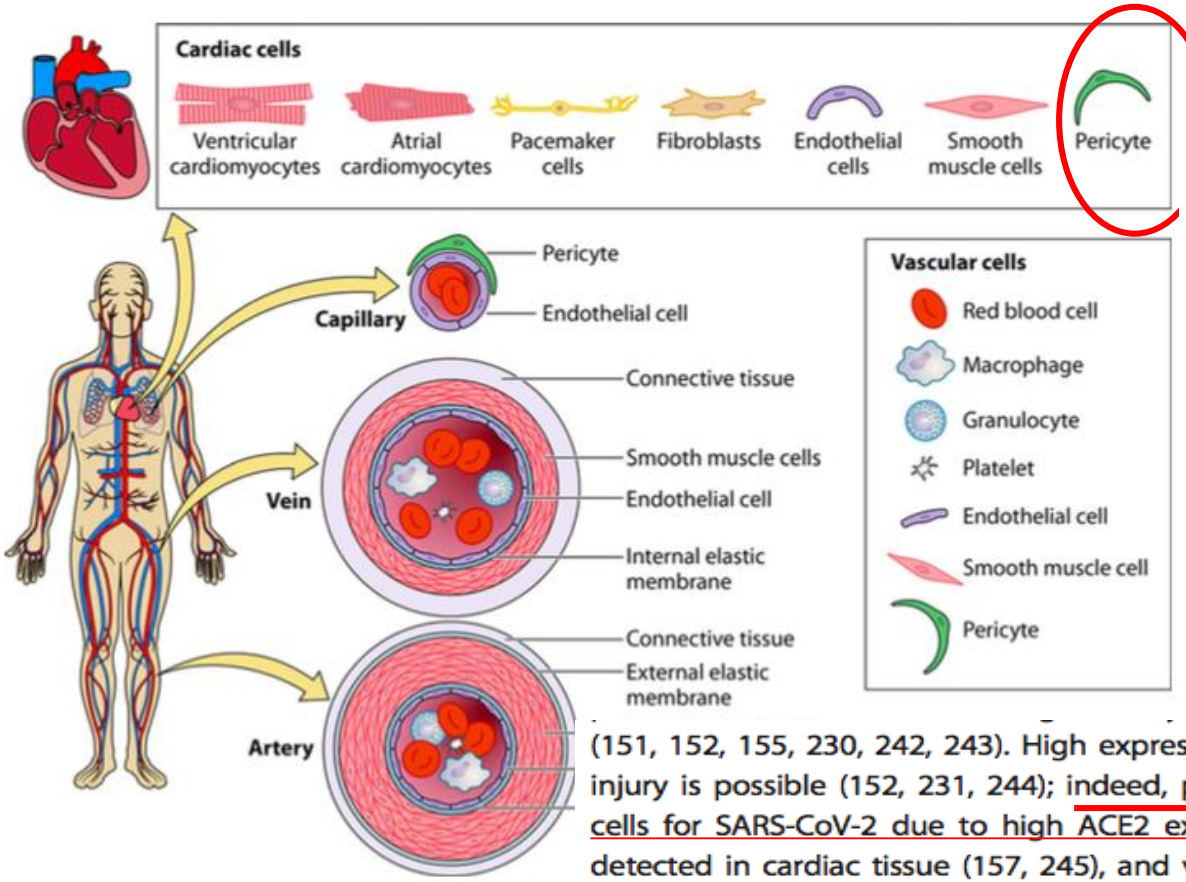

Fig. 1 | **Current understanding of predominant COVID-19 neurological disease mechanisms.** Mechanisms include a systemic inflammatory response (1), a prothrombotic state (2) and direct viral invasion (3).

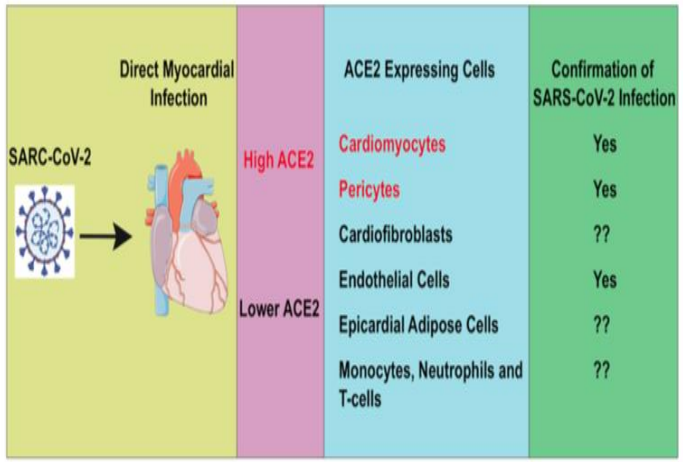
## Key advances

- 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].

# 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]




(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

# Cardiovascular involvement in patients with 2019 novel coronavirus disease

**Table 1: Cardiovascular involvements in patients with COVD-19**

| | Reference | Race | Study participants | No. of patients | Prevalence |
|---|---|---|---|---|---|
| **Pre-cardiovascular diseases** | | | | | |
| Hypertension | 31 | Chinese | COVID-19 | 138 | 31.2% |
| | 34 | Chinese | COVID-19 | 2068 | 34.2% |
| | 35 | Chinese | COVID-19 | 1,099 | 15.0% |
| | 36 | Caucasian | COVID-19 | 393 | 50.1% |
| | 39 | Caucasian | COVID-19 | 1,591 | 49.0% |
| Coronary heart disease | 34 | Chinese | COVID-19 | 2,068 | 8.8% |
| | 35 | Chinese | COVID-19 | 1,099 | 2.5% |
| | 36 | Caucasian | COVID-19 | 393 | 13.7% |
| Diabetes | 34 | Chinese | COVID-19 | 2,068 | 14.1% |
| | 35 | Chinese | COVID-19 | 1,099 | 7.4% |
| | 36 | Caucasian | COVID-19 | 393 | 25.2% |
| | 39 | Caucasian | COVID-19 | 1,591 | 17.0% |



Li C et al. J Transl Intern Med 2021; 9:152-160

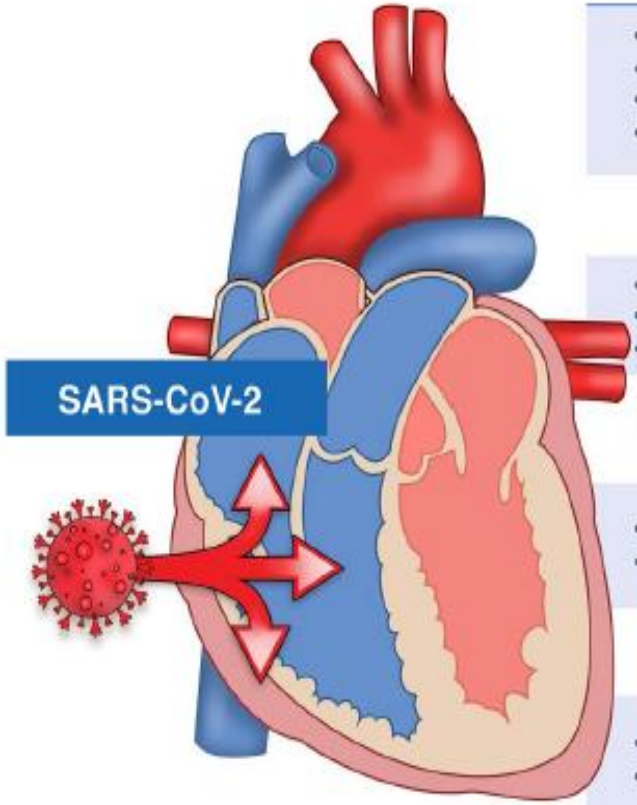
# Cardiovascular involvement in patients with 2019 novel coronavirus disease

| Cardiovascular complications | | | | | |
|---|---|---|---|---|---|
| Myocardial injury | 10 | Chinese | COVID-19 | 671 | 15.8% |
| | 34 | Chinese | COVID-19 | 2,068 | 8.8% |
| Acute coronary syndrome | 42 | Caucasian | COVID-19 with ST-segment elevation | 28 | 85.7% |
| | 34 | Chinese | COVID-19 | 2,068 | 0.2% |
| Heart failure | 45 | Chinese | COVID-19 | 799 | 49.0% |
| | 45 | Chinese | Died COVID-19 | 113 | 85.0% |
| | 34 | Chinese | COVID-19 | 2,068 | 64.3% |
| Arrhythmia | 31 | Chinese | COVID-19 | 138 | 16.7% |
| | 31 | Chinese | COVID-19 in intensive care unit | 36 | 44.4% |
| | 31 | Chinese | COVID-19 in non-intensive care unit | 102 | 6.9% |
| | 34 | Chinese | COVID-19 with elevated hs-cTnI | 227 | 47.1% |
| | 34 | Chinese | COVID-19 without elevated hs-cTnI | 249 | 12.4% |
| Coagulopathy | 35 | Chinese | COVID-19 | 1,099 | 46.4% |
| | 7 | Chinese | COVID-19 | 191 | 42.0% |
| | 34 | Chinese | COVID-19 | 2,068 | 58.6% |
| Myocarditis | - | - | - | - | - |



Li C et al. J Transl Intern Med 2021; 9:152-160

# Cardiac injury mechanisms in critically ill COVID-19 patients




## Pathogenic mechanisms

### Myocardial oxygen supply-demand imbalance

- Severe hypoxemia
- Hypoperfusion
- Shock
- Stress-induced cardiomyopathy

### Right ventricular dysfunction

- Acute respiratory distress syndrome
- Positive pressure mechanical ventilation
- Pulmonary thromboembolism

### Diffuse endotheliitis and procoagulant activity

- SARS-CoV-2 interactions with heart ACE-2 receptors
- Cytokine storm

### Myocardial injury

- Direct viral lesion of endothelial cells
- Direct viral lesion of myocardial cells

## Clinical Presentations

### Acute cardiac injury (ACI)

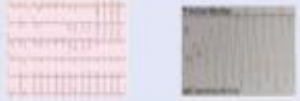
- Biomarkers abnormalities

### Acute coronary syndrome

- Chest pain
- Shock/cardiac arrest
- EKG abnormalities
- Troponin elevated

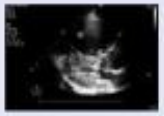
### Arrhythmias

- EKG abnormalities
- Shock
- Cardiac arrest



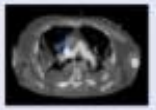
### Acute cor pulmonale

- Right heart failure
- Shock



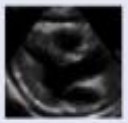
### Thromboembolism

- Deep venous thrombosis
- Chest pain/right heart failure
- Troponin elevated



### Myocarditis +/- pericardial effusion

- Chest pain
- Left/right heart failure
- Shock/cardiac arrest
- EKG abnormalities
- Troponin elevated



Helmes J et al. Intensive Care Med 2021

JAMA Network Open

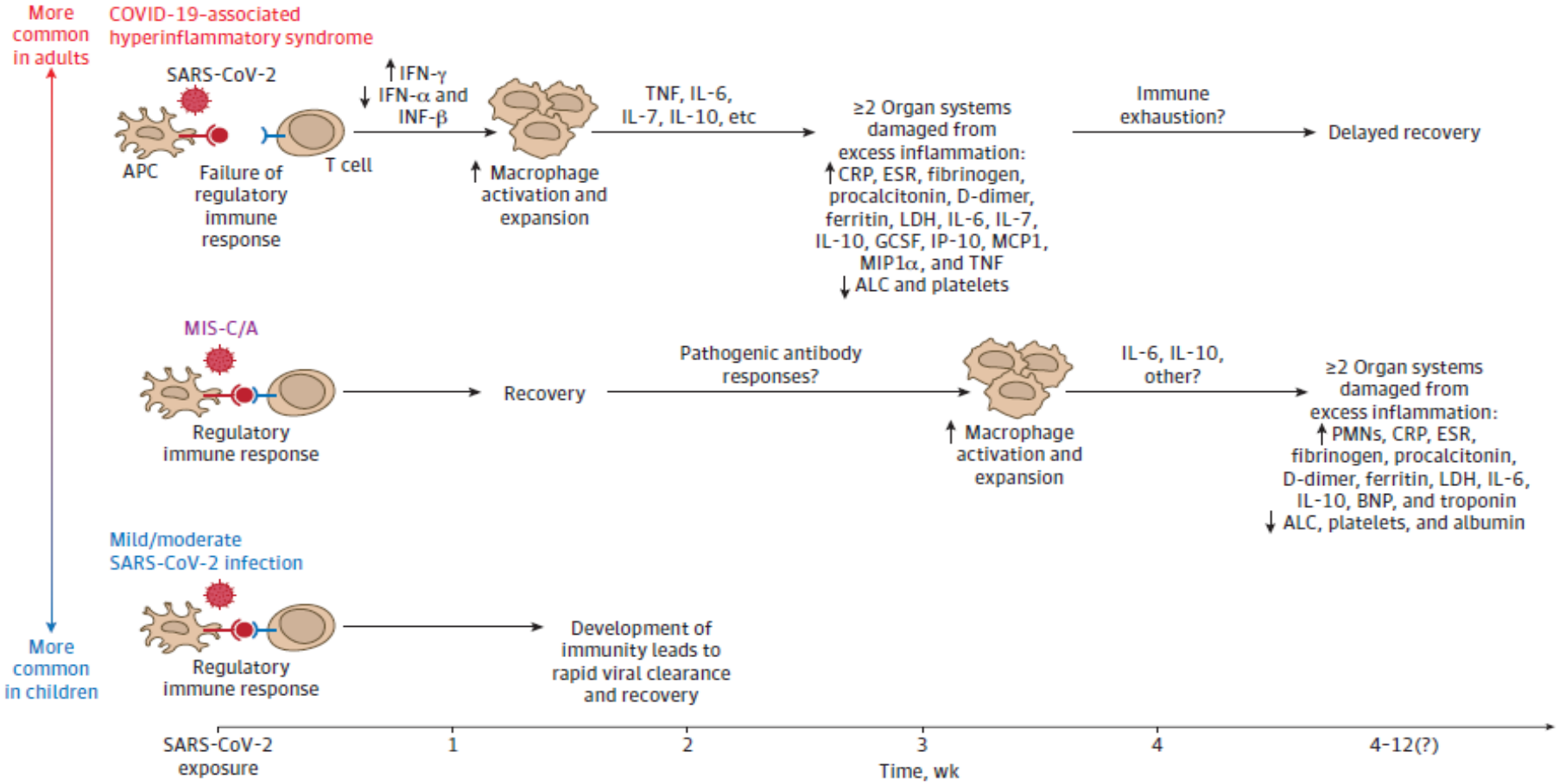
Original Investigation | Infectious Diseases

# Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults
## A Systematic Review

JAMA Network Open 2021;4:e2126456

Pragna Patel, MD, MPH; Jennifer DeCuir, MD, PhD; Joseph Abrams, PhD; Angela P. Campbell, MD, MPH; Shana Godfred-Cato, DO; Ermias D. Belay, MD

**Figure 3. Potential Mechanisms of Inflammatory Syndromes Associated With SARS-CoV-2**



JAMA Network | Open

Original Investigation | Infectious Diseases

# Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults
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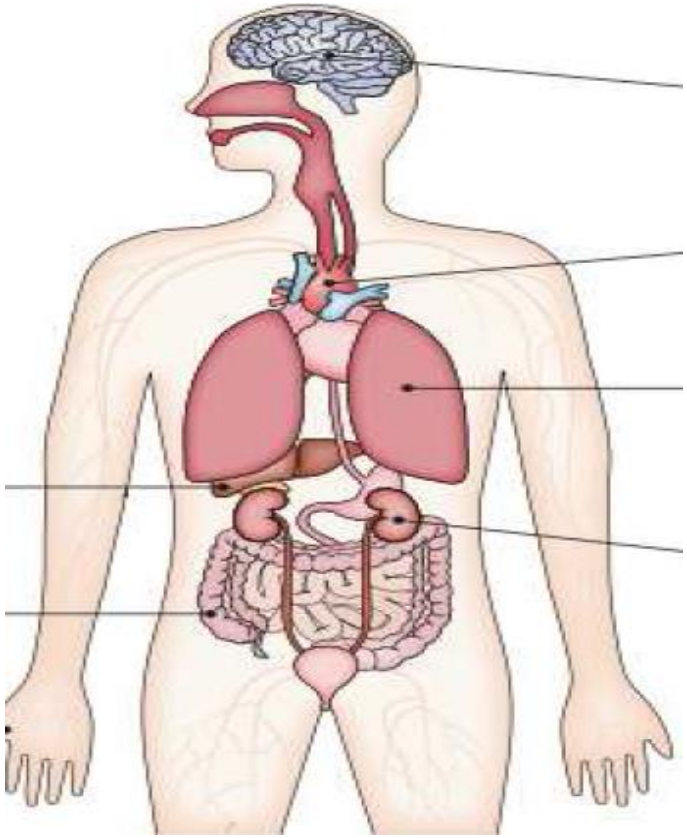

Median age 21 years

Male 70%

No underlying comorbidity 58%

COVID-like illness 4 weeks before

Median number of organ systems involved 5

# 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.