COLOURS OF SEPSIS

# Pathophysiology of COVID-19

Marcin Osuchowski

LUDWIG BOLTZMANN INSTITUTE
Traumatology
The Research Center in Cooperation with AUVA

AUVA

# Disclosures

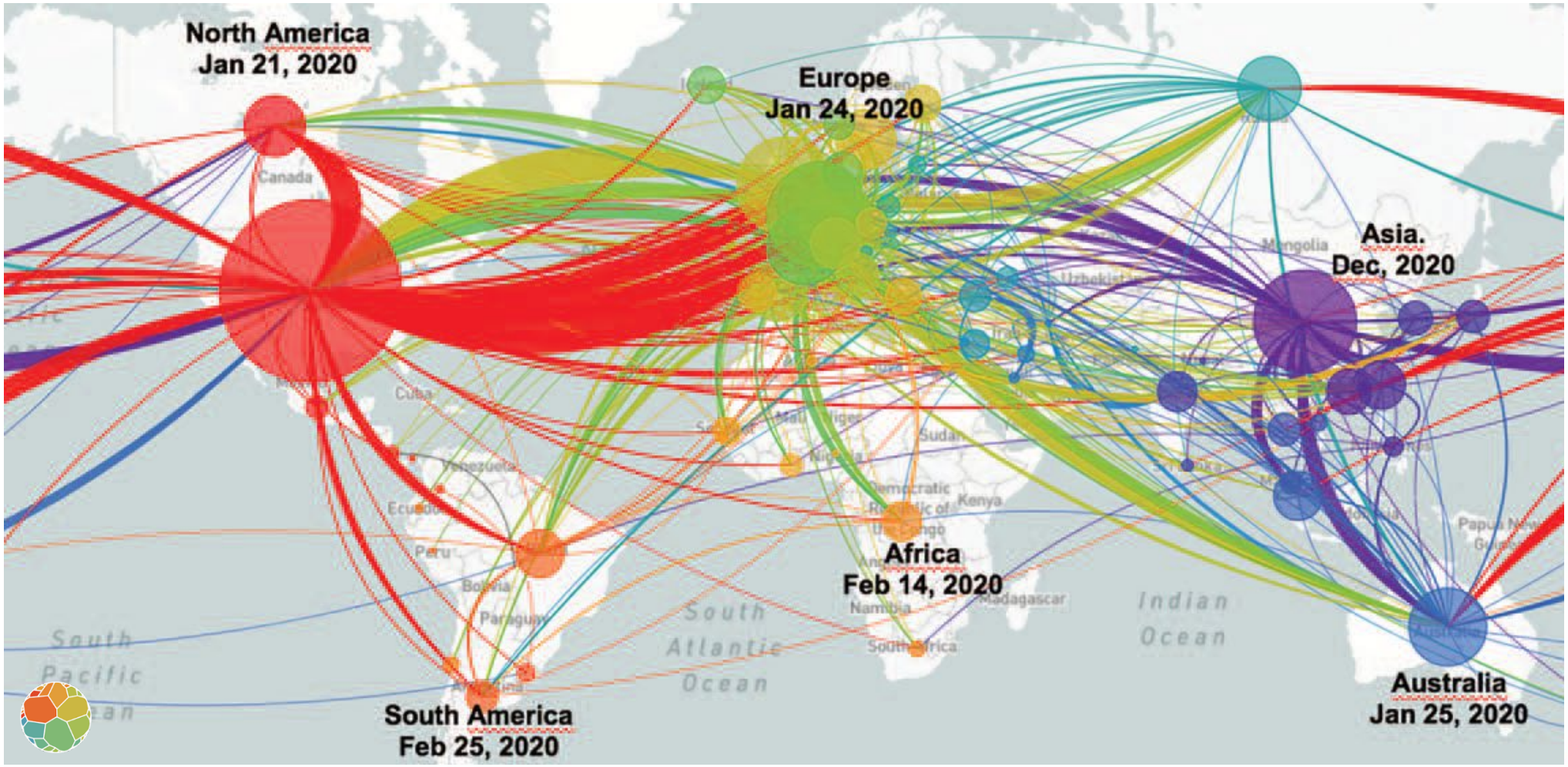
I do not have conflict of interest for this talk

I have never personally treated any COVID-19 patients

The Shock & Lancet Resp Med review interpretations of C-19 data presented here are a team effort as they largely stem from the collegial brainstorming of ESS and EGIS groups that created them.

**ESS**: European Shock Society, **EGIS**: European Group on Immunology of Sepsis

# COVID-19: the Beginning…

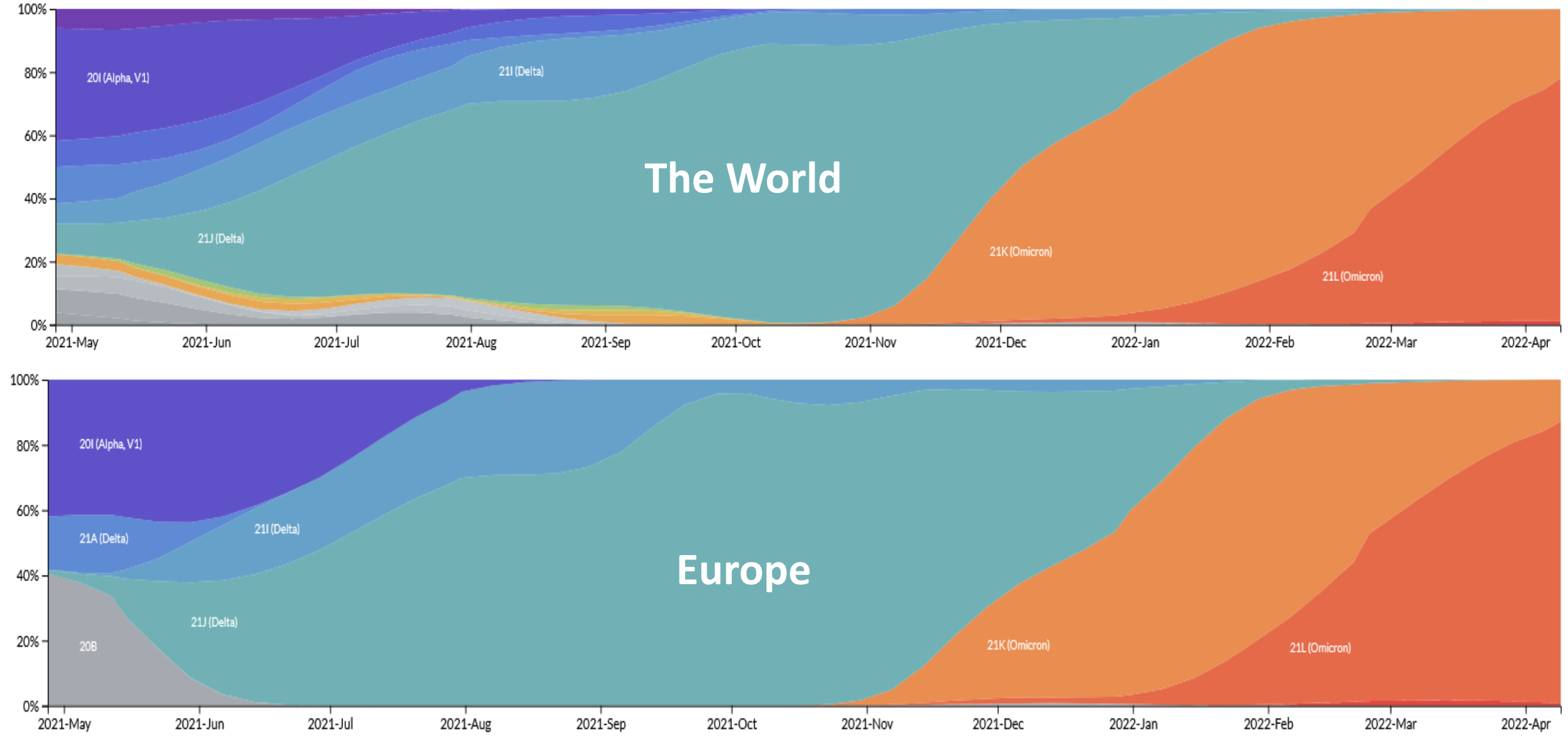



Variant

- 20I (Alpha, V1)
- 20H (Beta, V2)
- 20J (Gamma, V3)
- 21A (Delta)
- 21I (Delta)
- 21J (Delta)
- 21K (Omicron)
- 21L (Omicron)
- 21G (Lambda)
- 21H (Mu)

**SHOCK,** Vol. 54, No. 4, pp. 416–437, 2020

# SARS-CoV-2: the Evolution of the Variants

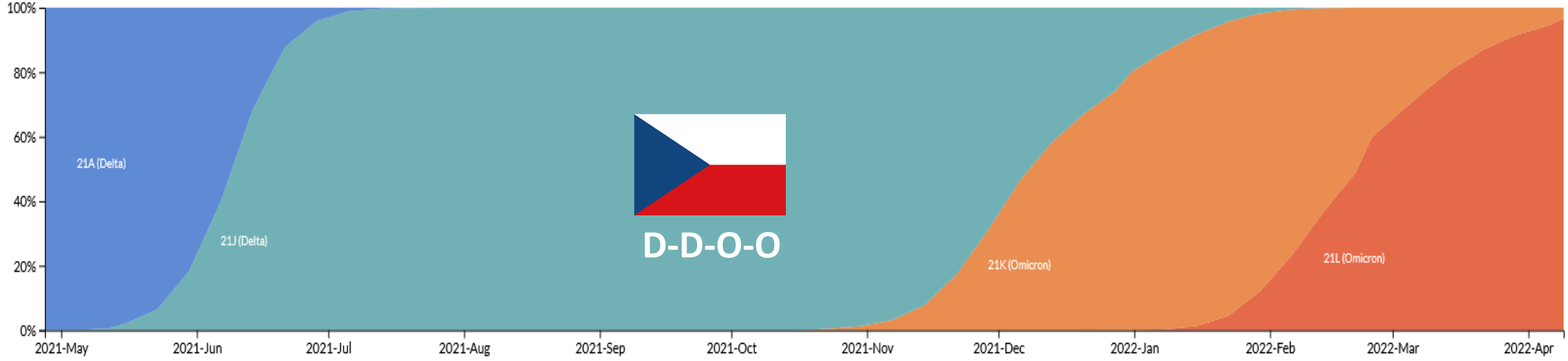






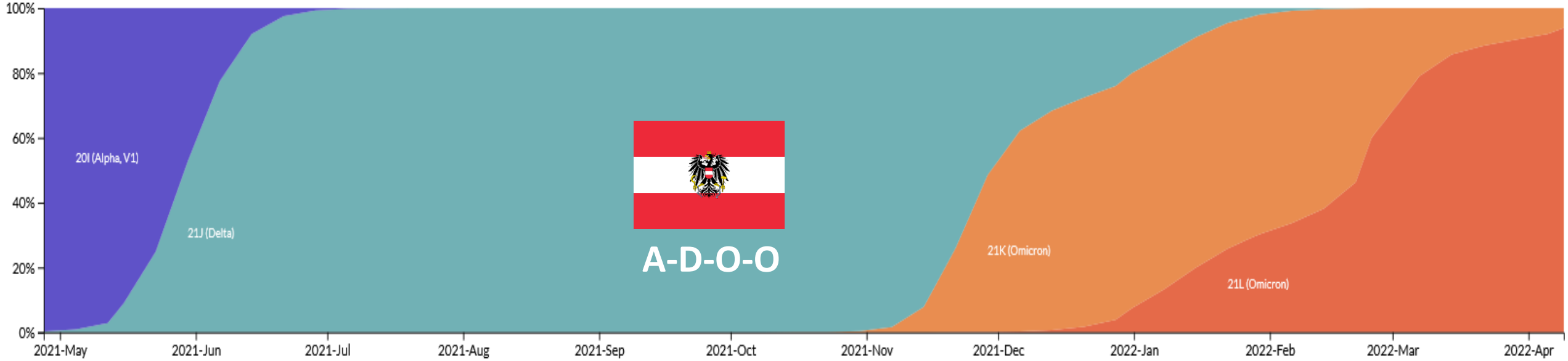
https://nextstrain.org/ncov

# SARS-CoV-2: the Evolution of the Variants






D-D-O-O

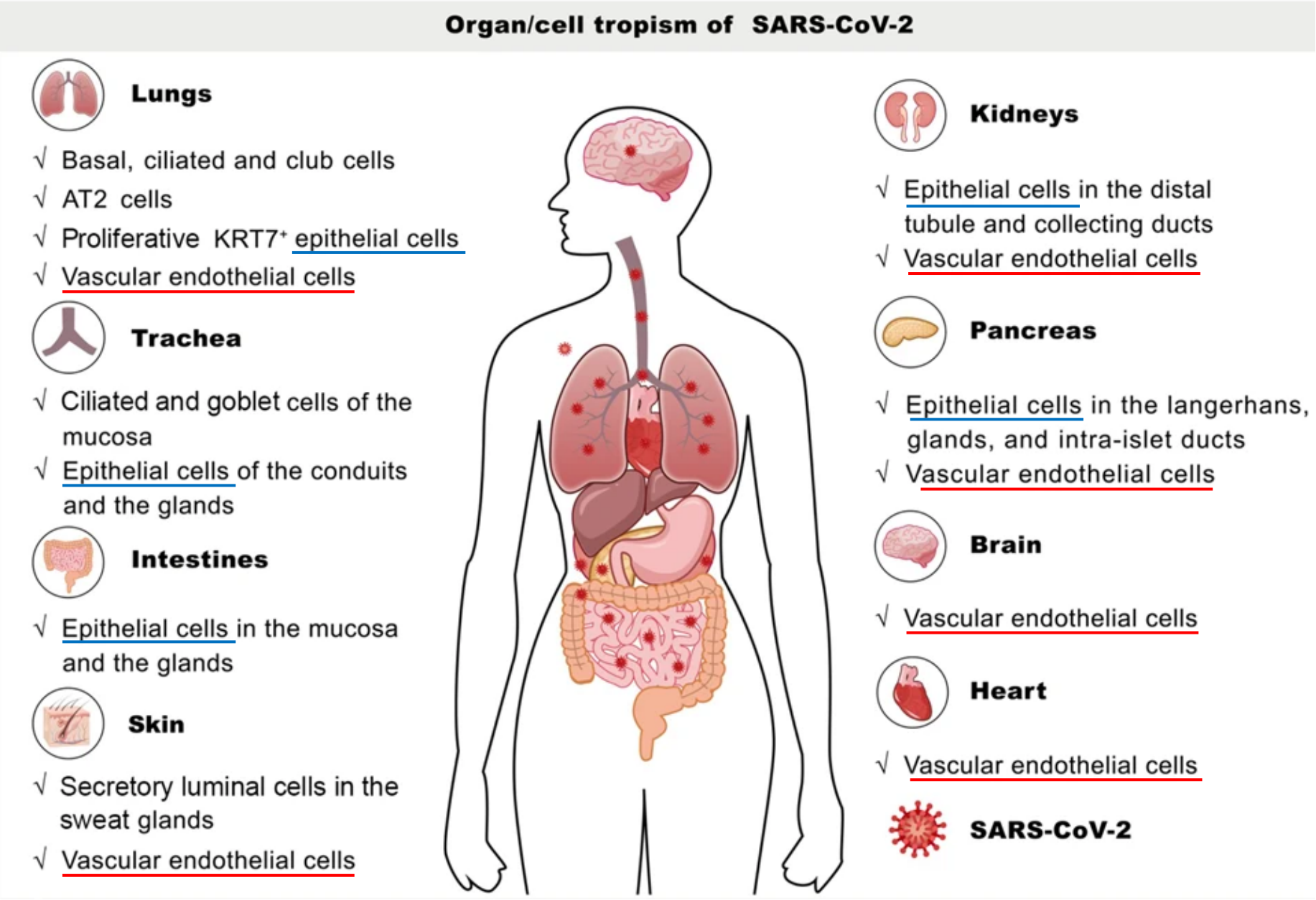





A-D-O-O

https://nextstrain.org/ncov

# Virus Tropism Mainly Correlates with ACE2 Tissue Distribution



# Schematic Diagram of SARS-CoV-2 Entry Pathways

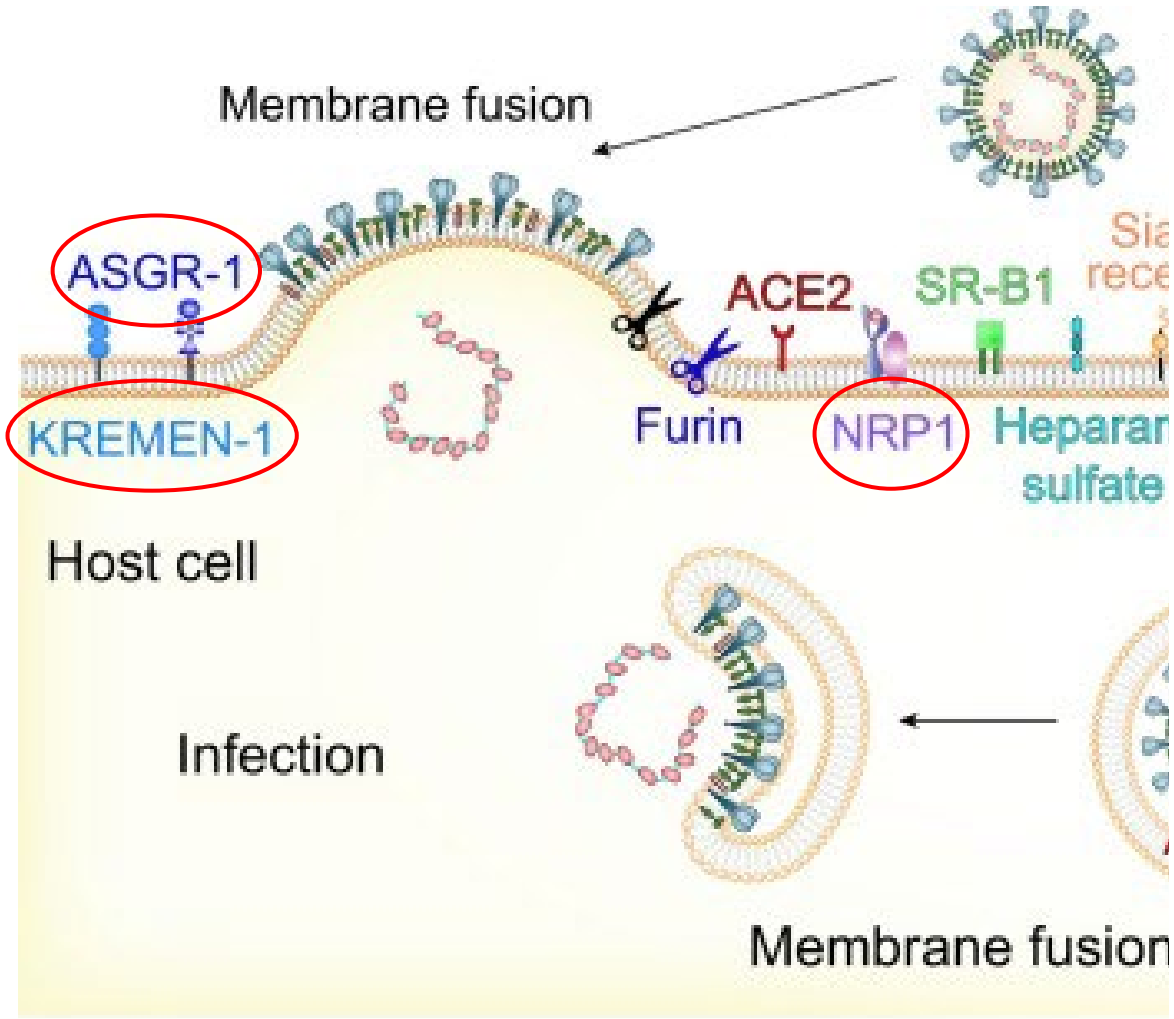



Table 1. Receptors, coreceptors, and cofactors involved in SARS-CoV-2 entry

| Molecule | Category | Functional annotation |
|---|---|---|
| ACE2 | Receptor | The major entry receptor |
| AXL | Receptor | A potential alternative receptor independent of ACE2 |
| KREMEN1 | Receptor | A potential alternative receptor independent of ACE2 |
| ASGL1 | Receptor | A potential alternative receptor independent of ACE2 |
| CD147 | Receptor | A potential alternative receptor independent of ACE2 |
| Heparan sulfate | Coreceptor | Auxiliary attachment receptor, dependent on ACE2 |
| Sialic acid | Coreceptor | Auxiliary attachment receptor, dependent on ACE2 |
| Lectin receptors | Coreceptor | Auxiliary attachment receptor, dependent on ACE2 |
| Neuropilin 1 | Coreceptor | Auxiliary attachment receptor, dependent on ACE2 |
| CD4 | Coreceptor | Potential auxiliary attachment receptor, dependent on ACE2 |
| SR-B1/ cholesterol | Cofactor | The S protein binds to cholesterol, and SR-B1 increases virion endocytosis by promoting cholesterol uptake |
| Furin | Cofactor | Proteolysis of S protein at the S1/S2 site |
| PC-1 | Cofactor | Proteolysis of S protein at the S1/S2 site |
| Trypsin | Cofactor | Proteolysis of S protein at the S1/S2 site |
| Matriptase | Cofactor | Proteolysis of S protein at the S1/S2 site |
| Cathepsins | Cofactor | Proteolysis of S protein at the S1/S2 and S2' sites |
| TMPRSS2 | Cofactor | Proteolysis of S protein at the S2' site |

**alternative/auxiliary (co)receptors**

NRP1: neuropilin 1
KREMEN-1: Kringle Containing Transmembrane Protein 1
ASGR-1: Asialoglycoprotein receptor 1

Peng et al.
Trends Biochem Sci. 2021

**SHOCK,** Vol. 54, No. 4, pp. 416–437, 2020

**May 5, 2020**

*Review Article*

# SARS-COV-2/COVID-19: EVOLVING REALITY, GLOBAL RESPONSE, KNOWLEDGE GAPS, AND OPPORTUNITIES

**Marcin F. Osuchowski,[*] Federico Aletti,[†] Jean-Marc Cavaillon,[‡] Stefanie B. Flohé,[§] Evangelos J. Giamarellos-Bourboulis,[‖] Markus Huber-Lang,[¶] Borna Relja,[#] Tomasz Skirecki,[**] Andrea Szabó,[††] and Marc Maegele[‡‡§§]**

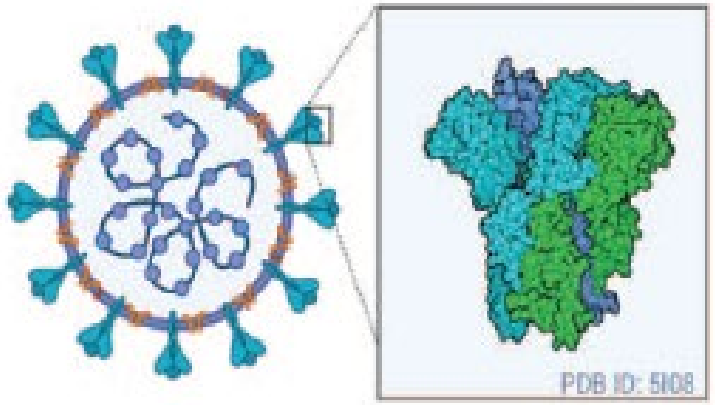
*[*]Ludwig Boltzmann Institute for Experimental and Clinical Traumatology in the AUVA Trauma Research Center, Vienna, Austria; [†]Department of Bioengineering, University of California San Diego, La Jolla, California; [‡]National Research Agency, Paris, France; [§]Department of Trauma, Hand, and Reconstructive Surgery, University Hospital Essen, University Duisburg-Essen, Essen, Germany; [‖]4th Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, Athens, Greece; [¶]Institute of Clinical and Experimental Trauma-Immunology, University Hospital Ulm, Ulm University, Ulm, Germany; [#]Experimental Radiology, Department of Radiology and Nuclear Medicine, Otto von Guericke University Magdeburg, Magdeburg, Germany; [**]Laboratory of Flow Cytometry, Centre of Postgraduate Medical Education, Warsaw, Poland; [††]Institute of Surgical Research, University of Szeged, Szeged, Hungary; [‡‡]Department of Trauma and Orthopaedic Surgery, Cologne-Merheim Medical Center (CMMC), University of Witten/Herdecke, Cologne-Merheim Campus, Cologne, Germany; and [§§]Institute for Research in Operative Medicine (IFOM), University of Witten/Herdecke, Cologne-Merheim Campus, Cologne, Germany*

Received 22 Apr 2020; first review completed 29 Apr 2020; accepted in final form 5 May 2020

# Defining "Goodness and Badness"

(on May 5, 2020)

- IFN I & III induction
- Coordinated monocyte response
- Induction of $T_{fh}$
- Activation of ASCs
- Seroconversion




- Inflammasome activation
- Endothelial & epithelial injury
- Coagulopathy
- CTL overactivation
- Inflammatory monocyte
- Activation of BM monocytes
- Failure to generate protective Abs

Beneficial response

Pathological response

**$T_{fh}$**: follicular helper T cells, **ASC**: antibody secreting cells, **CTL**: cytotoxic T-cells, **BM**: bone marrow

**SHOCK,** Vol. 54, No. 4, pp. 416–437, 2020

egis European Group on Immunology of Sepsis

May 6, 2021

# COVID-19: Pathophysiology of Acute Disease 1

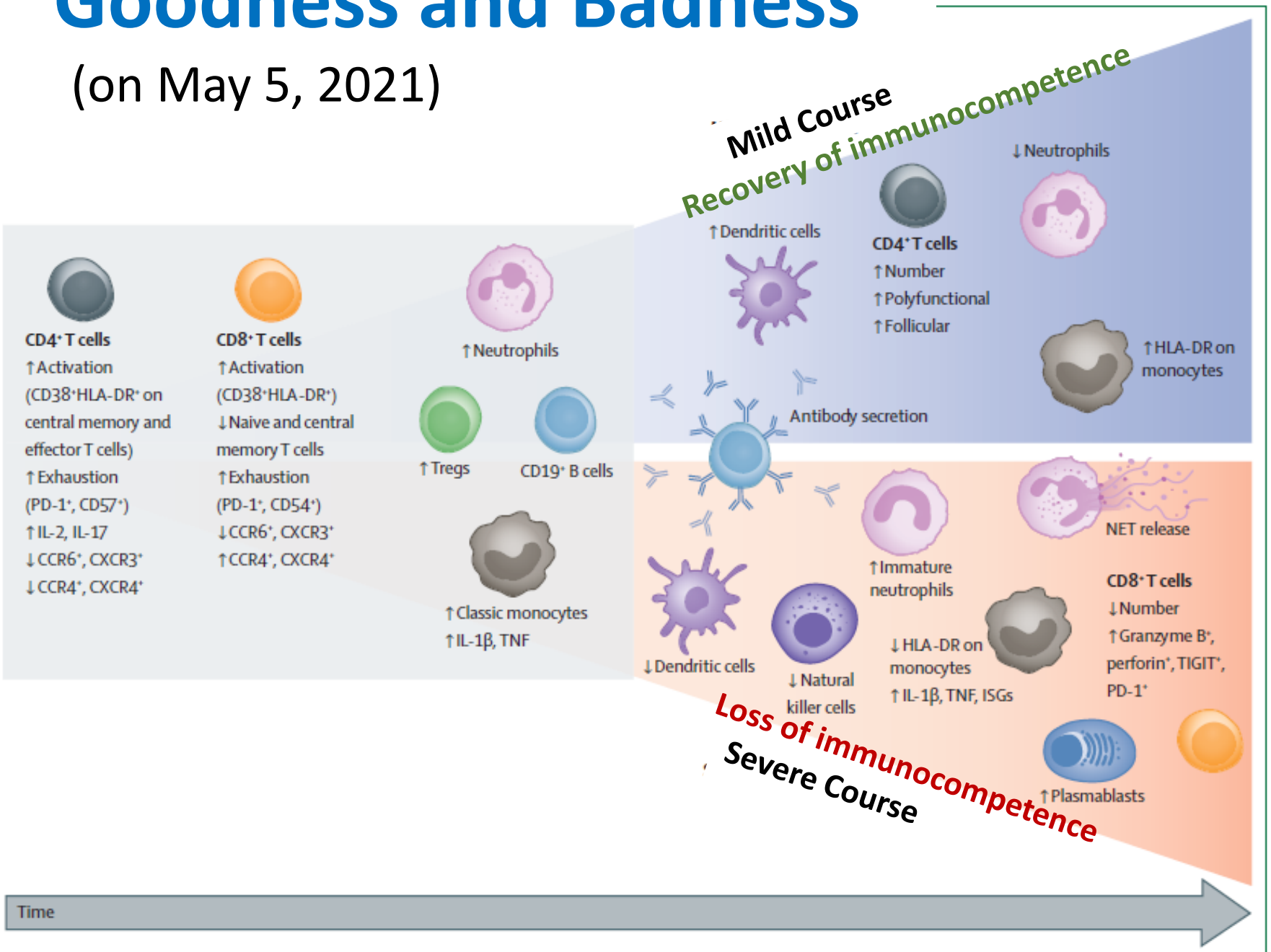
# The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity

*Marcin F Osuchowski*, Martin S Winkler*, Tomasz Skirecki, Sara Cajander, Manu Shankar-Hari, Gunnar Lachmann, Guillaume Monneret, Fabienne Venet, Michael Bauer, Frank M Brunkhorst, Sebastian Weis, Alberto Garcia-Salido, Matthijs Kox, Jean-Marc Cavaillon, Florian Uhle, Markus A Weigand, Stefanie B Flohé, W Joost Wiersinga, Raquel Almansa, Amanda de la Fuente, Ignacio Martin-Loeches, Christian Meisel, Thibaud Spinetti, Joerg C Schefold, Catia Cilloniz, Antoni Torres, Evangelos J Giamarellos-Bourboulis, Ricard Ferrer, Massimo Girardis, Andrea Cossarizza, Mihai G Netea, Tom van der Poll, Jesús F Bermejo-Martín, Ignacio Rubio*

Lancet Respir Med 2021; 9: 622–42

# Defining "Goodness and Badness"

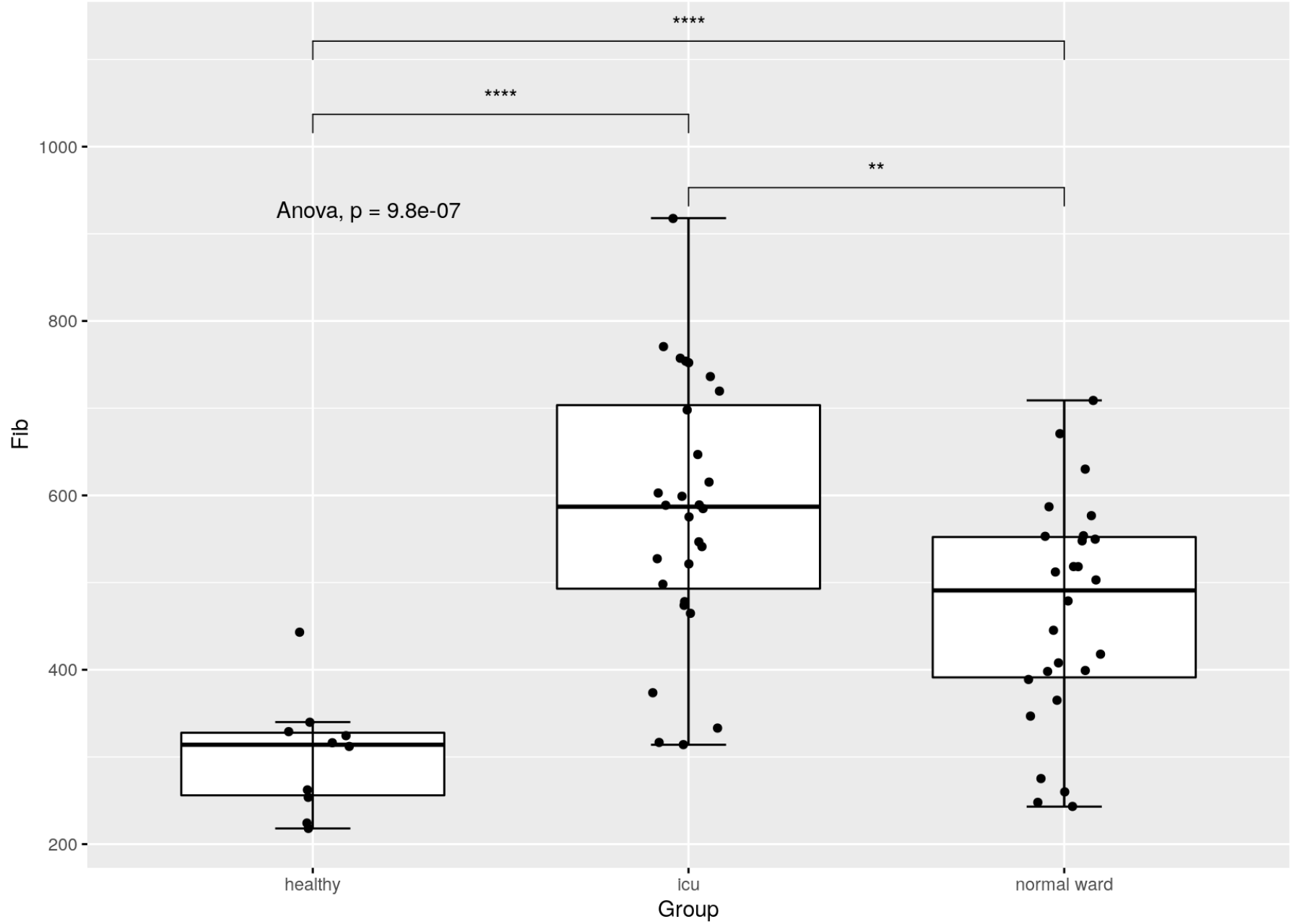
(on May 5, 2021)




*Lancet Respir Med* 2021; 9: 622–42

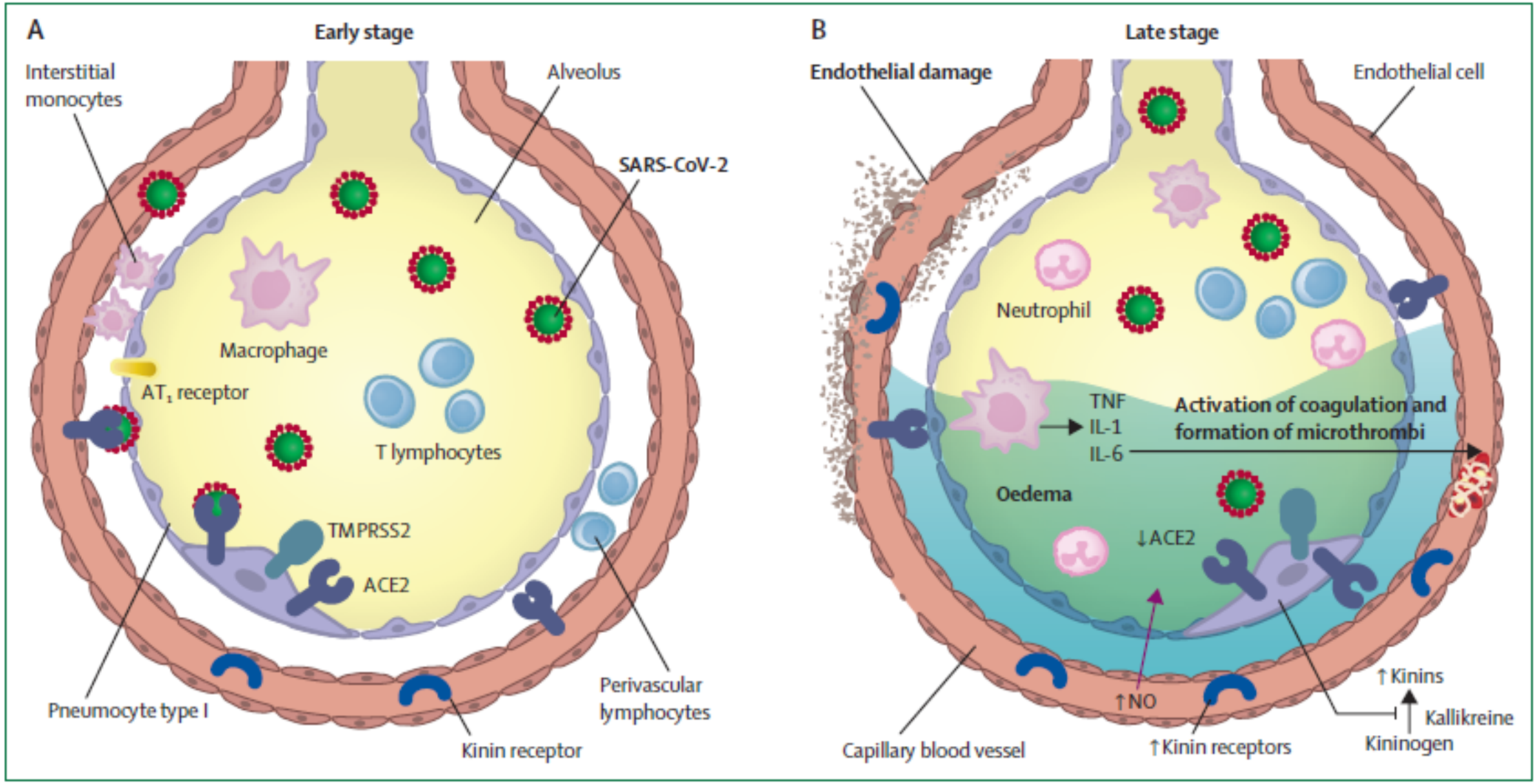
Fib

AUC: 0.7198




MEDICALNEWSTODAY

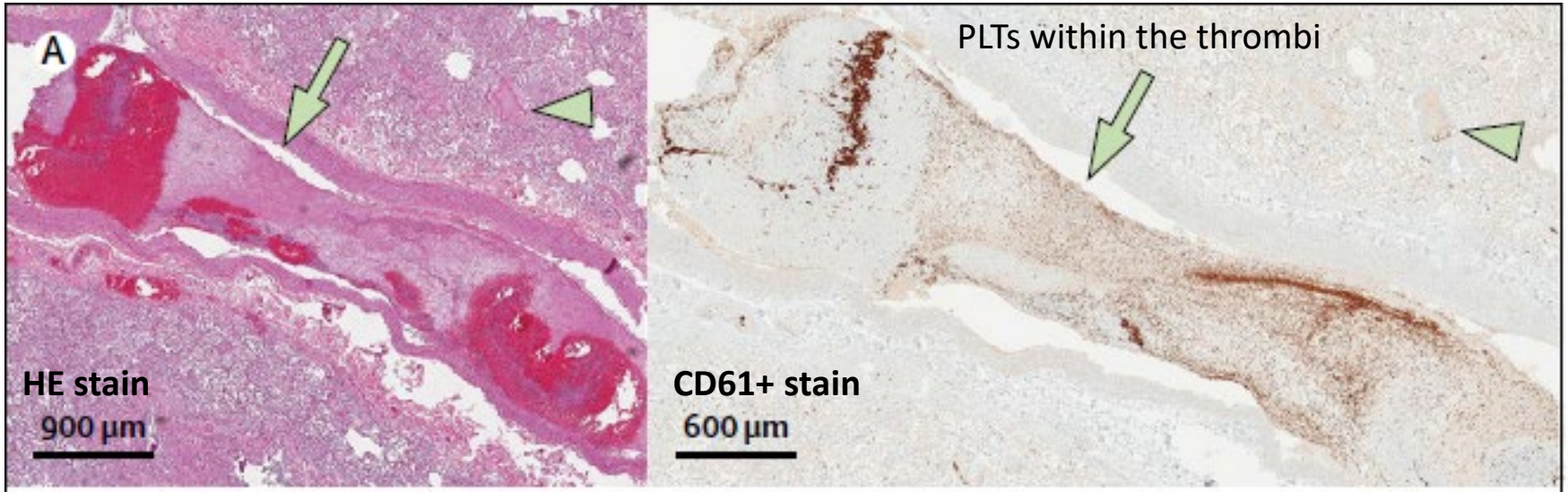
# Alveolar epithelial and endothelial damage, and coagulopathy in COVID-19




*Lancet Respir Med* 2021; 9: 622–42

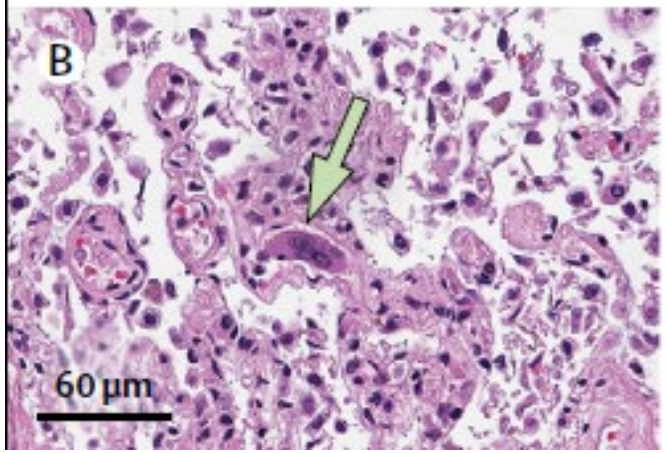
# Diffuse Alveolar Damage, Microangiopathy, Alveolar/Vascular Thrombosis

thrombus in a small pulmonary artery

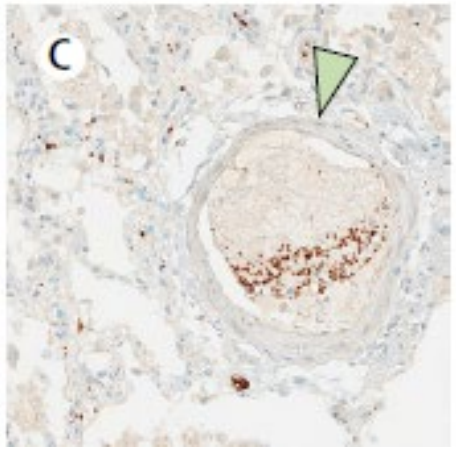




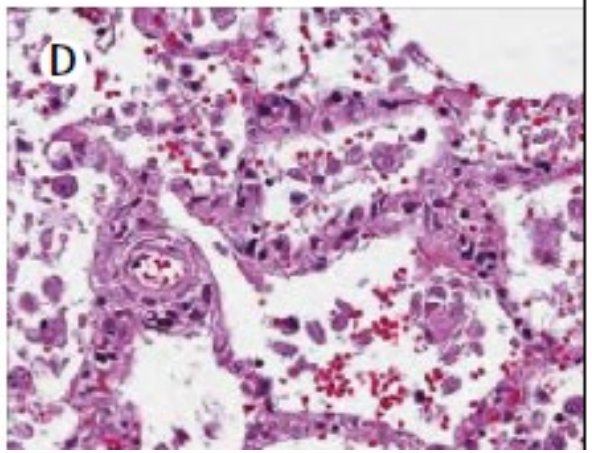





megakaryocytes in alveolar capillaries

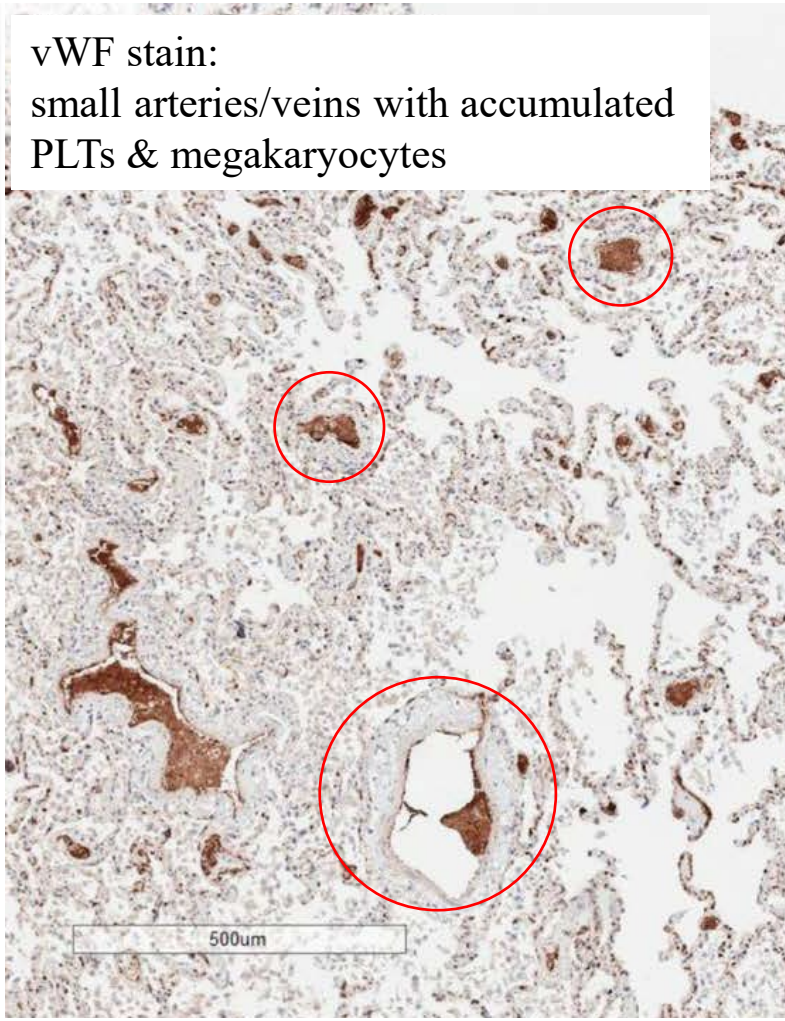



fibrin/PLT thrombus




perivascular LYM aggregates

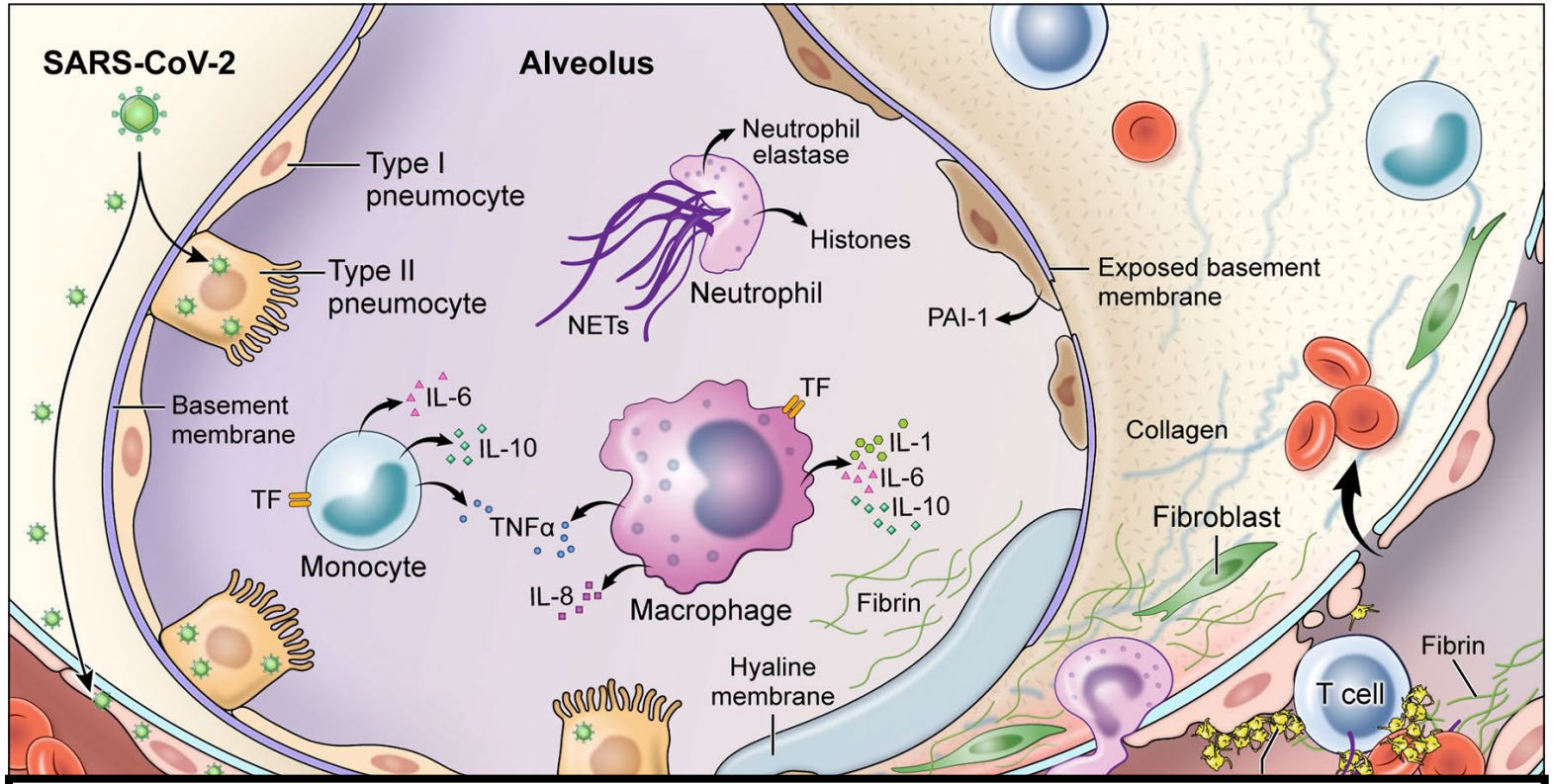
vWF stain:
small arteries/veins with accumulated PLTs & megakaryocytes




Sharon E Fox, Aibek Akmatbekov, Jack L Harbert, Guang Li, J Quincy Brown, Richard S Vander Heide **Lancet Respir Med** 2020; 8: 681–86

# Coagulopathy in the Alveolus & Capilary

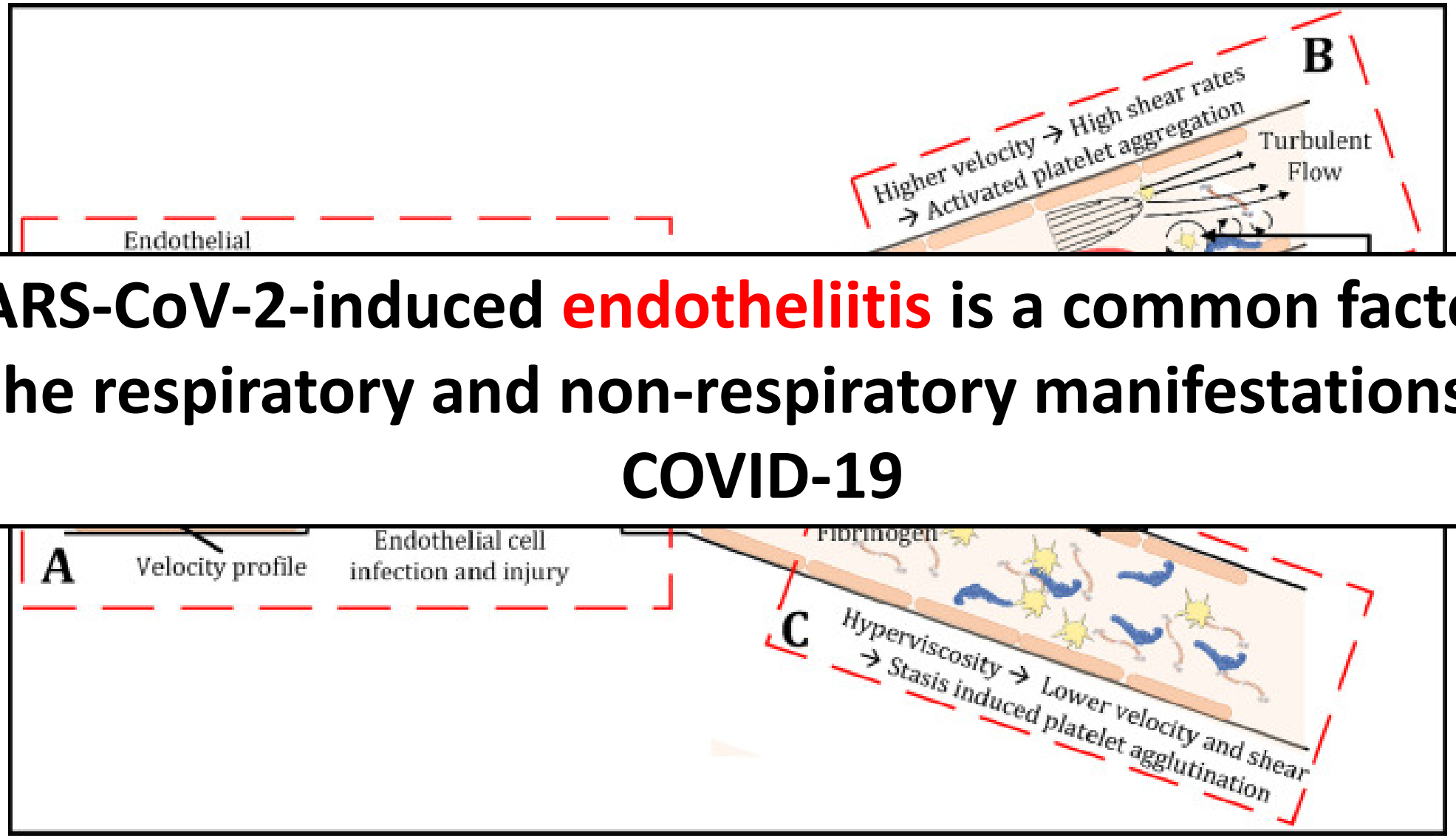
Immune activation and mechanisms of coagulopathy




# NOT a Classical DIC!

- mildly/not prolonged PT/aPTT
- Mild thrombocytopenia
- High/very high fibrinogen
- High D-dimers

# COVID-19 and thrombosis: The role of hemodynamics

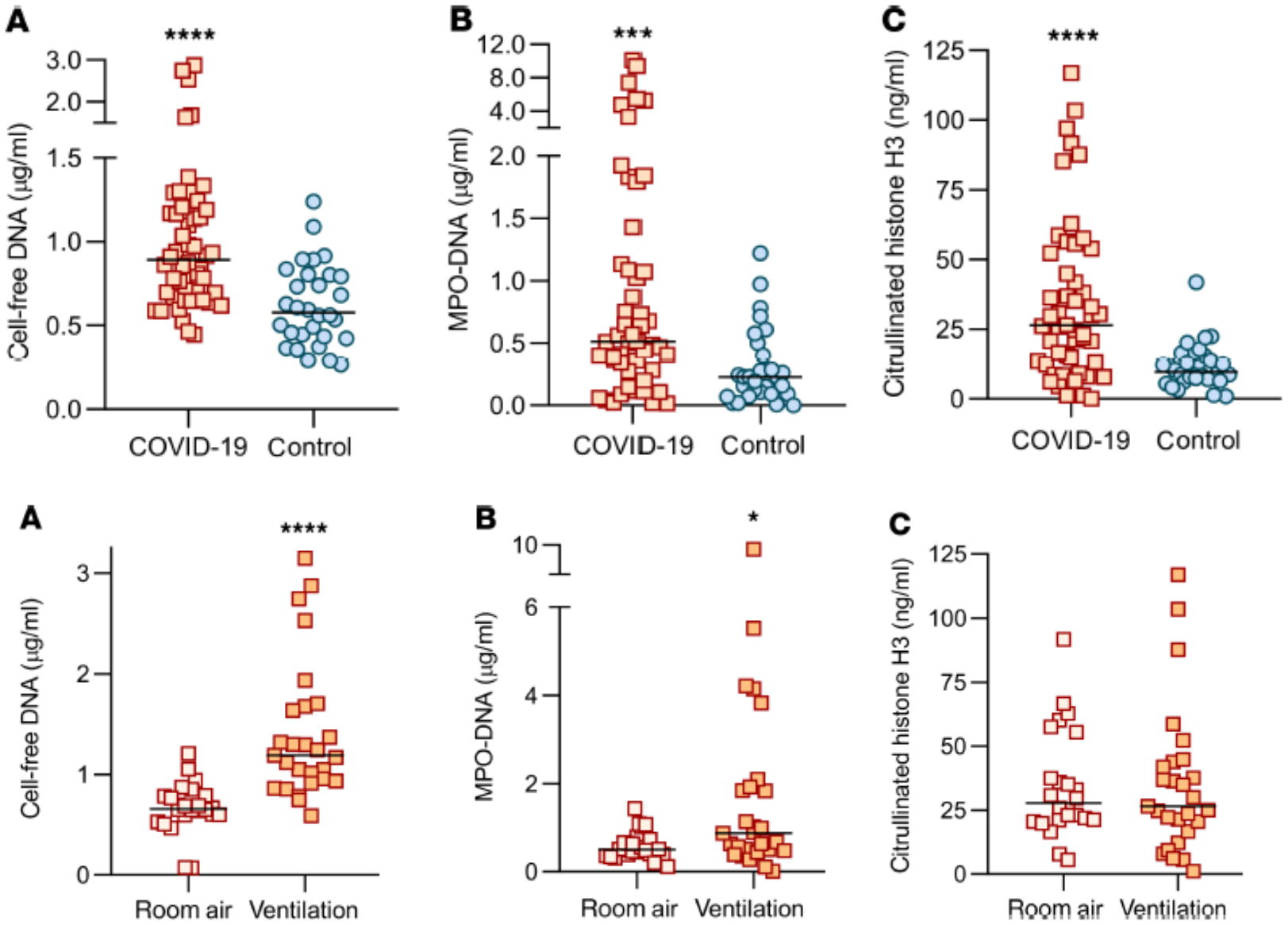



**SARS-CoV-2-induced endotheliitis is a common factor in the respiratory and non-respiratory manifestations of COVID-19**

Sastry et al. Thrombosis Research 212 (2022) 51–57

# Neutrophil extracellular traps in COVID-19

JCI insight



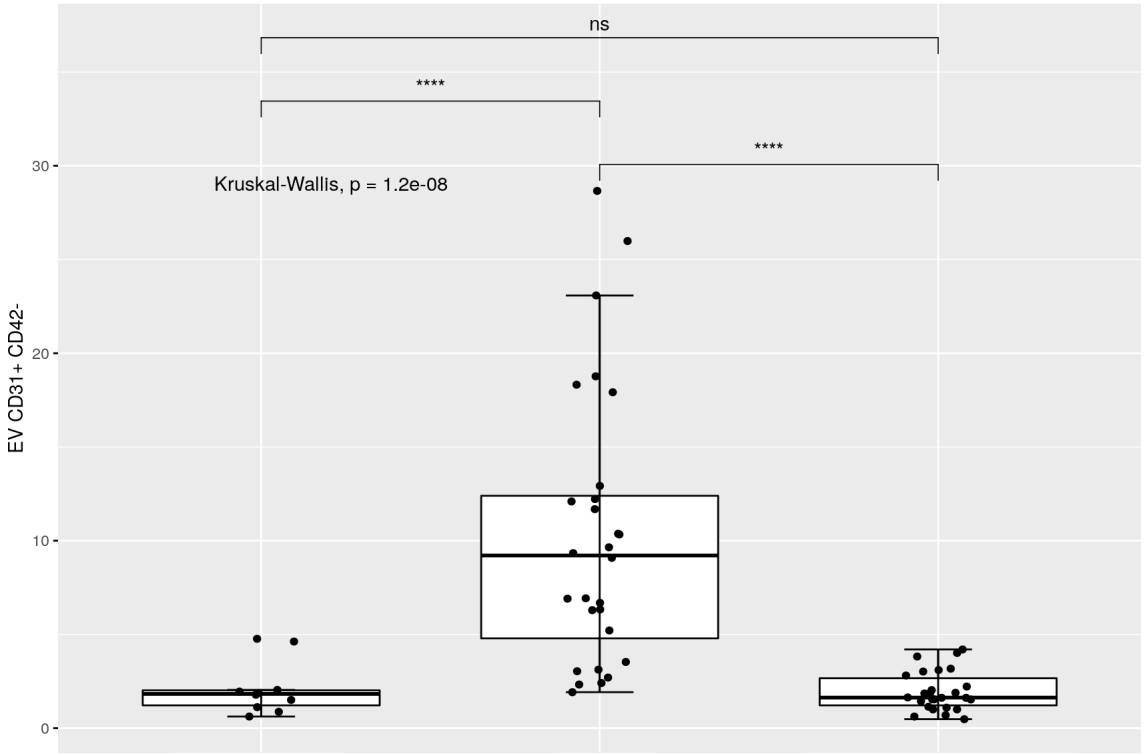

MPO-DNA: myeloperoxidase-DNA

Zuo at al. JCI Insights 2020

# High Release of Endoth./PLT-derived Extracellular Vesicles in Severe C-19

EV CD31+ endothelium

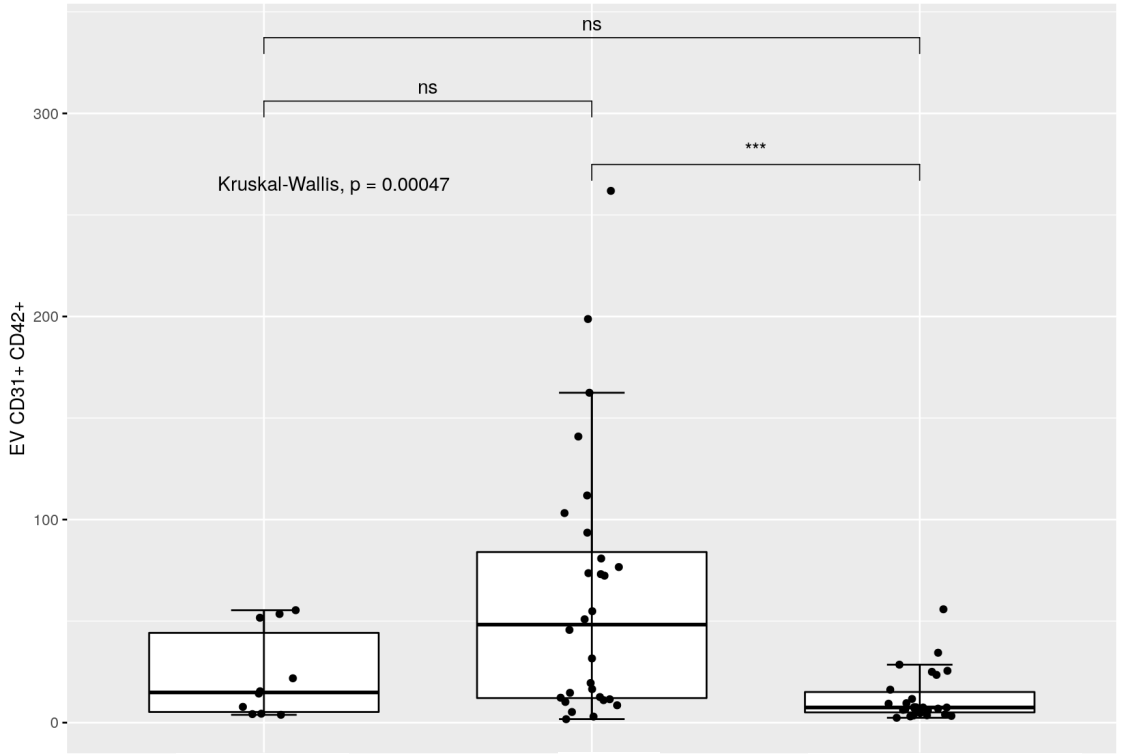
AUC: 0.9423




healthy control | ICU | normal ward

EV CD31+ CD42+ platelets

AUC: 0.8049



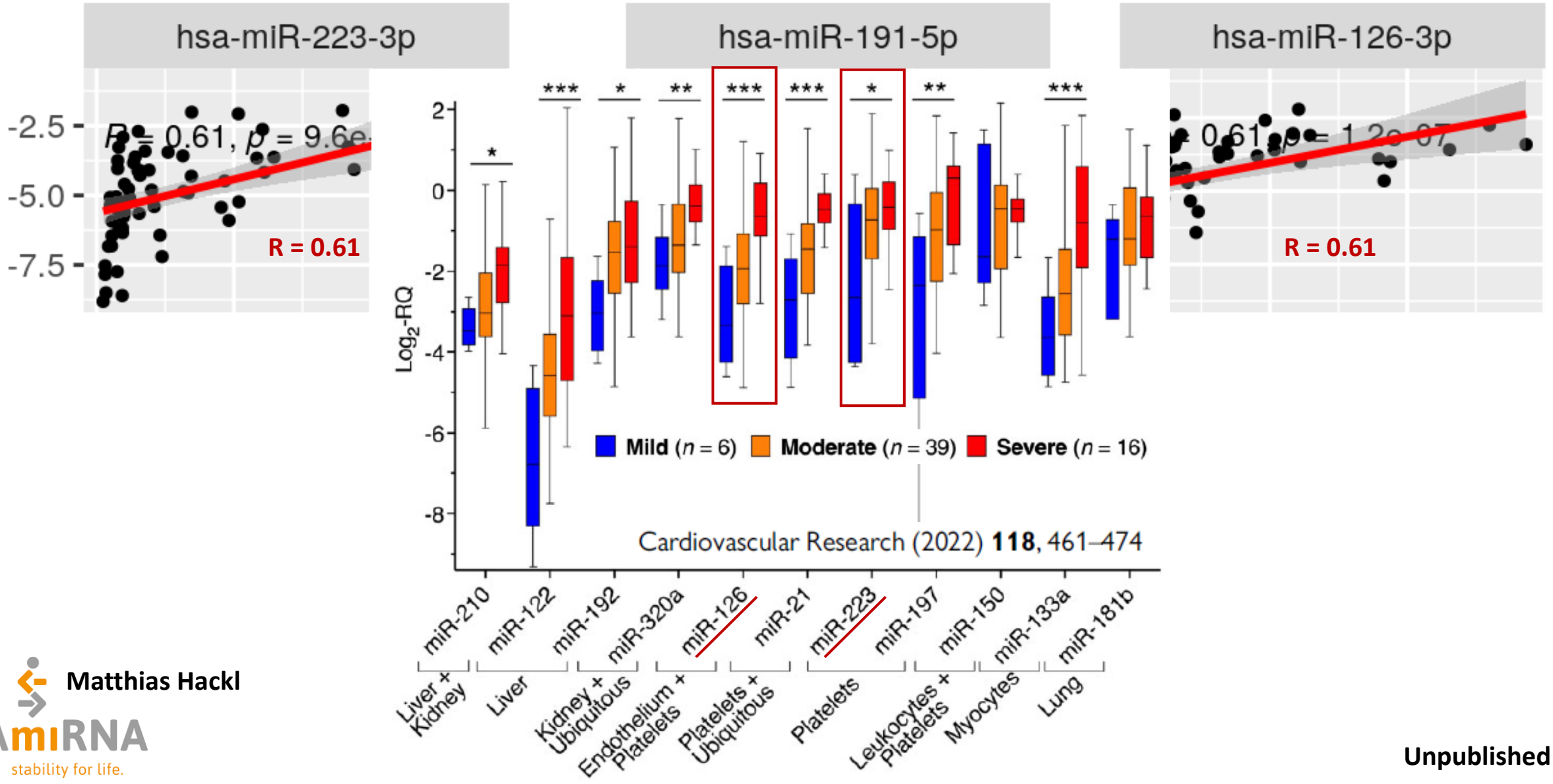

healthy control | ICU | normal ward


**Eva Schaden**
**Johannes Gratz**
**Marion Wiegele**
**Pierre Raeven**

MEDIZINISCHE UNIVERSITÄT WIEN
Allgemeines Krankenhaus der Stadt Wien


**Unpublished Data**

# microRNA signal well-correlated with the EV load in COVID-19 patients




Matthias Hackl

TAmiRNA
stability for life.

Unpublished Data

# A COVID-19 Cytokine Storm??

JCI insight 2020;5(17):e140329.

## Severe immunosuppression and not a cytokine storm characterizes COVID-19 infections

Kenneth E. Remy,[1,2,3] Monty Mazer,[1,3] David A. Striker,[4] Ali H. Ellebedy,[5] Andrew H. Walton, Jacqueline Unsinger,[3] Teresa M. Blood,[3] Philip A. Mudd,[6] Daehan J. Yi,[1] Daniel A. Mannion,[1] Dale F. Osborne,[3] R. Scott Martin,[4] Nitin J. Anand,[4] James P. Bosanquet,[4] Jane Blood,[3] Anne M. Drewry,[3] Charles C. Caldwell,[8] Isaiah R. Turnbull,[9] Scott C. Brakenridge,[10] Lyle L. Moldwawer,[10] and Richard S. Hotchkiss[2,3,9]

JOURNAL OF MEDICAL VIROLOGY WILEY J Med Virol. 2020;1–2.

## COVID-19: What type of cytokine storm are we dealing with?

Guillaume Monneret[1,2]
Ihsane Benlyamani[2]
Morgane Gossez[1,2]
Jesus F Bermejo-Martin[3,4]
Marta Martín-Fernandez[3,4]
Pierre Sesques[5]
Florent Wallet[6]
Fabienne Venet[1,2]

JAMA Internal Medicine September 2020 Volume 180, Number 9

EDITORIAL

## Is a "Cytokine Storm" Relevant to COVID-19?

Pratik Sinha, MB, ChB, PhD; Michael A. Matthay, MD; Carolyn S. Calfee, MD, MAS

SHOCK, Vol. 56, No. 5, pp. 667–672, 2021

*Review Article*

## CYTOKINE DRIZZLE—THE RATIONALE FOR ABANDONING "CYTOKINE STORM"

Allan E. Stolarski,*† Jiyoun Kim,† Qiuyang Zhang,† and Daniel G. Remick†

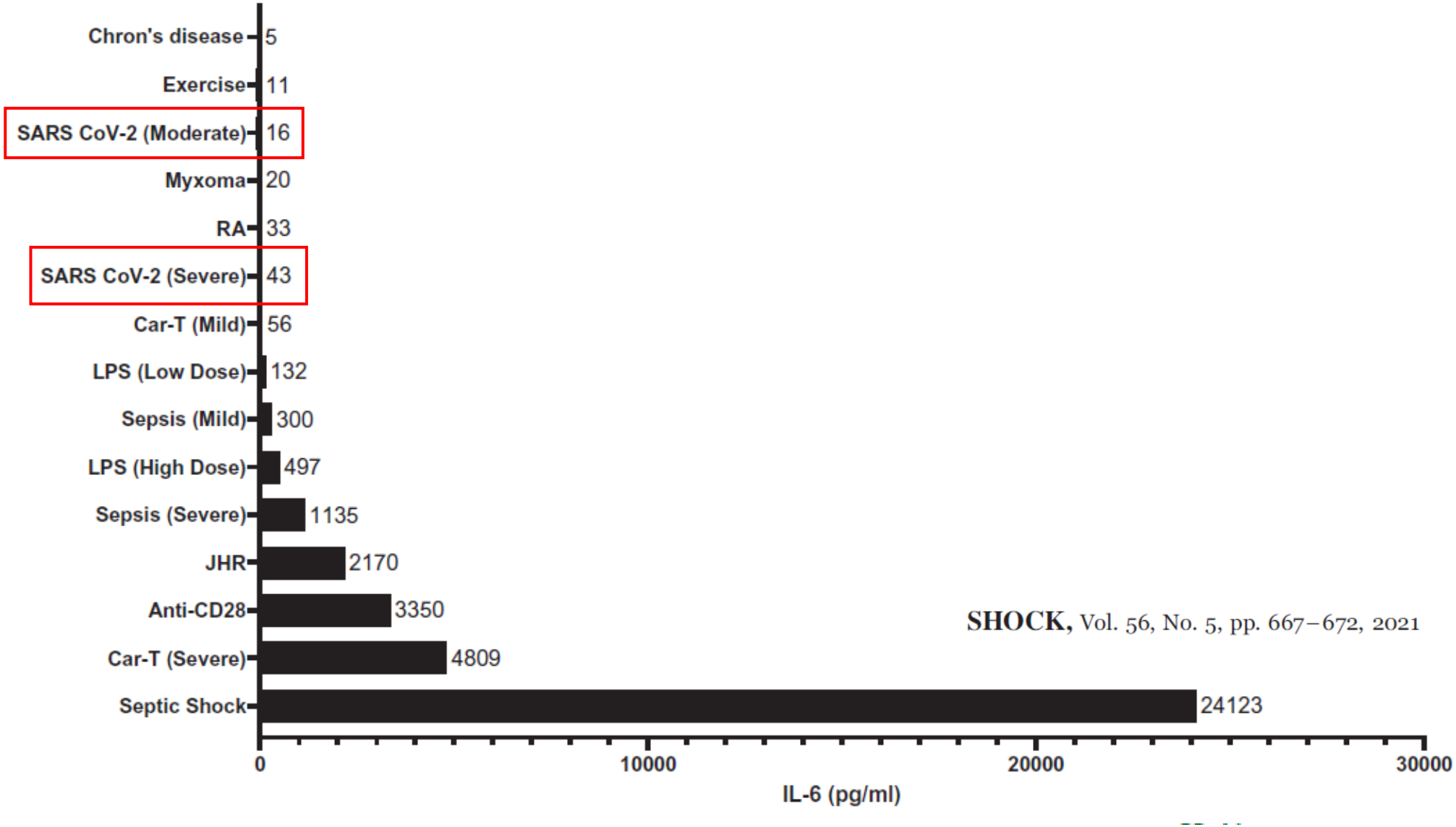
*Department of Surgery, Boston Medical Center, Boston University, Boston, Massachusetts; and †Department of Pathology and Laboratory Medicine, Boston University, Boston, Massachusetts

Lancet Respir Med 2020;
8: 1233–44

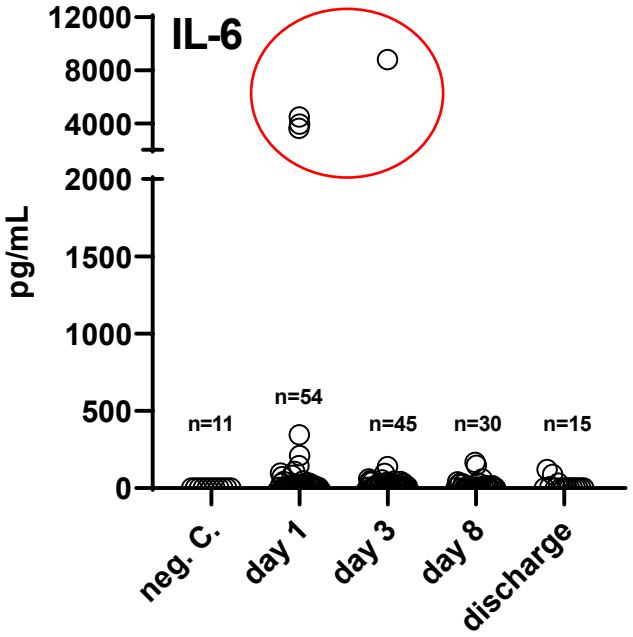
## Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes

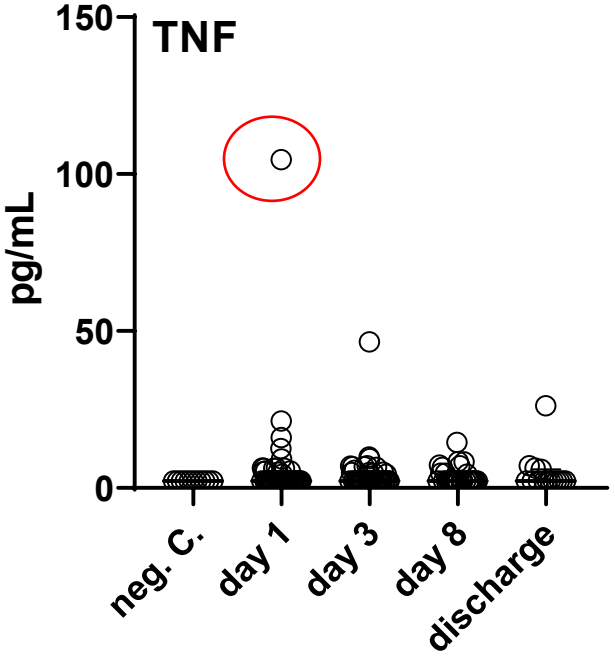
Daniel E Leisman*, Lukas Ronner*, Rachel Pinotti, Matthew D Taylor, Pratik Sinha, Carolyn S Calfee, Alexandre V Hirayama, Fiore Mastroiani, Cameron J Turtle, Michael O Harhay, Matthieu Legrand, Clifford S Deutschman

# Circulating IL-6 Across Various Severe Conditions

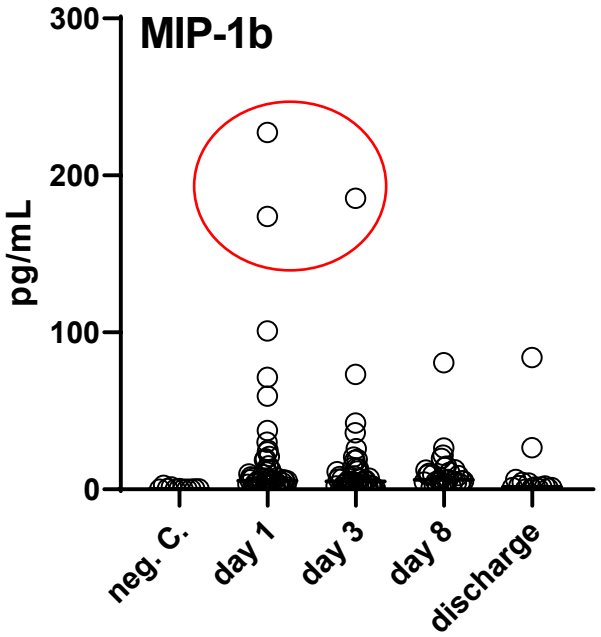


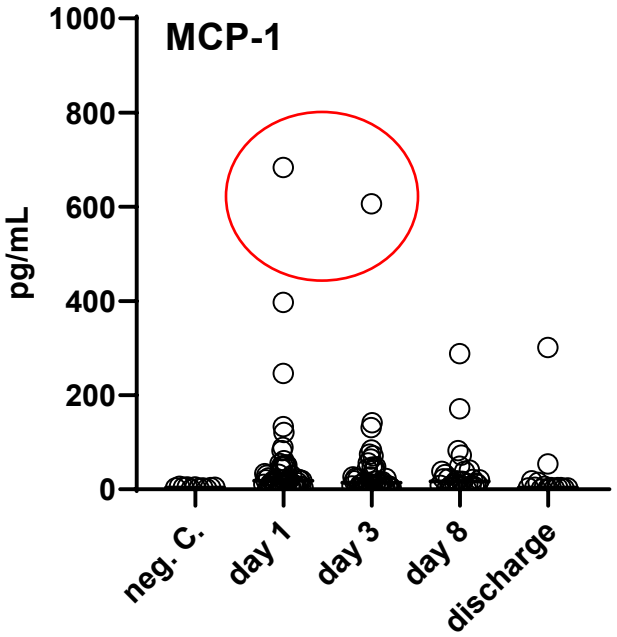

SHOCK, Vol. 56, No. 5, pp. 667–672, 2021




UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG



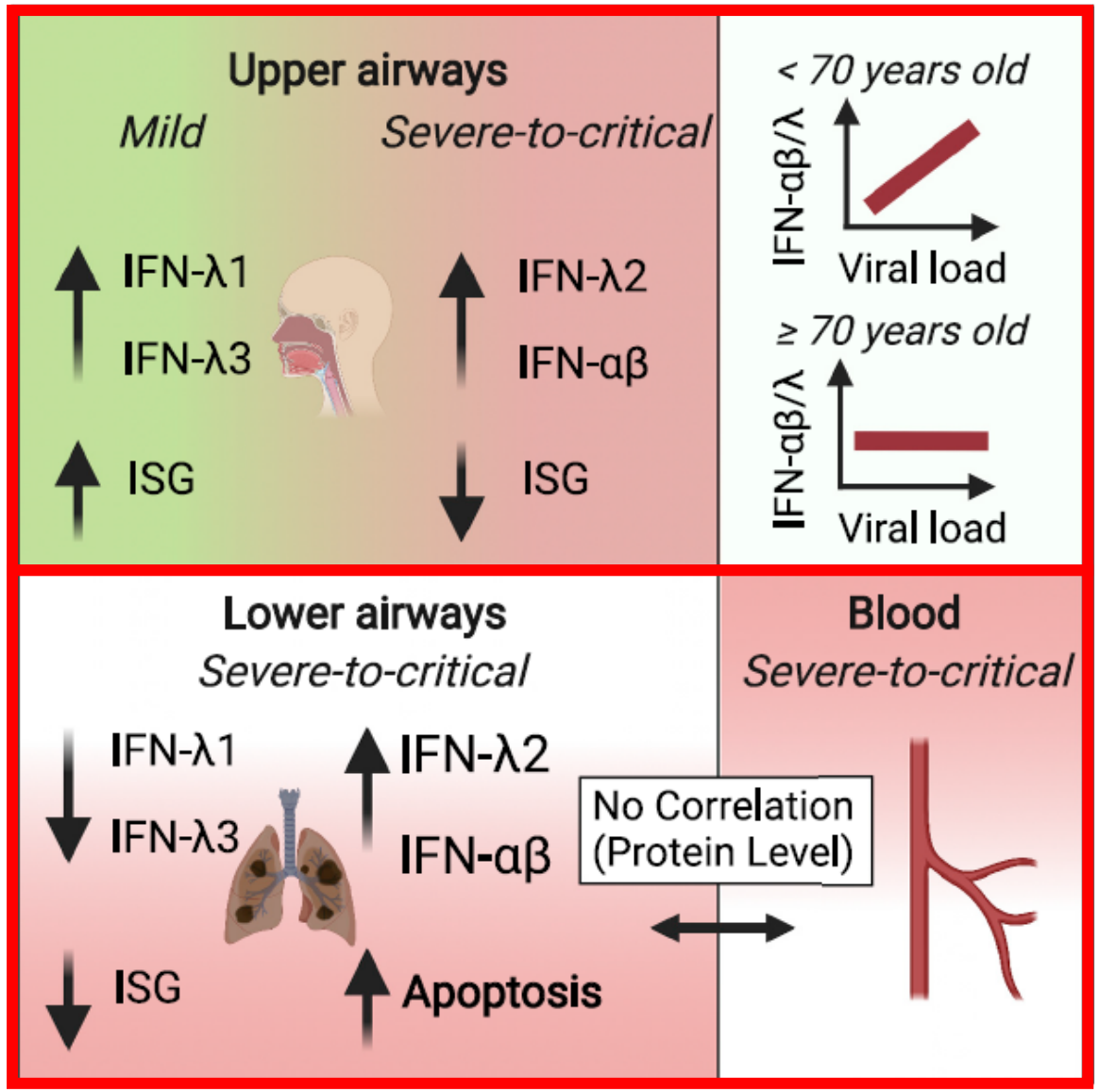



# Cytokine Storm??


# NOT Really!!

# The interferon landscape along the respiratory tract impacts the severity of COVID-19

Alpha/beta (α/β): IFN Type I
Lambda (λ): IFN Type III




**ISG: Interferon Stimulated Genes**

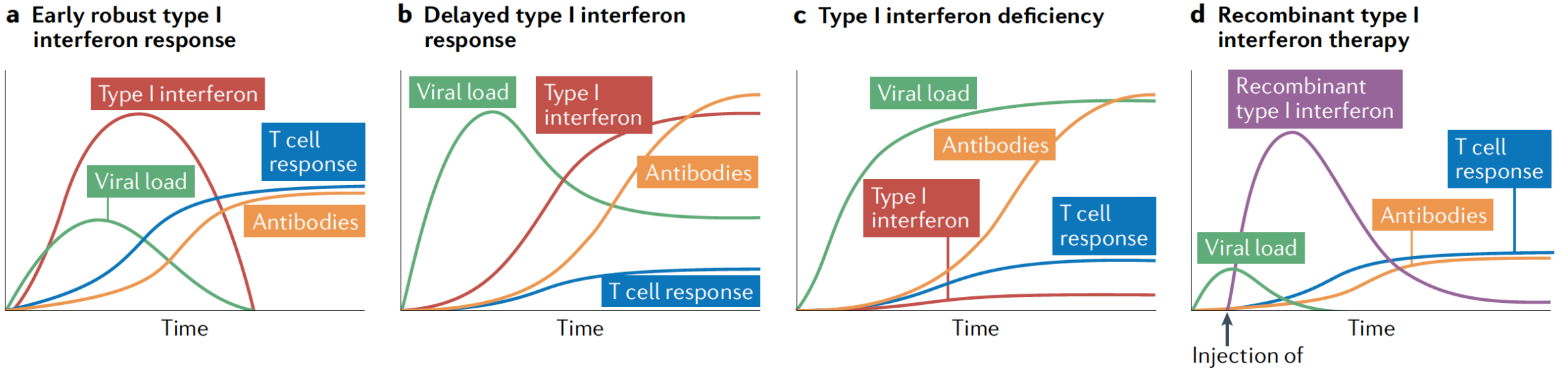
Sposito et al., 2021, Cell *184*, 4953–4968

# A VIRAL SEPSIS

NATURE REVIEWS | IMMUNOLOGY VOLUME 21 | APRIL 2021 | 245

## The first 12 months of COVID-19: a timeline of immunological insights

*Thiago Carvalho, Florian Krammer and Akiko Iwasaki*



## GENETIC PREDISPOSITION

Science 2020 Oct 23; 370(6515): eabd4585

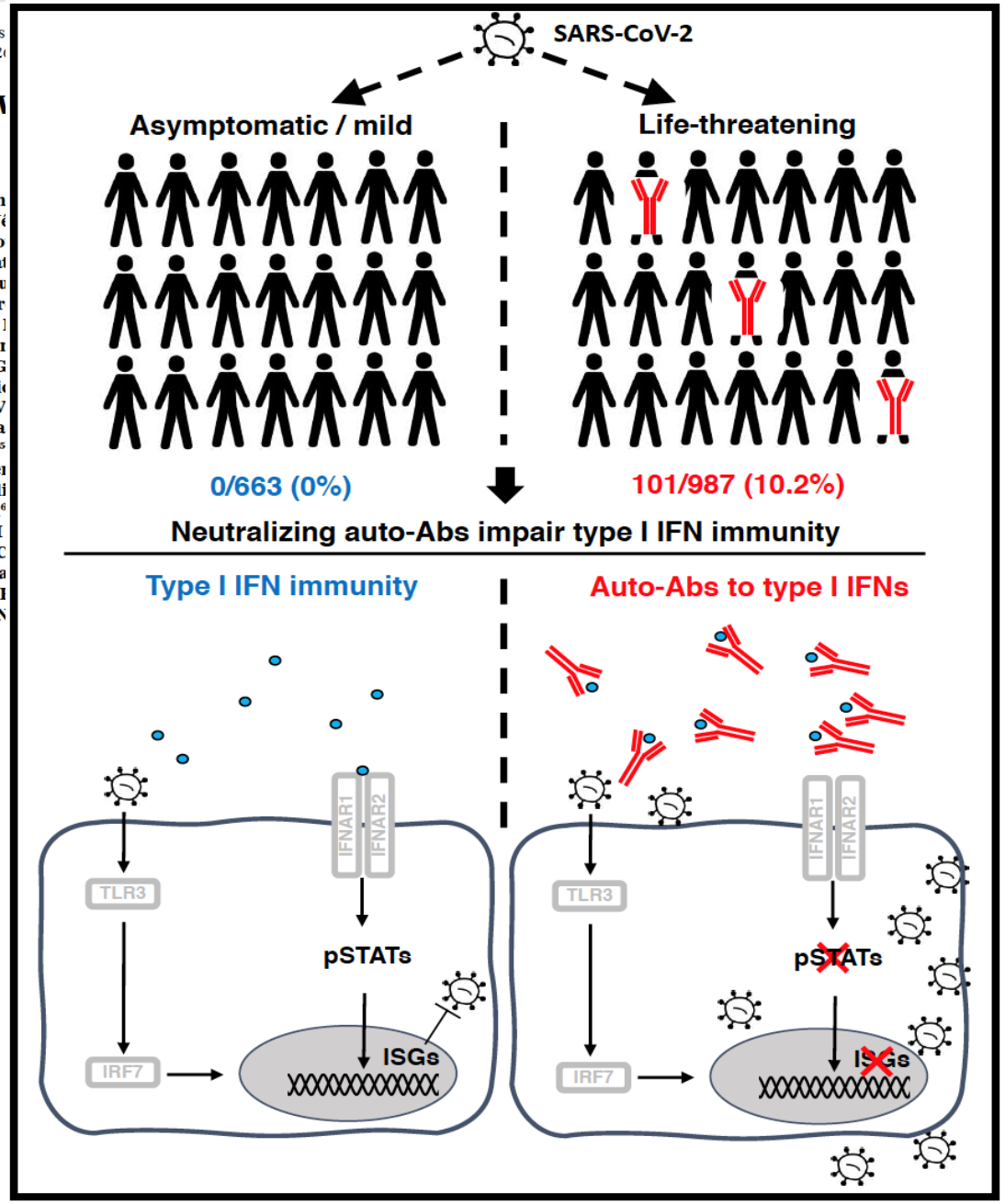
Cite as
10.112(

# Auto-antibodies against type I IFNs in patients w threatening COVID-19

Paul Bastard[1,2,3*†], Lindsey B. Rosen[4†], Qian Zhang[3‡], Eleftherios Michailidis[5‡], Hans-Hein Zhang[4‡], Karim Dorgham[6‡], Quentin Philippot[1,2‡], Jérémie Rosain[1,2‡], Vivien Béziat[1,2,3‡], Jé Elana Shaw[4], Liis Haljasmägi[7], Pärt Peterson[7], Lazaro Lorenzo[1,2], Lucy Bizien[1,2], Sophie Tro Kerry Dobbs[4], Adriana Almeida de Jesus[4], Alexandre Belot[10,11,12], Anne Kallaste[13], Emilie Cat Tandjaoui-Lambiotte[15], Jeremie Le Pen[5], Gaspard Kerner[1,2], Benedetta Bigio[3], Yoann Seeleu Alexandre Bolze[16], András N. Spaan[3,17], Ottavia M. Delmonte[4], Michael S. Abers[4], Alessandr Casari[18], Vito Lampasona[18], Lorenzo Piemonti[18], Fabio Ciceri[18], Kaya Bilguvar[19], Richard P. Vasse[22], David M. Smadja[23], Mélanie Migaud[1,2], Jérome Hadjadj[24], Benjamin Terrier[25], Darı Quintana-Murci[27,28], Diederik van de Beek[29], Lucie Roussel[30,31], Donald C. Vinh[30,31], Stuart G Filomeen Haerynck[34], David Dalmau[35], Javier Martinez-Picado[36,37,38], Petter Brodin[39,40], Mi Nussenzweig[41,42], Stéphanie Boisson-Dupuis[1,2,3], Carlos Rodríguez-Gallego[43,44], Guillaume V Mogensen[46,47], Andrew J. Oler[48], Jingwen Gu[48], Peter D. Burbelo[49], Jeffrey Cohen[50], Andrea Rachele Bettini[51], Mariella D'Angio[51], Paolo Bonfanti[52], Patrick Rossignol[53], Julien Mayaux[5] Laucat[24], Eystein S. Husebye[55,56,57], Francesca Fusco[58], Matilde Valeria Ursini[58], Luisa Imbe Sottini[59], Simone Paghera[59], Eugenia Quiros-Roldan[60], Camillo Rossi[61], Riccardo Castagnoli Montagna[63,64], Amelia Licari[62], Gian Luigi Marseglia[62], Xavier Duval[65,66,67,68,69], Jade Ghosn[6] NIAID-USUHS Immune Response to COVID Group§, COVID Clinicians§, COVID-STORM COVID Group§, French COVID Cohort Study Group§, The Milieu Intérieur Consortium§, C Amsterdam UMC Covid-19 Biobank§, COVID Human Genetic Effort§, John S. Tsang[70,71], Ra Mansky[4], Kai Kisand[7], Michail S. Lionakis[4], Anne Puel[1,2,3], Shen-Ying Zhang[1,2,3], Steven M. I Gorochov[6,72¶], Emmanuelle Jouanguy[1,2,3¶], Charles M. Rice[5¶], Aurélie Cobat[1,2,3¶], Luigi D. N Laurent Abel[1,2,3¶], Helen C. Su[4#], Jean-Laurent Casanova[1,2,3,42,73*#]

**"At least 10% of critical COVID-19 is an autoimmune attack."**

**Jean-Laurent Casanova**,
Rockefeller University




Slide by Jean-Marc Cavaillon, Institut Pasteur

# COVID-19 Consequences Can Be Widespread/Long-term…

| Body organs/parts | Damage/Consequences | Acts on/ Type of cell affected |
|---|---|---|
| **Gut Microbiota** | Gut dysbiosis | Decrease probiotic microorganisms |
| | Inflammation and diarrhoea | The small intestine, enterocytes, colon |
| **Kidney** | Acute Kidney Injury (AKI) | Podocytes and proximally straight tubular cells |
| | Rhabdomyolysis,hypoxemia,and coagulopathy | Glomerular cells, tubular epithelium, and podocytes |
| **Liver** | Irregular liver function | Cells of the bile duct |
| **Heart** | Microvascular disorders | Pericytes |
| | Myocarditis | Myocardium |
| | Acute Coronary Syndrome | Endothelial cells |
| **Lungs** | Alveolar damage, hypoxemia | Alveolar cell |
| | Acute Respiratory Distress Syndrome | Hyper fusion of alveolar cells |
| **Brain** | Cerebral haemorrhage | ACE-2 receptor affected due to amplified blood pressure |
| | Encephalitis | Neuronal destruction and nerve tissue lesions |
| | Puzzlement, loss of awareness, coma | Cerebral capillary endothelial cells |

# Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study

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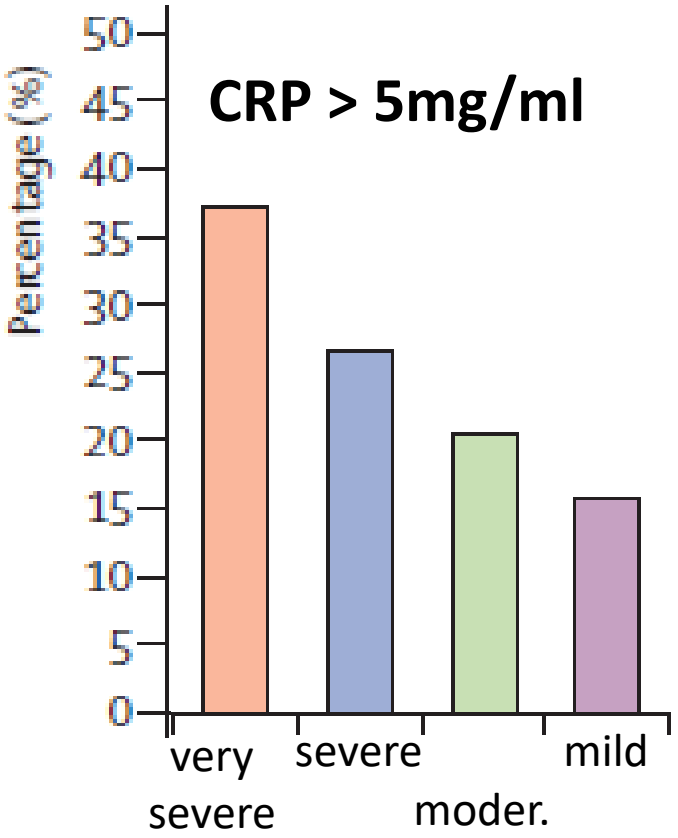
Published Online
April 23, 2022

*The PHOSP-COVID Collaborative Group**

## Covid-19: Only a quarter of patients admitted to hospital feel fully recovered after a year, study finds




The ten most common persistent symptoms at 1 year after discharge were fatigue (463 [60·1%] of 770 patients), aching muscles (442 [54·6%] of 809), physically slowing down (429 [52·9%] of 811), poor sleep (402 [52·3%] of 769), breathlessness (395 [51·4%] of 769), joint pain or swelling (382 [47·6%] of 803), slowing down in thinking (377 [46·7%] of 808), pain (359 [46·6%] of 770), short-term memory loss (360 [44·6%] of 808), and limb weakness (341 [41·9%] of 813; appendix p 35). Overall,

*Panel 2:* Priorities for future research

The proposed research aims will be achieved most effectively with a complementary combination of preclinical and clinical research.

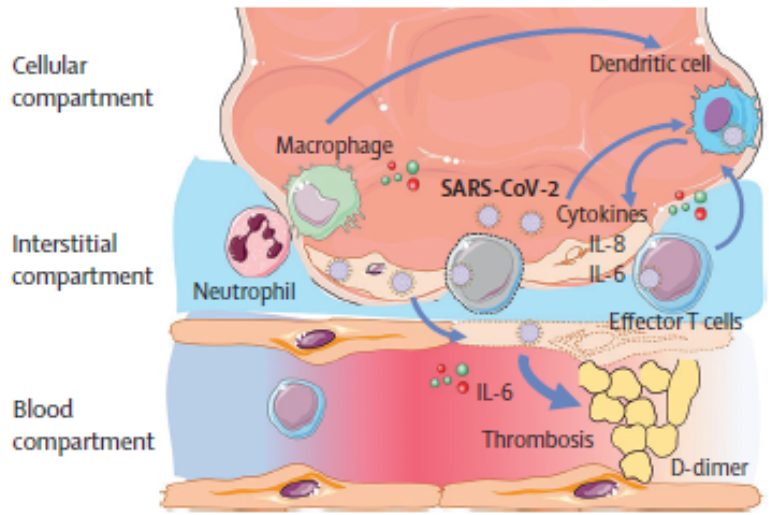
- Establish the molecular basis for lower pathogenicity of SARS-CoV-2 compared with SARS-CoV
- Define the role of pre-existing and acquired T-cell immunity in COVID-19 development and progression
- Establish precise predictive thresholds for known biomarkers of COVID-19 severity, outcomes, and complications
- Develop novel prognostic biomarkers and risk predictors for COVID-19 pneumopathy, acute respiratory distress syndrome, and fibrosis
- Elucidate compartmentalisation profiles of soluble inflammatory mediators and cell subsets (ie, in individual organs and systems)
- Characterise immunological deficiencies secondary to ageing and comorbidities that impair efficient immunological responses against SARS-CoV-2
- Characterise short-term and long-term COVID-19 vasculopathies and their sequelae
- Develop a unified post-COVID-19 monitoring platform to characterise long-term outcomes and immune derangements after SARS-CoV-2 infection
- Conduct high-quality, prospective clinical studies to identify optimum anti-coagulative and immunomodulatory strategies for patients with SARS-CoV-2 infection

# A Wishful Thinking To-Do List…

- some evidence emerging
- some evidence emerging
- robust evidence emerging; needs standardization
- little evidence emerging
- v. difficult; mostly evidence from blood/lung
- some evidence emerging; need of Big Data
- Robust evid. for short-term; poor for long-term
- Difficult to organize; some local initiatives
- mixed quality evidence: both robust & poor RCTs

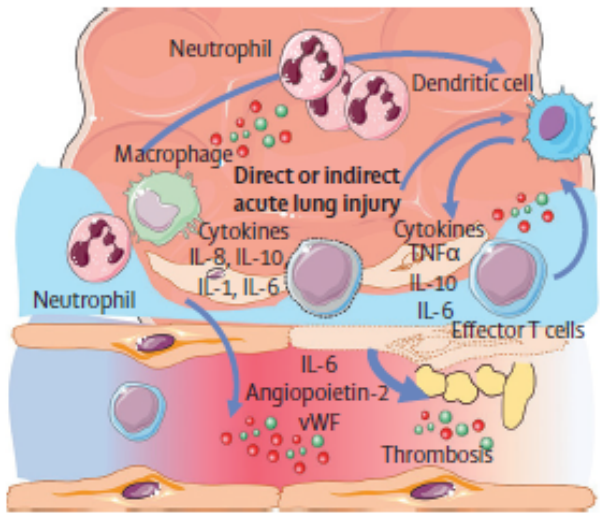

Thanks
Thanks
Thanks
Thanks


EUROPEAN SHOCK SOCIETY
ESS
1983
20th
Congress
September 21-23, 2023
STUDII SAPIENTIAE VIENNENSIS
University of Vienna



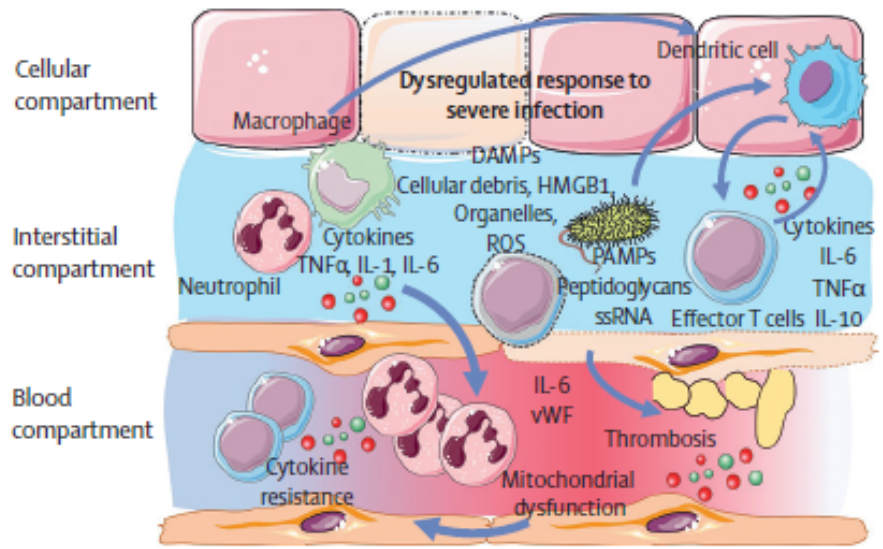

**COVID-19**

| | |
|---|---|
| **Acute-phase reactants** | |
| D-dimer | +++++ |
| CRP | +++ |
| Ferritin | ++ |
| LDH | ++ |
| PCT | - |
| **Leucocytes** | |
| Lymphocytes | ↓↓ |
| Neutrophils | ↑ |
| Effector function* | ↓↓ |
| **Cytokines** | |
| IL-6 | + |
| TNFα | + |
| Chemokines | ++ |
| IFNs | ↓ |



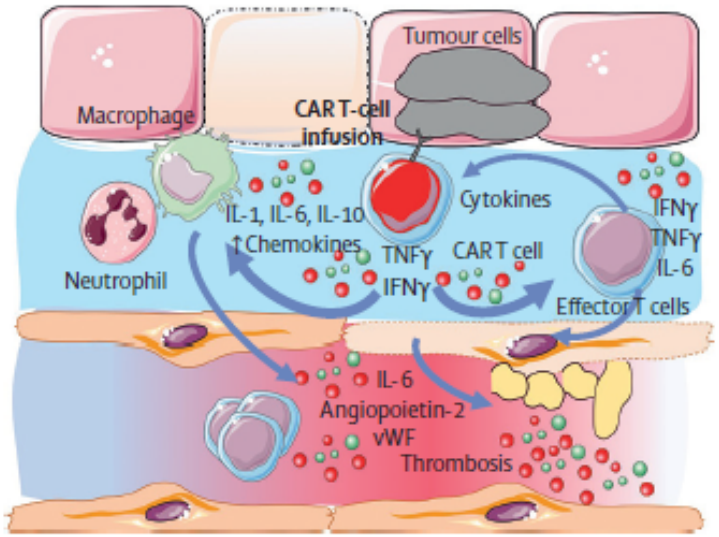

**ARDS**

| Acute-phase reactants | Hyper-inflammatory | Hypo-inflammatory |
|---|---|---|
| D-dimer | +++ | + |
| CRP | ++ | ++ |
| Ferritin | +/++ | +/++ |
| **Leucocytes** | | |
| Lymphocytes | -- | -- |
| Neutrophils | -- | -- |
| Effector function* | ? | ? |
| **Cytokines** | | |
| IL-6 | ++++ | ++ |
| TNFα | ++++ | ++ |
| Chemokines | ++++ | ++ |
| IFNs | ? | ? |




**Sepsis**

| | |
|---|---|
| **Acute-phase reactants** | |
| D-dimer | +/++ |
| CRP | +++ |
| Ferritin | +/+++ |
| PCT | ++ |
| **Leucocytes** | |
| Lymphocytes | ↔ or ↓ |
| Neutrophils | ↑ or ↓ |
| Effector function* | ↓↓ |
| **Cytokines** | |
| IL-6 | +++ |
| TNFα | +++ |
| Chemokines | +++ |
| IFNs | ↑ |




**CAR T cell-induced CRS**

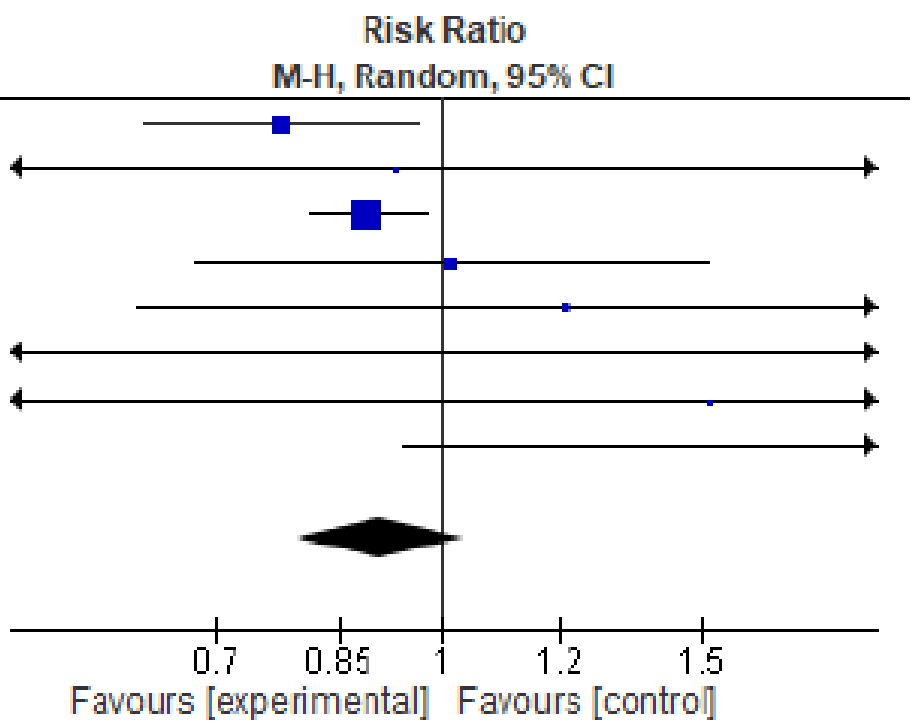
| | |
|---|---|
| **Acute-phase reactants** | |
| D-dimer | ++ |
| CRP | ++++ |
| Ferritin | ++++ |
| LDH | ++++ |
| **Leucocytes** | |
| Lymphocytes | ↓ |
| Neutrophils | ↑ |
| Effector function* | ↑ |
| **Cytokines** | |
| IL-6 | +++++ |
| TNFα | +++++ |
| Chemokines | +++++ |
| IFNs | ↑↑↑ |

**Figure s6a.** Forest plot for the outcome of mortality for tocilizumab vs. no tocilizumab

| Study or Subgroup | Tocilizumab Events | Tocilizumab Total | No tocilizumab Events | No tocilizumab Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Gordon 2021 | 98 | 366 | 142 | 412 | 25.4% | 0.78 [0.63, 0.96] |
| Hermine 2020 | 7 | 63 | 8 | 67 | 1.9% | 0.93 [0.36, 2.42] |
| Horby 2021 | 596 | 2022 | 694 | 2094 | 55.8% | 0.89 [0.81, 0.97] |
| Rosas 2020 | 58 | 294 | 28 | 144 | 9.5% | 1.01 [0.68, 1.52] |
| Salama 2020 | 26 | 249 | 11 | 128 | 3.8% | 1.22 [0.62, 2.38] |
| Salvarani 2020 | 2 | 60 | 1 | 63 | 0.3% | 2.10 [0.20, 22.56] |
| Stone 2020 | 9 | 161 | 3 | 82 | 1.1% | 1.53 [0.43, 5.49] |
| Veiga 2021 | 14 | 65 | 6 | 64 | 2.2% | 2.30 [0.94, 5.61] |
| **Total (95% CI)** | | **3280** | | **3054** | **100.0%** | **0.91 [0.79, 1.04]** |
| Total events | 810 | | 893 | | | |

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.32$, $df = 7$ ($P = 0.31$); $I^2 = 16\%$

Test for overall effect: $Z = 1.43$ ($P = 0.15$)



# Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity