COVID 19 Immunology Risk Factors and Treatment

WHY ARE CERTAIN POPULATION GROUPS MORE VULNERABLE TO COMPLICATIONS

Objectives

1. Review at risk population groups

2. Discuss potential innate and adaptive immune responses that may explain risk

3. Provide overview of treatment options

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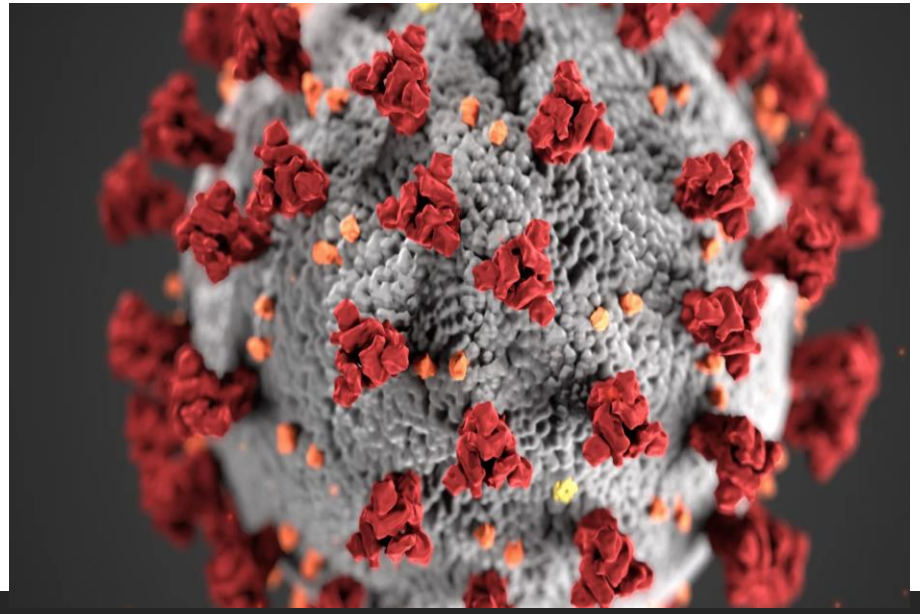
Competing Interests

- Research paid to institution: AstraZeneca, Genentech/Roche, Novartis
- Consultancy: GSK, BioCryst, AbbVie
- Promotional Speaking: ALK, AstraZeneca, Genentech/Roche, Sanofi/Genzyme/Regeneron
- Legal Opinion: Indoor mold exposure, Drug allergy, Radiocontrast reactions, Asthma (all for defense except one)

COVID 19 Risk

- 10% of infected subjects have more severe disease and 2% of infected subjects have life-threatening disease
- Risk varies in populations with select high risk groups
  - Ethnicity: People of color including African American, Native American and select Hispanic groups
  - Older age
  - COPD and cigarette smoking
  - Diabetes melitis
  - Hypertension and other cardiovascular disease
  - Chronic renal disease
  - Immunodeficiency
  - Lower socieoeconomic status



JACI In Practice 2021

Rostrum

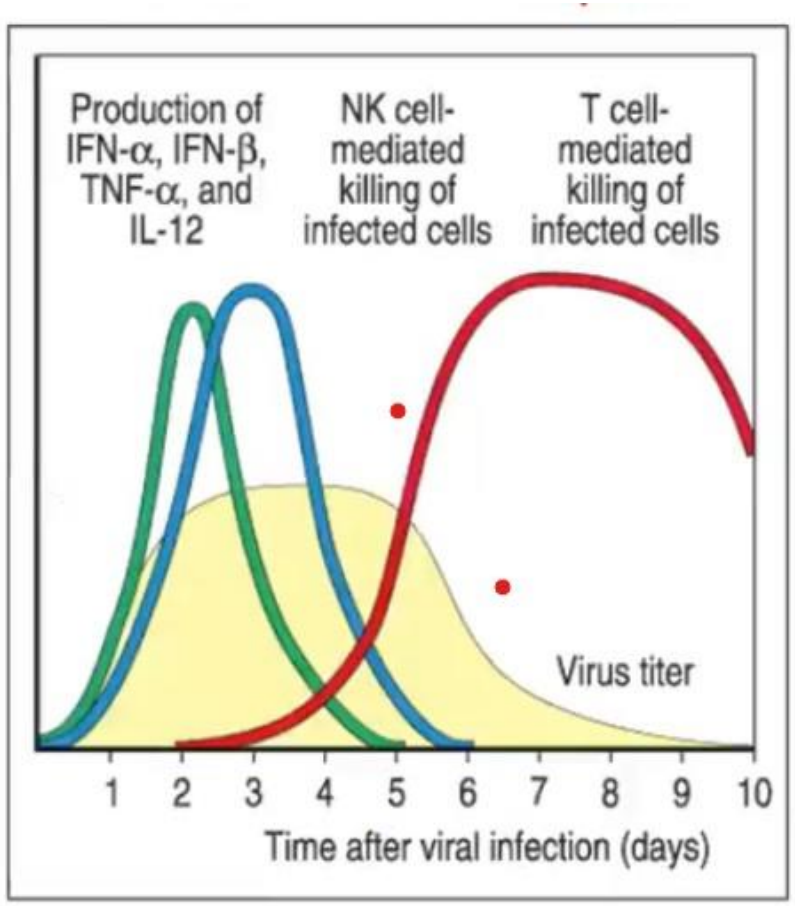
Why Do Some People Develop Serious COVID-19 Disease After Infection, While Others Only Exhibit Mild Symptoms?

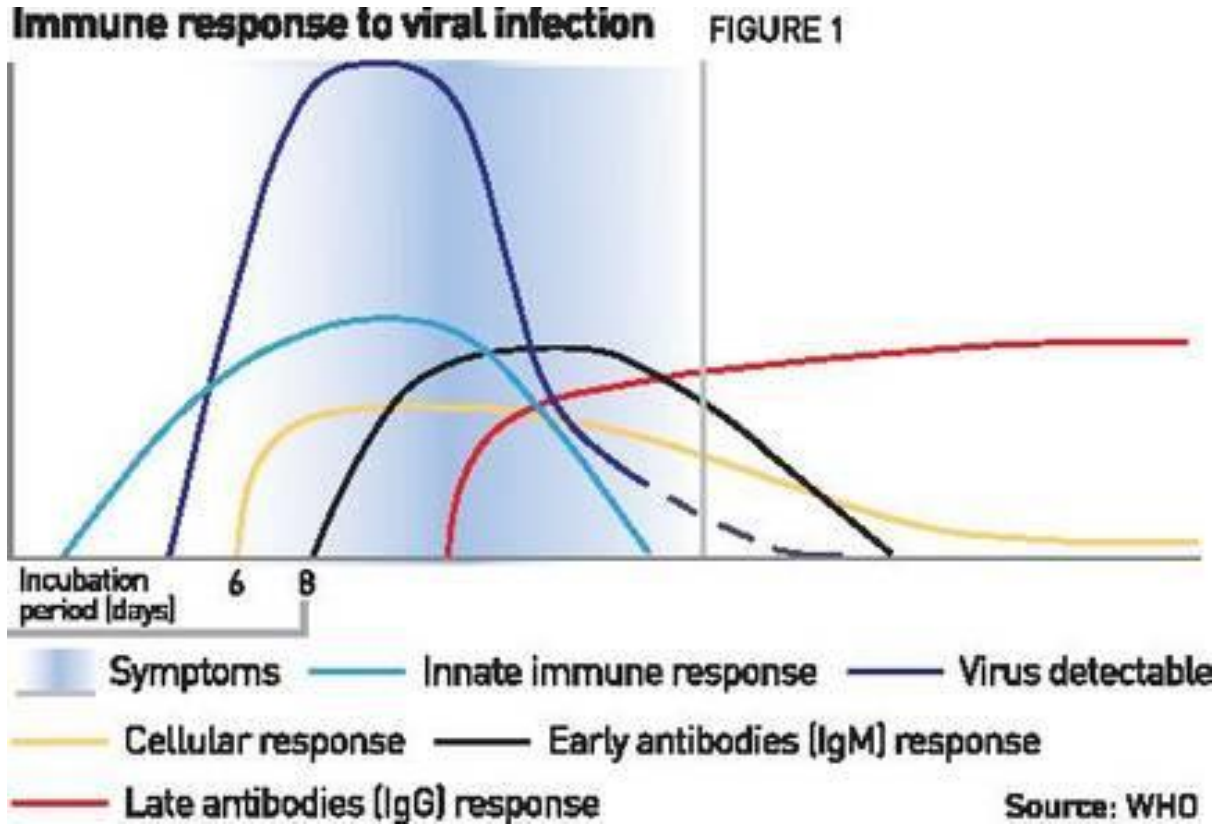
Mark Ballow, MD[a], and Christopher L. Haga, PhD[b] *St. Petersburg and Jupiter, Fla*

Innate and Adaptive Mechanisms Linked to COVID to be Reviewed

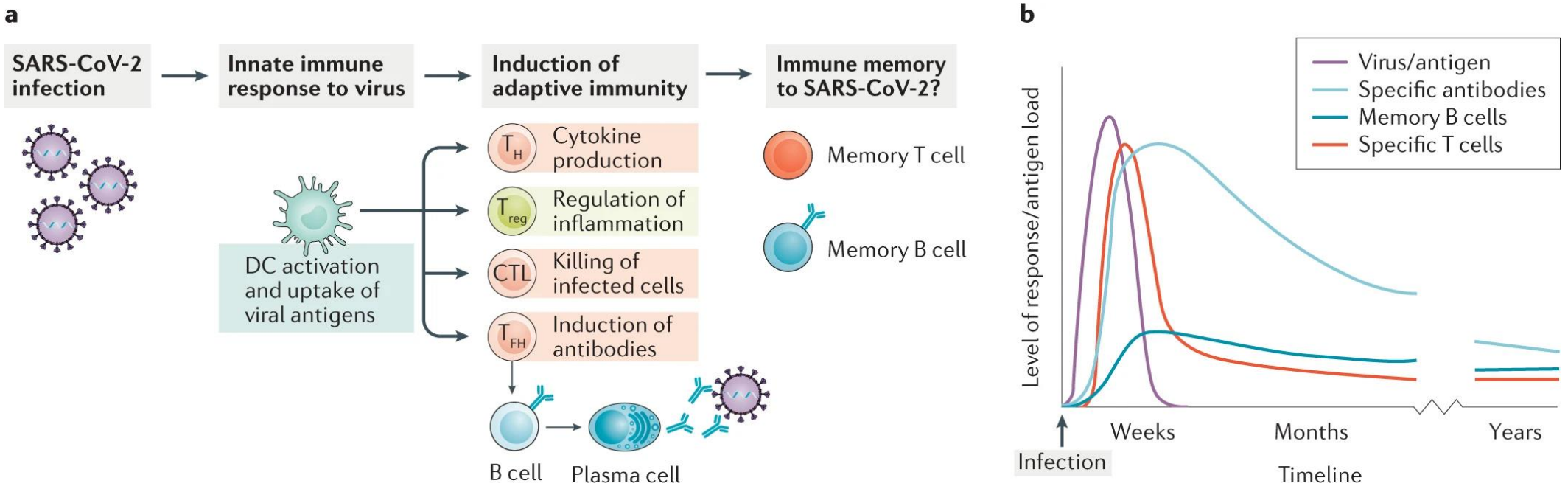
- ACE2 role in immune modulation and anti-inflammatory effects
- Reduced Type I interferon response in early infection with dysregulated late immune response
- Reduced or dysregulated adaptive immunity
  - T cell
  - Extrafollicular B cells
  - Glycosalation of immunoglobulin
  - Autoimmunity
- Pre-existing, cross-reactive immune response to coronaviruses associated with common cold

Normal COVID 19 Immune Response



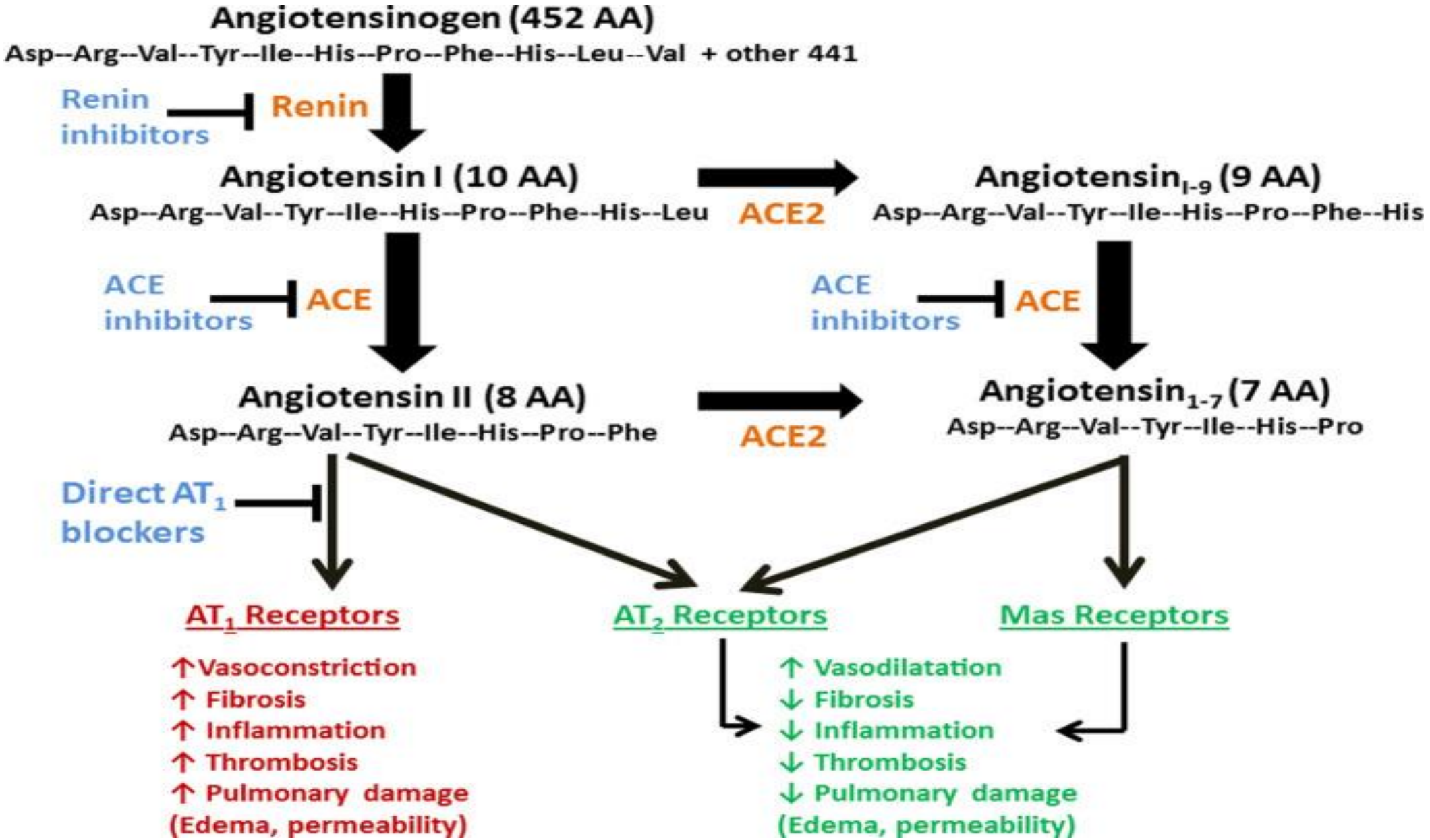


COVID 19 Immune Response More Than Antibody (Cox R et al. Nature Rev Immunol 2020)



What Is Angiotensin Converting Enzyme 2(ACE2)?

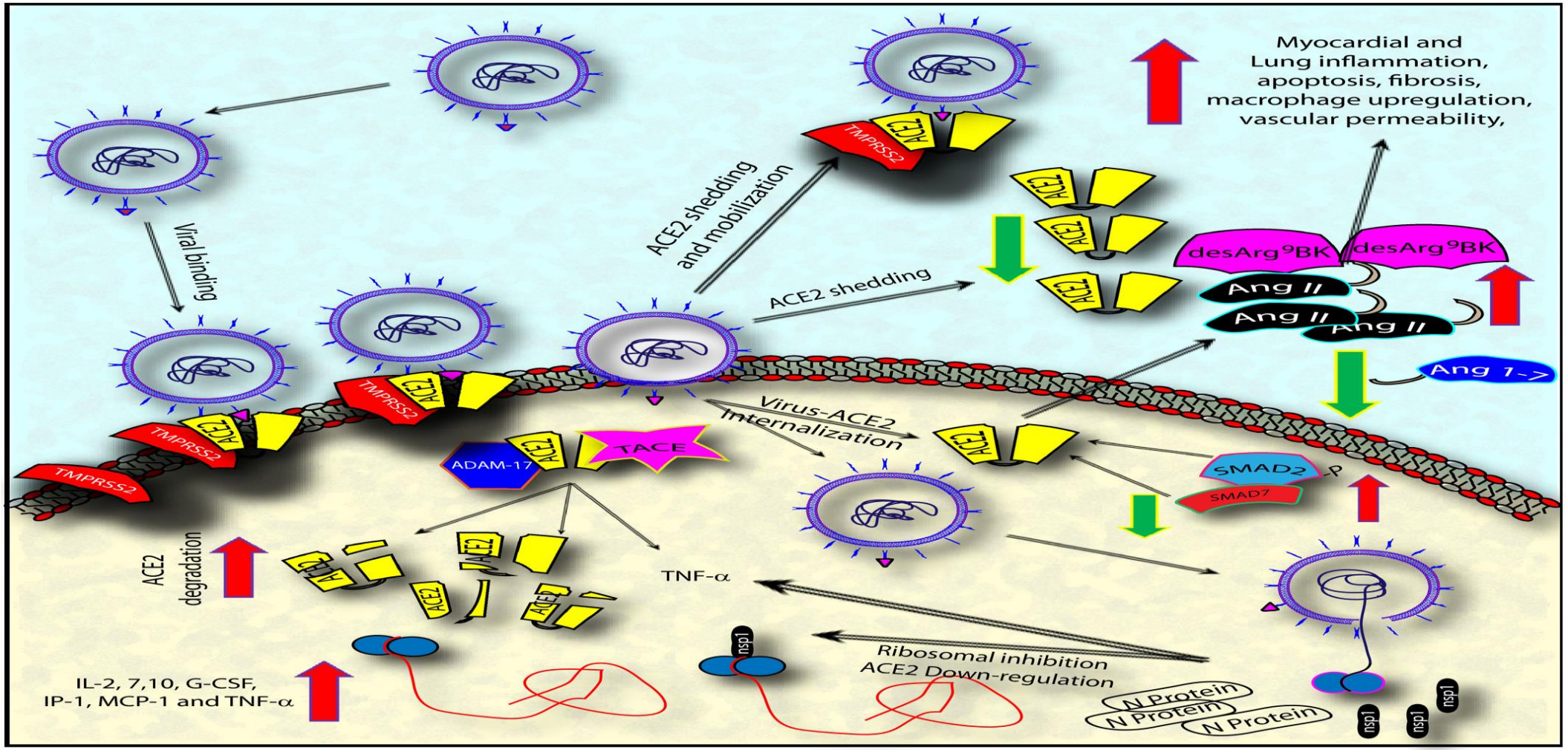
- Dipeptidase that cleaves Angitotensin II (AngII) to Ang 1-7
- Expressed on apical surface of nasal, oral, pharyngeal mucosal cells, alveolar type II cells, endothelial cells, myocardiam, renal tubular cells, enterocytes in small intestine
- Expression higher in women and lower with age and atopy
- Upregulated by ARB/ACEi and IFN-I
- Soluble form results from ADAM17 and TACE
- AngII acting via ATR1 is proinflammatory, thus reducing AngII via ACE2 is anti-inflammatory


Angiotensinogen (452 AA)
Asp--Arg--Val--Tyr--Ile--His--Pro--Phe--His--Leu--Val + other 441
Renin inhibitors
Renin
Angiotensin I (10 AA)
Asp--Arg--Val--Tyr--Ile--His--Pro--Phe--His--Leu
ACE2
Angiotensin I-9 (9 AA)
Asp--Arg--Val--Tyr--Ile--His--Pro--Phe--His
ACE inhibitors
ACE
ACE inhibitors
ACE
Angiotensin II (8 AA)
Asp--Arg--Val--Tyr--Ile--His--Pro--Phe
ACE2
Angiotensin 1-7 (7 AA)
Asp--Arg--Val--Tyr--Ile--His--Pro
Direct AT1 blockers
AT1 Receptors
↑Vasoconstriction
↑ Fibrosis
↑ Inflammation
↑ Thrombosis
↑ Pulmonary damage
(Edema, permeability)
AT2 Receptors
Mas Receptors
↑ Vasodilatation
↓ Fibrosis
↓ Inflammation
↓ Thrombosis
↓ Pulmonary damage
(Edema, permeability)

ACE2's Role In Inflammation

- Interacts with innate immune response by reducing AngII and
  - AngII signals through MAPKinase, JAK and STAT3
- Soluble ACE2 levels inversely correlate with viral titer
- Ang1-7, product of ACE2 on AngII, binds Mas receptor and reduces inflammation and negatively regulates RAS
- Decreases bradykinin by degrading to des-arg (9) bradykinin

COVID-19 and renin-angiotensin system inhibition: role of angiotensin converting enzyme 2 (ACE2) - Is there any scientific evidence for controversy?

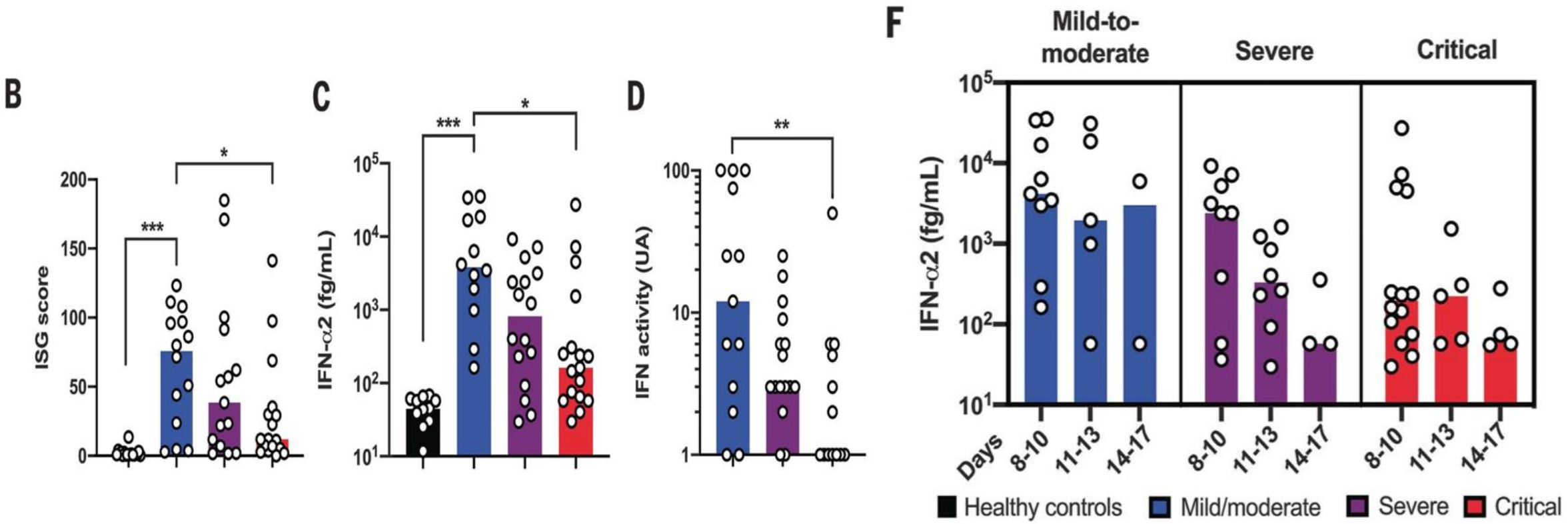


Journal of Internal Medicine, Volume: 288, Issue: 4, Pages: 410-421, First published: 27 May 2020, DOI: (10.1111/joim.13101)

Reduced Type I Interferon Early and Increased Interferon Late in Infection

- IFN-I impaired early in severely affective COVID subjects (Trouillet-Assant et al; Hadjadj et al)
- IFN-I reduced in viral illness such as influenza in older populations and IFN I inversely related to influenza viral load
- Non-structural SARS-CoV-2 proteins target INF I (nsp13, nsp6, ORF6) by reducing IFN Regulatory Factor 3 (IRF3)
- IFN-I reduced in obese subjects but not DMII or renal transplant patients
- Pro-inflammatory response and reduced viral clearance by macrophages with ACE2 expression in risk groups
- IFN-I increased in post-mortem COVID 19 lung samples (Nienhold et al)
- Pattern of decreased early and excess late may explain innate immune system susceptibility

Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients



Hadjadj J et al Science 369:718, 2020

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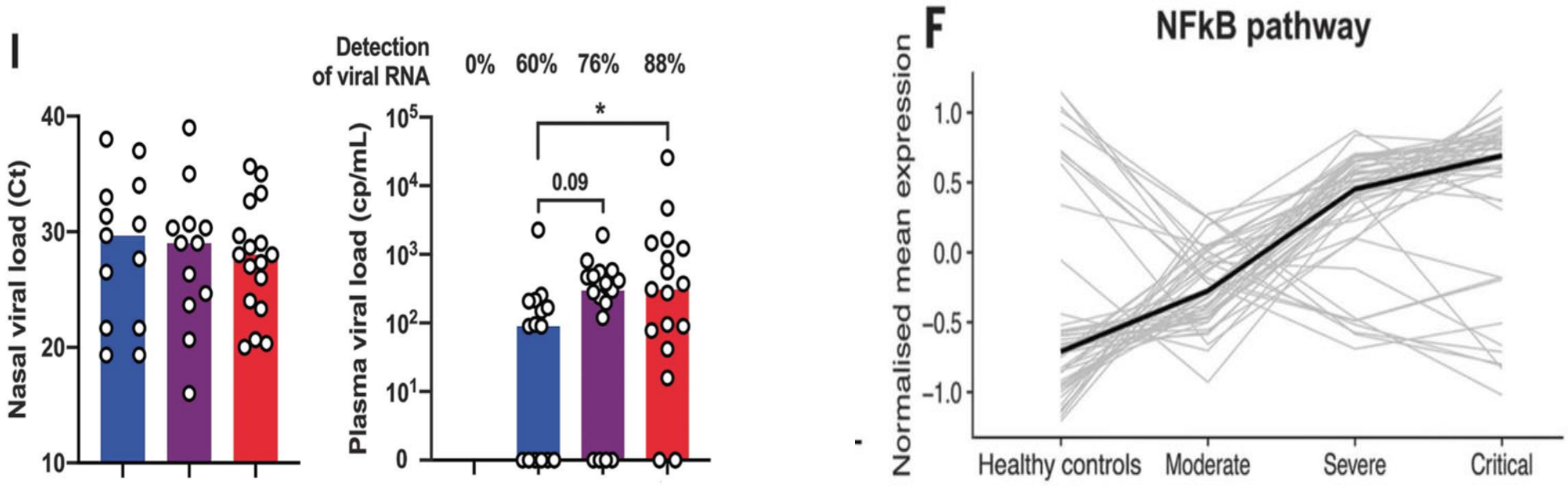
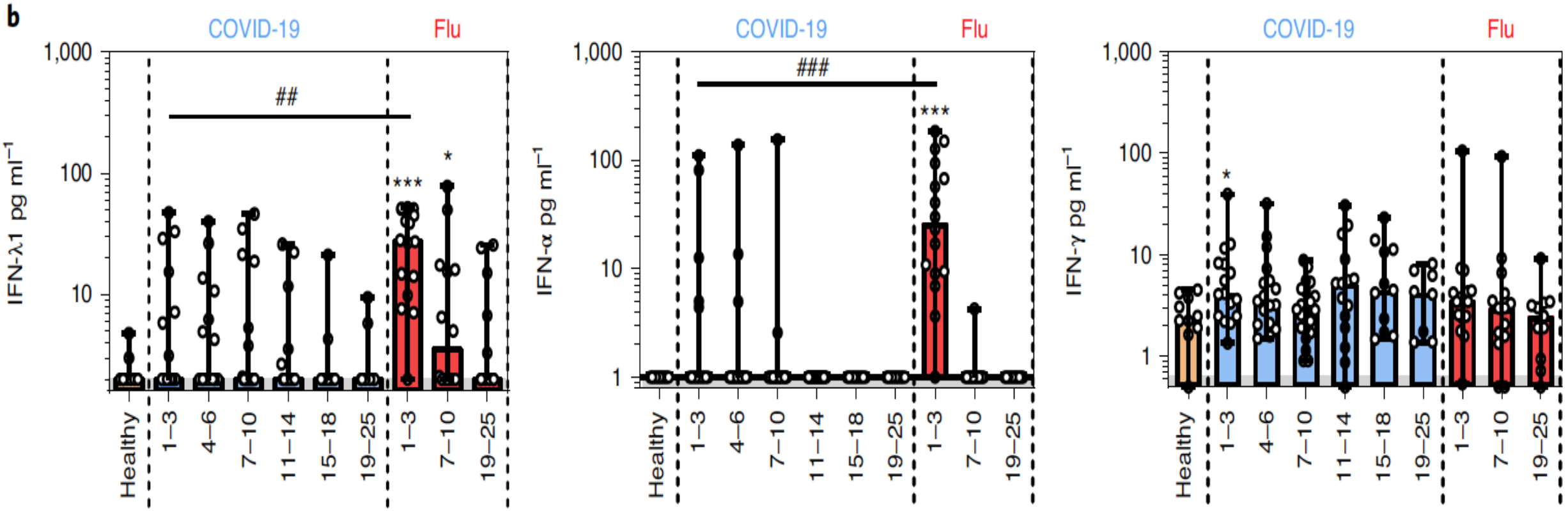


Hadjadj J et al Science 369:718, 2020

Temporal IFN and inflammatory cytokine patterns of patients with COVID-19 and flu in relation to hospital admission



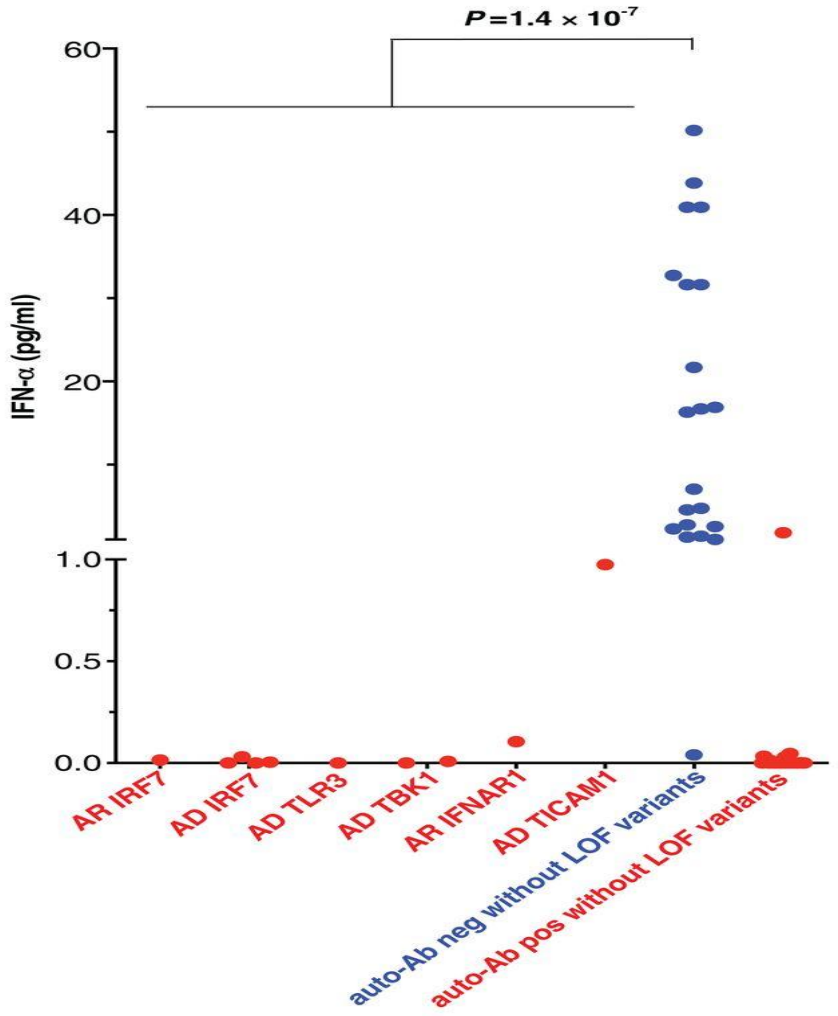
16 out of the 32 patients with COVID developed critical disease, 3 died, **vs** only 3 of the 16 patients with flu

Galani I et al Nature Immunol Jan 2021

In vivo type I IFN responses to SARS-CoV-2 infections.

Measured the levels of the 13 types of IFN-α in the blood of patients during the acute phase of COVID-19.

10 of the 23 patients with mutations for whom samples were available, had serum IFN-α levels <1 pg/ml



Qian Zhang et al. Science 2020;370:eabd4570

Science AAAS

Susceptibility Due to Adaptive Immune Response Dysfunction

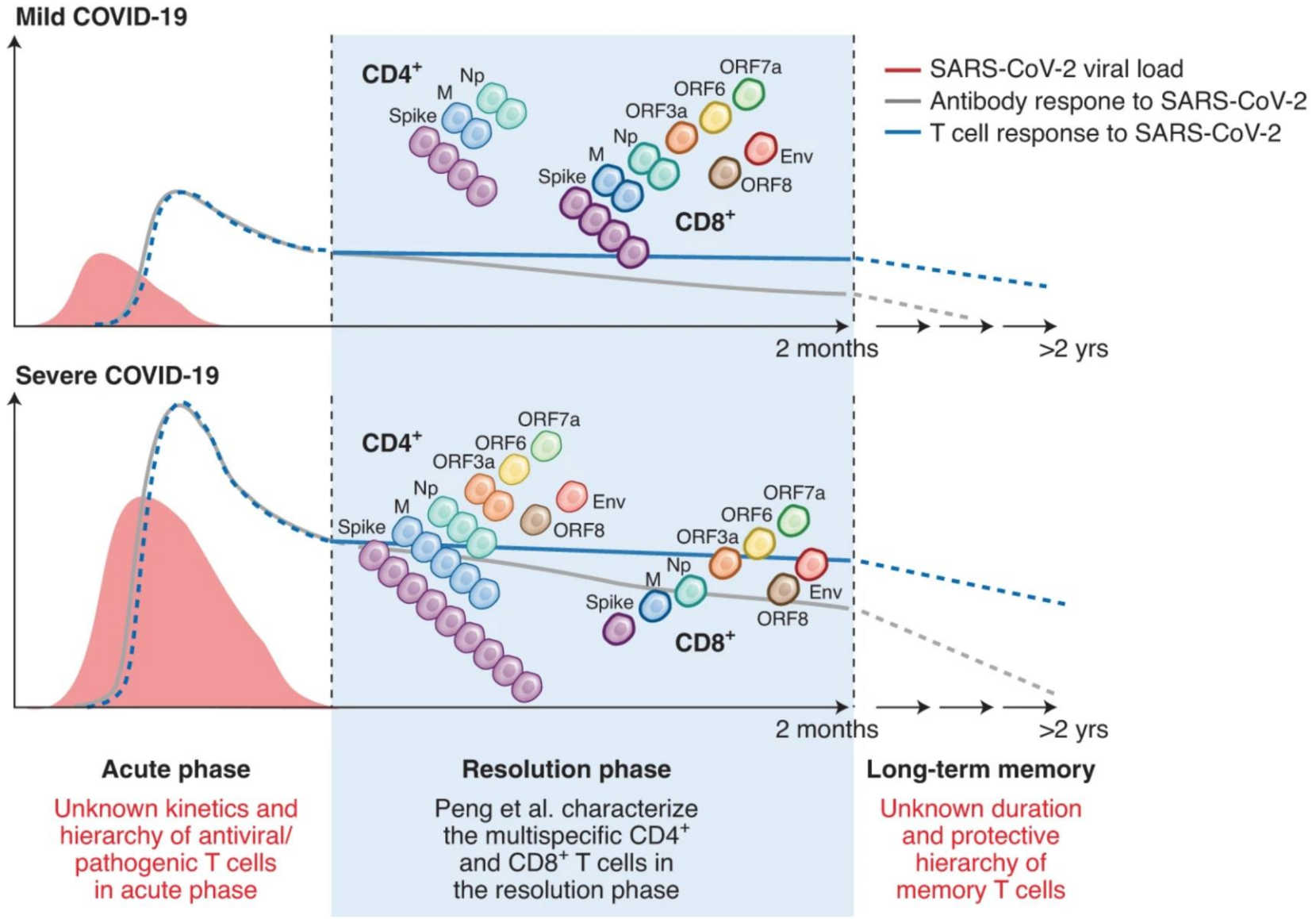
- Risk groups often have less than optimal adaptive immune response and immunosenescence associated with more severe disease
- Immunodeficient patients are at slightly greater risk of severe disease (Gao J of Infection 2020)
- CD8 T cell responses likely more significant than CD4
- Autoimmunity or immune dysregulation may play a role in disease
- Extrafollicular B cell responses with altered glycosalation of IgG associated with more severe disease

Ping et al charactered circulating SAR-CoV-2 specific CD4+ and CD8+ T-cells during convalescent phase of disease recovery.

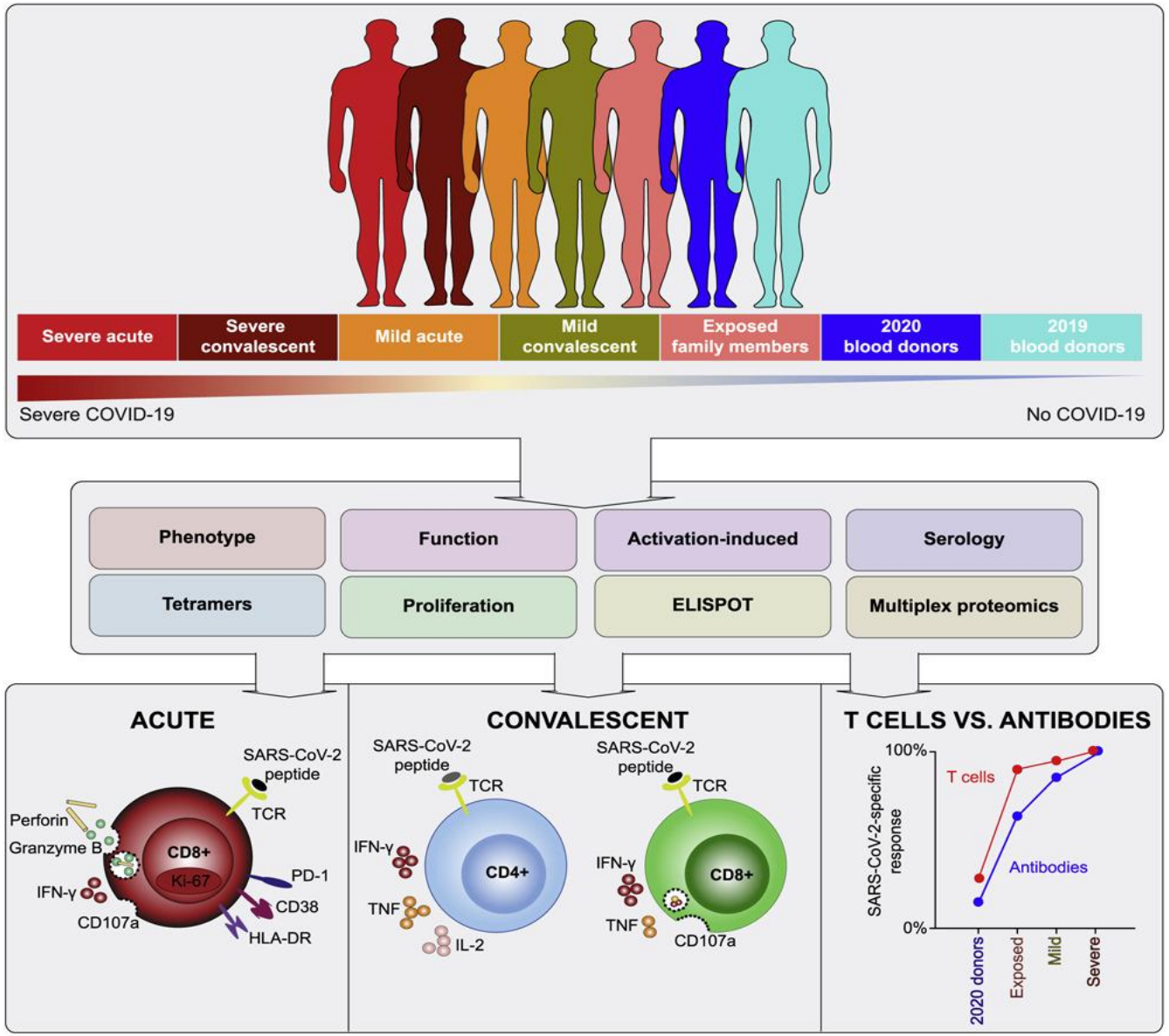
Robust T cell response to multiple structural and nonstructured regions.

Mapped parts of the virus response using overlapping peptides spanning the whole viral genome (except ORF-1 region)

Breath and magnitude greater in more severe COVID-19. **However, T-cell response attributable to CD8+ T-cells is increased in mild infections**

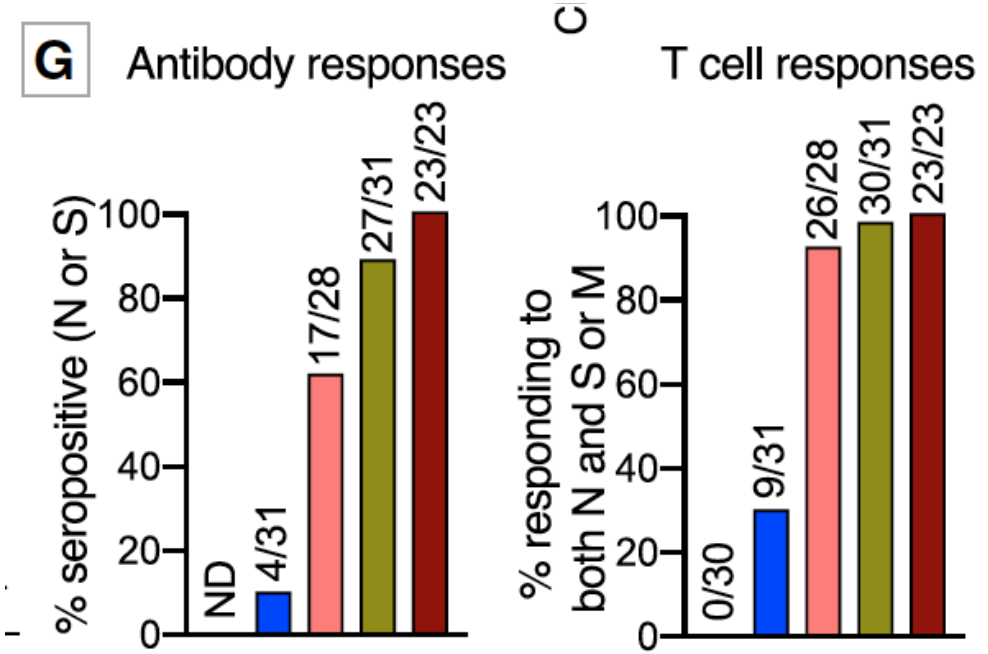


Peng, Y. et al. Nat. Immunol. https://doi.org/10.1038/s41590-020-0782-6 (2020).



Sekine et al Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19 Cell Oct 2020

- Studied subjects with acute moderate or severe COVID, convalescent phase, healthy individuals who donated blood before 2019
- Many activated/cycling T cells in the acute phase were functionally replete and specific for SARS-CoV-2.
- Subjects with mild COVID showed robust memory T cell responses, even in the absence of specific antibodies
- 28% of unexposed healthy blood donors had detectable cross reactive T cell responses



Sekine T et al Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19 Cell 2020 183158-168

The Humoral Immune Response to SAR- CoV-2

The Fc structure, dictates interactions with Fcγ receptors (FcγRs) - Activating, low-affinity FcγRs (FcγRIIa and FcγRIIIa) and the inhibition motif (ITIM) signaling through the inhibitory FcγRIIb

Some antibody responses are highly activating/proinflammatory repertoires enriched for features such as IgG1, IgG3 and/or reduced core fucosylation of the IgG1 Fc domain

Higher levels of IgG2 and/or sialylated Fcs that have reduced or inhibitory activating/ inflammatory FcγR signaling potential, and signal thru FcγRIIb receptor on effector cells

Critically ill patients with SAR-CoV-2 have extra follicular (EF) B cell responses similar to what has been reported for autoimmune diseases, e.g. SLE

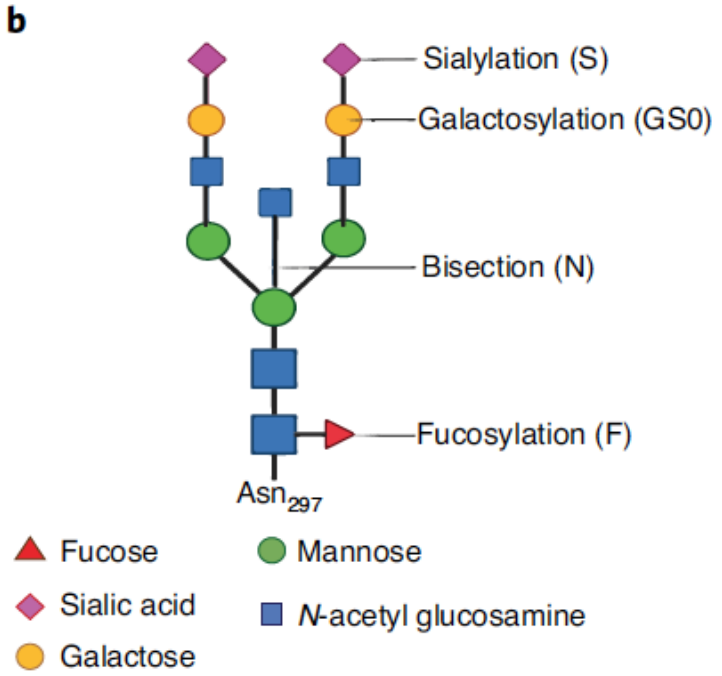
Woodruff MC et al Nature Immunol 2020; Kaneko N et al Cell Oct 2020

Proinflammatory IgG Fc structures in patients with severe COVID-19

Profiled anti-RBD (antibodies against the receptor-binding domain) immunoglobulin isotype titers in sera from patients with COVID-19 (ICU, inpatient, outpatients) or from seropositive children

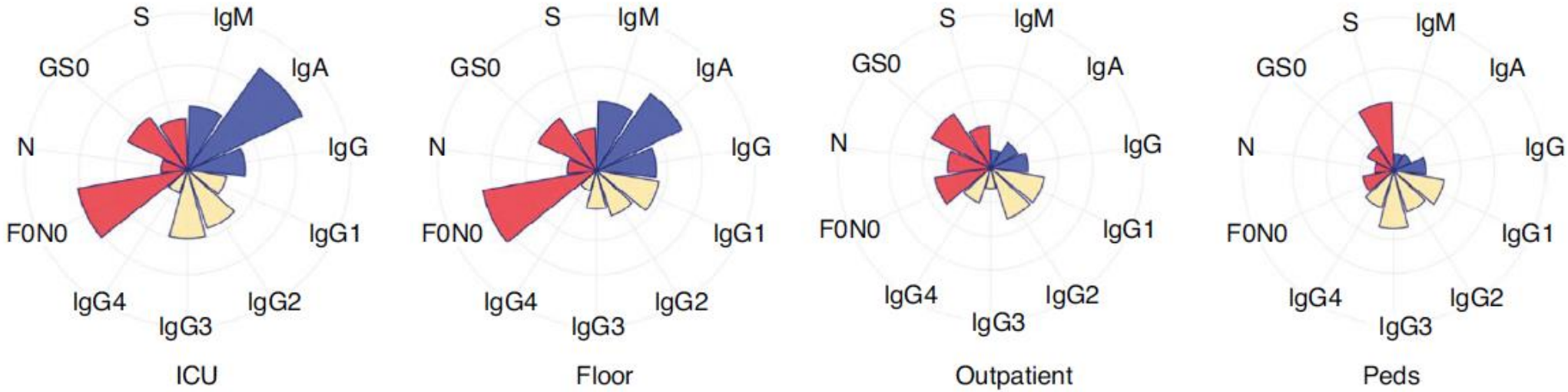
Patients with severe COVID-19 (ICU and floor) had significantly higher serum titers of IgM and IgA RBD-binding antibodies compared to patients with mild COVID-19 and seropositive children.

The anti-RBD IgG titers were not significantly different among the groups



Chakraborty S Nature Immunology | VOL 22 | January 2021 | 67–73

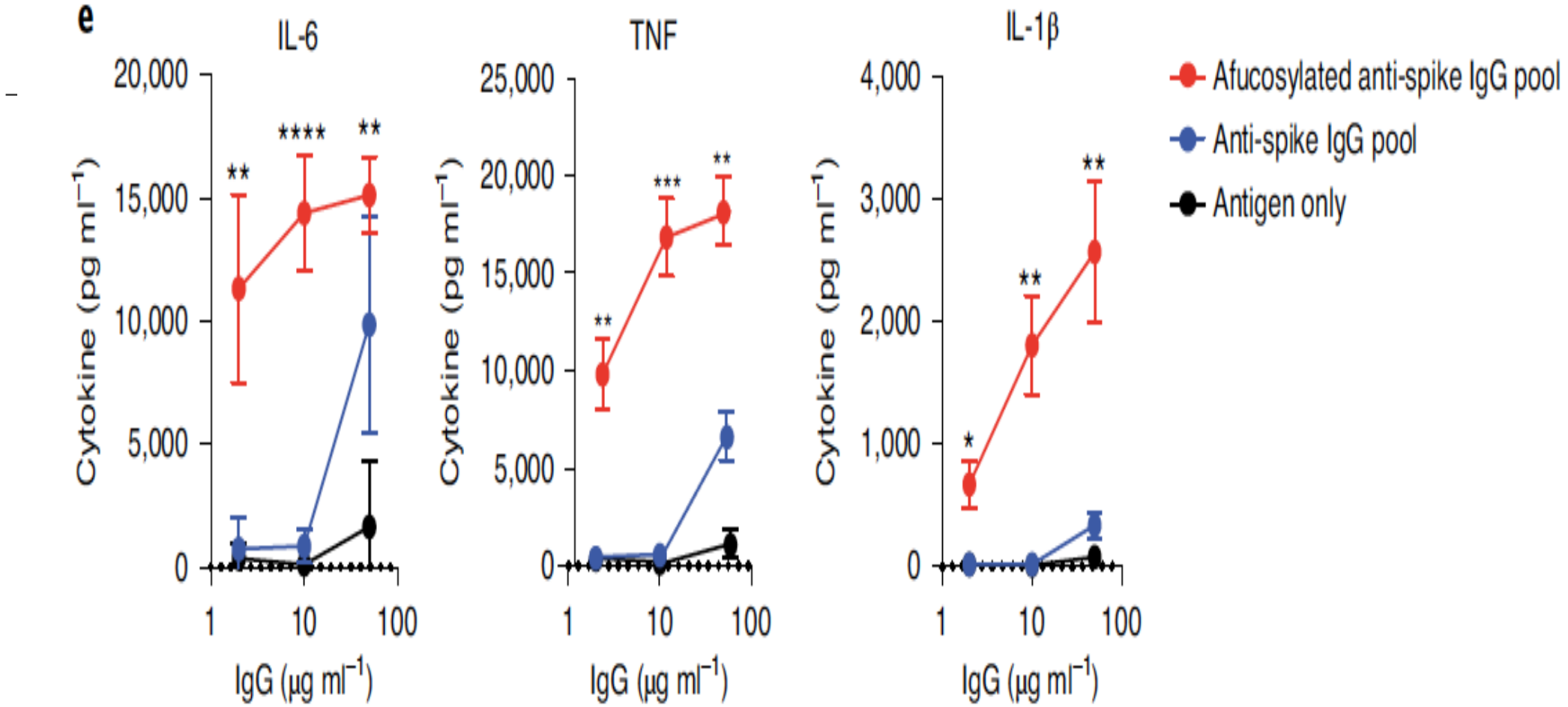
Structural properties of anti-RBD IgG Fc domains in adult patients with COVID-19 and in seropositive children



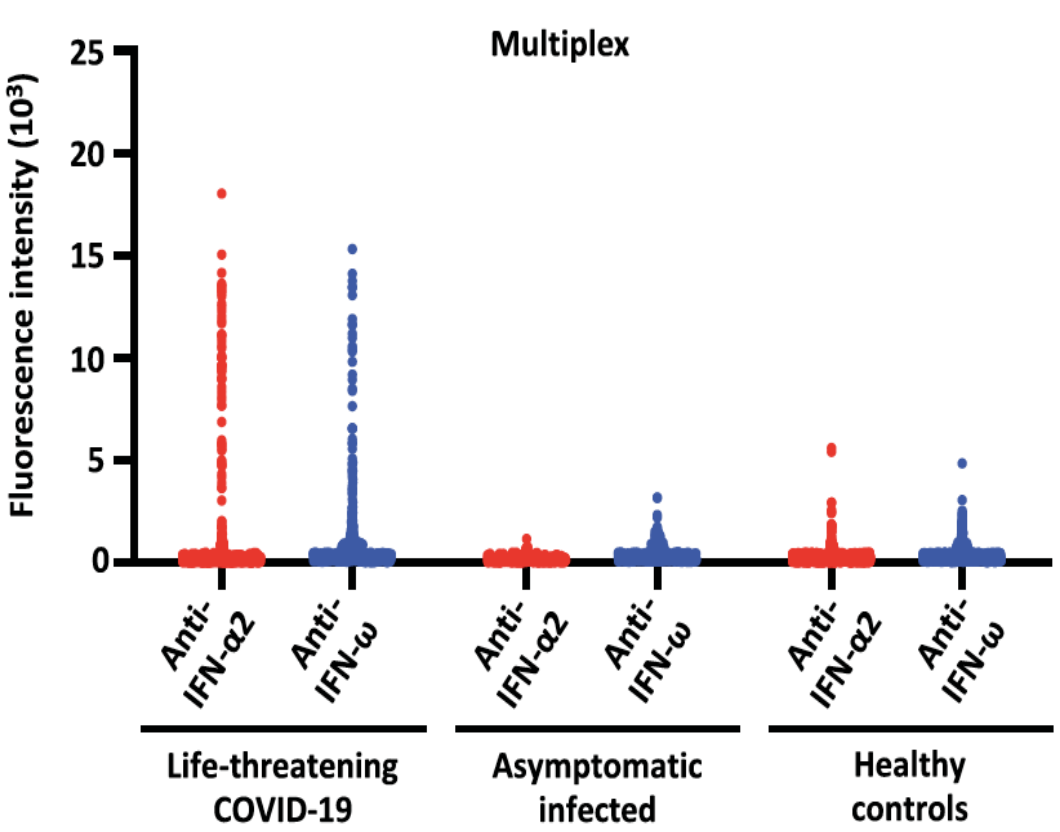
F0N0 – lack both core fucose and bisecting N-acetyl glucosamine, Fc galactosylation (GS0), sialylation (S)

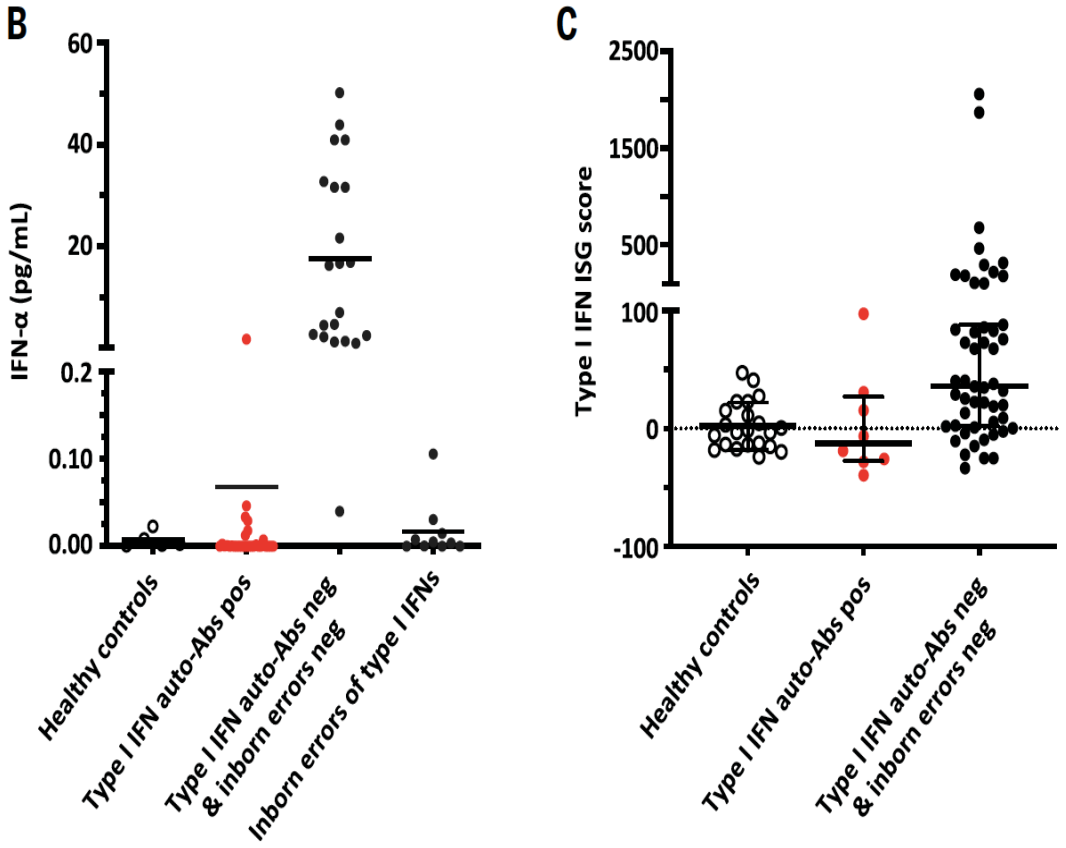
Patients with severe COVID-19 were more likely to produce significantly higher titers of anti-RBD IgM and IgA isotypes, increased IgG3 (ICU patients) and increased afucosylated (F0N0) Fc glycoforms compared to patients with mild COVID-19 (Fig. 3). The IgG3 subclass and afucosylated IgG1 modifications are features that increase Fc interactions with activating/proinflammatory FcγRs

Afucosylated SARS-CoV-2 immune complexes can promote FcγRIIIa interactions and inflammatory cytokine production



Neutralizing auto-Abs to type I IFNs underlie life-threatening COVID-19 pneumonia





Paul Bastard et al. Science 2020;370:eabd4585

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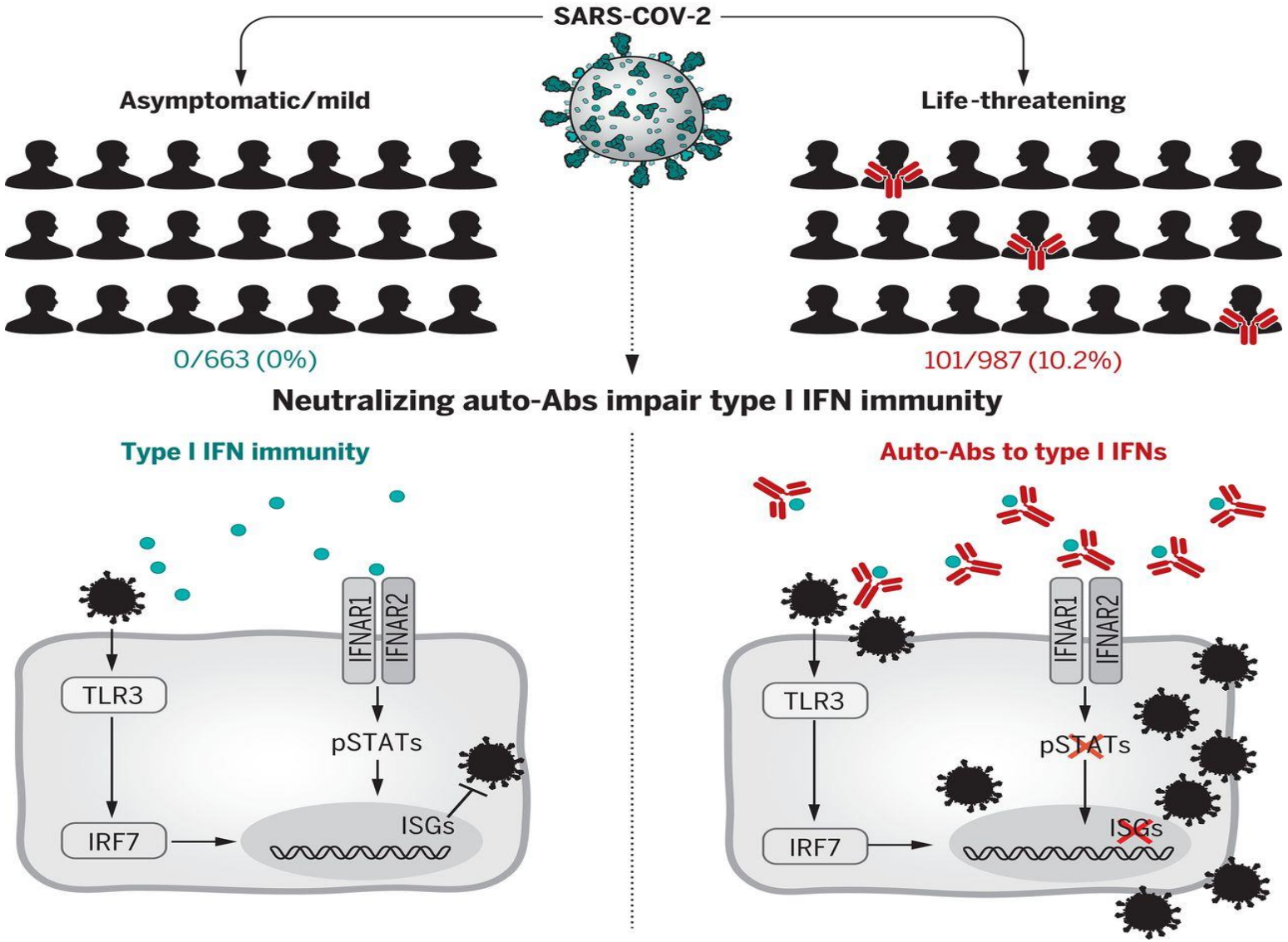


Paul Bastard et al. Science 2020;370:eabd4585

Role of Immunity to Circulating Coronovirus Infections

- Several coronaviruses are in population, likely greater in younger age groups, causing acute URIs
- Duration of immunity to these less pathogenic viruses likely short-lived
- Presence of pre-existing, cross-reactivity immunity may play a role in reducing disease severity of SAR-CoV-2

Table 2. SARS-CoV-2 infection and COVID-19 outcomes in the patients with and without a documented endemic coronavirus[a]

	eCoV- (n = 15,053)	eCoV+ (n = 875)	OR (95% CI) eCoV+/eCoV-	Adjusted OR (95% CI)
SARS-CoV-2 tested, no. (% of total)	1,679 (11.2)	133 (15.2)	1.4 (1.2 – 1.7)	1.4 (1.2 – 1.7)[b]
SARS-CoV-2+, no. (% of tested)	437 (26.0)	33 (24.8)	0.9 (0.6 – 1.4)	
Hospitalized, no. (% of SARS-CoV-2+)	231 (52.9)	21 (63.6)	1.6 (0.8 – 3.2)	
Intensive care unit, no. (% of hospitalized)	65 (28.1)	1 (4.8)	0.1 (0.0 – 0.7)	0.1 (0.1 – 0.9)[c]
Mechanical ventilation, no. (% of hospitalized)	38 (16.4)	0 (0)	0.0 (0.0 – 1.0)	

Abbreviations include eCoV: endemic coronavirus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: coronavirus disease-19; OR: odds ratio; CI: confidence interval

Four different endemic coronaviruses (eCoVs) are etiologic agents for the seasonal “common cold,” and these eCoVs share extensive sequence homology with COVID-19. the patients with a previously detected eCoV had less severe COVID.

Pre-existing immune responses against endemic human coronaviruses can mitigate disease manifestations from SARS-CoV-2 infection.

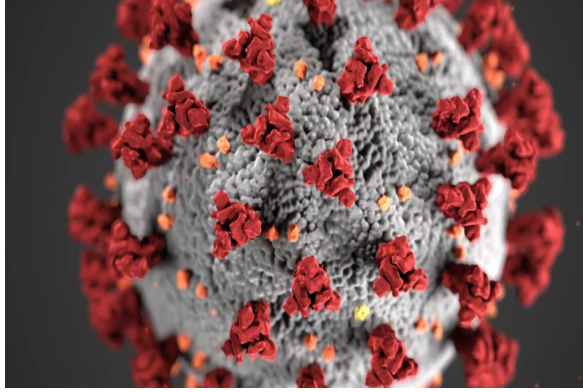
Sagar et al J Clin Invest in press Dec 2020

Immune Response and Variabilty

- Lack of prospective trials complicate interpretation of data (associations vs causations)
- Variability likely multifactorial and/or multi-mechanism dependent
- Efficacy of corticosteroids supports the role of excessive inflammation and/or immune response in more severe disease
- Efficacy of monoclonal antibody, though modest, supports the importance of specific immune response early in disease
- Most likely there is an early decrease in innate and IFN response coupled with immune dysregulation, autoimmunity or loss of anti-inflammatory factors in late severe disease
- Pre-existing immunity to coronaviruses likely mitigate SAR-CoV-2 disease

What About Treatment?

COVID-19 Treatment Guidelines (nih.gov)



- Treatment is **Antiviral** or **Anti-Inflammatory/Immunomodulator/Supportive**
- Antiviral
  - Remdesivir (nucleoside analogue)
  - Convalescent plasma (?)
  - Monoclonal antibody (Bamalinivimab + Etesevimab OR Casirivimab + Imdevimab)
  - Nanobody (investigational)
- Anti-Inflammatory/Immunomodulator/Supportive
  - Dexamethasone
  - Vitamin D (?)
  - Anticoagulation
  - Oxygen
  - Tocilizumab (anti-IL6 receptor)

Wang et al. BMJ 2021;11:45-52.

Gupta S et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med*. 2021;181(1):41-51.

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3. Ballo M, Haga CL. Why do some people develop serious COVID-19 after infection while others only exhibit mild symptoms. JACI In Pract 2021

4. COVID 19 Treatment Guidelines (COVID-19 Treatment Guidelines (nih.gov))

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