



دانشگاه علوم پزشکی و خدمات بهداشتی درمانی گیلان

# ایمونوپاتولوژی کووید-۱۹

## (التهاب شدید)

دکتر آرشی پور غلامی نژاد

متخصص ایمونولوژی

عضو هیئت علمی دانشگاه علوم پزشکی گیلان

دانشکده پزشکی - گروه ایمونولوژی



# مرگ و میر جهانی به دلایل عفونت‌ها



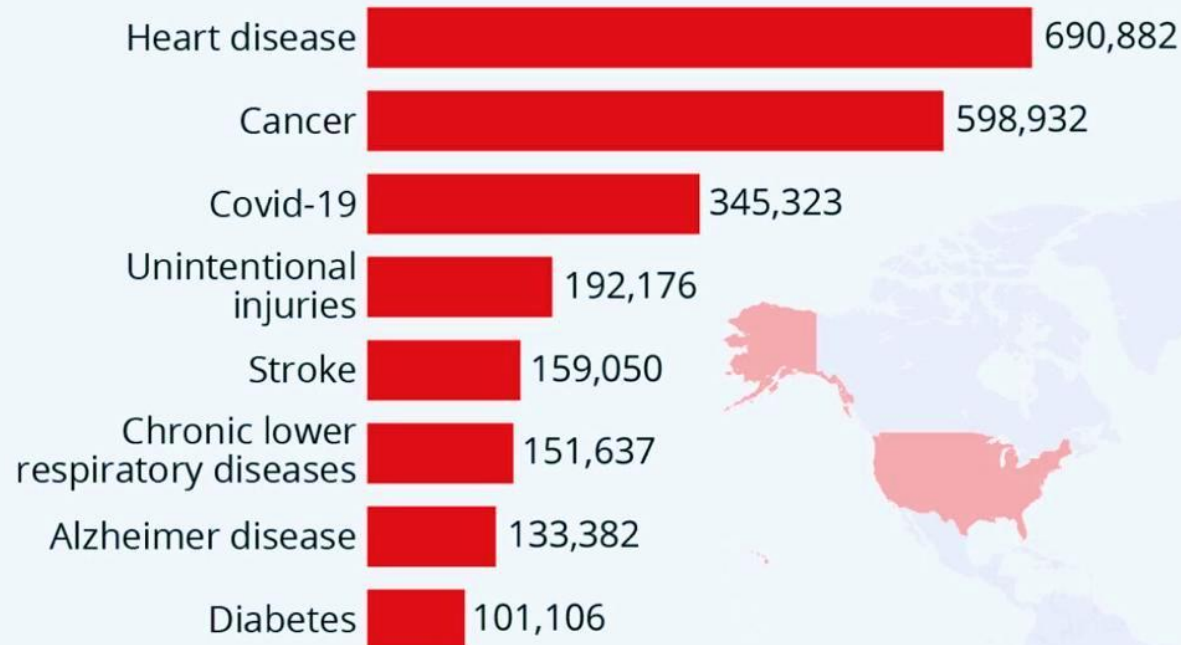
- قرن پنجم قبل از میلاد - آتن
- ۶۲۷-۶۲۸ میلادی: طاعون در زمان شاهنشاهی ساسانیان
- سده ۱۳۰۰ میلادی: طاعون سیاه - تا ۲۰۰ میلیون نفر مرگ مردم اروپا (۱/۳ ایرانیان کشته شدند)
- ۲۵۰ سال پیش - دوران کریم خان زند (۱۱۵۱) در ایران همه گیری طاعون - ۲ میلیون مرگ
- ۱۸۷۰ (زمان ناصرالدین شاه قاجار): قحطی ۱ بزرگ ایران: مرگ ۱/۱۰ جمعیت ایران از وبا و گرسنگی
- ۱۹۱۸ (زمان احمد شاه قاجار): آنفوانزای اسپانیایی ۵۰ میلیون مرگ
- (قحطی ۲ بزرگ ایران: تا ۵ میلیون مرگ ایرانی)
- ۱۹۵۸: آنفوانزای آسیایی ۲ میلیون مرگ
- ۱۹۶۸: آنفلوانزای هنگ کنگی ۱ میلیون مرگ
- قرن بیستم: ۵۰۰-۳۰۰ میلیون مرگ بواسطه آبله!

۲۰۱۹: کووید-۱۹ تا بحال بیش از ۴ میلیون مرگ



# Covid-19 Was America's Third Leading Cause Of Death In 2020

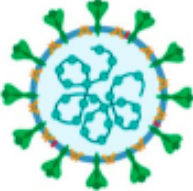
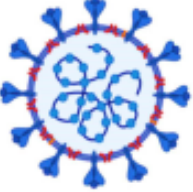

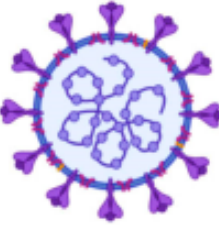
Number of deaths for all leading causes of death in the U.S. in 2020



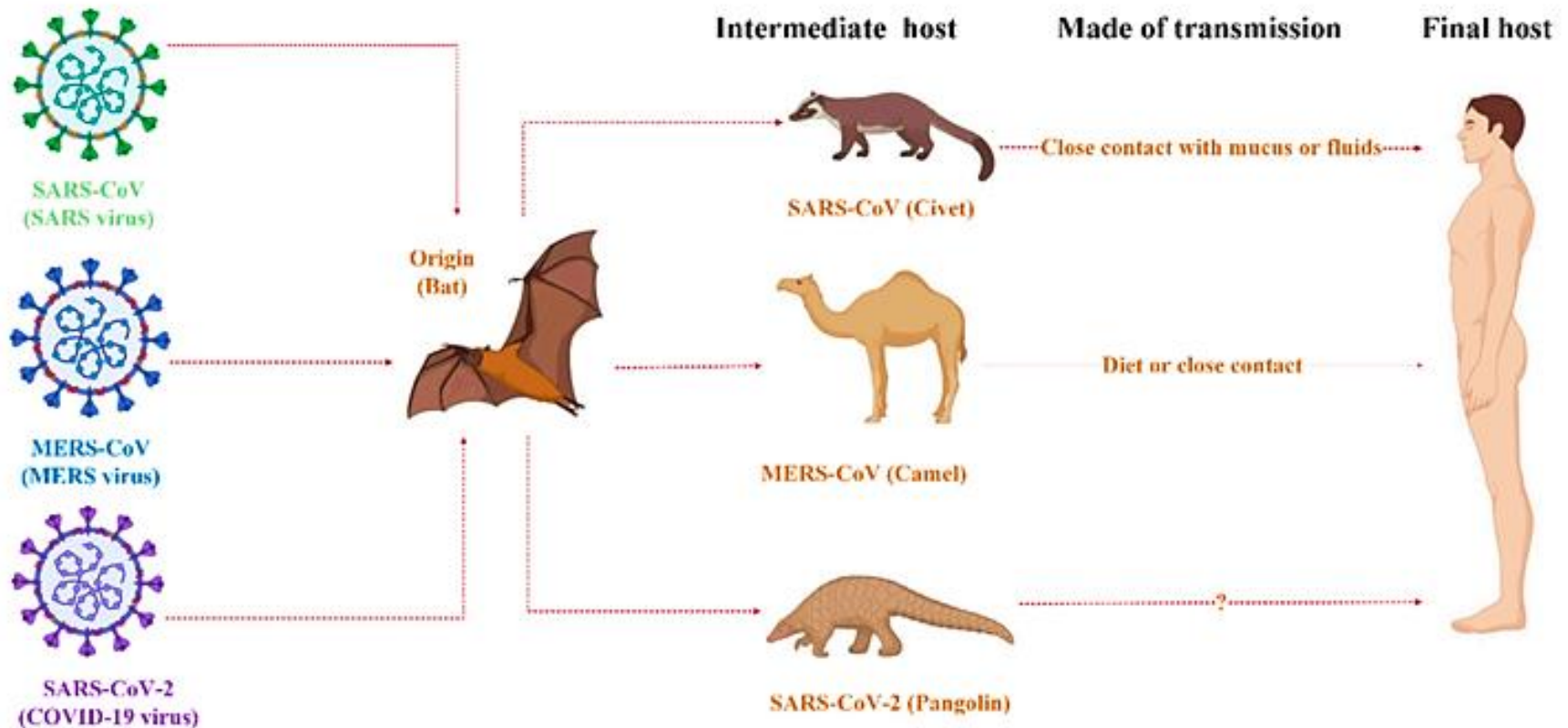
Source: Centers for Disease Control and Prevention



Table 2. Epidemiological comparison of respiratory viral infection [70–73].

Disease	Disease-Causing Pathogen	R <sub>0</sub> Basic Reproductive Number	CFR Case Fatality Rate	Incubation Time	Hospitalization Rate	Community Attack Rate	Annual Infected Global
SARS	 SARS-CoV	3	9.6–11%	2–7 days	Most cases	10–60%	8098 (in 2003)
MERS	 MERS-CoV	0.3–0.8	34.4%	6 days	Most cases	4–13%	420
Flu	 Influenza virus	1.3	0.05–0.1%	1–4 days	2%	10–20%	~1 billion
COVID-19	 SARS-CoV-2	2.0–2.5	~3.4%	4–14 days	~19%	30–40%	N/A ongoing

# Animal Resource of SARS



**Figure 1.** Animal origins of human coronaviruses (Created with [BioRender.com](https://BioRender.com), accessed on 1 August 2020).

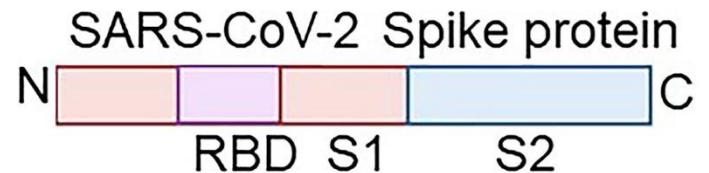
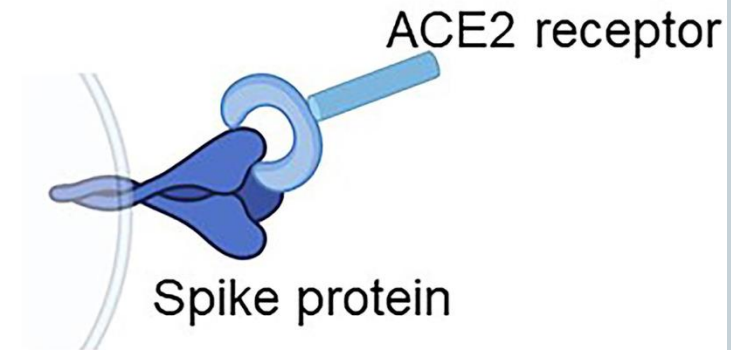
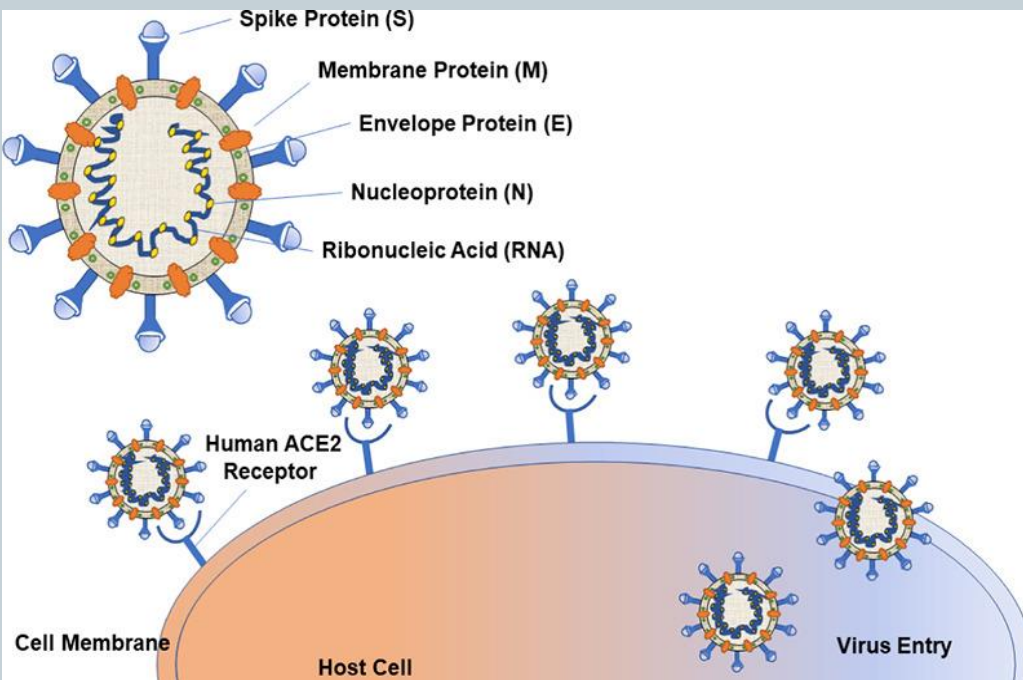
## Review

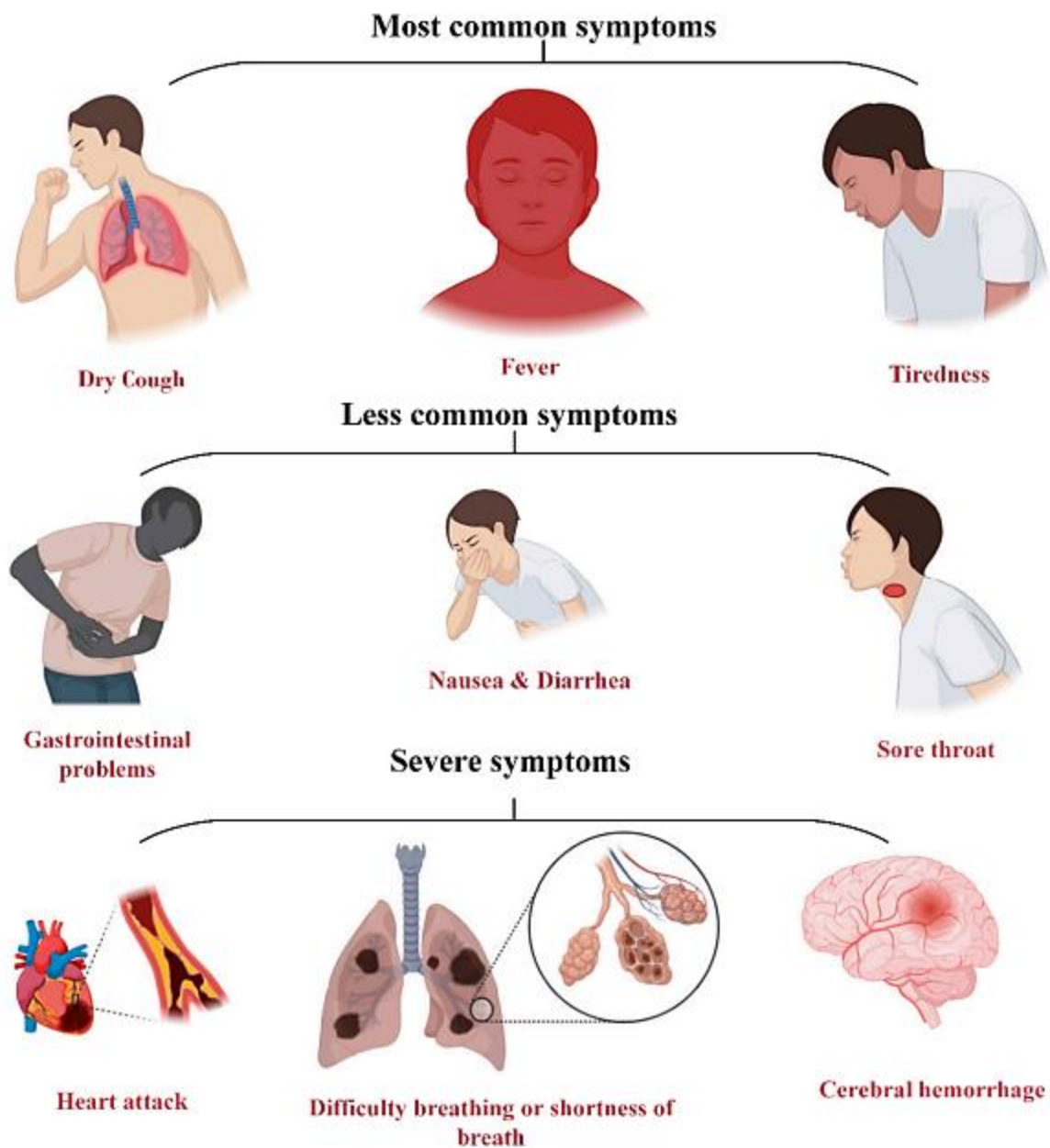
### Overview of COVID-19 Disease: Virology, Epidemiology, Prevention Diagnosis, Treatment, and Vaccines

Iman Salahshoori <sup>1,\*</sup>, Noushin Mobaraki-Asl <sup>2,\*</sup>, Ahmad Seyfaee <sup>3,\*</sup>, Nasrin Mirzaei Nasirabad <sup>2</sup>, Zahra Dehghan <sup>4</sup>, Mehrdad Faraji <sup>5</sup>, Mina Ganjkhani <sup>4</sup>, Aziz Babapoor <sup>4,\*</sup>, Seyede Zahra Shadmehr <sup>6</sup> and Ali Hamrang <sup>6</sup>



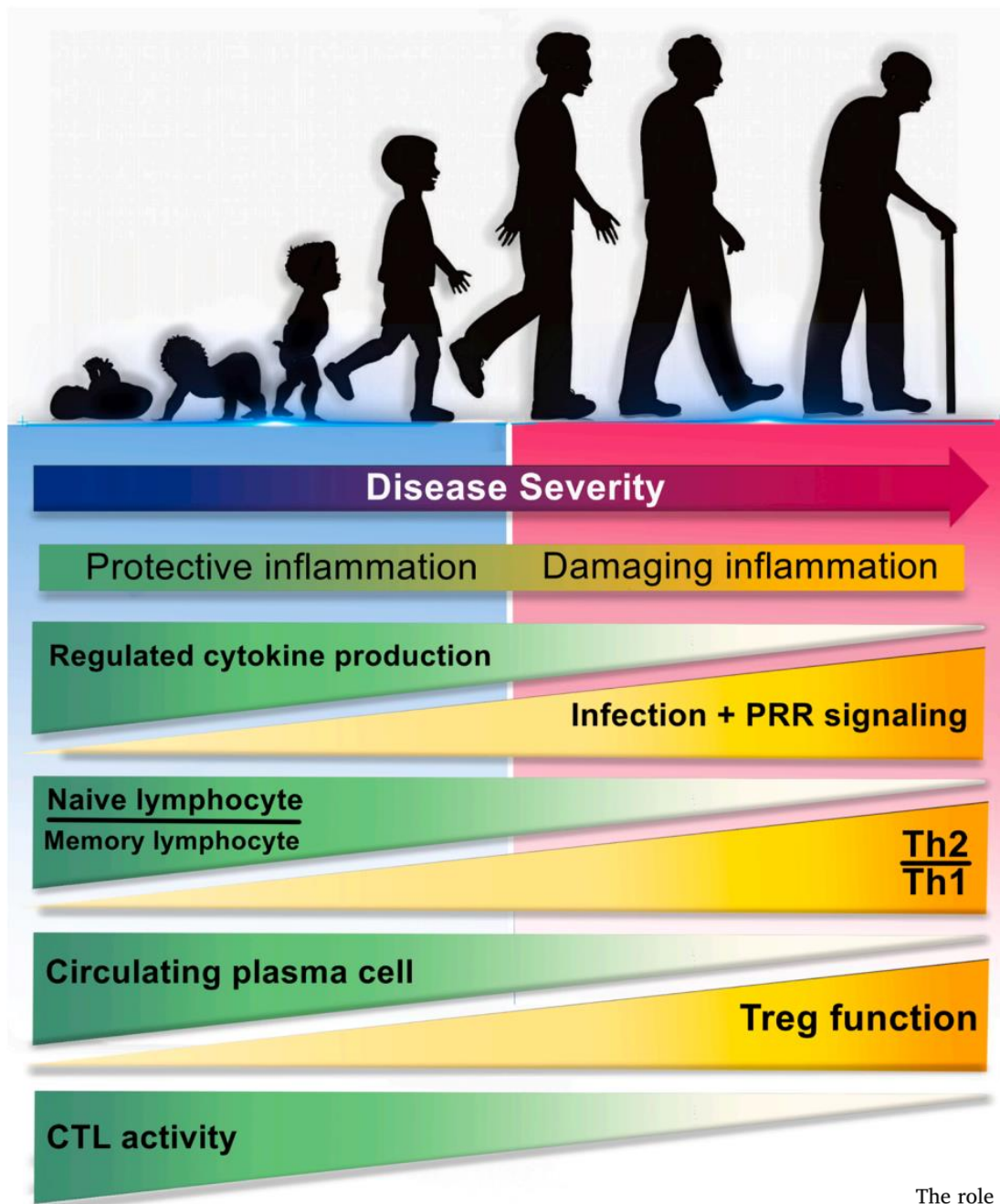
# Spike (S) Protein & ACE2





**Figure 5.** The most minor and major symptoms of COVID-19 (Created with [BioRender.com](https://www.biorender.com), accessed on 15 March 2021)

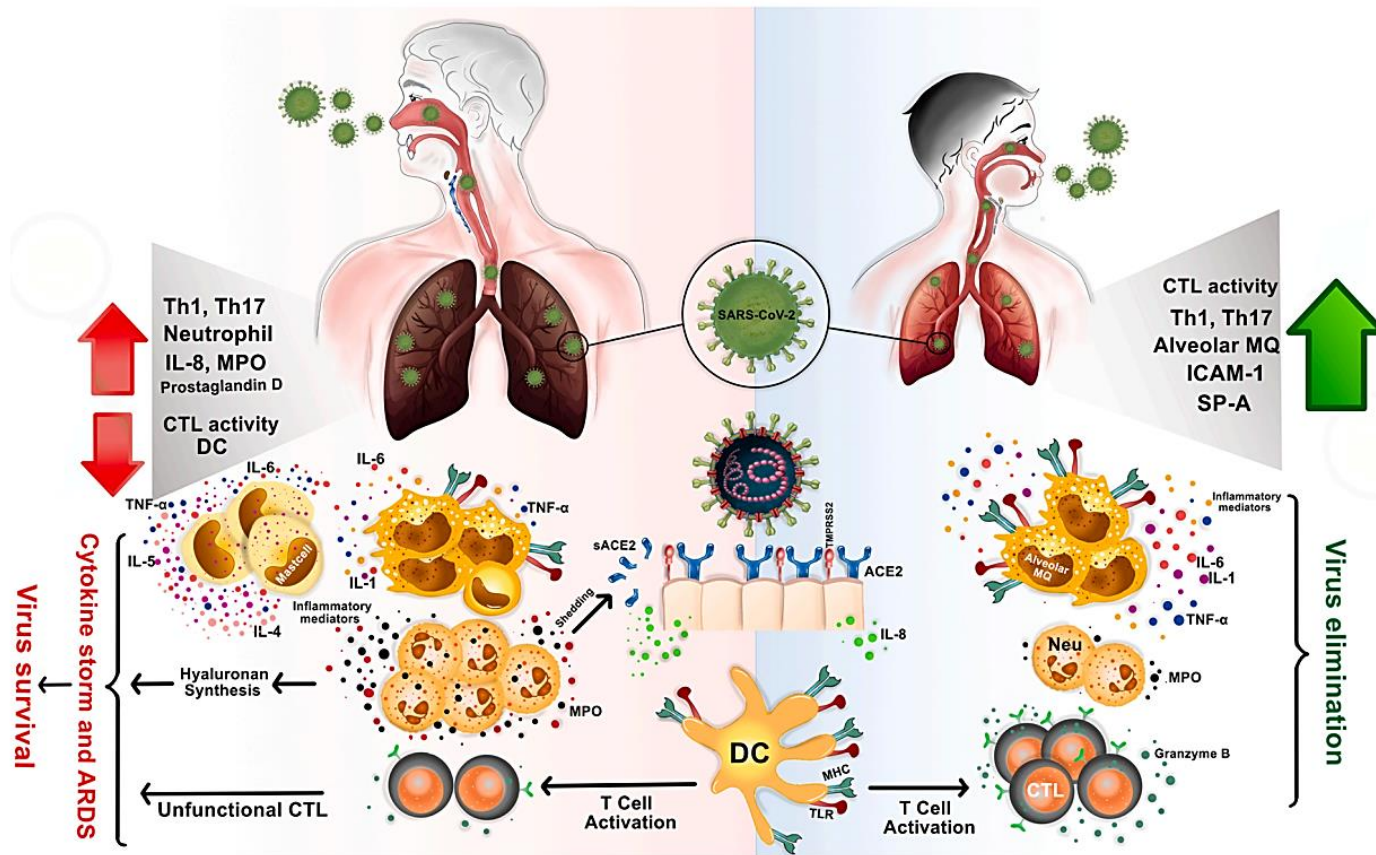




**Fig. 1.** The relationship between age-dependent changes in immune responses with the severity of COVID-19 disease.

Differences in the immune system of children and adults may be the reasons for clinical differences in the severity of COVID-19. During aging, immune responses undergo changes that lead to more severe disease, some of which are include: a) depletion of well-ordinated innate immunity and regulative cytokines, b) diminished ability of the innate immune cells to recognize PAMPs, followed by strong activation of PRRs, influx of pathogenic immune cells and excessive release of proinflammatory cytokines for compensation, c) reduction ratio of naïve lymphocyte/memory lymphocyte, d) induce of negative regulation and the predominance of Th2 to Th1 responses, e) decrement of circulating plasma cells, f) increase of regulatory T cells (CD4<sup>+</sup> CD25<sup>+</sup> FOXP3<sup>+</sup>) function, and g) decrease of CTLs activity and diminish of CTL-mediated immunity. PAMP: Pathogen associated molecular pattern; PRR: Pathogen recognition receptor; Th: T helper; CTL: Cytotoxic T lymphocyte.

# Adults & Children COVID-19



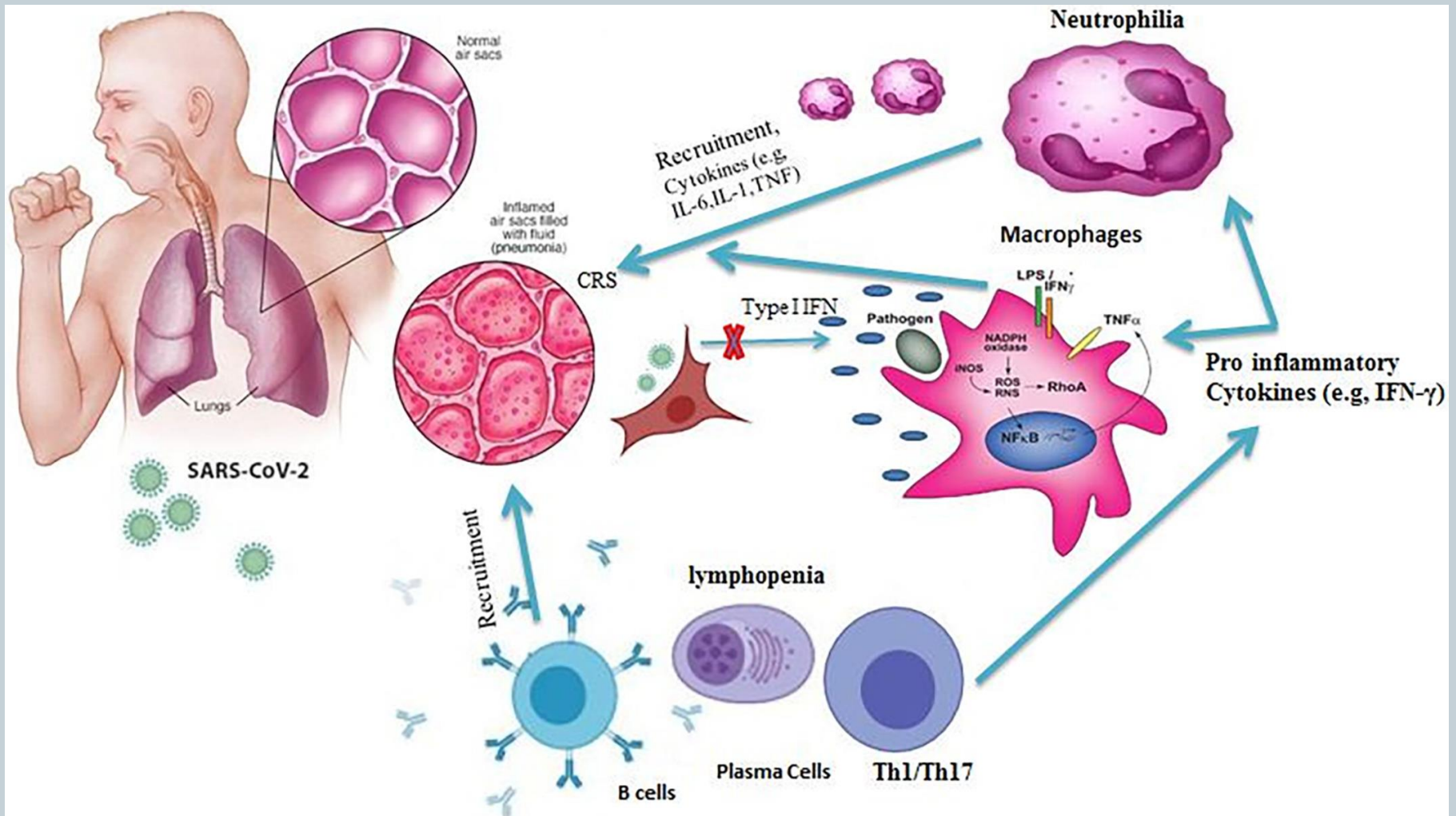
**Fig. 2.** The difference in immune responses in the lungs of children and adults to SARS-CoV-2 is the reason for the different clinical manifestations. In children, SARS-CoV-2 infection may be quickly eradicated due to having less mature ACE2 receptors and rapid activation of immunocompetent immune cells (right side). In adults, the negative regulation of the immune response in the respiratory tract, late changes in the nature of the immune responses, decrease in population of immunocompetent cells, increase of ACE2 expression, ACE2 shedding and sACE2 production, all can lead to an uncontrolled immune response, widespread ineffective inflammation, immune dysregulation, cytokine storm and ARDS (left side). ACE2: Angiotensin-CONverting enzyme 2; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; ARDS: Acute respiratory distress syndrome.

The role of dysregulated immune responses in COVID-19 pathogenesis

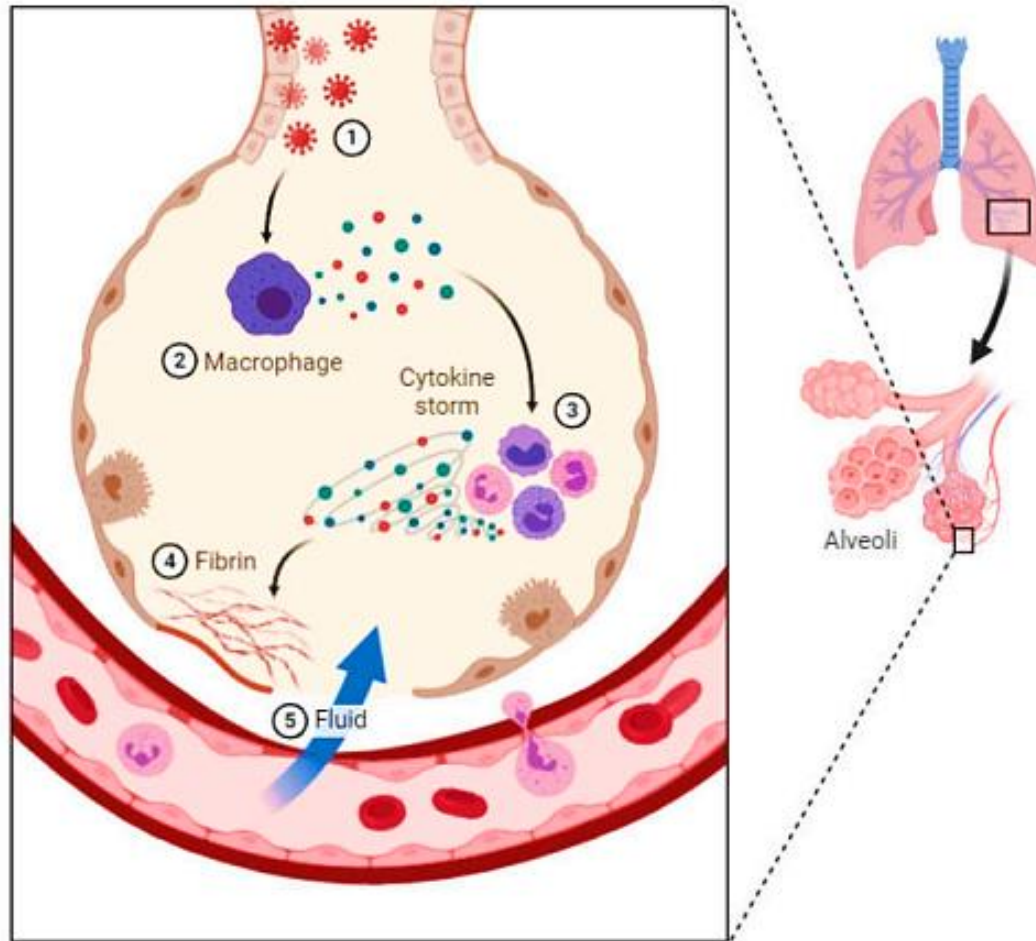
Tahaghoghi-Hajghorbani S<sup>a,b</sup>, Zafari P<sup>a,b</sup>, Masoumi E<sup>c,d,e</sup>, Rajabinejad M<sup>a,b</sup>, Jafari-Shakib R<sup>f,g</sup>, Hasani B<sup>a</sup>, Rafiei A<sup>h,\*</sup>



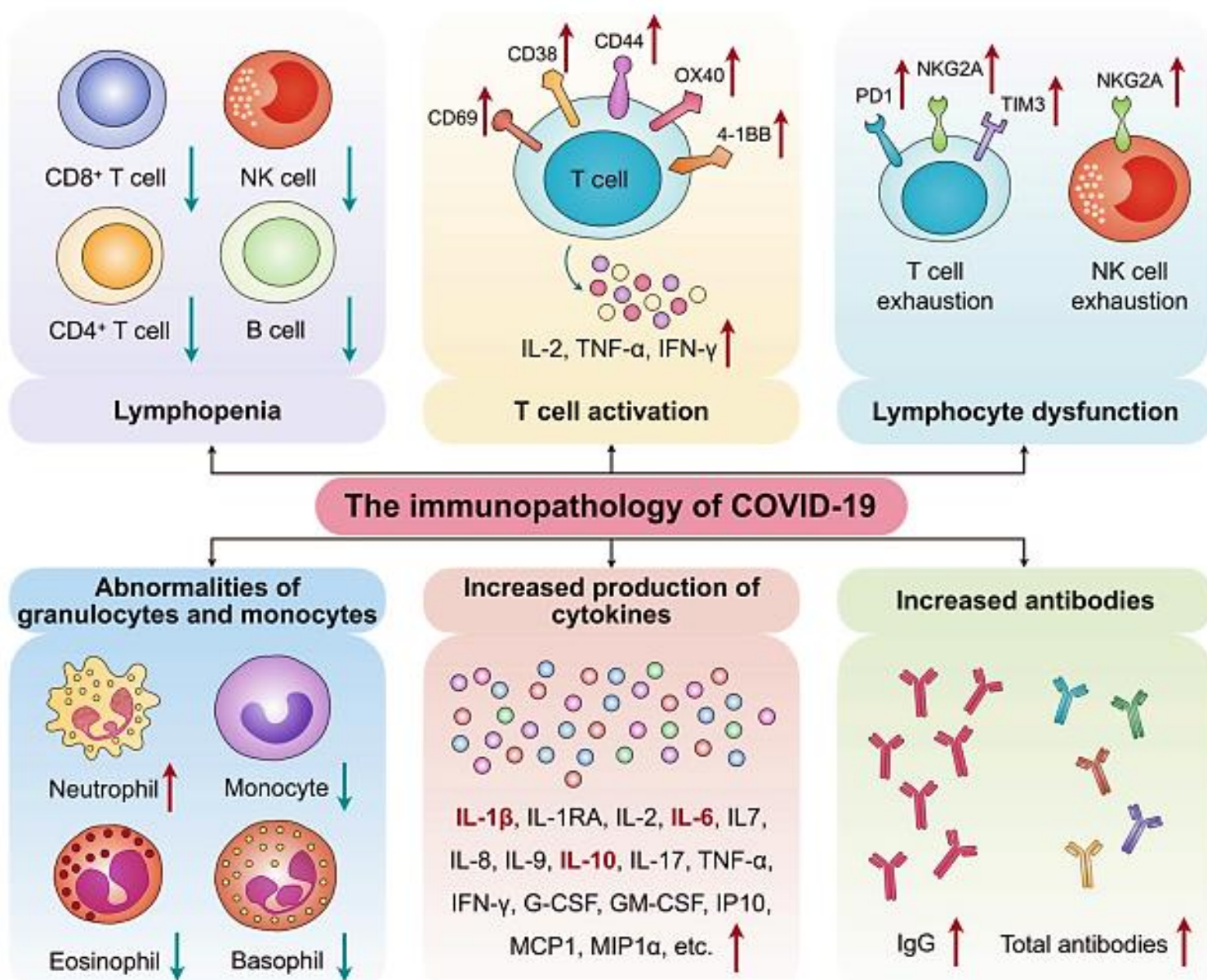
# COVID-19-associated Hyper-inflammation



# CYTOKINE STORM & ARDS



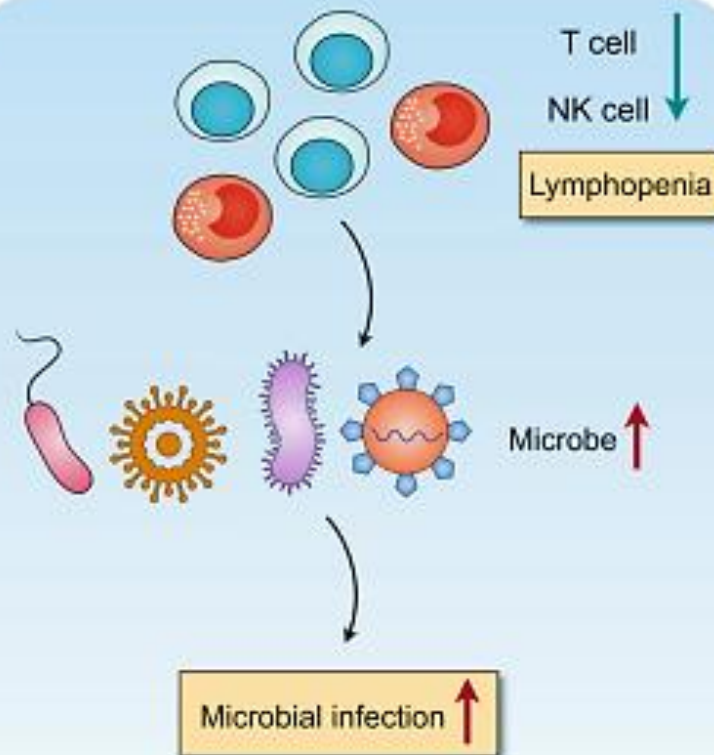
**Figure 6.** A cytokine storm in the lungs due to COVID-19 disease: (1) infection, (2) Cytokine production, (3) Creating a cycle of inflammation in lung cells, (4) Fibrin formation and (5) Filling of the lung cavities (Reprinted from "Cytokine Storm", by [BioRender.com](https://www.biorender.com), accessed on 3 July 2020) [38].



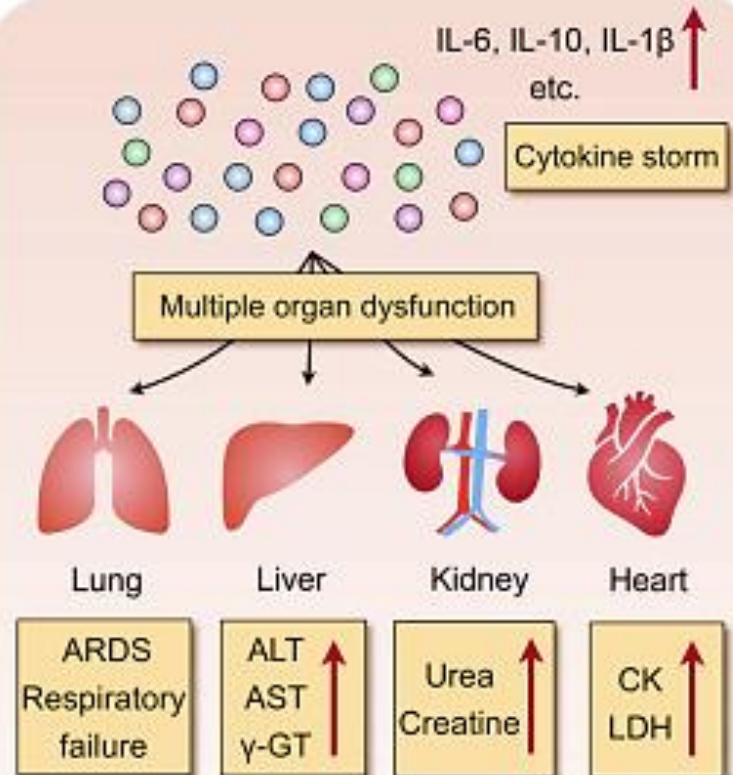


## Clinical implications of SARS-CoV-2-induced immunopathology

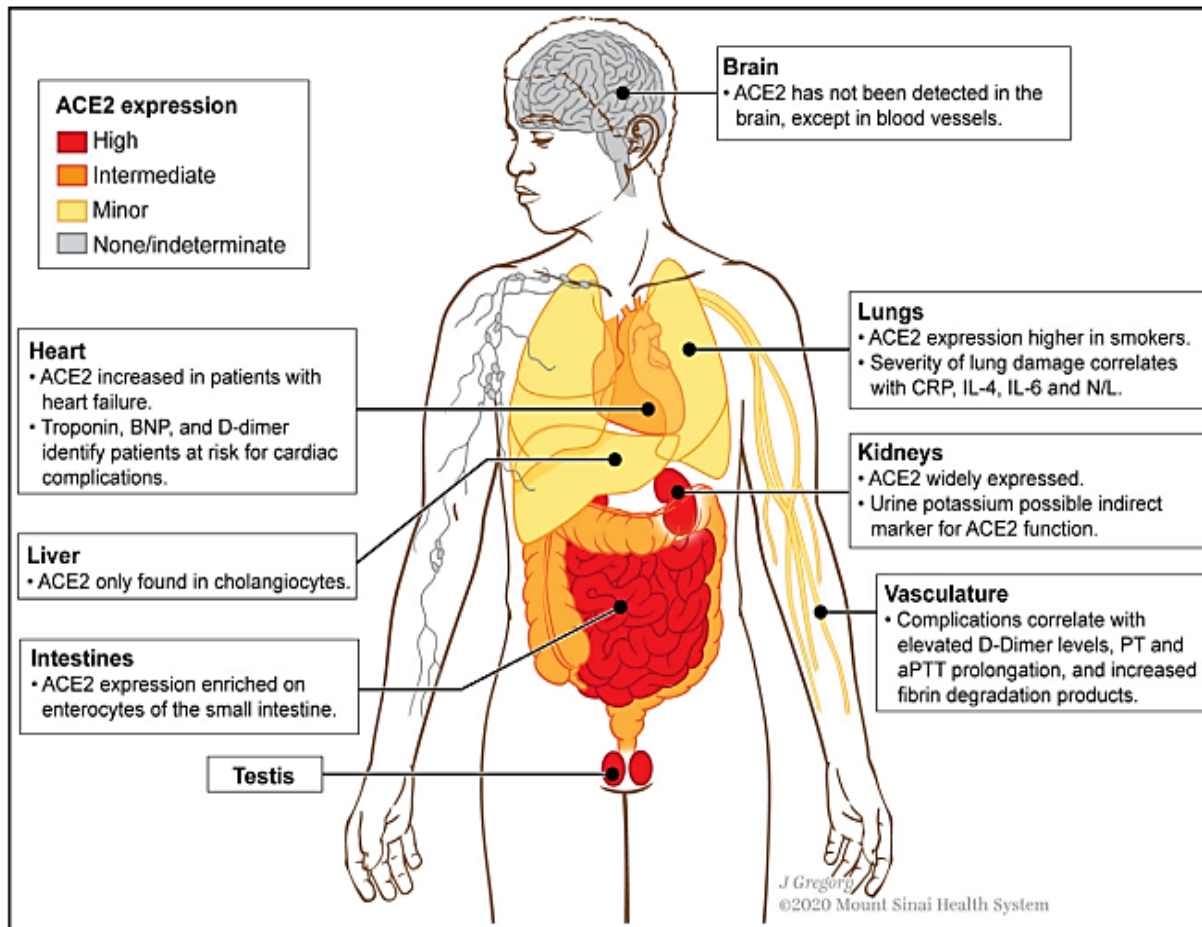
### The effect of lymphopenia on microbiota infection



### The effect of elevated cytokine production on severe syndromes



# ACE2 Expression in Most Organs

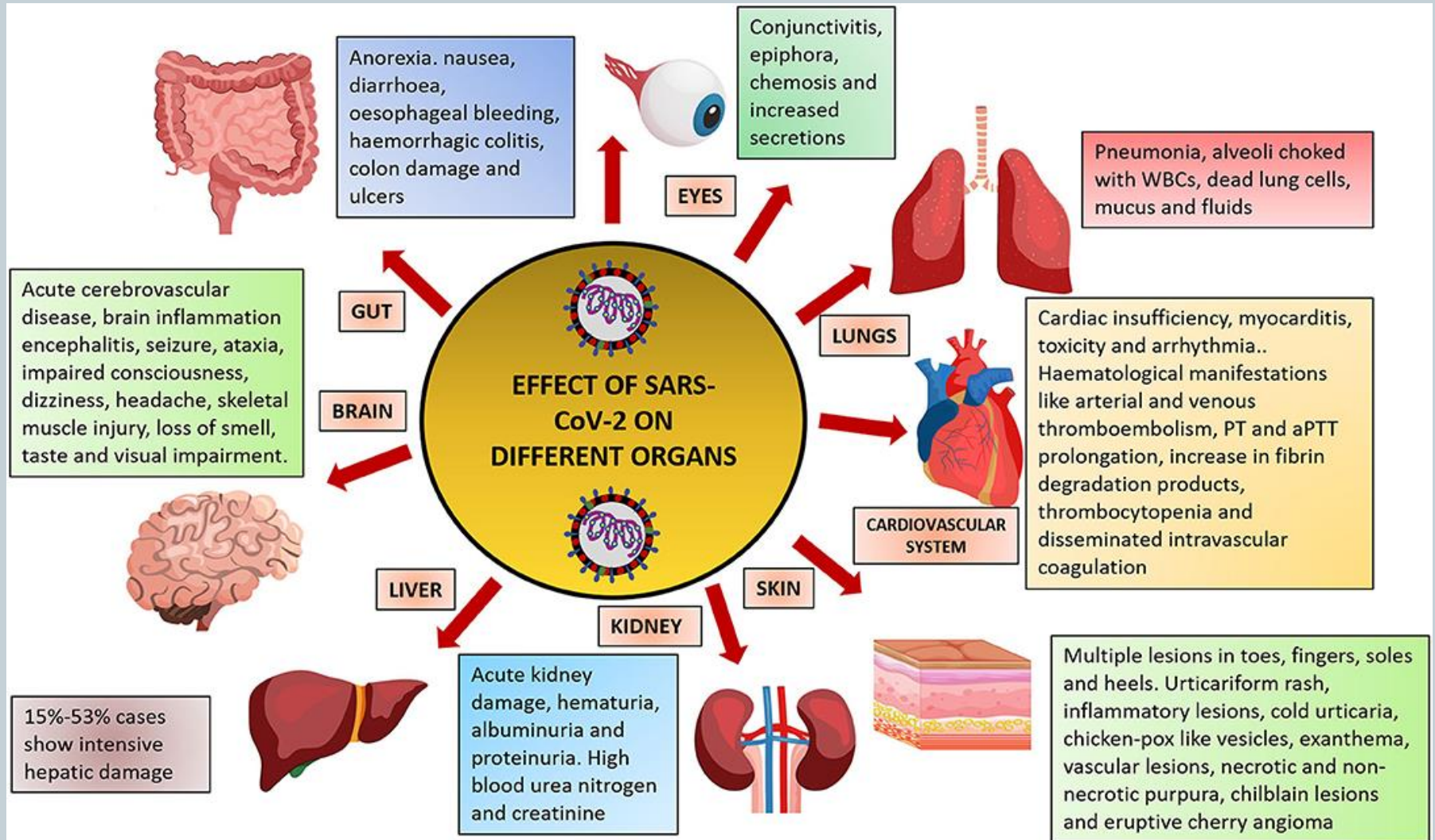


**Figure 5. ACE2 Expression in Organs and Systems Most Frequently Implicated in COVID-19 Complications**

The gastrointestinal tract, kidneys, and testis have the highest ACE2 expressions. In some organs, different cell types have remarkably distinct expressions; e.g., in the lungs, alveolar epithelial cells have higher ACE2 expression levels than bronchial epithelial cells; in the liver, ACE2 is not expressed in hepatocytes, Kupffer cells, or endothelial cells but is detected in cholangiocytes, which can explain liver injury to some extent. Furthermore, ACE2 expression is enriched on enterocytes of the small intestine compared to the colon. ACE2, angiotensin-converting enzyme 2; BNP, B-type natriuretic peptide; CRP, C-reactive protein; IL, interleukin; N/L, neutrophil-to-lymphocyte ratio; PT, prothrombin time; aPTT, activated partial thromboplastin time.

of similarities between different virus replication mechanisms, some antivirals can be repurposed against various viral infections. Currently, most of the available

# Multi-Organ Failure due to COVID-19

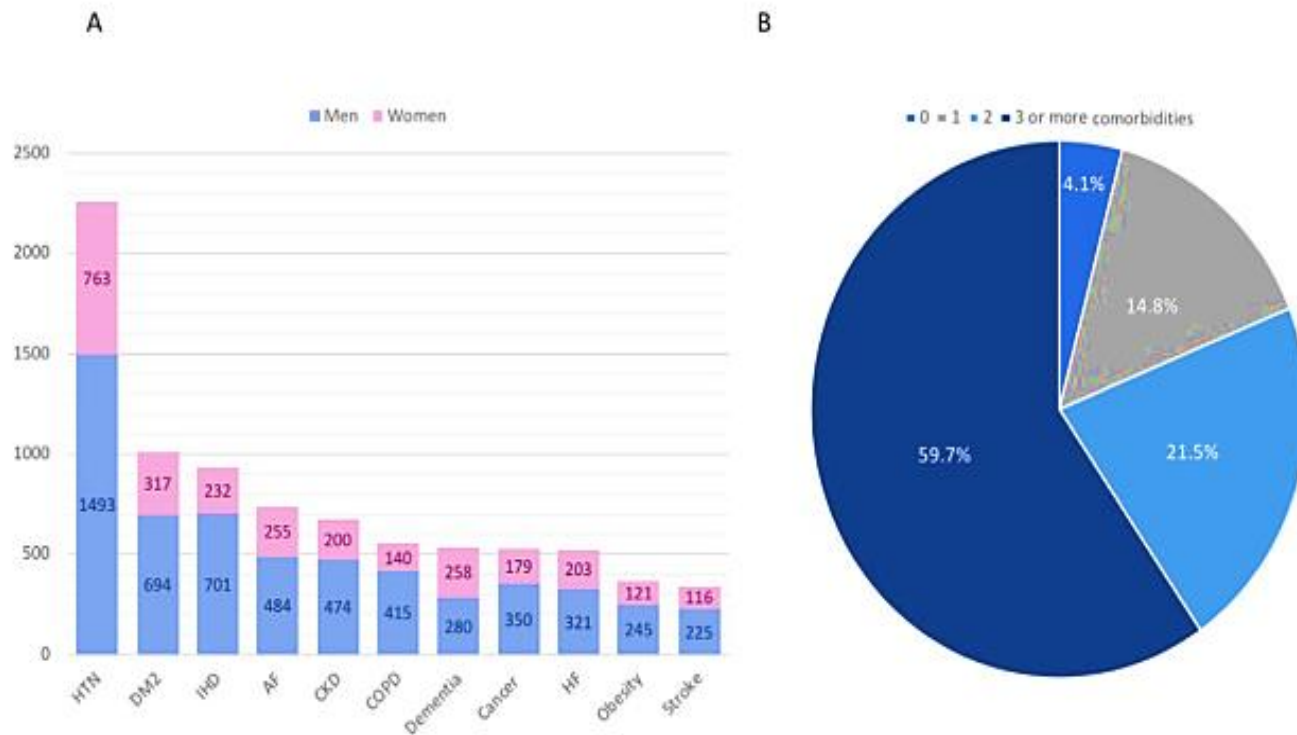




# Chronic Comorbidities Among 3335 Deceased COVID-19 Patients in Italy

454

F. Mai et al./Journal of Cardiology 76 (2020) 453–458

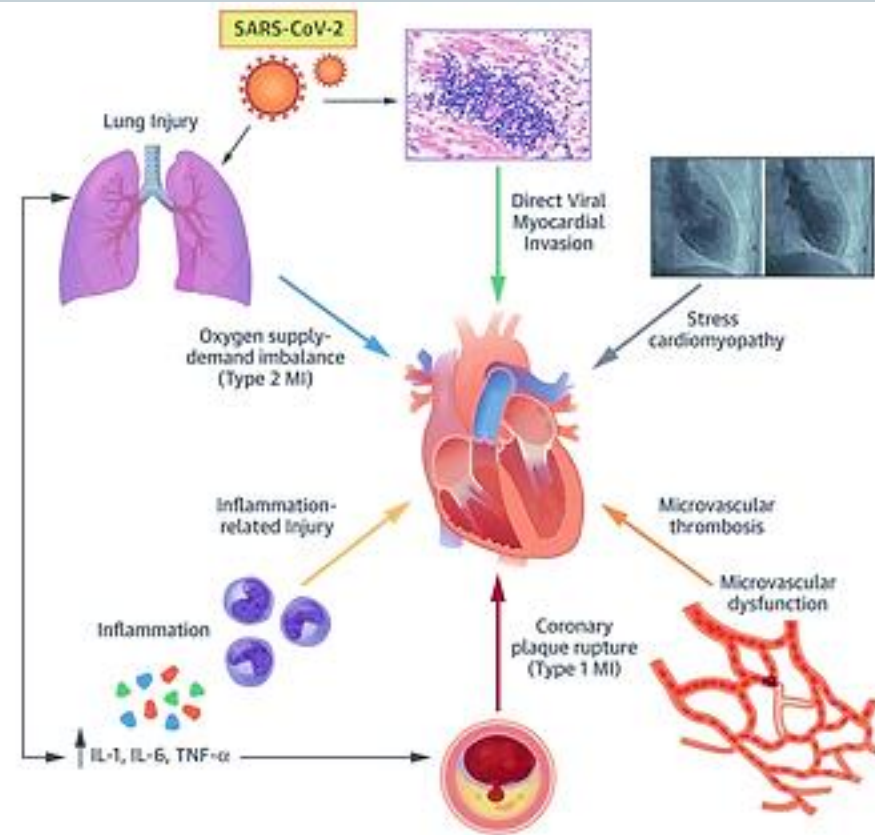


**Fig. 1.** Chronic comorbidities among 3335 deceased COVID-19 patients in Italy as of June 4th, 2020. (A) Comorbidities by gender. (B) Proportion of patients with 0, 1, 2, or at least 3 comorbidities: 4.1%, 14.8%, 21.5%, and 59.7%, respectively. HTN, hypertension; DM2, diabetes mellitus type 2; IHD, ischemic heart disease; AF, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure.

## COVID-19 and cardiovascular diseases

Francesca Mai (MD)<sup>1</sup>, Rita Del Pinto (MD, PhD)<sup>1</sup>, Claudio Ferri (MD)\*

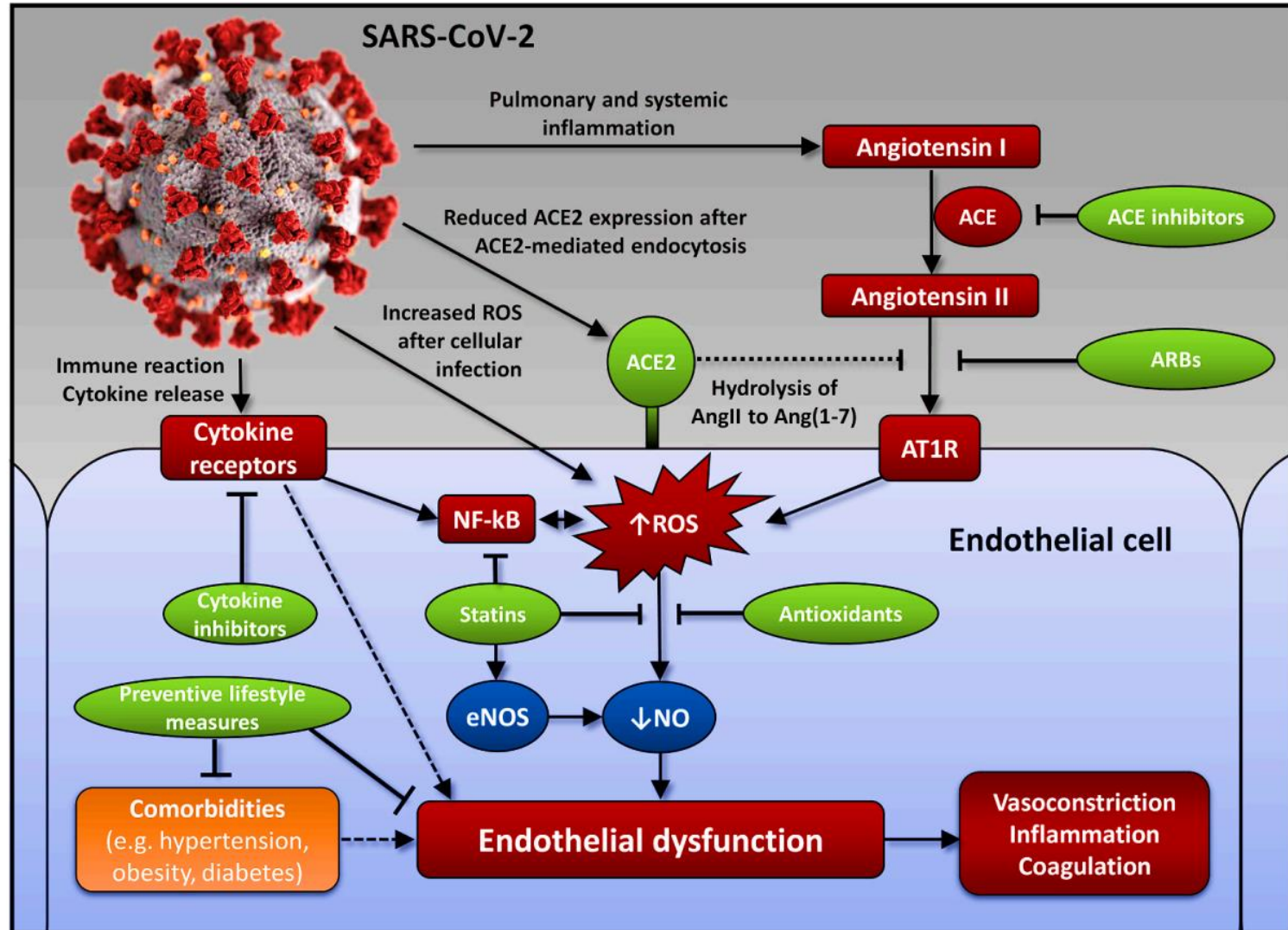
# Mechanisms of Myocardial Injury in COVID-19 patients



Giustino, G. et al. J Am Coll Cardiol. 2020;76(17):2011-23.



# Mechanisms of *Endothelial Dysfunction* in COVID-19



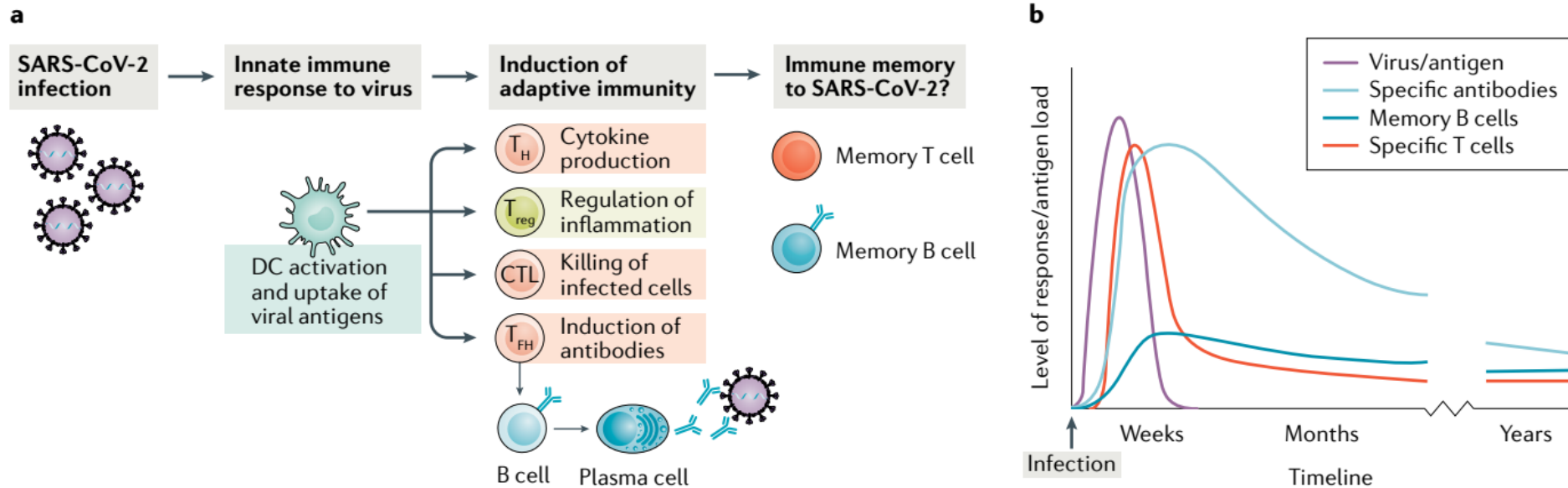
Endothelial dysfunction in COVID-19: Current findings and therapeutic implications

Matthias P. Nägele, Bernhard Haubner, Felix C. Tanner, Frank Ruschitzka, Andreas J. Flammer

# **Immune Response to SARS-CoV-2**

# Not just antibodies: B cells and T cells mediate immunity to COVID-19

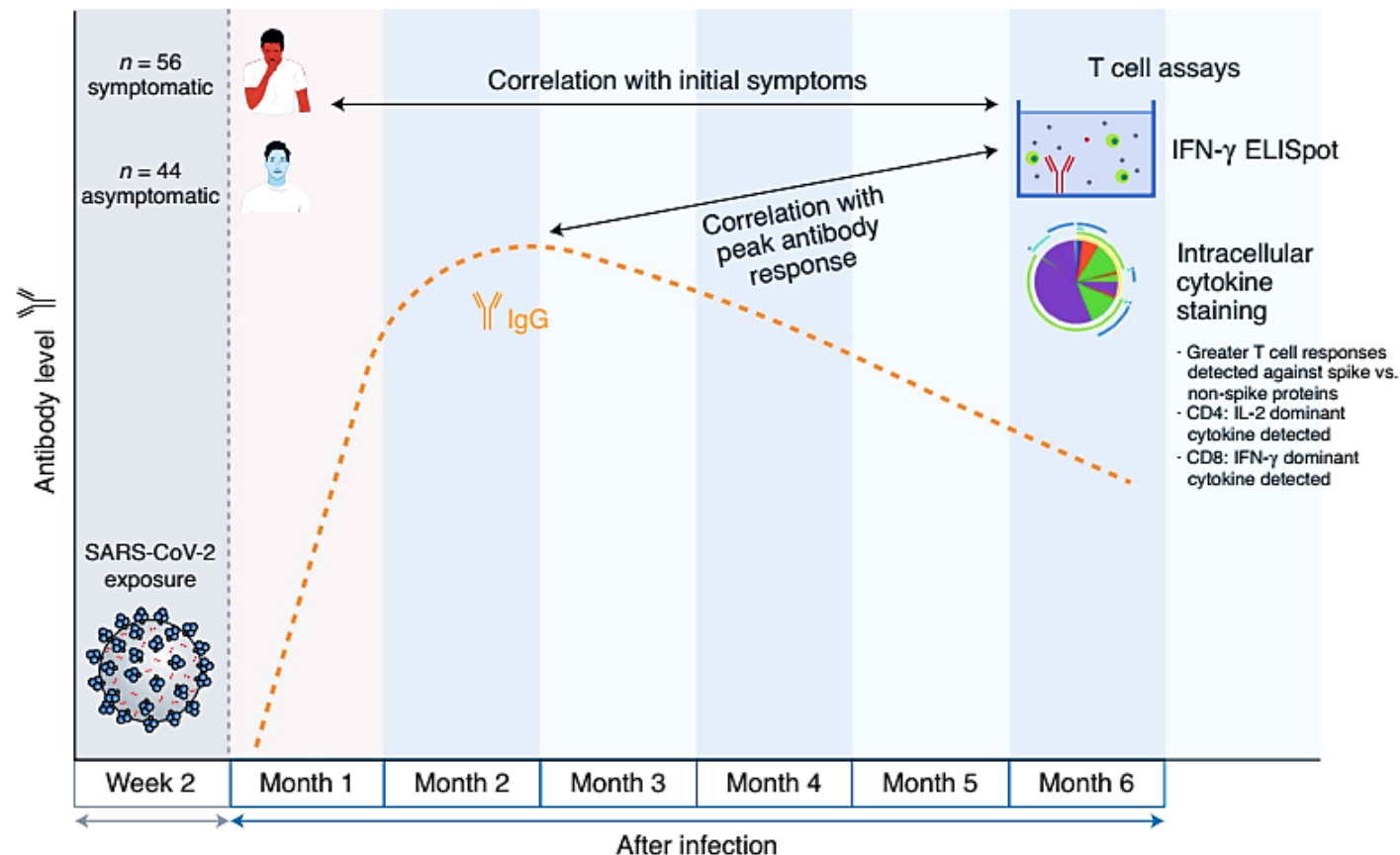
Rebecca J. Cox<sup>1</sup> and Karl A. Brokstad<sup>2</sup>



**Fig. 1 | T cells and B cells in immunity to SARS-CoV-2. a** | Infection with SARS-CoV-2 leads to activation of innate immunity and dendritic cells (DCs), which will drive the induction of virus-specific T cell and B cell responses. Little is currently known concerning the memory response to SARS-CoV-2, but this will be important for developing an effective vaccine. **b** | A predicted time-course of adaptive immunity to SARS-CoV-2. CTL, cytotoxic T lymphocyte;  $T_{FH}$ , T follicular helper cell;  $T_H$ , T helper cell;  $T_{reg}$ , regulatory T cell.

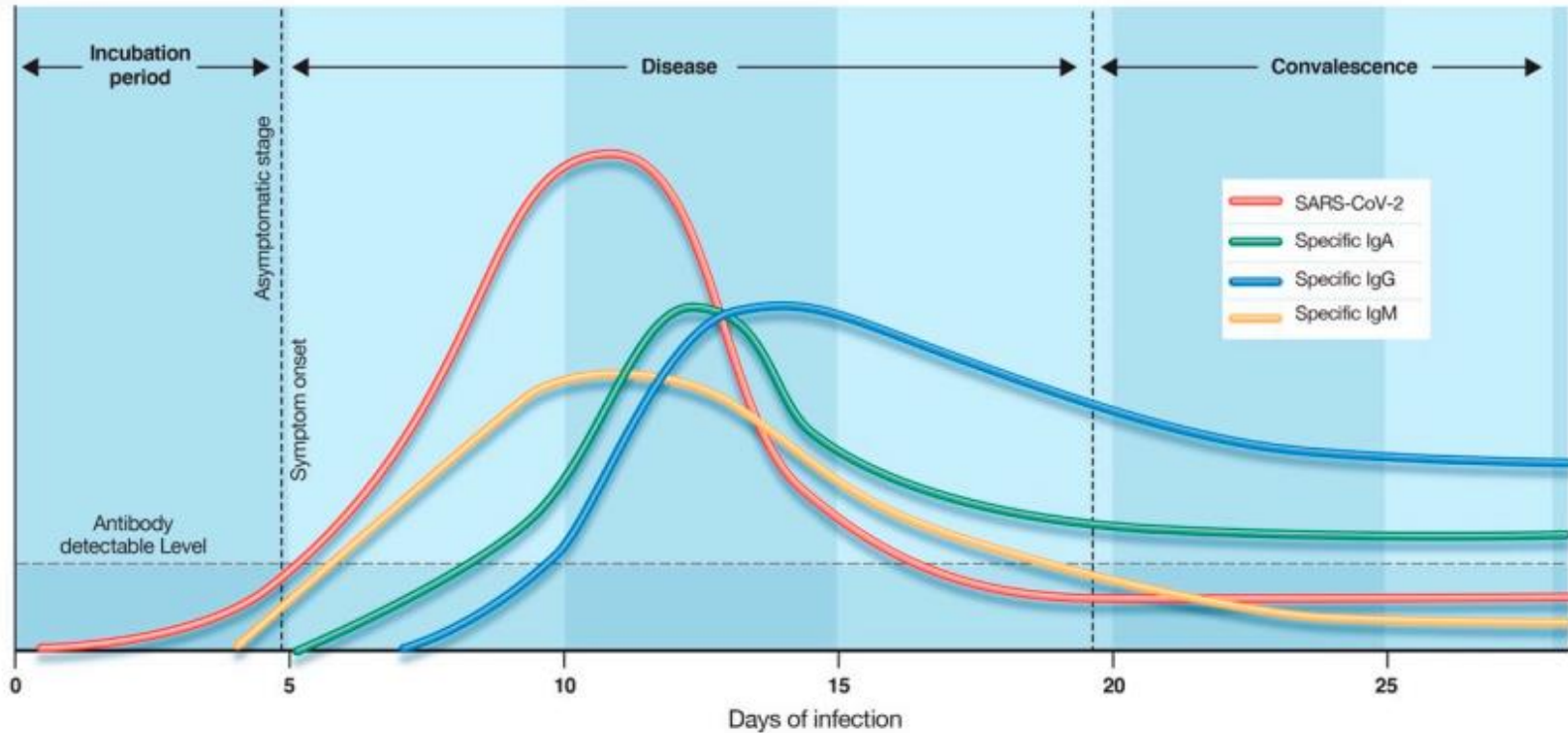
# Immunity after SARS-CoV-2 infections

NATURE IMMUNOLOGY | VOL 22 | MAY 2021 | 537-544 | [www.nature.com/natureimmunology](http://www.nature.com/natureimmunology)



**Fig. 1 | Correlations between SARS-CoV-2-specific T cell responses, disease severity and peak antibody response.** Zuo et al. measured SARS-CoV-2-specific T cell responses in 100 individuals six months after infection. SARS-CoV-2-specific T cell responses were measured by IFN- $\gamma$  ELISpot and intracellular cytokine staining and correlated with both initial symptoms and the peak antibody response.

# Antibody Response in COVID-19



**Figure 4.** Time kinetics of antibody response in coronavirus disease 2019 (COVID-19). The illustration demonstrates the relative levels of host immunoglobulins (IgM, IgG, IgA) and SARS-CoV-2 viral load at different stages of COVID-19. Antibody-specific seroconversion occurs when the antibody reaches a detectable level in blood. Disclaimer: This graphic is for illustrative purposes only and does not represent actual levels of each antibody.



# Laboratory Diagnosis of COVID-19

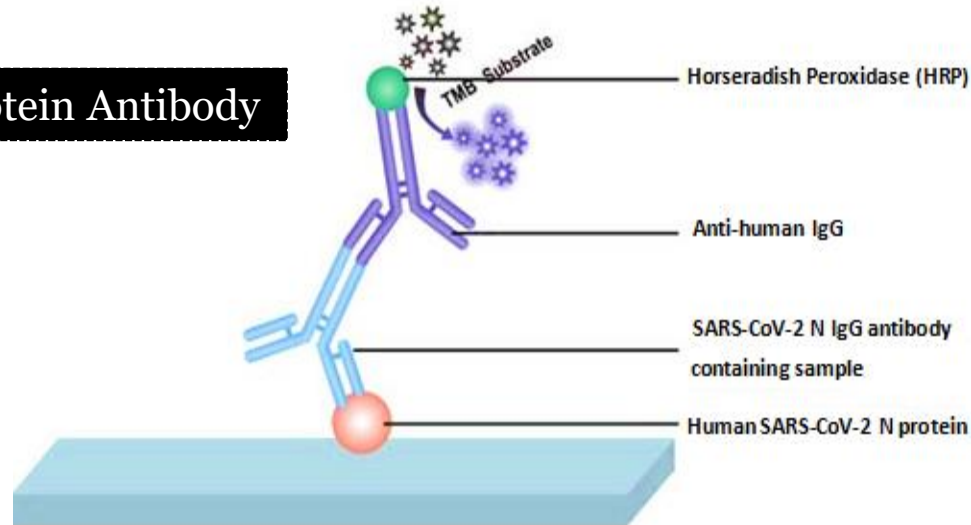
- *Molecular Assays (PCR)*
- *Immunologic Assays (ELISA)*

**Figure 9.** The protocol template COVID-19 diagnostic testing through real-time RT-PCR: (1) Nasopharyngeal swab, (2) Collected specimen, (3) RNA extraction, (4) purified RNA and (5) Test results real-time (Adopted from “COVID-19 Diagnostic Test through RT-PCR”, by BioRender.com, accessed on 9 April 2020) [98].

**Figure 9.** The protocol template COVID-19 diagnostic testing through real-time RT-PCR: (1) Nasopharyngeal swab, (2) Collected specimen, (3) RNA extraction, (4) purified RNA and (5) Test results real-time (Adopted from “COVID-19 Diagnostic Test through RT-PCR”, by [BioRender.com](https://www.biorender.com), accessed on 9 April 2020) [98].

# Immunologic Assays (ELISA)

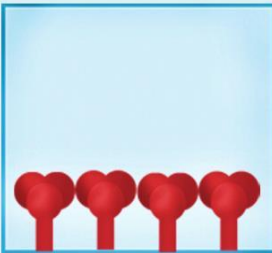
## 1) Anti-Nucleoprotein Antibody



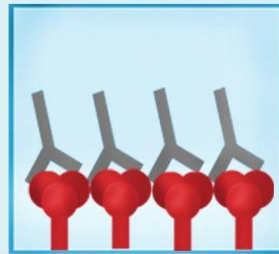
## 2) Anti-Spike Glycoprotein Antibody

### Anti-Spike Trimer IgG Detection Kit *Colorimetric*

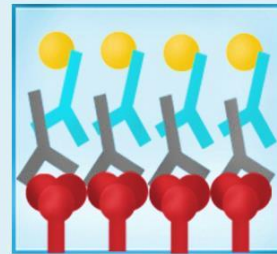
BPS #79975



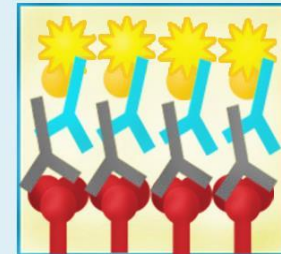
Spike  
Trimer



Serum  
Sample

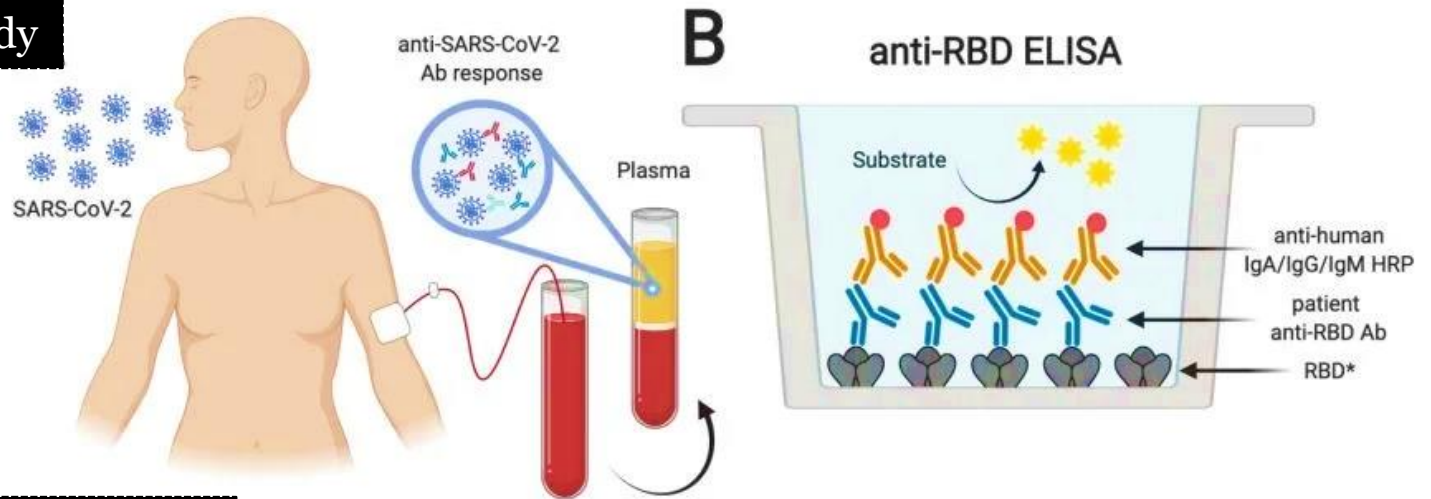


Anti-Fc-HRP

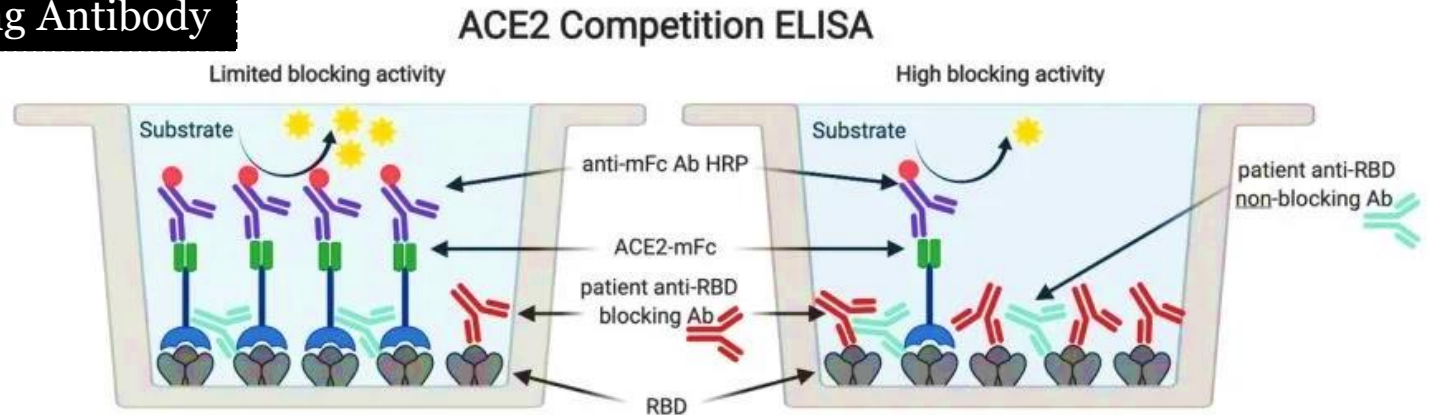


HRP Substrate

### 3) Anti-RBD Antibody



### 4) ACE2 Neutralizing Antibody



# جمع‌بندی و نتیجه‌گیری



- اهمیت طوفان سایتوکایینی و التهاب شدید در پاتولوژی ویروس سارس-۲ بالاست.
- تغییرات ایمنولوژیک یکی از مهمترین دلایل اختلالات چندعضوی است.
- بیماری کووید-۱۹ منحصرأ پنومونی نیست و یک بیماری سیستمیک میتواند باشد.
- مشکلات ایمنوترومبوز، کواگولوپاتی و اختلالات عملکردی اندوتلیوم میتواند در ایجاد بیماریهای کاردیوواسکولار تاثیر بسزایی داشته باشد.
- تشخیص های ایمنولوژیک کووید-۱۹ رو به پیشرفت است و با انواع سنجش‌های مبتنی بر روش الایزا آشنا شدیم.