دانشگاه علوم پزشکی و خدمات بهداشتی درمانی گیلان

ایمونوپاتولوژی کووید-۱۹

(التهاب شدید تا مشکلات قلبی)

دکتر آرش پورغلامی‌نژاد

متخصص ایمونولوژی

عضو هیئت علمی دانشگاه علوم پزشکی گیلان

دانشکده پزشکی- گروه ایمونولوژی

مرگ و میر جهانی به دلایل عفونت‌ها

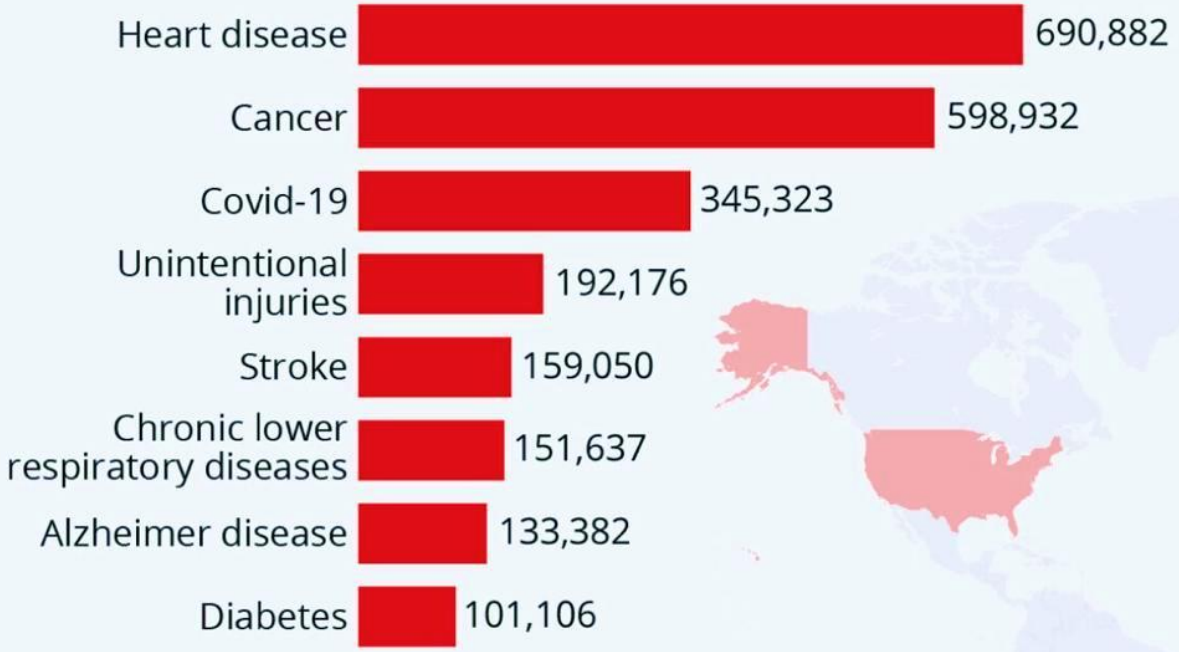
- قرن پنجم قبل از میلاد- آتن
- ۶۲۸-۶۲۷ میلادی: طاعون در زمان شاهنشاهی ساسانیان
- سده ۱۳۰۰ میلادی: طاعون سیاه- تا ۲۰۰ میلیون نفر مرگ مردم اروآسیا (۱/۳ ایرانیان کشته شدند)
- ۲۵۰ سال پیش-دوران کریم‌خان‌زند (۱۱۵۱) در ایران همه گیری طاعون- ۲ میلیون مرگ
- ۱۸۷۰ (زمان ناصرالدین شاه قاجار) : قحطی ۱ بزرگ ایران: مرگ ۱/۱۰ جمعیت ایران از وبا و گرسنگی
- ۱۹۱۸ (زمان احمدشاه قاجار): آنفوآنزای اسپانیایی ۵۰ میلیون مرگ

  (قحطی ۲ بزرگ ایران: تا ۵ میلیون مرگ ایرانی)
- ۱۹۵۸: آنفوآنزای آسیایی ۲ میلیون مرگ
- ۱۹۶۸: آنفلوآنزای هنگ کنگی ۱ میلیون مرگ
- قرن بیستم: ۵۰۰-۳۰۰ میلیون مرگ بواسطه آبله!

۲۰۱۹: کووید-۱۹ تا بحال بیش از ۳ میلیون مرگ

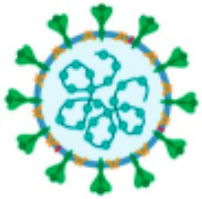
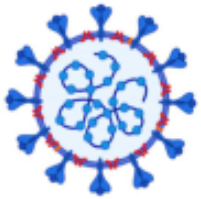
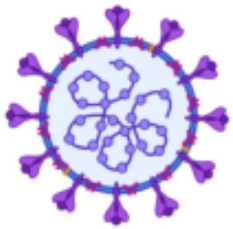
Covid-19 Was America's Third Leading Cause Of Death In 2020

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_O 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

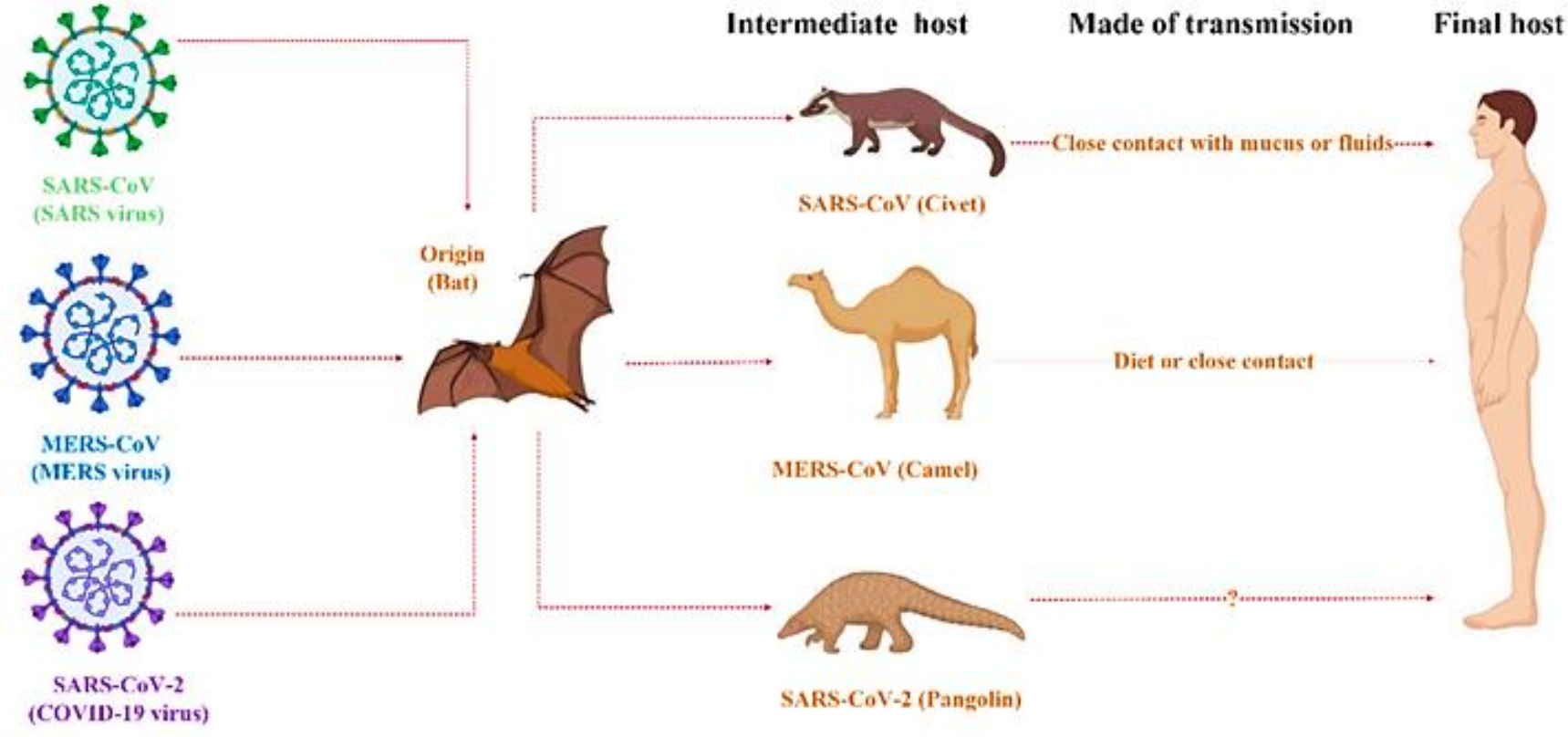


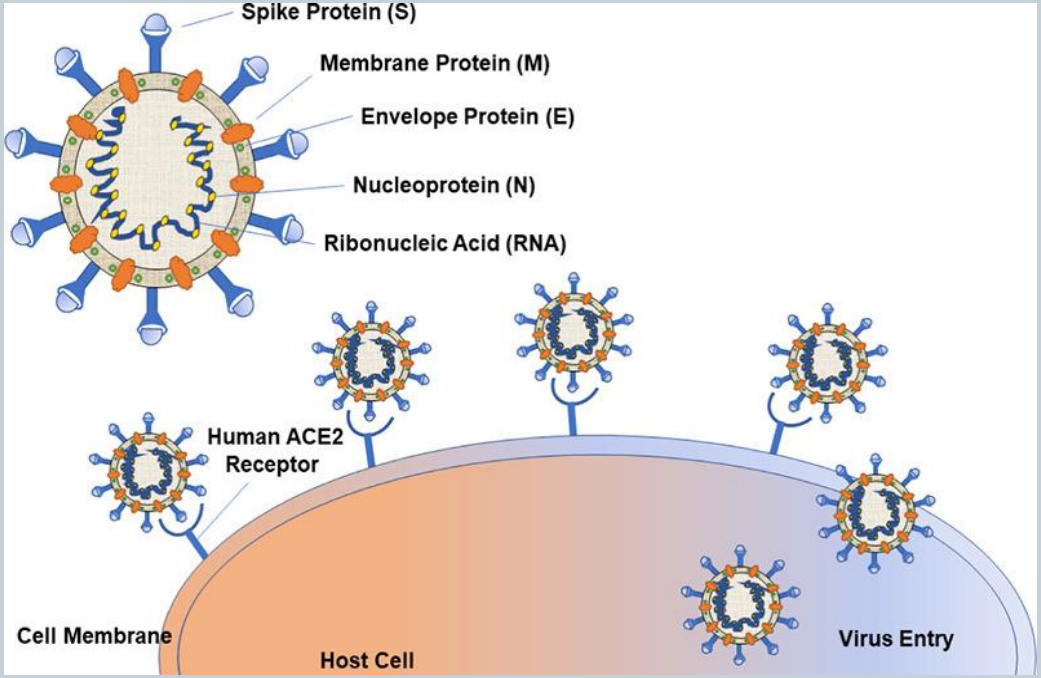
Figure 1. Animal origins of human coronaviruses (Created with BioRender.com, accessed on 1 August 2020).

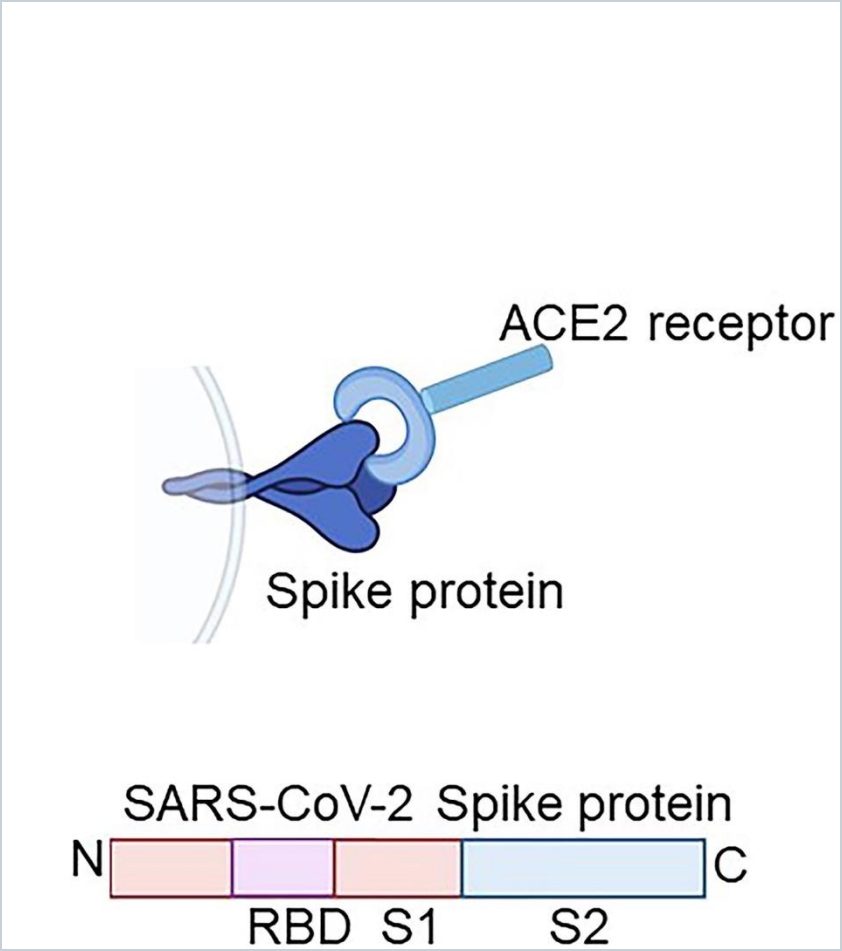
Review

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

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

Spike (S) Protein & ACE2





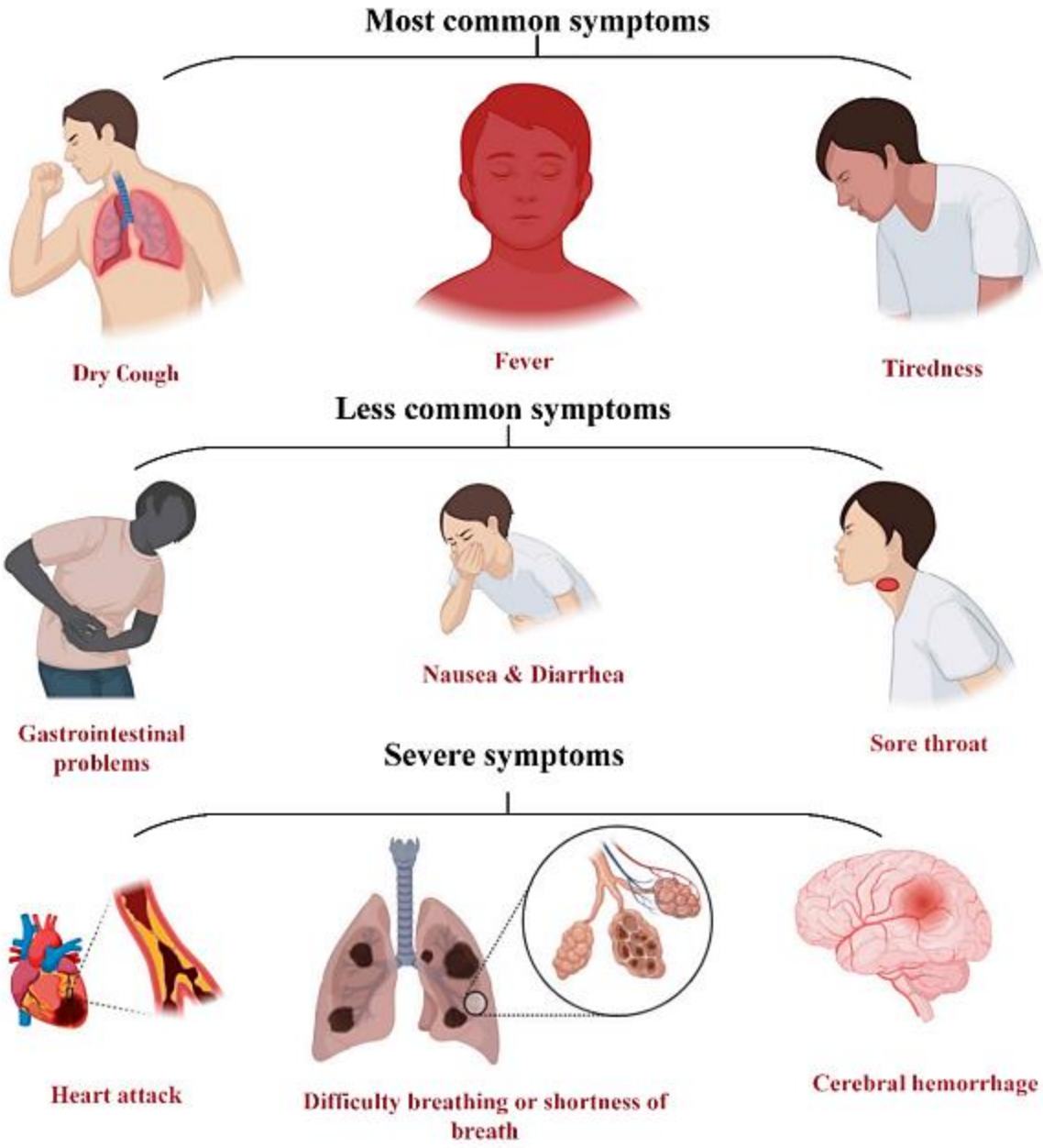


Figure 5. The most minor and major symptoms of COVID-19 (Created with BioRender.com, accessed on 15 March 2021)

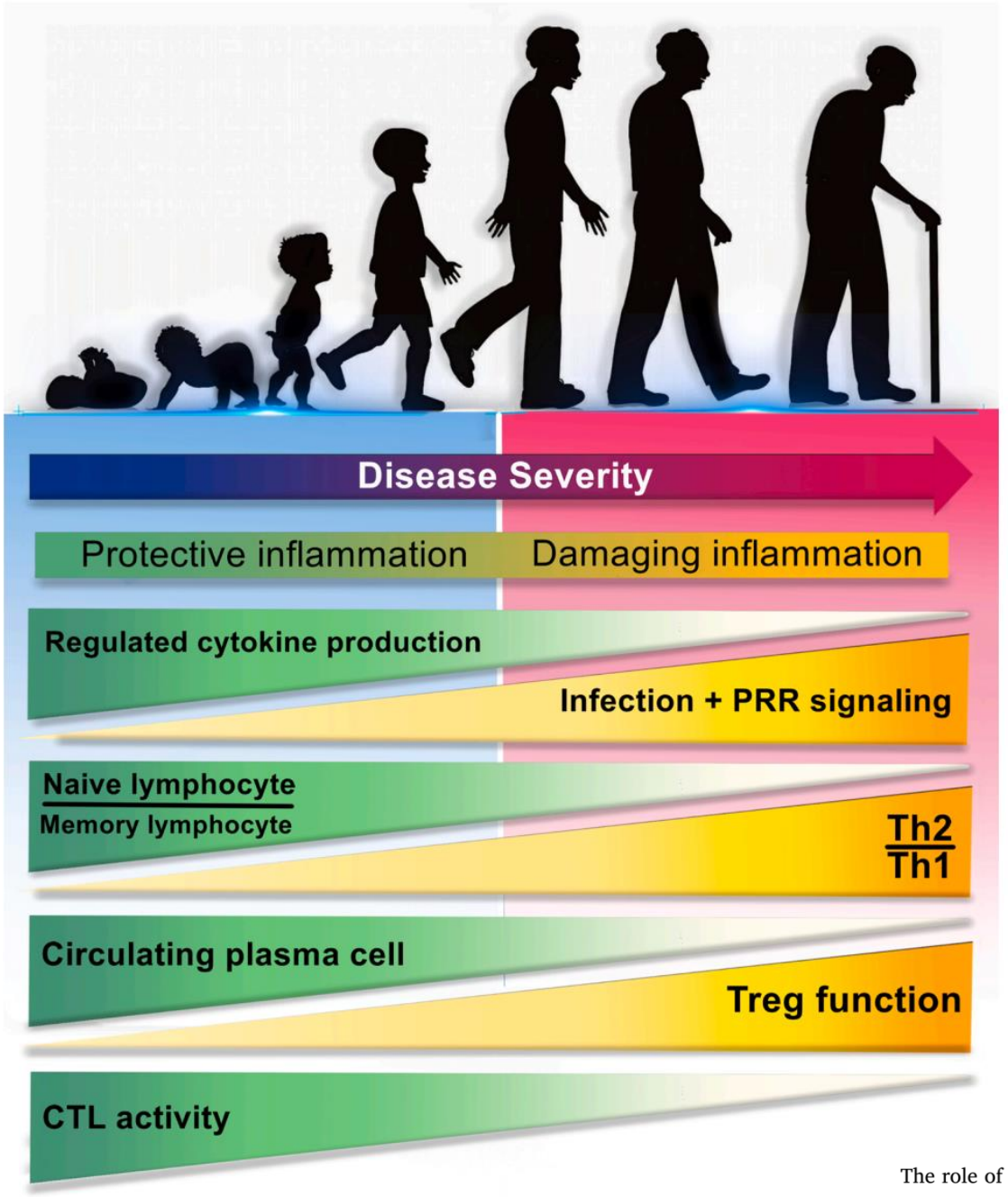


Fig. 1. The relationship between age-dependent changes in immune responses with the severity of COVID-19 disease.
Differences in the immune system of children and adults may be the reasons for clinical differences in the severity of COVID-19. During aging, immune responses undergo changes that lead to 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+ CD25+ FOXP3+) 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.

The role of dysregulated immune responses in COVID-19 pathogenesis

Tahaghoghi-Hajghorbani S[a,b], Zafari P[a,b], Masoumi E[c,d,e], Rajabinejad M[a,b], Jafari-Shakib R[f,g], Hasani B[a], Rafiei A[h,*]

Adults & Children COVID-19

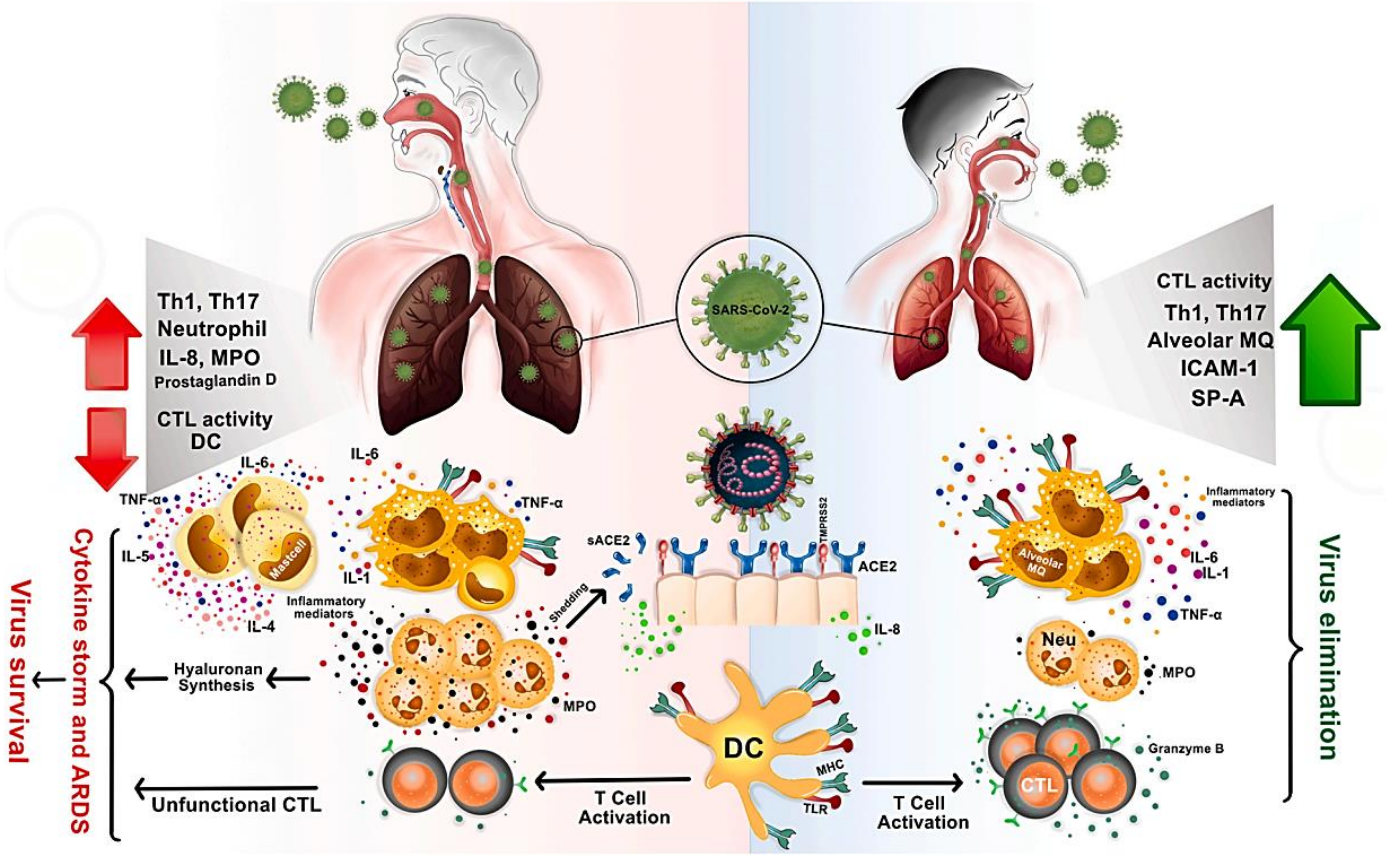
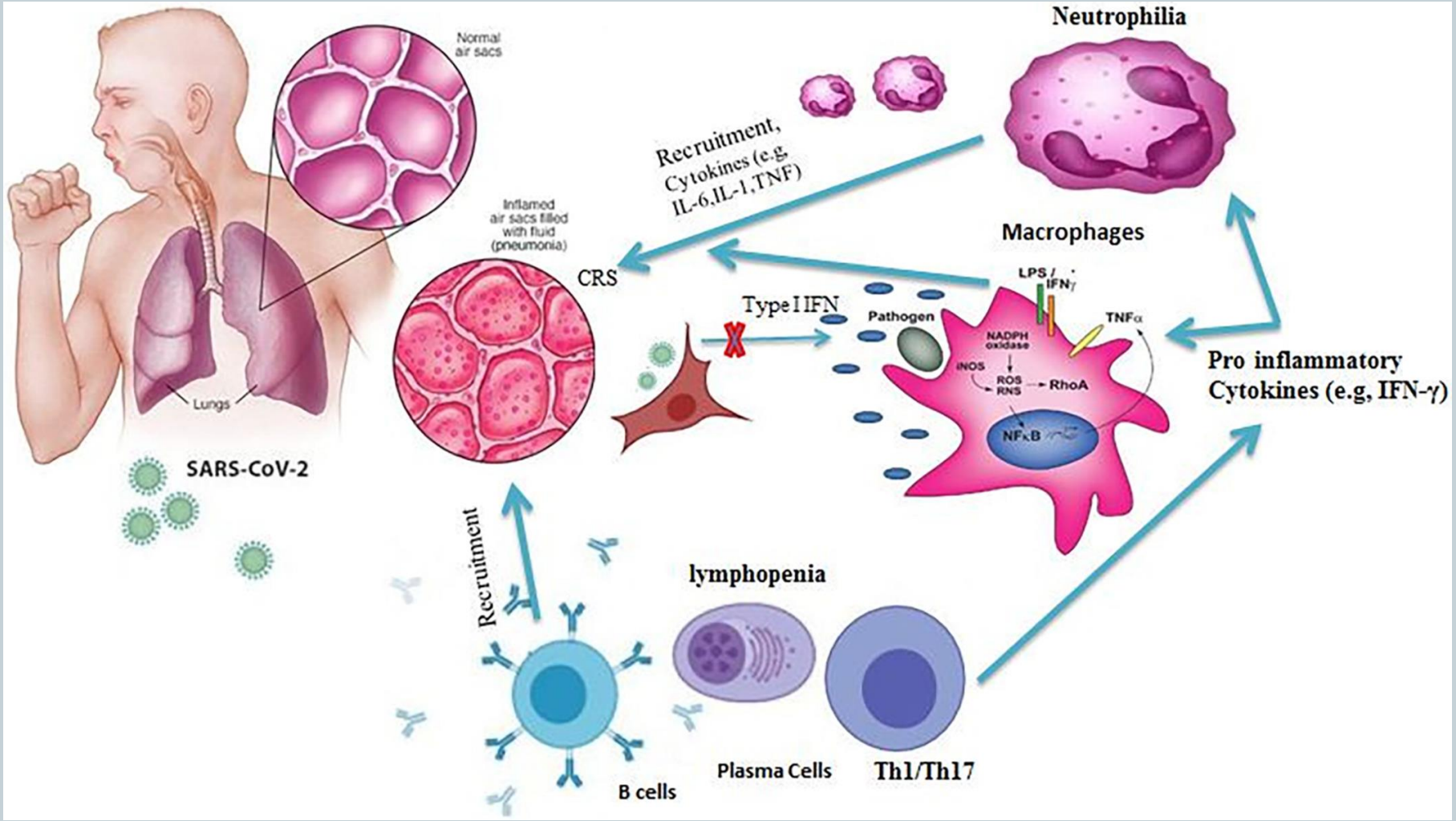


Fig. 2. The difference in immune responses in the lungs of children and adults to SARS-CoV-2 is the reason for the different clinical manifestations. In children, SARS−COV-2 infection may be quickly eradicated due to having less mature ACE2 receptors and rapid activation of immunocompetent immune cells (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[a,b], Zafari P[a,b], Masoumi E[c,d,e], Rajabinejad M[a,b], Jafari-Shakib R[f,g], Hasani B[a], Rafiei A[h,*]

COVID-19-associated Hyper-inflammation



CYTOKINE STORM & ARDS

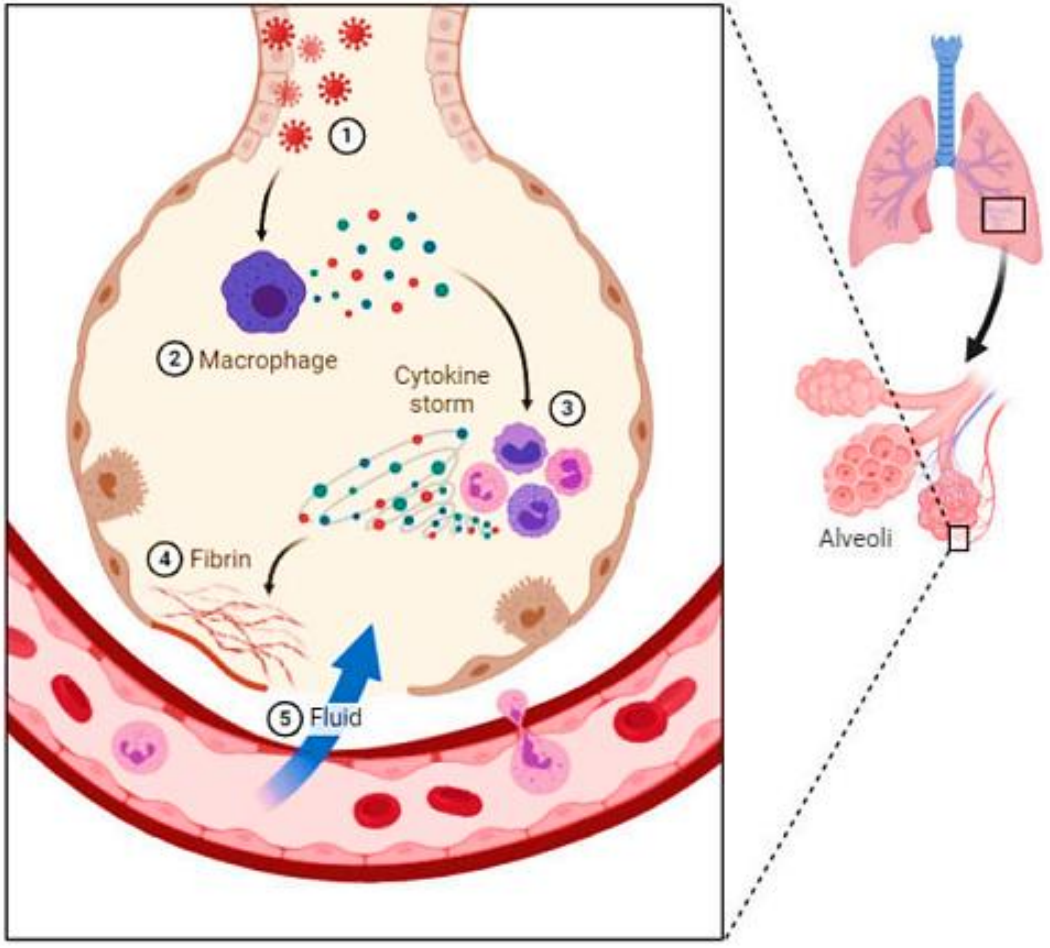
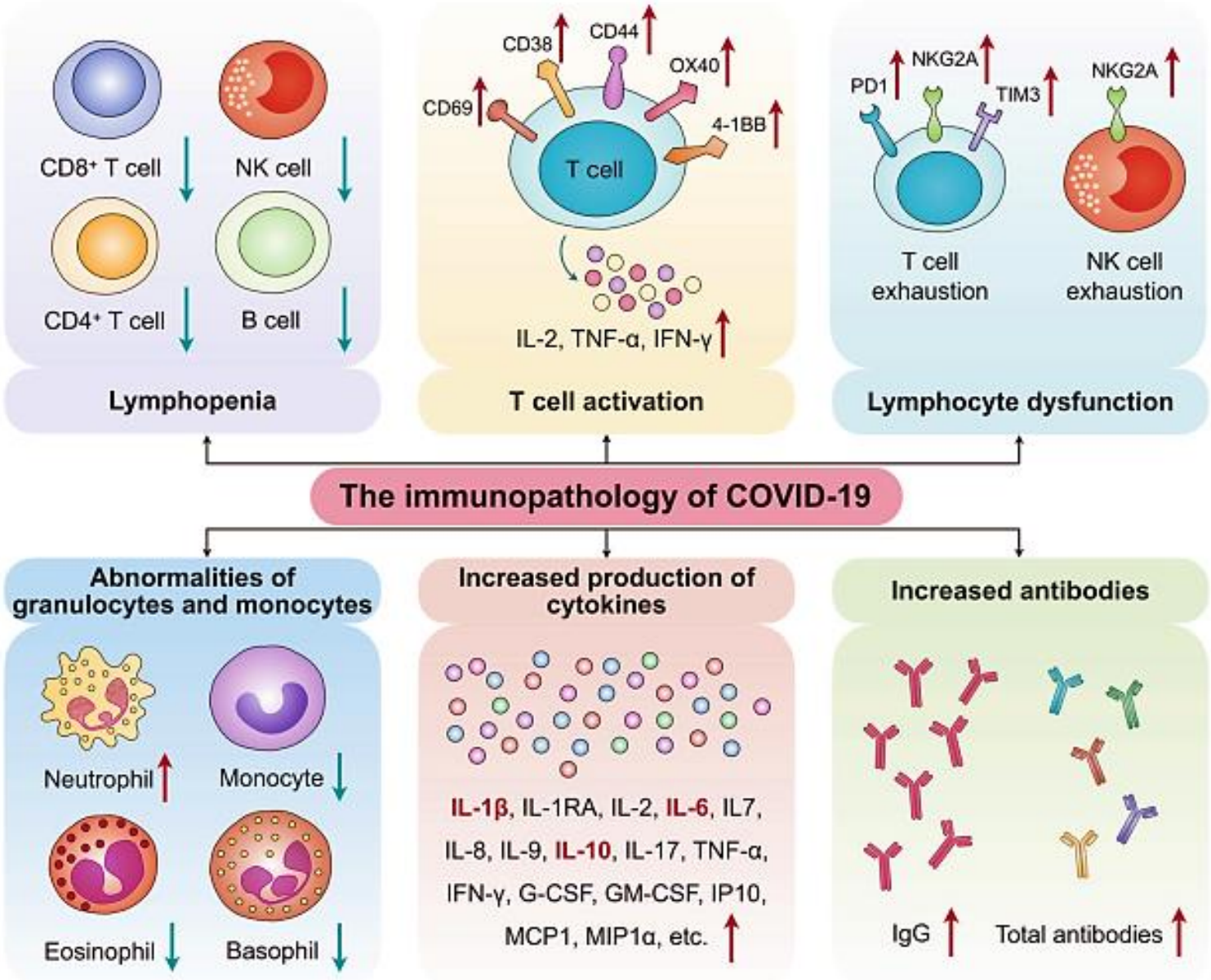
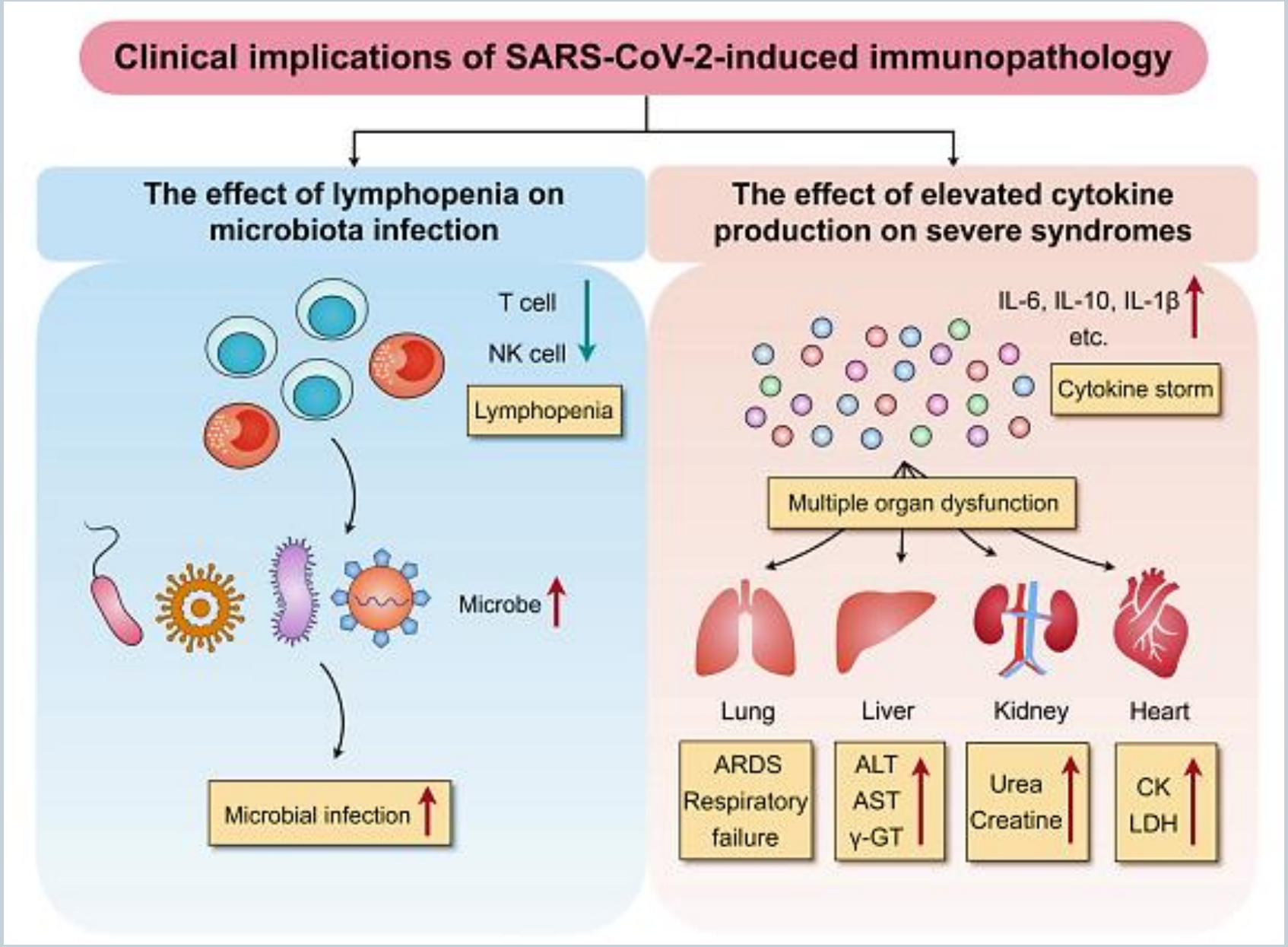


Figure 6. A cytokine storm in the lungs due to COVID-19 disease: (1) infection, (2) Cytokine production, (3) Creating a cycle of inflammation in lung cells, (4) Fibrin formation and (5) Filling of the lung cavities (Reprinted from "Cytokine Storm", by BioRender.com, accessed on 3 July 2020) [38].

COVID-19: immunopathogenesis and Immunotherapeutics
Yang et al.




Clinical implications of SARS-CoV-2-induced immunopathology
The effect of lymphopenia on microbiota infection
The effect of elevated cytokine production on severe syndromes
T cell
NK cell
Lymphopenia
Microbe
Microbial infection
IL-6, IL-10, IL-1β
etc.
Cytokine storm
Multiple organ dysfunction
Lung
Liver
Kidney
Heart
ARDS
Respiratory failure
ALT
AST
γ-GT
Urea
Creatine
CK
LDH

ACE2 Expression in Most Organs

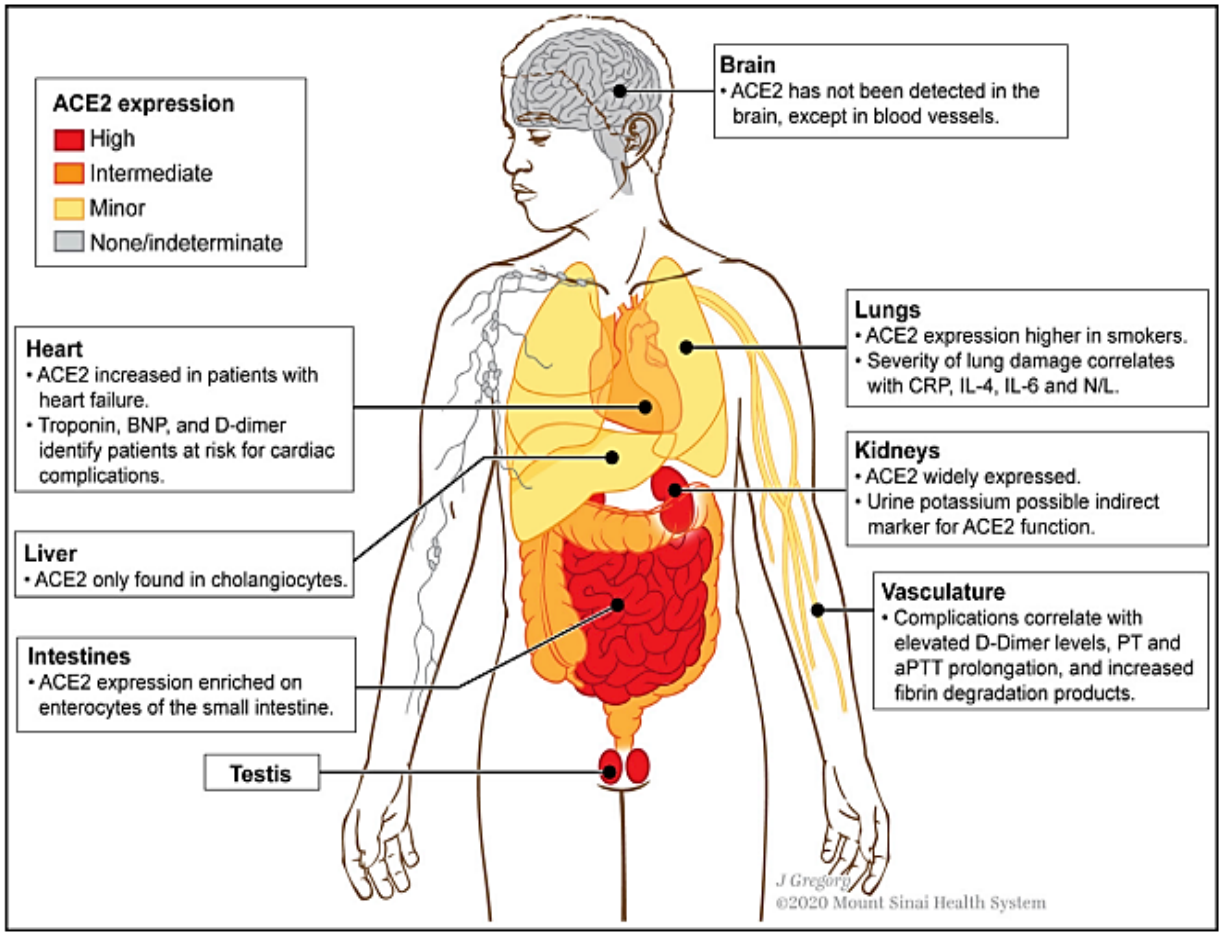


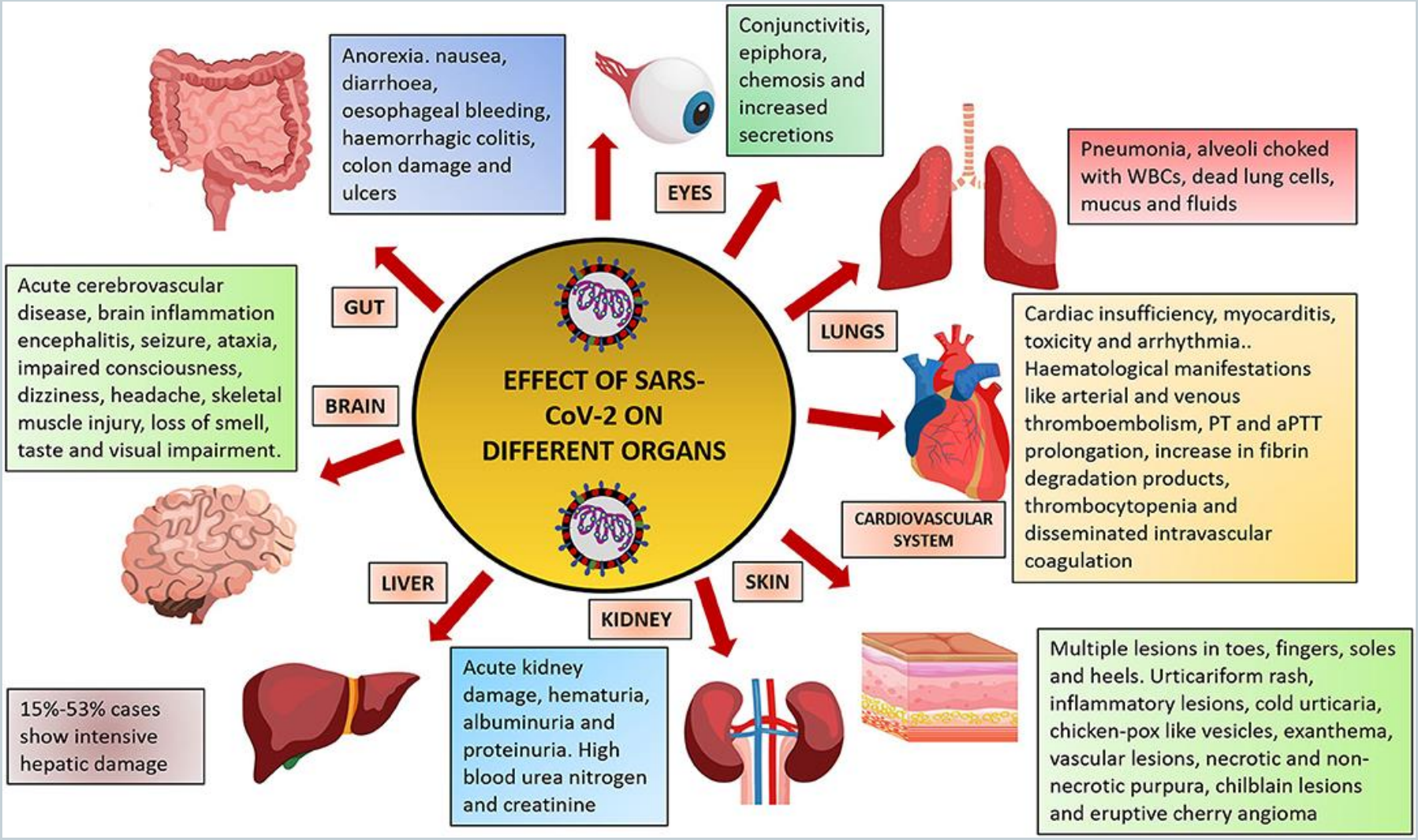
Figure 5. ACE2 Expression in Organs and Systems Most Frequently Implicated in COVID-19 Complications

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

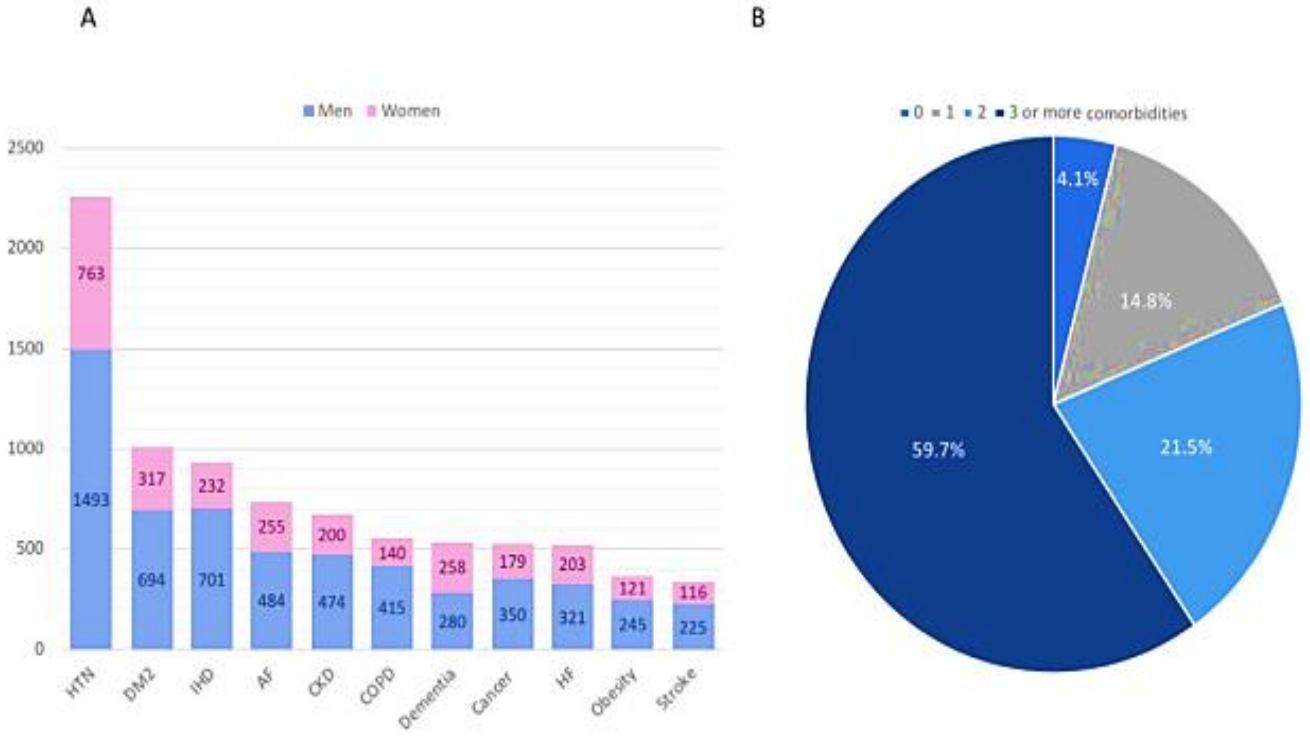
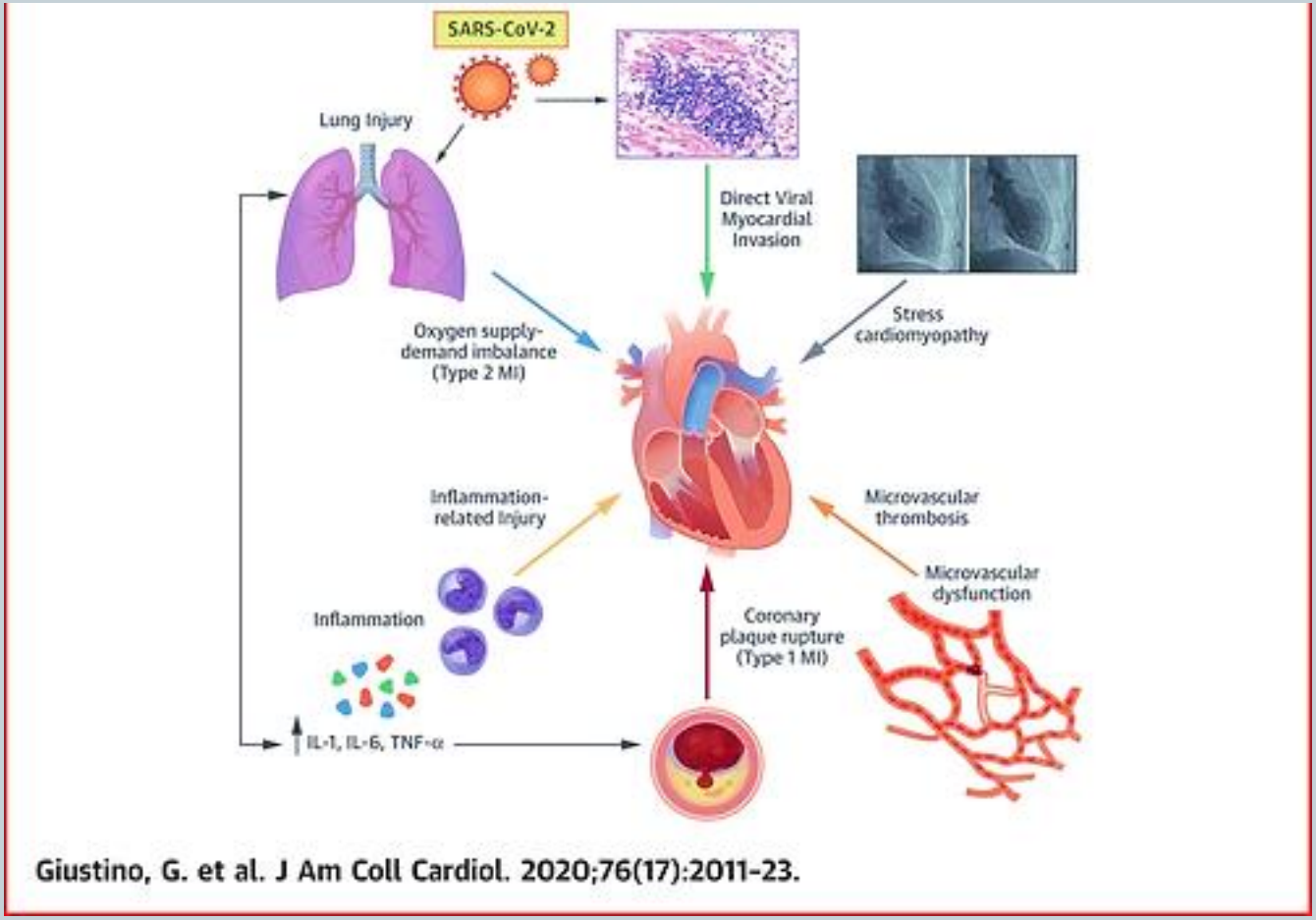


Fig. 1. Chronic comorbidities among 3335 deceased COVID-19 patients in Italy as of June 4th, 2020. (A) Comorbidities by gender. (B) Proportion of patients with 0, 1, 2, or at least 3 comorbidities: 4.1%, 14.8%, 21.5%, and 59.7%, respectively. HTN, hypertension; DM2, diabetes mellitus type 2; IHD, ischemic 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)[1], Rita Del Pinto (MD, PhD)[1], Claudio Ferri (MD)*

Mechanisms of Myocardial Injury in COVID-19 patients



Masataka Nishiga[1,2,3], Dao Wen Wang[4], Yaling Han[4], David B. Lewis[5] and Joseph C. Wu[1,2,6]

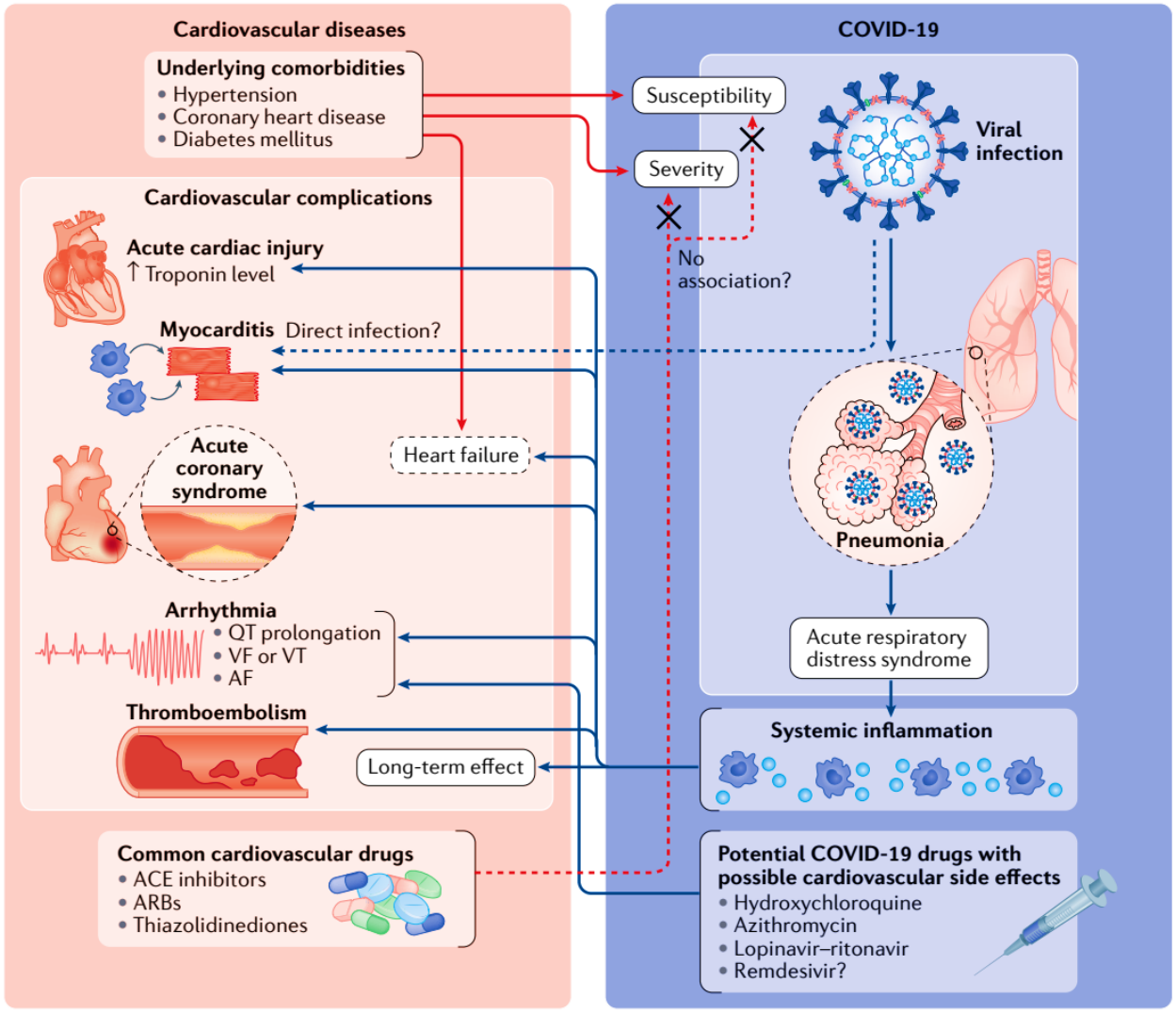
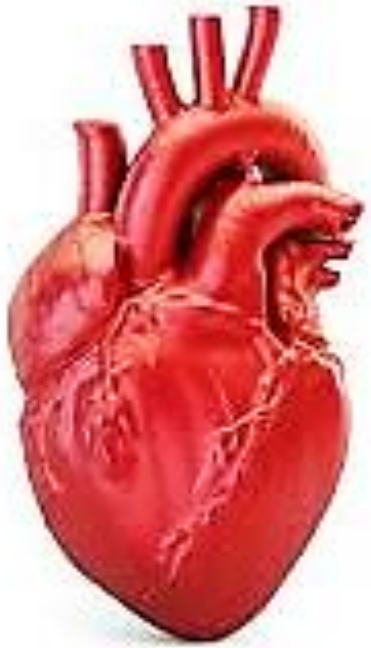


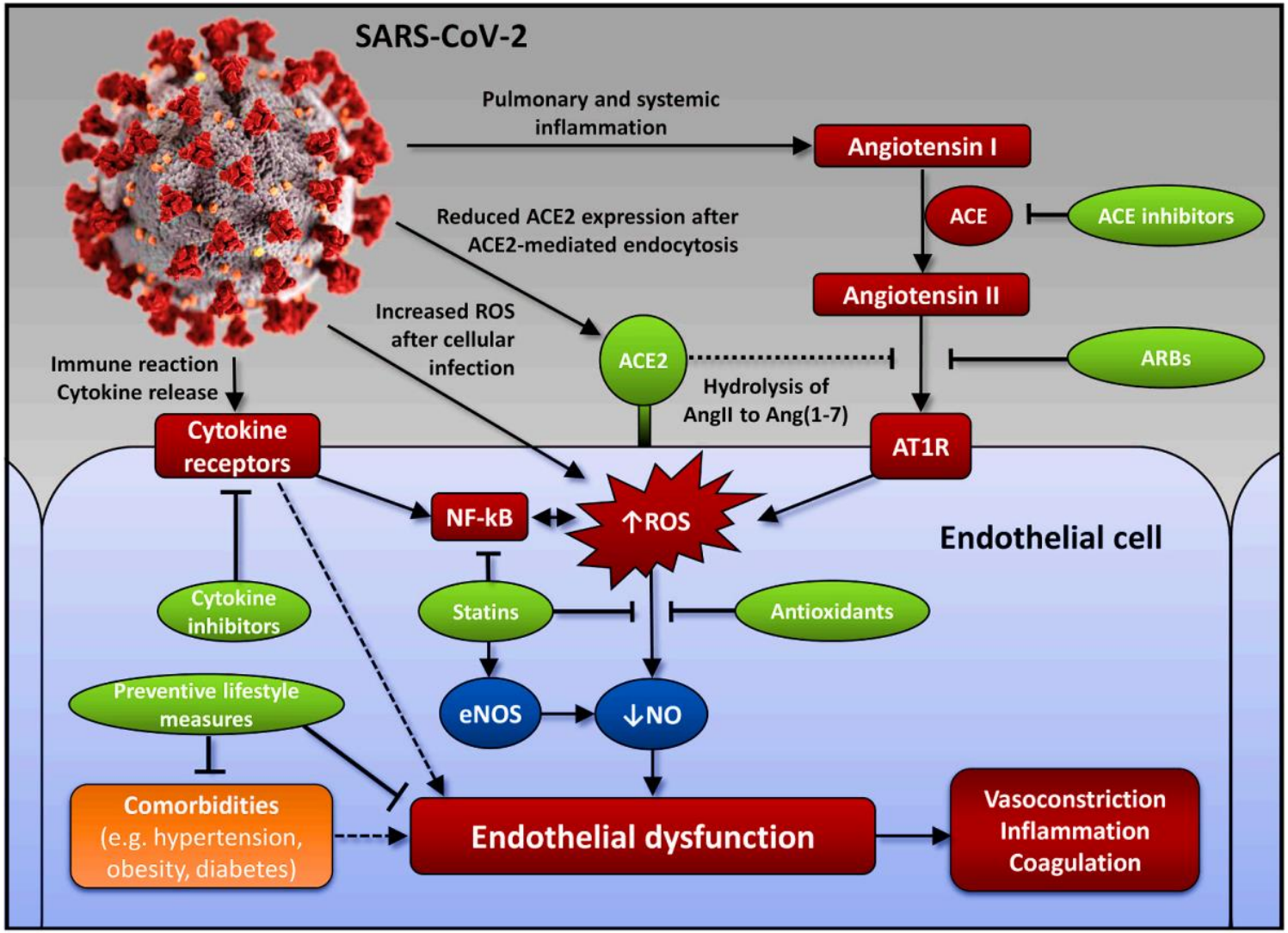
Fig. 2 | **Bidirectional interaction between cardiovascular diseases and COVID-19.** Cardiovascular comorbidities such as hypertension and coronary artery disease are associated with high mortality in patients with coronavirus disease 2019 (COVID-19). Drugs used to reduce cardiovascular risk such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have numerous effects that might influence susceptibility to or the severity of COVID-19. Furthermore, although the main presentation of COVID-19 is viral pneumonia, COVID-19 can also induce cardiovascular manifestations including myocardial injury, myocarditis, arrhythmias, acute coronary syndrome and thromboembolism. Among these cardiovascular manifestations, myocardial injury has been independently associated with high mortality among patients with COVID-19 (REF.[23]). Finally, medications that have been proposed as treatments for COVID-19 such as hydroxychloroquine and azithromycin have pro-arrhythmic effects. AF, atrial fibrillation; VF, ventricular fibrillation; VT, ventricular tachycardia.

Immunothrombosis **in COVID-19**

1. COVID-19-associated ***hyper-inflammation***
2. COVID-19-associated ***endothelial dysfunction***
3. COVID-19-associated ***coagulopathy***
4. COVID-19-associated ***ARDS***



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 *

Yuefei Jin[1], Wangquan Ji[1], Haiyan Yang[1], Shualyin Chen[1], Weiguo Zhang[1,2] and Guangcai Duan[1]

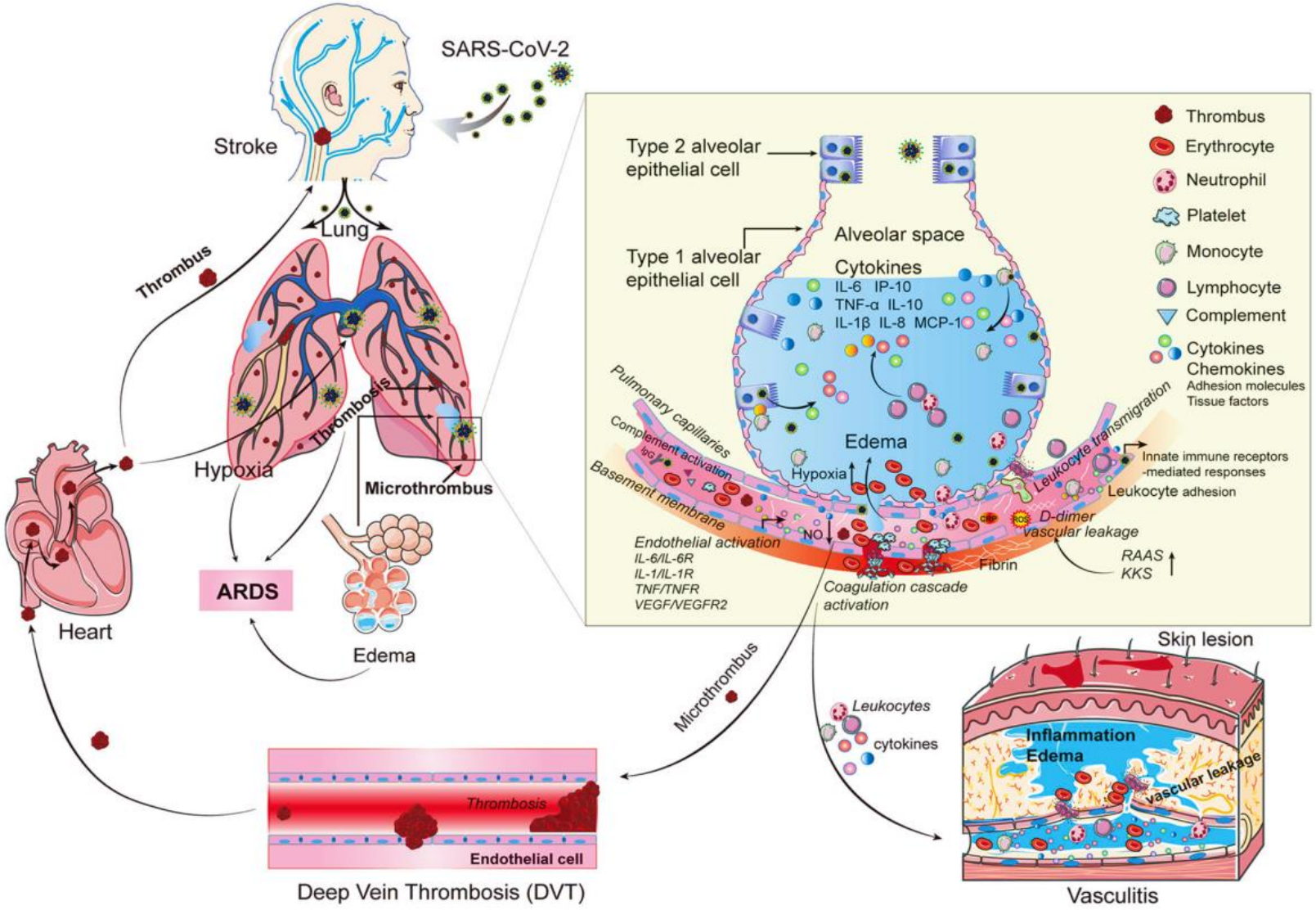
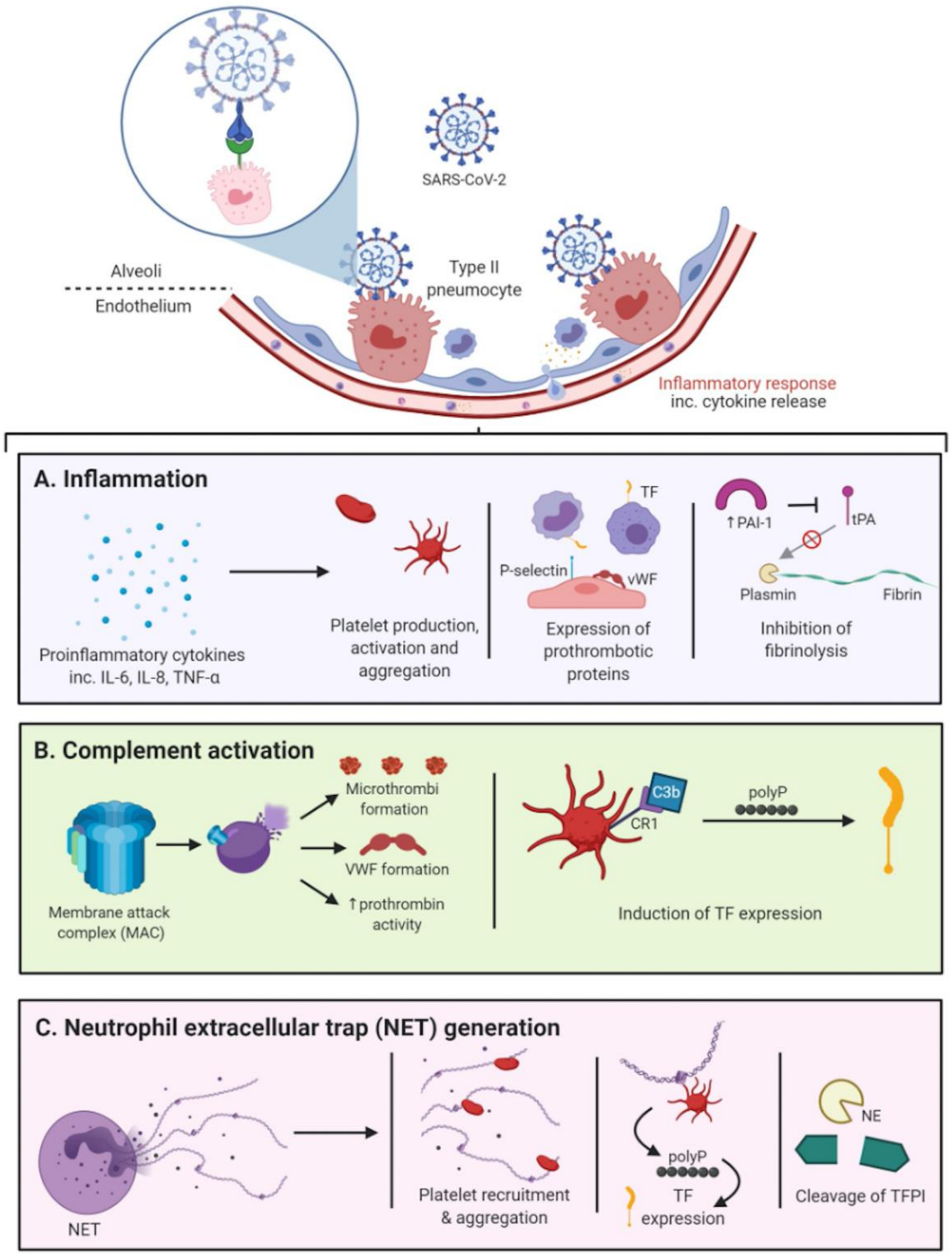


Fig. 2 Overview of endothelial activation and dysfunction in the pathogenesis of COVID-19. In the initial stage of severe COVID-19 patients, SARS-CoV-2 infection causes acute lung injury, and then excessive cytokines are released from immune cells, bronchial epithelial cells, and alveolar cells. SARS-CoV-2 infection and various cytokines are predicted to cause endothelial activation and dysfunction by multiple pathways, leading to vascular inflammation and permeability. Then more immune cells enter or migrate into alveoli and enhance lung inflammation. With vascular permeability, erythrocytes enter into alveoli, leading to edema. Moreover, with the release of pro-inflammatory cytokines and inflammatory cells to circulation, vasculitis occurs. The disruption of vascular integrity and EC apoptosis leads to the exposure of the thrombogenic basement membrane and the activation of the clotting cascade. Endothelial cells release relevant cytokines that further augment platelet production. Platelet activation is the primary cause of thrombosis. Inflammation, edema, and microthrombus work together to cause ARDS. The transfer of microthrombi into the blood circulation increases the risk of the formation of deep vein thrombosis, which may further cause pulmonary embolism and stroke

Immunothrombosis in COVID-19



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Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19

Aldo Bonaventura, Alessandra Vecchié, Lorenzo Dagna, Kimberly Martinod, Dave L. Dixon, Benjamin W. Van Tassell, Francesco Dentali, Fabrizio Montecucco, Steffen Massberg, Marcel Levi and Antonio Abbate

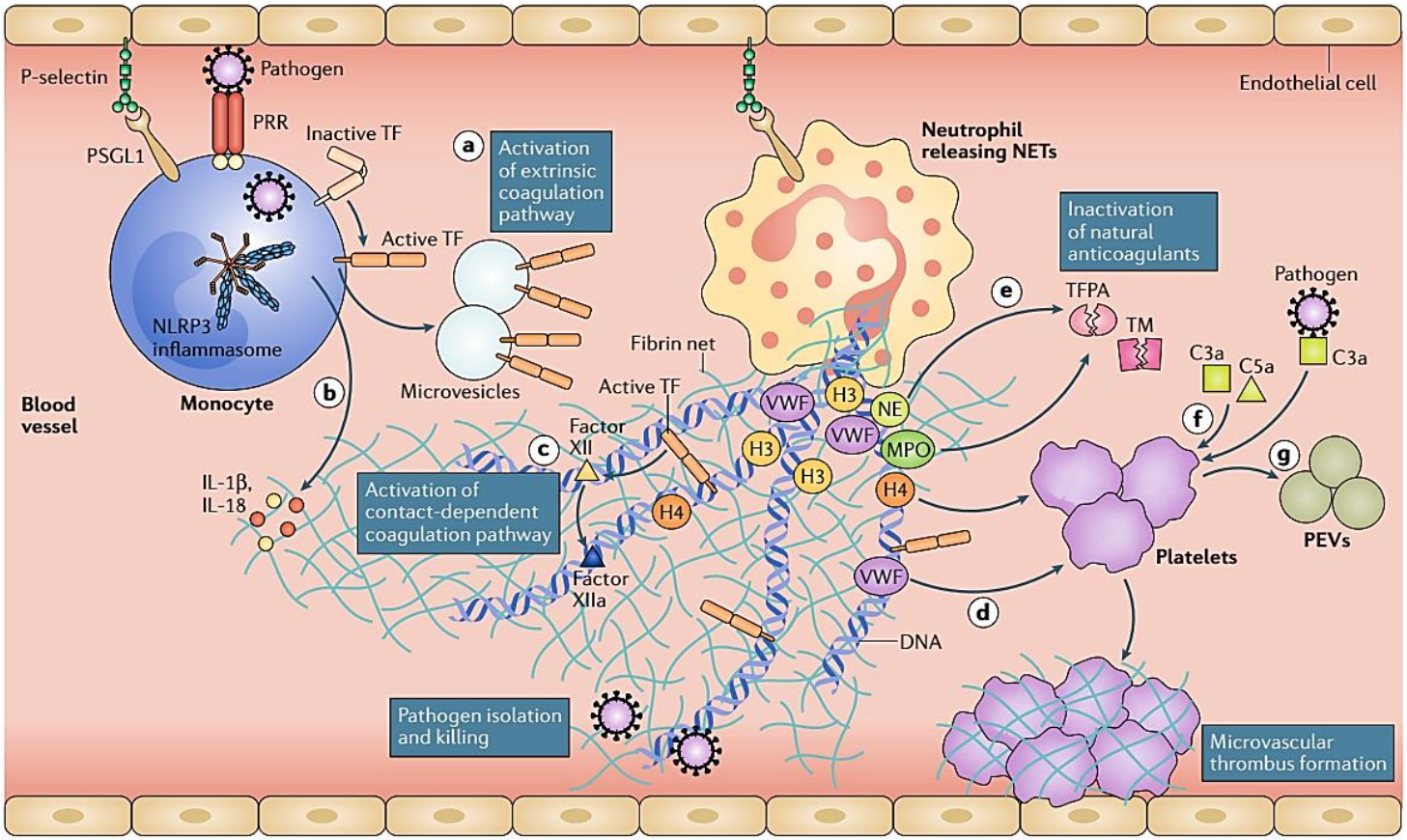


Fig. 1 | **Immunothrombosis is important in promoting immune defence.** Following recognition of a pathogen through pattern recognition receptors (PRRs), monocytes and monocyte-derived microvesicles present activated tissue factor (TF) on their surfaces and release it at sites of pathogen localization, thus activating the extrinsic pathway of coagulation (path **a**). Pathogens also stimulate the NLRP3 inflammasome in monocytes and/or macrophages, leading to the release of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and IL-18 (path **b**). Neutrophils are recruited and contribute to this process through the release of neutrophil extracellular traps (NETs), which directly activate factor XII and, thus, the contact-dependent pathway of coagulation (path **c**). NETs also bind von Willebrand factor (VWF) and help to recruit platelets (path **d**). Histones, in particular H3 and H4, trigger activation of platelets. In addition, neutrophil elastase (NE) and myeloperoxidase (MPO) in NETs cleave and inactivate natural anticoagulants (tissue factor pathway inhibitor (TFPA) and thrombomodulin (TM)) (path **e**). Finally, NETs can externalize and bind TF, promoting activation of the extrinsic pathway of coagulation. Platelets support the immunothrombotic process by activating the contact-dependent pathway of coagulation through the release of polyphosphates and, along with endothelial cells, may promote fibrin generation. Platelets can also be activated by C3a and C5a (path **f**). Activated platelets release large amounts of pro-inflammatory cytokines in platelet extracellular vesicles (PEVs) (path **g**). Through this mechanism, pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) become trapped within the fibrin-based NETs and killed. The immunothrombotic process allows pathogen killing to be restricted to the intravascular compartment, thus limiting injury to organs. Although it is clear that immunothrombosis participates in SARS-CoV-2 pathogenesis, the exact mechanisms are still under investigation. These may include the following: direct injury of endothelial cells by the virus and consequent activation of the coagulation cascade; infiltration of neutrophils that lead to NET formation; induction of hypoxaemia causing upregulation of TF expression by hypoxia-inducible transcription factors and formation of clots; activation of complement that promotes coagulation and recruits and activates platelets, monocytes and neutrophils, thus triggering TF expression; and an abnormal increase in the levels of pro-inflammatory cytokines causing direct cell damage.

Immune Response to SARS-CoV-2

NATURE REVIEWS | IMMUNOLOGY

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

Rebecca J. Cox[1] ✉ *and Karl A. Brokstad*[2]

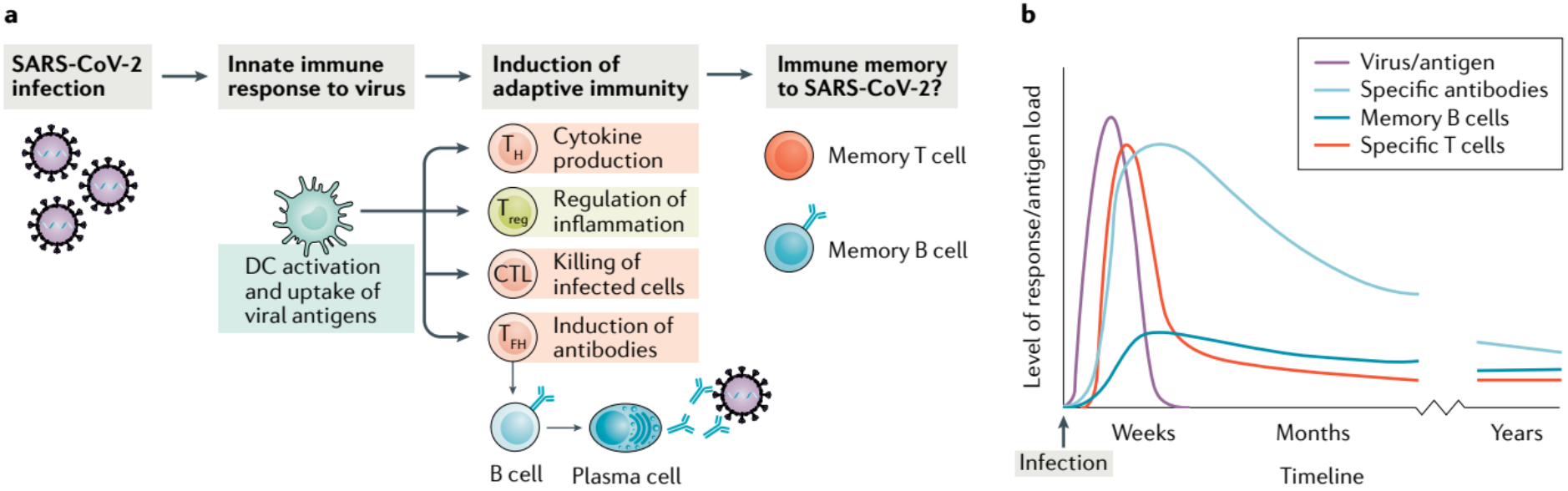


Fig. 1 | **T cells and B cells in immunity to SARS-CoV-2. a** | Infection with SARS-CoV-2 leads to activation of innate immunity and dendritic cells (DCs), which will drive the induction of virus-specific T cell and B cell responses. Little is currently known concerning the memory response to SARS-CoV-2, 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

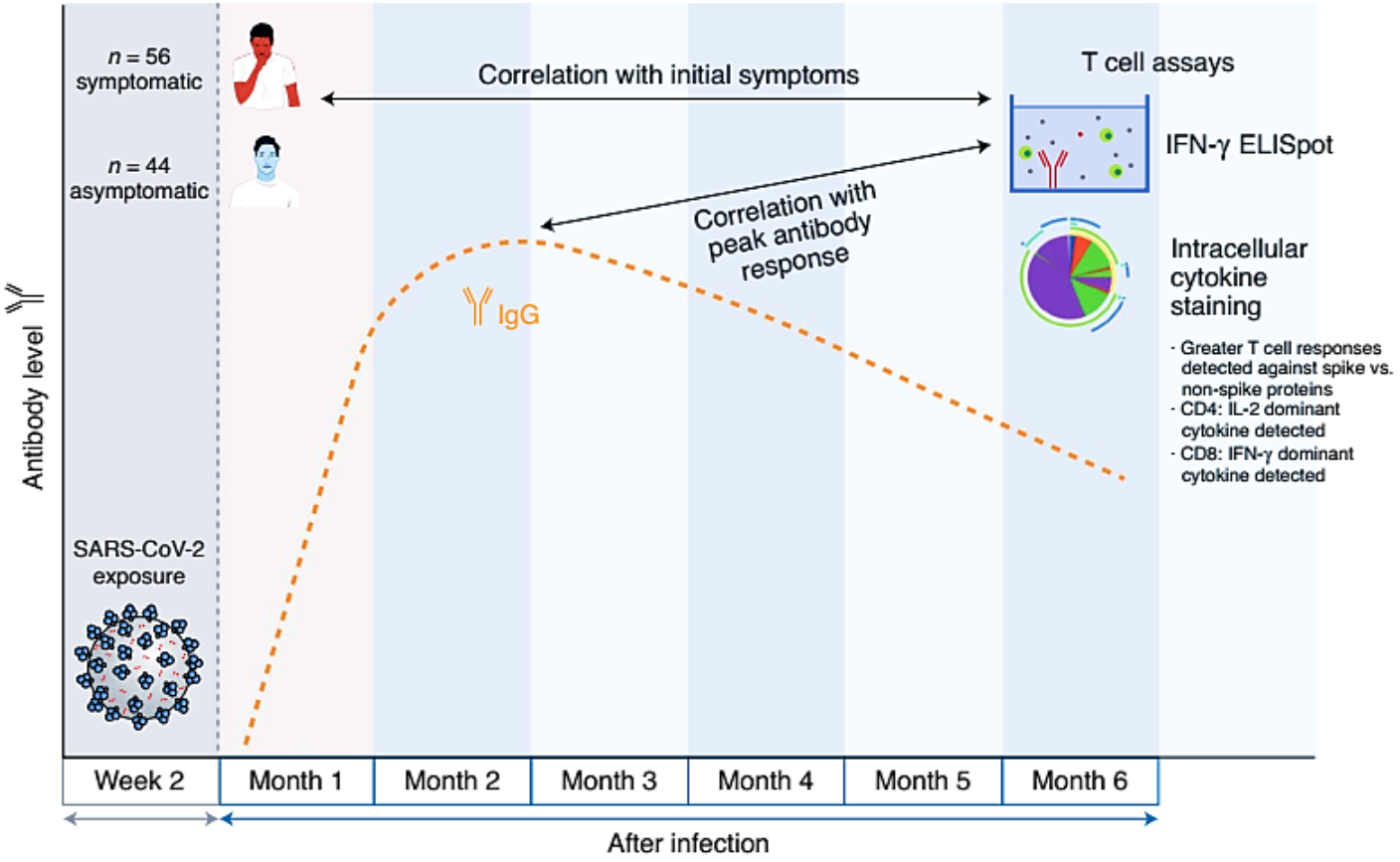


Fig. 1 | Correlations between SARS-CoV-2-specific T cell responses, disease severity and peak antibody response. Zuo et al. measured SARS-CoV-2-specific T cell responses in 100 individuals six months after infection. SARS-CoV-2-specific T cell responses were measured by IFN-γ ELISpot and intracellular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

Antibody Response in COVID-19

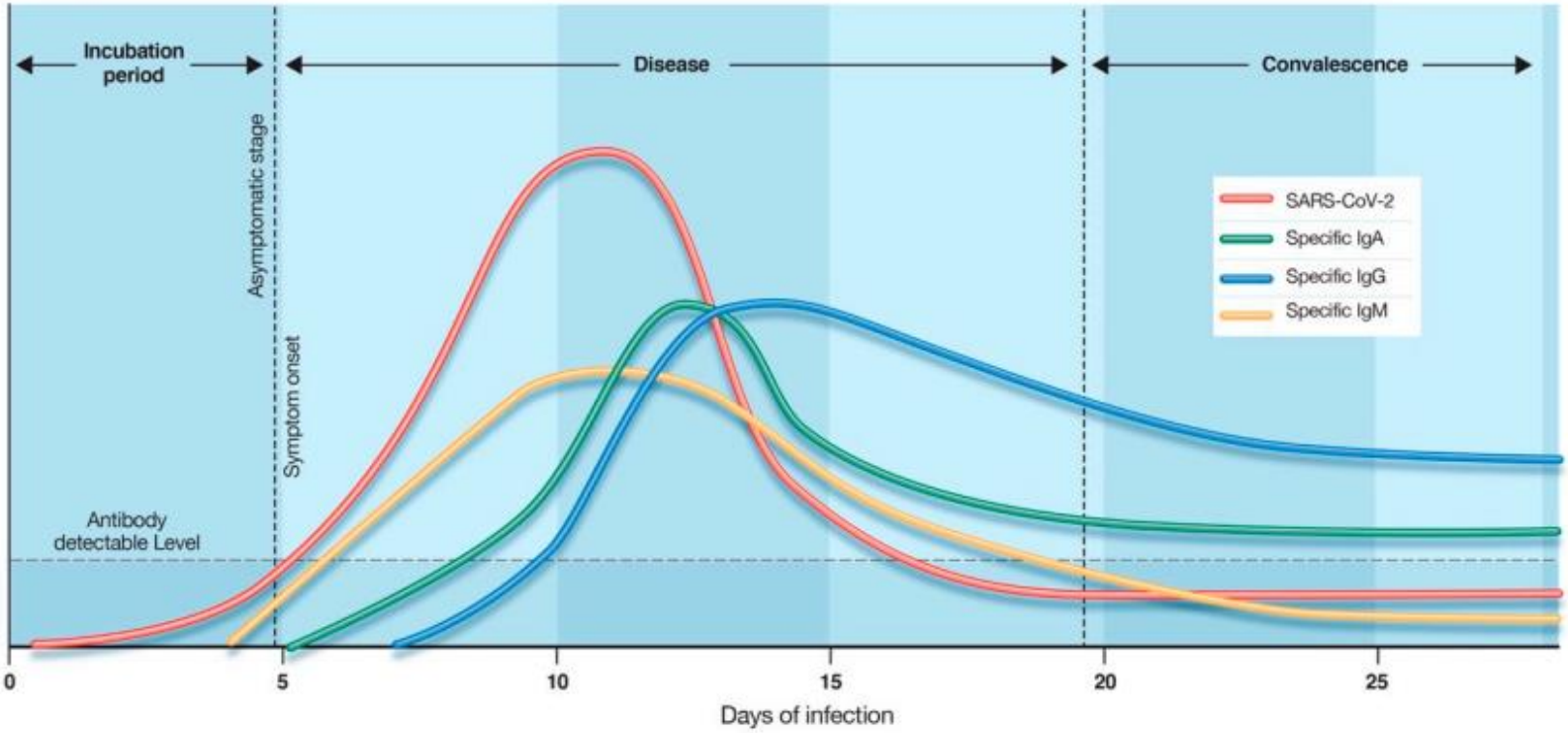


Figure 4. Time kinetics of antibody response in coronavirus disease 2019 (COVID-19). The illustration demonstrates the relative levels of host immunoglobulins (IgM, IgG, IgA) and SARS-CoV-2 viral load at different stages of COVID-19. Antibody-specific seroconversion occurs when the antibody reaches a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

Review

COVID-19 Serological Tests: How Well Do They Actually Perform?

Back to the SARS-2 Structure and SPIKE

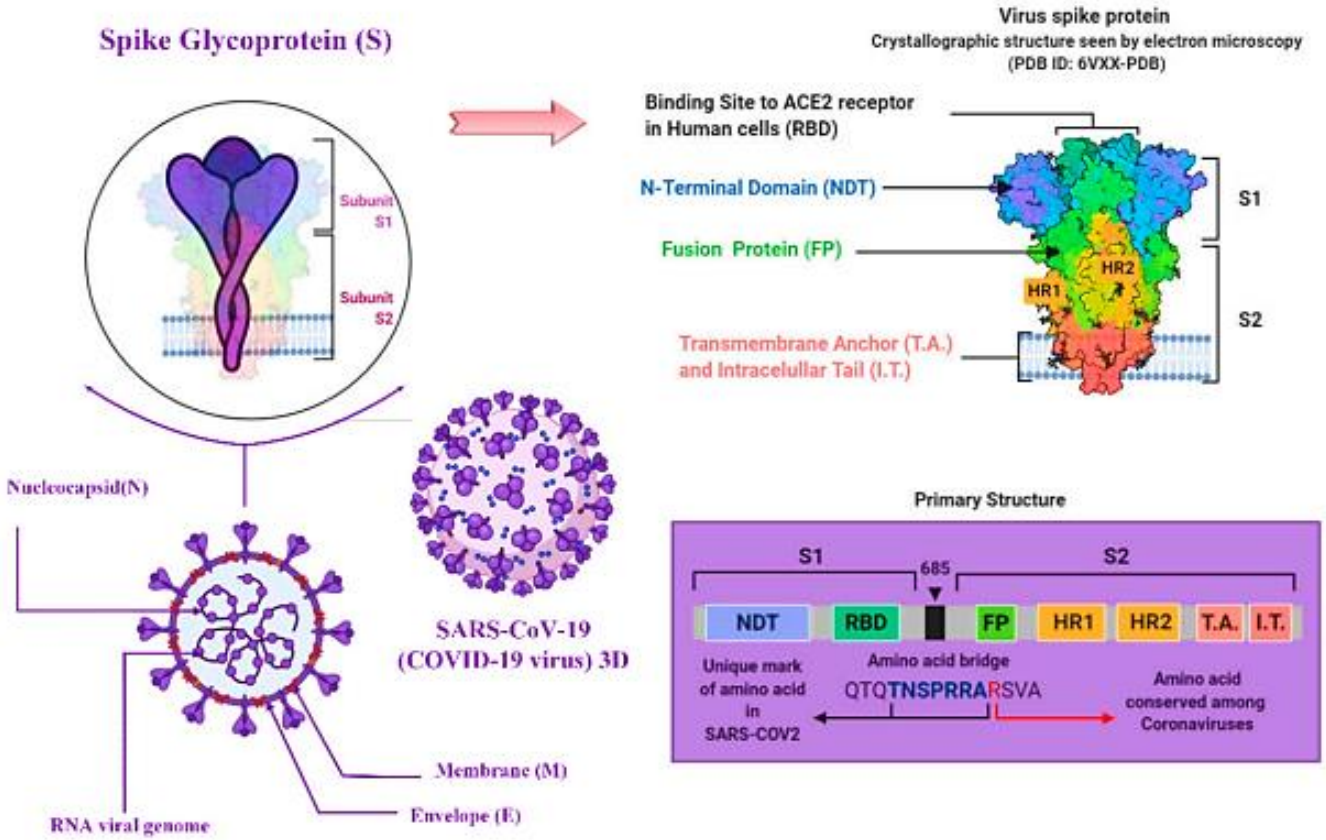


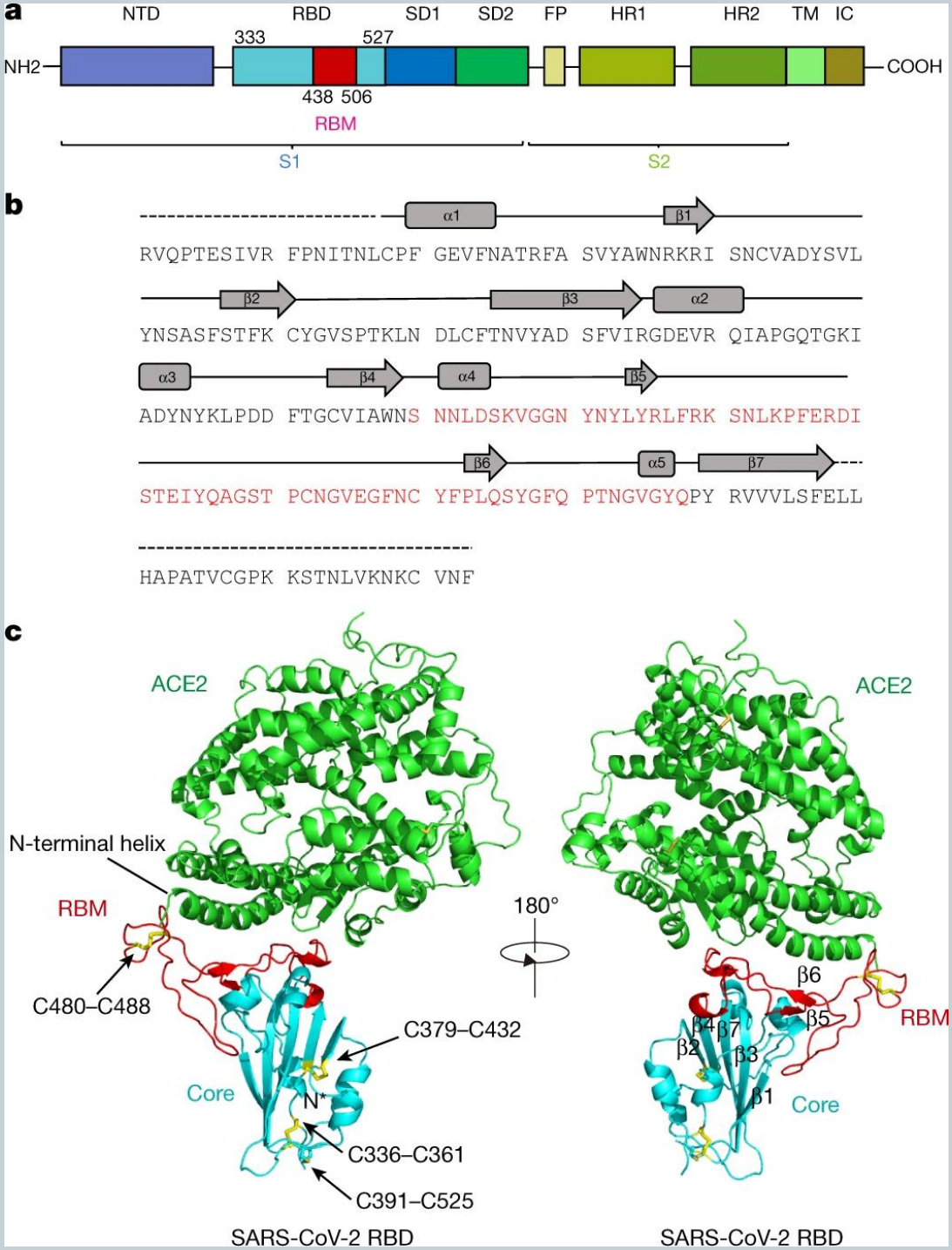
Figure 2. An in-depth look into the SARS-CoV-2 Spike Glycoprotein (Reprinted from "An In-depth Look into the Structure of the SARS-CoV-2 Spike Glycoprotein", by BioRender.com, accessed on 1 August 2020) [20].

Article | Published: 30 March 2020

Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor

Jun Lan, Jiwan Ge, Jinfang Yu, Sisi Shan, Huan Zhou, Shilong Fan, Qi Zhang, Xuanling Shi, Qisheng Wang, Linqi Zhang ✉ & Xinquan Wang ✉

Nature **581**, 215–220 (2020) | Cite this article

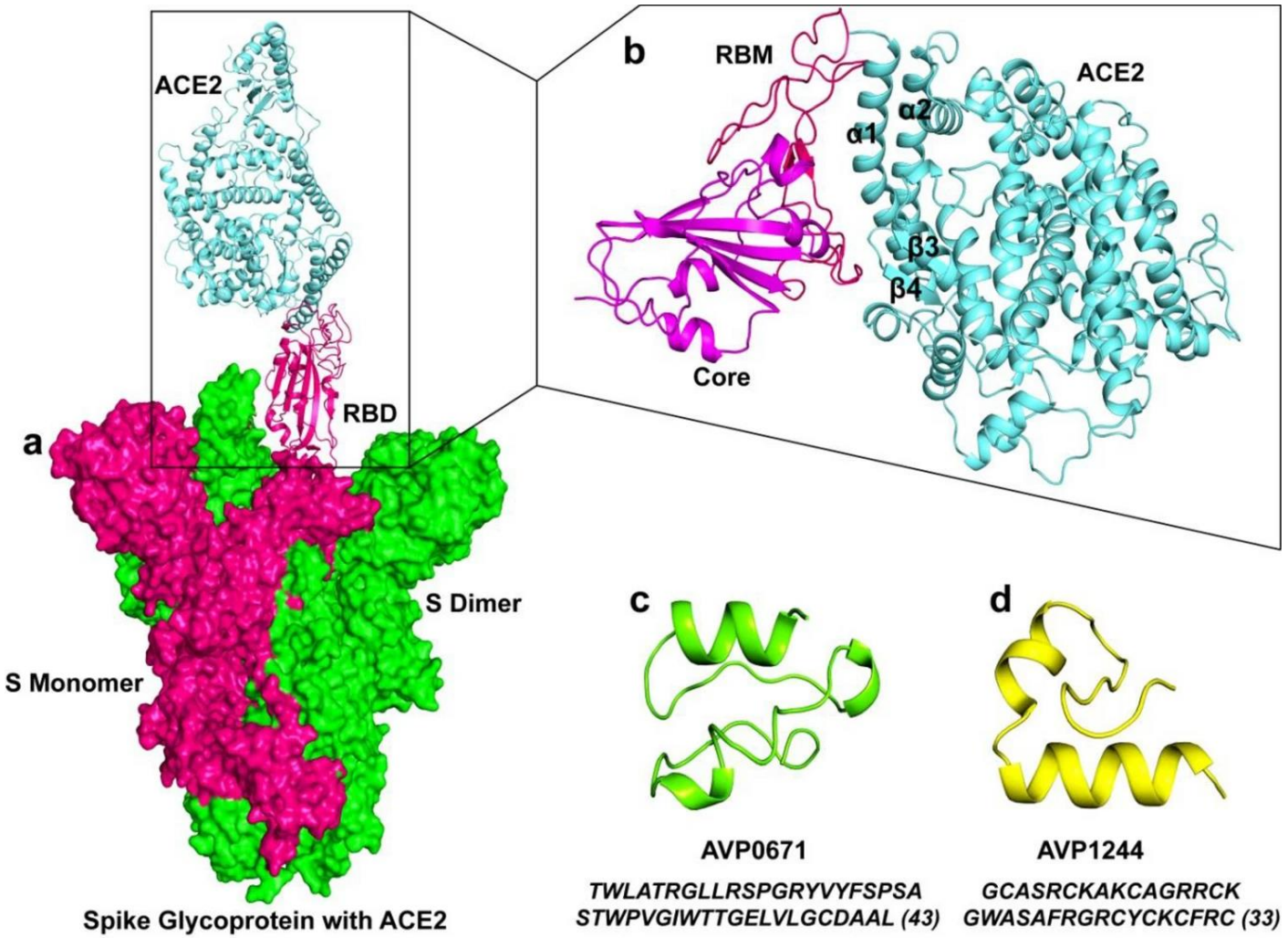


Original Research | Published: 09 November 2020

Peptide modelling and screening against human ACE2 and spike glycoprotein RBD of SARS-CoV-2

Shravan B. Rathod ✉, Pravin B. Prajapati, Lata B. Punjabi, Kuntal N. Prajapati, Neha Chauhan & Mohmedyasin F. Mansuri

In Silico Pharmacology **8**, Article number: 3 (2020) | Cite this article



Laboratory Diagnosis of COVID-19

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

COVID-19 Diagnosis by PCR

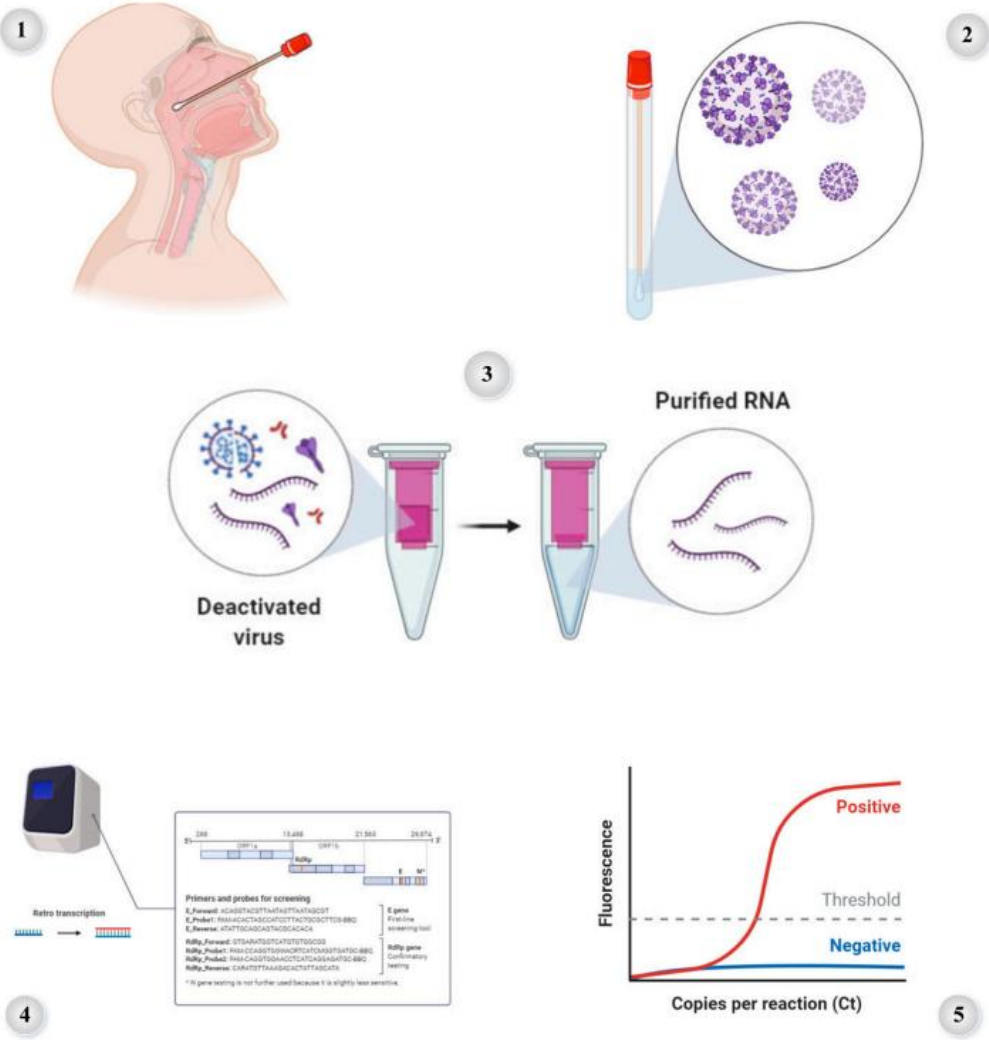
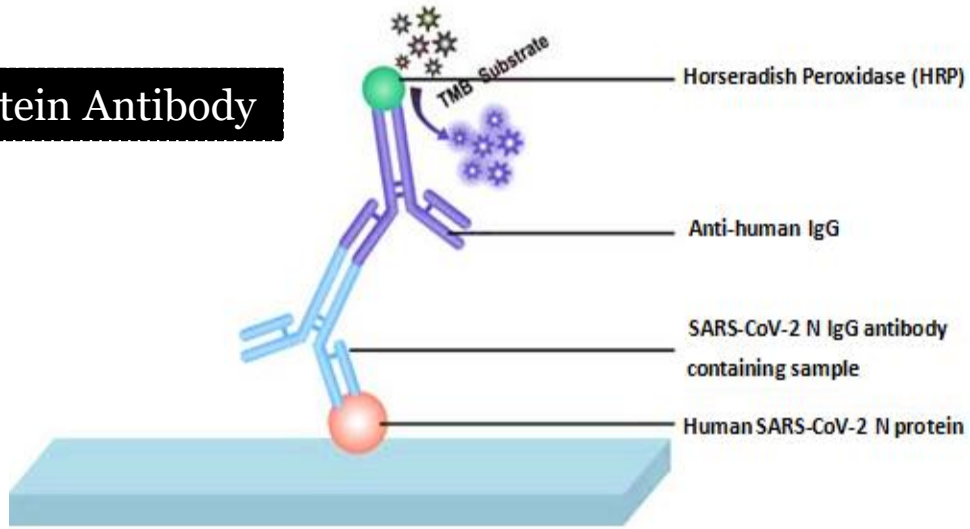


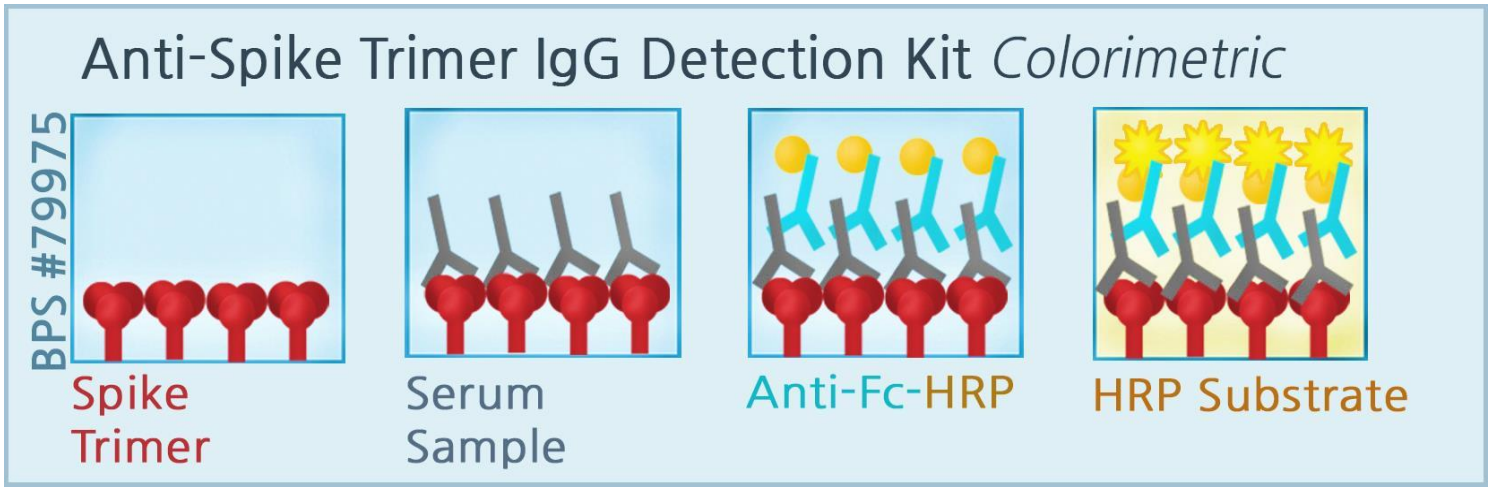
Figure 9. The protocol template COVID-19 diagnostic testing through real-time RT-PCR: (1) Nasopharyngeal swab, (2) Collected specimen, (3) RNA extraction, (4) purified RNA and (5) Test results real-time (Adopted from "COVID-19 Diagnostic Test through RT-PCR", by BioRender.com, accessed on 9 April 2020)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

Immunologic Assays (ELISA)

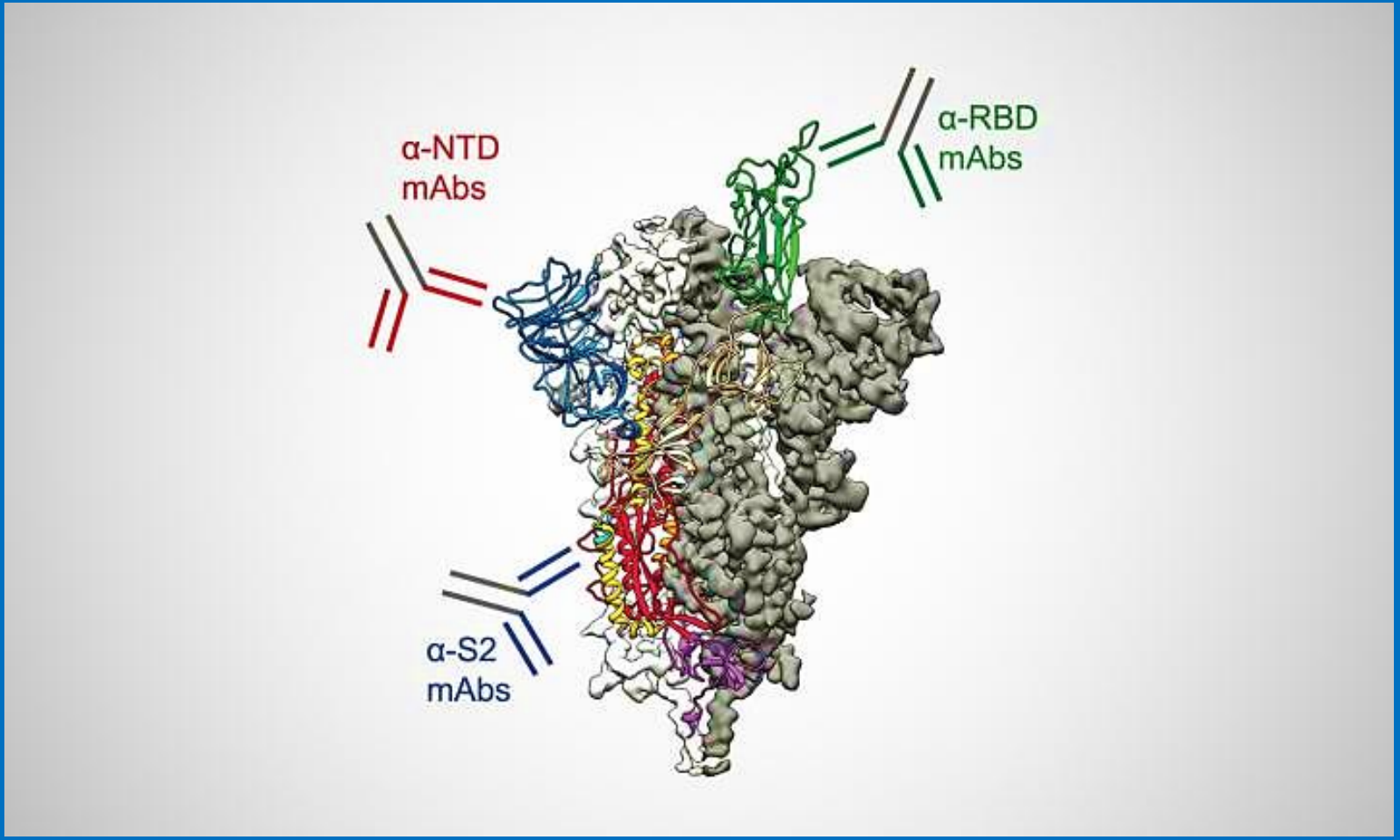
1) Anti-Nucleoprotein Antibody



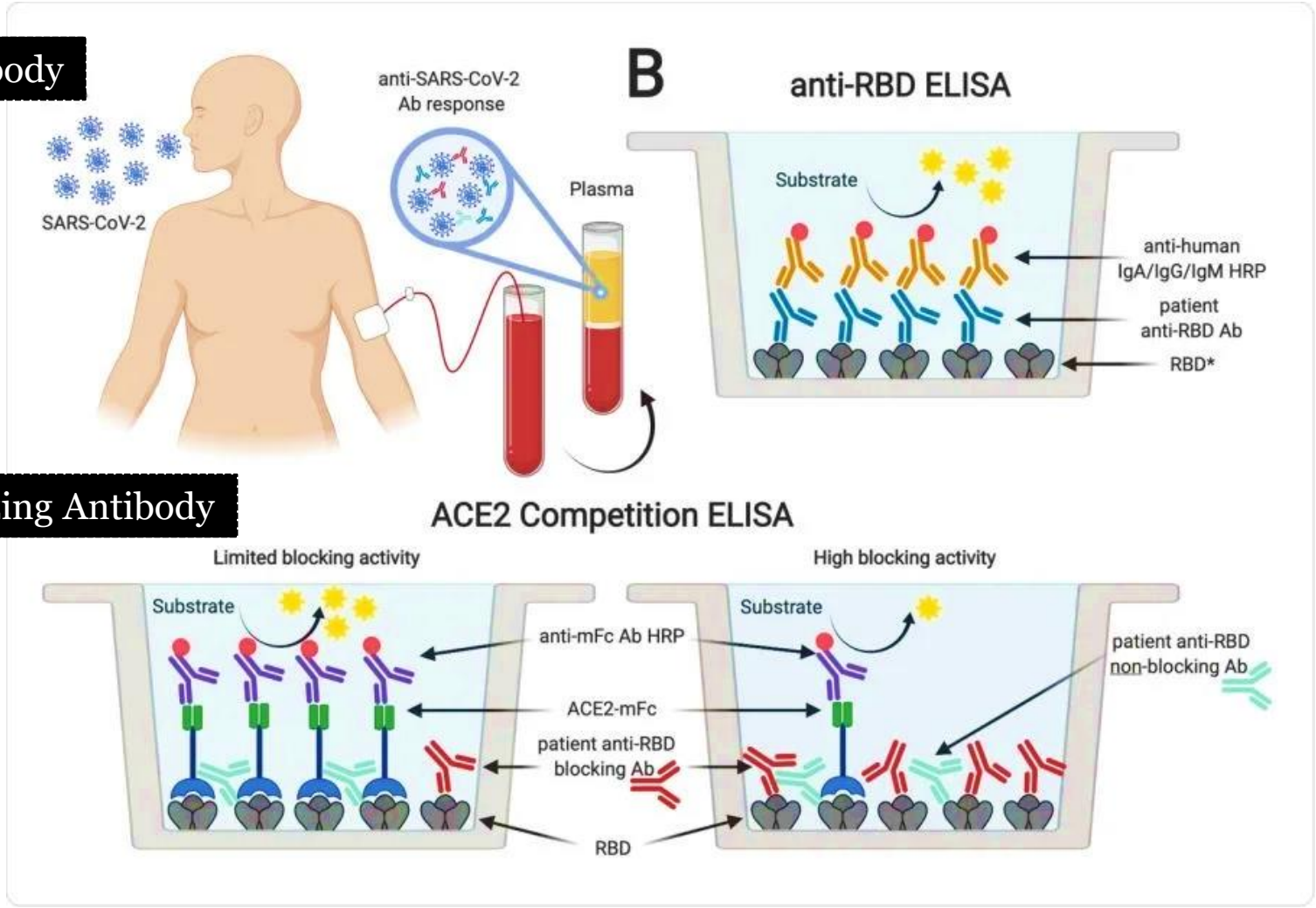
2) Anti-Spike Glycoprotein Antibody



Anti-Spike Protein Antibody



3) Anti-RBD Antibody



4) ACE2 Neutralizing Antibody

https://www.news-medical.net

جمع‌بندی و نتیجه‌گیری

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