

Biochemical, molecular genetic and clinical aspects of COVID-2019

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ABSTRACT

The 2020 coronavirus infection pandemic has potentiated a large number of studies in the world on the etiopathogenesis and clinical and morphological manifestations of COVID-2019 infection. This review presents biochemical, molecular genetic, and clinical aspects of COVID-2019.

Key words: COVID-19, coronavirus, cytokines, polymorphism.

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Биохимические, молекулярно-генетические и клинические аспекты COVID-2019

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РЕЗЮМЕ

Пандемия коронавирусной инфекции в 2020 г. потенцировала проведение большого числа исследований в мире в области этиопатогенеза и клинко-морфологических проявлений COVID-2019. Представлены биохимические, молекулярно-генетические и клинические аспекты COVID-2019.

Ключевые слова: COVID-19, коронавирус, цитокины, полиморфизм.

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INTRODUCTION

The causative agent of the infection, a new coronavirus SARS-CoV-2, which was previously undetected, was identified by Chinese researchers on January 7, 2020 [1]. On February 11, 2020, the new coronavirus infection was named COVID-2019 (Corona Virus Disease 2019), and the virus causing it was renamed to SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) [2]. The coronavirus pandemic in 2020 has potentiated a large number of studies in the world on the etiopathogenesis and clinical and morphological manifestations of COVID-2019 infection.

CHARACTERISTICS AND PATHOGENESIS OF COVID-2019

The first stage of the virus life cycle is receptor adsorption of the viral particle on the surface of the target cell as a result of specific binding of the first subunit of the S1 spike protein to the cell receptor. For SARS-CoV-2, this is the angiotensin-converting enzyme 2 (ACE2) [3–10]. The mechanism of virus-ACE2 binding depends on the cellular serine protease TMPRSS2 [9, 10].

The *ACE* gene is characterized by genetic deletion/insertion (D/I) polymorphism in intron 16, which is associated with changes in circulating and tissue ACE protein concentrations. The D allele is associated with reduced ACE2 expression. Although ACE2 and ACE have only 42% amino acid identity, they both act as carboxypeptidases, cleaving the amino acids from the carboxyl end of the peptides [11]. The D/I polymorphism has significant geographical differences [12]. J.R. Delanghe et al. compared the frequency of the D allele of the *ACE1* gene obtained in 25 different European countries with the prevalence and mortality of COVID-2019. The prevalence and mortality from COVID-2019

infection are inversely correlated with the frequency of the D allele [13].

After receptor binding to the surface of the target cell, the subsequent stages begin. The receptor-mediated endocytosis ends with the penetration of a viral nucleocapsid into the cytoplasm of the host cell, where virion RNA acts as an mRNA for the synthesis of two extended polyproteins pp1a and pp1ab with a length of about 2,000 and 7,000 amino acid residues, respectively. The pp1ab polyprotein includes pp1a and is formed as a result of the ribosome ignoring the stop signal in 20–30% of cases due to a hairpin that displaces the reading frame. Polyproteins pp1a and pp1ab do not exist in the cell as single molecules and are cotranslationally cut by proteases into 16 non-structural (i.e., not part of the virion) proteins that regulate further replication and, in particular, transform the folds of the endoplasmic reticulum into a kind of “factory” for the later stages of virus replication.

One of the most important non-structural proteins is RNA-dependent RNA-polymerase (RdRp), which synthesizes a complementary virion strand of negative-sense RNA, which, in turn, acts as a matrix for synthesis of genomic RNAs that will enter daughter virions. In addition, RdRp synthesizes a series of subgenomic negative-sense RNAs (sgRNAs) on a genomic RNA matrix with a chain break and its transfer to the 3'-end of the matrix, as a result of which all sgRNAs in this series have the same 5' and 3' flanks and central parts of varying degrees of nesting in each other. After that, sgRNAs are used as a matrix for synthesis of positive-sense subgenomic matrix RNAs, from which structural proteins are read. Assembly of daughter virions occurs in the endoplasmic reticulum, and they then leave the host cell by exocytosis [14–17].

Previously, several proteins that can interact with the SARS coronavirus nucleocapsid protein

(SARS-CoV) had been identified. Glycoprotein α -2-Heremans-Schmid (AHS_G), required for macrophage deactivation by endogenous cations, was associated with inflammatory process regulation. Rs2248690 variant of the *AHS_G* gene (AOR, 1.63; 95% CI, 1.30–2.04) was associated with susceptibility to atypical pneumonia. Rs2248690 affects the transcriptional activity of the *AHS_G* gene promoter and, thus, regulates the level of AHS_G in the blood. The AA rs2268690 genotype, which leads to a higher concentration of AHS_G protein in the blood, is protective for the development of SARS [18].

The site of entry of the pathogen SARS-CoV-2 is the epithelium of the upper respiratory tract and epithelial cells of the stomach and intestines. The initial stage of infection is the penetration of SARS-CoV-2 into target cells that have ACE2 receptors, which are represented on the cells of the respiratory tract, kidneys, esophagus, bladder, ileum, heart, and central nervous system. However, the main and quickly achievable target is the alveolar cells of type II (AT2) in the lungs, which determines the development of pneumonia. The role of CD147 in SARS-CoV-2 cell invasion was also discussed [19].

The pathogenesis of coronavirus infection begins with colonization and destruction of upper respiratory tract epithelial cells by coronavirus. With insufficient immunity, the process passes to the alveoli and is accompanied by the destruction of the surfactant, excessive exudation, and a drastic decrease in gas exchange. In patients who had the disease, type-specific immunity develops and the affected areas of the alveolar walls are replaced with connective tissue [20].

CLINICAL FEATURES OF COVID-2019

Clinical variants and manifestations of COVID-2019 are acute respiratory viral infection (only the upper respiratory tract lesion); pneumonia without respiratory failure; pneumonia with acute respiratory failure; acute respiratory distress syndrome; sepsis and septic (infectious-toxic) shock [19]. At the same time, more than 30% of patients develop hypoxemia (SpO₂ is less than 88%) [19]. COVID-2019 can have various manifestations, ranging from no symptoms or mild illness to severe pneumonia [21].

Clinical symptoms of COVID-2019 are fever (in 87.9% of those seeking medical help), usually low-

grade temperature (up to 37.5 °C in 56.2%); respiratory symptoms, such as cough (67.7%); in severe cases, shortness of breath (18.6%) and symptoms of intoxication: fatigue and weakness (38.1%), headache (13.6%), dyspepsia (5%) and diarrhea (3.7%). The most frequent manifestations of severe cases are pneumonia (76%) and hypoxia (38%) [22].

Clinical forms of COVID-2019 are the following: asymptomatic (1–3% of cases); mild (with only upper respiratory tract damage); moderate (pneumonia without respiratory failure); severe (pneumonia with respiratory failure, respiratory rate (RR) $\geq$ 30 per minute, saturation $\leq$ 93%, PaO₂ / FiO₂ oxygenation index $<$ 300, or the appearance of infiltrates in the lungs in the form ground-glass opacity, occupying more than 50% of the lungs within 24–48 hours); and very severe (critical) form (pneumonia, sepsis, septic shock, multiple organ failure).

Approximately 10–15% of mild and moderate cases (81–82% of all infected patients) develop into severe ones [23]. About 15–20% of severe cases become very severe. A group of high-risk mortality from COVID-2019 should include elderly patients with concomitant diseases, especially with cardiovascular system damage [24]. In patients over 60 years of age, more severe clinical manifestations, greater severity, and a longer course of the disease were detected compared to patients under 60 years of age [21].

The morphological substrate of COVID-2019 infection is diffuse alveolar damage. The virus causes increased permeability of cell membranes and increased transport of albumin-rich fluid to interstitial lung tissue and alveolar lumen; thus, interstitial and alveolar edema develops. In this case, the surfactant is destroyed, which leads to the collapse of the alveoli. Acute respiratory distress syndrome (ARDS) develops following drastic gas exchange disturbances [25–27]. ARDS is very often confirmed in fatal cases of human SARS-CoV-2 infection [28].

Stages of ARDS development are the following. The exudative (acute) stage is manifested through alveolar type I cell damage, increased alveolar-capillary membrane permeability, interstitial and alveolar edema, and filling of the alveoli with leucocytes, red blood cells, and products of damaged cells (alveolar flooding, impaired function and production of endogenous surfactant). The second stage proliferative (subacute) with alveolar type II cell dam-

age, fibroblast migration in the alveolar exudates, proliferation of alveolar type II cells, and reduction of lung edema. The third stage is a fibroproliferative (chronic) phase with obliteration of the alveoli and advanced fibrosis of the pulmonary parenchyma.

BIOCHEMICAL AND MOLECULAR GENETIC ASPECTS OF COVID-2019

Genetic susceptibility and inflammatory cytokines have been shown to be associated with ARDS. More than 40 genes, especially *ACE2*, *IL-10*, *TNF*, and *VEGF*, are closely associated with ARDS development [29]. Elevated blood levels of interleukin-6 (IL-6) and interleukin-8 (IL-8) were shown to be associated with an adverse ARDS outcome [30].

It was demonstrated that rapid virus replication and cell damage caused by the virus down-regulation of *ACE2* and antibody buildup are responsible for aggressive uncontrolled lung inflammation caused by SARS-CoV-2 [31]. The beginning of rapid replication of the virus can lead to the mass death of epithelial and endothelial cells, causing excessive production of proinflammatory cytokines and chemokines. Research data show that SARS-CoV-2 infection increases markers of inflammation, such as CRP, IL-6, IFN γ , and TNF α [32, 33, 34], which is assumed to be facilitated by a sustained inflammatory response and cytokine storm [35, 36].

It was found that patients infected with COVID-2019 have high blood levels of IL-1 β , IFN γ , IP10, and MCP-1, which probably results in activated responses of type 1 helper cells (Th1). In addition, patients requiring hospitalization have higher concentrations of GCSF, IP10, MCP-1, MIP-1 α , and TNF α than patients who do not require hospitalization, suggesting that the cytokine storm is associated with the severity of the disease. COVID-2019 infection also initiates increased secretion of type 2 helper (Th2) cytokines (for example, IL-10), which suppress inflammation [33]. To characterize the effect of coronavirus on cytokine and chemokine production in the acute phase of the disease, the blood levels of cytokines and chemokines in patients who were confirmed to have COVID-2019 were analyzed. These data were compared in patients in the intensive care unit (ICU) and patients with a milder form of the disease (comparison group) [33]. Blood cytokines and chemokines (IL-1 β , IL-1RA, IL-2,

IL-4, IL-5, IL-6, IL-7, IL-8 (CXCL8), IL-9, IL-10, IL-12 p70, IL-13, IL-15, IL-17A, eotaxin (CCL11), FGF2, GCSF (CSF3), GMCSF (CSF2), IFN γ , IP10 (CXCL10), MCP-1 (CCL2), MIP-1 α (CCL3), MIP-1 β (CCL4), DGFB, RANTES (CCL5), TNF α , and VEGFA) were measured using the 27-PLEX panel for human cytokine analysis of the Bio-PLEX200 system (Bio-Rad, Hercules CA, USA). Blood samples were also taken from 4 healthy people as a control for cross-comparison. It was shown that the initial concentrations of IL-1 β , IL-1RA, IL-7, IL-8, IL-9, IL-10, FGF, GCSF, GMCSF, IFN γ , IP10, MCP-1, MIP-1 α , MIP-1 β , PDGF, TNF α and VEGF were increased both in ICU patients and in the comparison group, as opposed to the controls. Blood levels of IL-5, IL-12, p70, IL-15, eotaxin, and RANTES (CCL5) were the same in healthy individuals and in patients infected with COVID-2019. Further comparison between ICU patients and comparison group showed that blood concentrations of IL-2, IL-7, IL-10, GCSF, IP10, MCP-1, MIP-1 α and TNF α were higher in ICU patients than in the comparison group [33]. J. Lei et al. showed that patients infected with COVID-2019 had increased neutrophils, proinflammatory cytokines, C-reactive protein, D-dimer, and ESR in the blood [37].

Although the mechanism of heart damage is not fully described, there is evidence documenting the effect of COVID-2019 on the cardiovascular system. Thus, a study by C. Chen et al. confirmed that among a group of patients ($n = 120$) with COVID-2019, there was an increase in troponin ($n = 12$, 10%) and NT-ProBNP ($n = 33$, 27.5%), which indicated myocardial damage [38]. Two studies of patients in critical condition demonstrated that 23% ($n = 12$) of people developed myocardial damage [39], and 33% ($n = 7$) of patients developed cardiomyopathy [40]. In a study of 138 patients with COVID-2019, 10 patients (7.2%) were diagnosed with acute myocardial damage based on an increase in highly sensitive cardiac troponin I (hs-cTnI), and 8 of them were admitted to the ICU [41]. In another retrospective study, cardiac troponin I (cTnI) was significantly elevated in 33.3% of severe and 100.0% of critical patients [42]. C. Huang et al. and co-authors also identified an increase in the number of COVID-2019 patients with acute myocardial damage and critical conditions leading to ICU ad-

mission [33]. It was also shown that the mortality rate from COVID-2019 pneumonia was significantly higher among patients with cardiovascular or cerebrovascular diseases, which contributed to high mortality in these patients [43].

An increase in the biomarkers of myocardial necrosis in patients with COVID-2019 can provide predictive information for assessing the progression of the disease and the development of adverse events. Since some of the biomarkers are not specific to the myocardium, an increase in these indicators in the blood during the development of adverse events in COVID-2019 patients may reflect damage not only to the myocardium but also to other vital organs or tissues. Thus, in a study of 99 patients with COVID-2019, 75 patients had an increase in the lactate dehydrogenase level, and 13 patients had an increase in creatine kinase [44]. Elevated levels of lactate dehydrogenase were also shown in other studies of patients with laboratory-confirmed COVID-2019 [22, 32]. Renal dysfunction in patients with COVID-2019 was expressed by increased levels of urea and creatinine [41, 45], which was associated with direct exposure to the virus and hypoxia.

Increasing evidence suggest that abnormal biochemical processes in the liver are closely related to the severity of COVID-2019. A study of a cohort of 1,099 patients with COVID-2019 showed that 39.4% of individuals had AST > 40 U / l and 28.1% of individuals had ALT > 40 U / l, and most of the patients had a severe course of the disease [22]. In another multicenter retrospective study involving 32 patients, the average levels of ALT, AST, and bilirubin in the blood of severe and critical patients were significantly higher than in the controls [46]. ALT and AST levels in the blood of patients in severe and critical cases were significantly higher than in mild and moderate cases in other studies [33, 41, 47–49]. According to some data [45, 49], about a quarter of the deceased patients had elevated levels of procalcitonin. It was shown that an increased procalcitonin level (more than 0.5 µg / l) was associated with a fatal outcome (93% probability). Other authors demonstrated that the procalcitonin level was usually within normal values upon admission to the hospital but might increase in patients admitted to the ICU [33, 41, 44].

A retrospective analysis of 99 patients with COVID-2019, held in Wuhan Jinyintan hospital, showed that 36% of patients had increased D-dimer, 16% – a decrease in activated partial thromboplastin time (APTT), 6% – in increase in APTT, 30% – shortened prothrombin time (PT) and 30% – an increase in PT [44]. A retrospective analysis of routine parameters of the coagulation system in 183 patients with COVID-2019 showed that fibrin degradation products (FDP) and D-dimer in the blood of non-survivors were significantly higher than in survivors, whereas PT and APTT were significantly prolonged [50]. A retrospective analysis of 138 patients with COVID-2019 also confirmed that blood levels of D-dimer increased after admission to the hospital [41].

Previous studies demonstrated that elevated D-dimer is an independent risk factor for acute respiratory distress syndrome and mortality in patients with COVID-2019 [48]. Analysis of literature data shows that patients with a severe course of the disease than in patients with mild COVID-2019 [32, 45, 48, 49]. In a series of cases from China, an increase in the concentration of D-dimer in the blood during hospitalization (> 1 µg / ml) was associated with the risk of in-hospital mortality, which was 18 times higher than among patients with normal D-dimer concentrations [49].

It is reported that COVID-2019 should be considered as a disease that leads to increased thrombosis, and it is even proposed to rename COVID-2019 to MicroCLOTS (microvascular COVID-2019 lung vessel obstructive thromboinflammatory syndrome). The authors suggest that in predisposed people, viral alveolar damage is followed by an inflammatory reaction and microvascular pulmonary thrombosis. This progressive endothelial thrombo-inflammatory syndrome can also affect the microvascular bed of the brain and other vital organs, leading to multiple organ failure and death [51].

It was found that severe coronavirus disease can be complicated by coagulopathy, namely disseminated intravascular coagulation, which is quite prothrombotic in nature with a high risk of venous thromboembolism. The incidence of venous thromboembolism among patients with COVID-2019 in the ICU is high. D-dimer level can help in early recognition of these high-risk patients, as well as in prediction of the outcome. Preliminary data show

that in patients with severe COVID-2019, anticoagulant therapy appears to be associated with lower mortality in a subpopulation that meets the criteria for sepsis-induced coagulopathy, or with a markedly elevated D-dimer. Recent recommendations suggest that all hospitalized COVID-2019 patients should receive thromboprophylaxis or full anticoagulant therapy if such indications are present [52]. It is also advisable to use thromboprophylaxis in patients with confirmed coagulation system activation (increased concentration of D-dimer in the blood) upon admission [53].

A number of studies demonstrated a possible link between human leukocyte antigen (HLA) polymorphism and SARS-CoV susceptibility. HLA-B*4601, HLA-B*0703, HLA-DRB4*01010101, HLA-DRB1*1202, and HLA-Cw*0801 are associated with a genetic predisposition to SARS-CoV infection. A possible protective effect was observed for several other HLA alleles, including HLA-Cw*1502 and HLA-DRB1*0301. Genetic variation of HLA A, B, and C, may affect the sensitivity and severity of SARS-CoV-2. It was found that HLA-B*4601 has the smallest number of predicted peptides binding SARS-CoV-2, it is likely that individuals with this allele may be particularly vulnerable to COVID-2019 [54]. HLA-B*1503 demonstrated the greatest ability to represent highly conserved SARS-CoV-2 peptides that are common to human coronaviruses, suggesting that it may provide cross-protective T-cell-based immunity.

Individual genetic variations can help explain different immune responses to the virus in a population. Determining the type of HLA with simultaneous testing for COVID-2019 can improve assessment of the severity of the disease in patients. After developing a vaccine against the SARS-CoV-2 virus that causes COVID-2019, people with high-risk HLA types may have priority for vaccination [55]. In addition to HLA polymorphism, SARS-CoV and MERS-CoV infection susceptibility is also correlated with mannose-binding lectin (MBL) gene polymorphism associated with antigen presentation [56].

A group of researchers from the University of New York identified three signs indicating likely (70–80%) development of acute respiratory distress syndrome and pneumonia: the presence of myalgia, increased hemoglobin levels, and a slight increase in alanine aminotransferase [57].

Researchers at Wuhan University claim that the role of red blood cells in the pathophysiology of COVID-2019 is underestimated. The coefficient of variation in the width of the distribution of red blood cells (RDW) is a predictor of the severity of the condition [58]. According to the new data [59], the SARS-CoV-2 virus is able to secrete non-structural proteins ORF1ab, ORF10, and ORF3a, which easily penetrate the cell membrane of the red blood cell and displace the bivalent iron atom from the porphyrin core of the beta chain of the hemoglobin molecule. A single iron atom is able to transport 4 molecules of oxygen. Thus, destruction of hemoglobin inside the red blood cell takes place. The released iron ion contributes to further oxidation of organic molecules. Microhemolysis and hemolytic anemia occur. The authors attribute the occurrence of respiratory failure primarily to the resulting hemoglobin deficiency and oxidative damage initiated by iron ions and hemolysis. In addition to these three non-structural proteins that displace iron from the porphyrin core, the surface glycoprotein of the virus and the protein ORF8 can bind to the heme, which further strengthens the hemolytic potential of the virus. Excess porphyrins in red blood cells can accelerate cell lysis and development of hemolytic anemia [60]. It is hypothesized that critical COVID-2019 patients may experience a form of acquired acute porphyria [61]. Iron settles in the lung tissues, catalyzing oxidative processes and fibrosis [61, 62].

In a meta-analysis of 9 publications containing data from 1,779 COVID-2019 patients, mild thrombocytopenia ($140 \times 10^9/l$, an average decrease by $31 \times 10^9/l$) was observed in patients with a more severe course and was associated with a risk of mortality and severe complications with a five-fold relative risk (OR 5.1) [63]. In the deceased patients, there was an even more pronounced decrease in the number of platelets ($123 \times 10^9/l$, decrease by $48 \times 10^9/l$).

Z. Varga et al. presented data indicating that SARS-CoV-2 infection contributes to the induction of endotheliitis in several organs as a direct consequence of the virus (noted in the presence of viral bodies) and an inflammatory response of the host. In addition, induction of apoptosis and pyroptosis may play an important role in endothelial cell damage in patients with COVID-2019 [64].

Due to the dominance in the pathogenesis of acute distress syndrome and pneumonia caused by COVID-2019, oxygen delivery disorders associated with intra-erythrocyte and microcirculatory disorders, intravascular coagulation, erythrocyte hemolysis, microthrombosis in lung vessels and intralveolar fibrin formation, endotheliitis, the clinical and laboratory presentation fits into the framework of chronic hemolytic microthrombovasculitis and secondary chronic disseminated intravascular coagulation (DIC) syndrome.

Rs12252-C/C single-nucleotide polymorphism in the *IFITM3* gene (interferon-induced transmembrane protein 3) is a risk factor for severe influenza and was also detected in a patient with COVID-2019. Interferon-induced transmembrane protein-3 of the rs12252-C genetic variant is associated with disease severity in COVID-2019. Homozygotes for the rs12252 allele in the *IFITM3* gene are associated with a more severe course of the disease depending on age. This confirms the role of *IFITM3* in the pathogenesis of the disease and the possibility of early targeted intervention in high-risk individuals [65]. Susceptibility to the development of pulmonary fibrosis after COVID-2019 may also have a genetic component [66–68].

Molecular genetic studies of patients who have undergone COVID-2019 of varying severity can reveal host body features that explain why some patients carry the disease asymptomatically or in a mild form, while other patients are in a critical condition [69]. The causative agent of the COVID-2019 pandemic outbreak, SARS-CoV-2, is a member of the Coronaviridae family of shell viruses with a single-stranded (ss) RNA genome [70]. SsRNA viruses are recognized by the host's immune system, its first line of defense, through innate pattern recognition (PRR) receptors, such as Toll-like receptor 7 (TLR7), which is a primary sensor for extracellular or endosomal structures of virus-derived nucleic acids.

Gender differences in TLR7 responses were reported for people: female individuals are able to better tolerate hepatitis C, which is also typical of COVID-2019 [71–73]. When binding viral nucleic acid motifs, TLR7 induces expression of type I IFNs (IFN- α and IFN- β) and expression of the recently described type III IFN family (IFN- λ 1–4). Type III IFN is activated during viral infection of

the lung and liver epithelium [74]. It was shown that common genetic variations of the germ line at the locus of the type III *IFN* gene determine the host's ability to cope with infection caused by the hepatitis C virus (HCV), a type of ssRNA virus that is tropic to liver epithelial cells. It is assumed that one of the possible variants is a dinucleotide polymorphism in the *IFML4* gene (rs368234815/rs11322783 [TT/GG]), which determines the host's ability to encode the functional protein IFN- λ 4 [75].

The knockout variant TT of the *IFNL4* gene is favorable for destroying the virus and resolving the infection, presumably by deactivating the control mechanism of IFN α -desensitizing action that antagonizes the effectiveness of IFN α [76]. In the world, the frequency of favorable knockout variant TT is 0.841, 0.689, and 0.293 among Asian, European, and African populations, respectively. People of different populations may differ in their susceptibility to other RNA viruses, not just to hepatitis C. The study of genetic predictors of disease severity will reveal new targets for intervention against SARS-CoV-2 and COVID-19 infection.

Several international online platforms have been created to concentrate the genetic data of patients obtained by different groups of researchers (<https://covid19-hpc-consortium.org>; <https://www.covid19hg.org/>; <https://bigd.big.ac.cn/>). Platforms involve the exchange of data for their comprehensive analysis.

CONCLUSION

Despite the fact that the lung is the main organ damaged by the virus, COVID-2019 is currently considered a systemic disease affecting a wide range of other vital organs, such as the heart, liver, and kidneys [46, 77, 78]. However, it remains largely unclear whether organ and tissue damage in patients with COVID-2019 is a direct or indirect consequence of viral infection. The clinical features and prognosis of the disease differ in patients of different ages, which can help clinicians worldwide establish risk stratification for all patients with COVID-2019.

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