

## AGE AND SARS-COV2 INFECTION

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SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2), a novel virus of the beta coronavirus group RNA viruses, is responsible for a zoonotic disease named COVID-19 (coronavirus disease from 2019). The main receptor through which the virus enters the host cell is angiotensin-converting enzyme 2 (ACE2), known as a multifunctional protein. ACE2 expression has been found in oral and nasal mucosa, lungs, adipose tissue, heart, brain, kidneys, vascular tissue, stomach, liver. Upon entry of the virus into the target host cells, two processes are initiated, the host's immune response and the inflammatory cascade. As immune (innate and adaptive) and inflammatory responses change throughout life both qualitatively and quantitatively, both processes are responsible for varying degrees of disease severity depending on the patient's age. Short-time experience with SARS-CoV-2 infection has shown that: (i) children and adolescents develop the disease with mild symptoms, mainly on upper respiratory airways; (ii) the disease has a more severe course in adult patients with associated chronic diseases such as cardiovascular and renal diseases, chronic respiratory diseases, diabetes, etc.; and (iii) the most severe, often fatal disease occurs in the elderly, due to more pronounced processes of immunosenescence and inflamm-aging.

**Key words:** age, angiotensin-converting enzyme 2 (ACE2), coronaviruses, COVID-19, SARS-CoV-2

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### INTRODUCTION

The beginning of 2020 was marked by the emergence of the 2019 COVID-19 pandemic (**Corona Virus Disease from 2019**) caused by the new corona virus, SARS-CoV-2 (also known as new CoV, 2019-nCoV or COVI-19), a name derived from the syndrome name, i.e. **Severe Acute Respiratory Syndrome**, which first appeared in China at the end of 2019 (1) and then spread rapidly around the world. So far, the animal from which the SARS-CoV-2 was transmitted to humans is not known yet with certainty. In addition to the previously known MERS-CoV and SARS-CoV, which can cause severe clinical presentation (**Middle East Respiratory Syndrome** and **Severe Acute Respiratory Syndrome**), four other human coronaviruses (229E, NL63, OC43 and HKU1) have been shown to cause infection only in the upper respiratory tract and

cause relatively minor symptoms. SARS-CoV-2 has the ability to infect and actively reproduce in the upper respiratory tract.

In recent months, physicians and scientists have faced new challenges regarding COVID-19 and are focused on the investigation of a number of unknown characteristics of the novel coronavirus (its ability to infect and reproduce in the respiratory tract) (1), the receptor through which it enters human cells, the immune response and accompanying inflammation, new drugs and vaccines (2). As with other pathogens, the outcome of infection with SARS-CoV-2 depends on the amount of virus exposure at the start of infection, and on the innate and adaptive immune capabilities of the host, as well as the ability to overcome inflammation. Generally, the immune response is conditioned by age, genetic inheritance, and health condition of the host (3).

Although COVID-19 initially appeared to be a disease of the elderly and individuals whose immune system is already compromised by various chronic diseases and conditions, it was soon shown that middle-aged persons, younger persons and some children can be affected by this new viral disease.

The aim of this paper is to present literature data on the relationship between age and outcome of SARS-CoV-2 infection. In search of the review and scientific papers on the PubMed free search engine, the following key words were used: age, angiotensin-converting enzyme 2 (ACE2), coronaviruses, COVID-19, SARS-CoV-2. Articles published in English between 2003 and May 2020 were included and selected according to the relevance to the topic.

### SARS-COV-2

Like other coronaviruses, SARS-CoV-2 belongs to the betaCoV group of positive-sense single-stranded RNA viruses (4,5), diameter of approximately 60-140 nm, having four major structural proteins: the spike (S), membrane/matrix (M), small envelope (E) and nucleocapsid (N) proteins, essential to produce a structurally complete viral particle and for infection. Trimeric S glycoprotein comprises two subunits, S1 and S2 subunits. The S1 subunit contains an amino-terminal domain and a receptor-binding domain (RBD), which binds to ACE2 on the surface of epithelial cells in the lungs and other tissues. As the S glycoprotein through its RBD interacts with human ACE2 as a receptor on the target cell and mediates virus-cell fusion, it is responsible for viral entry into human cells (6). The S2 subunit comprises a fusion peptide region and two heptad repeat regions, HR1 and HR2. According to the research of other CoVs (7), the M protein defines the shape of the viral envelope, binds to the S protein and the host surface receptors, and therefore it improves membrane fusion. In addition, M protein is involved in virus replication, and is also important for virus antigenicity (8). The N protein has multiple functions: it allows virus replication, the host cellular response to viral infection, and acts as an antagonist of interferon alpha (IFN- $\alpha$ ), a major effector cytokine in the innate antiviral response (9). The majority of E protein is localized at the site of intracellular trafficking. It seems that protein E participates in viral assembly, intracellular trafficking and pathogenesis of the virus infection (10). After SARS-CoV infection, B lymphocytes produce antibodies against these four structural proteins crucial to the development of diagnostic tests and vaccine (11).

### ANGIOTENSIN-CONVERTING ENZYME 2 AND SARS-COV2 INFECTION

The monocarboxypeptidase ACE2 is a multifunctional protein that acts in several ways: (i) as an enzyme it degrades angiotensin (Ang) 2 to biologically active peptide Ang (1-7) in the renin-angiotensin system (RAS); (ii) as a receptor for SARS-CoVs, it allows the virus to penetrate the cells of various tissues (Figure 1); (iii) as an acid transporter plays an essential role in the absorption of amino acids in the kidney and gut; and (iv) in the soluble form (sACE2) present in serum, it degrades angiotensin Ang 2 to Ang (1-7) (12, 13). Although Kuba *et al.* suppose that the function of ACE2 as a SARS-CoV receptor takes place independently of its peptidase activity (12), this hypothesis needs to be proven in the future. ACE2 expression has been found in oral and nasal mucosa, lungs, adipose tissue, heart, brain, kidneys, vascular tissue, stomach, liver (13-15). Also, ACE2 is bound to peptides in circulation (both maternal and fetal), renal tubular fluid, cerebrospinal fluid, interstitial and bronchial fluid.

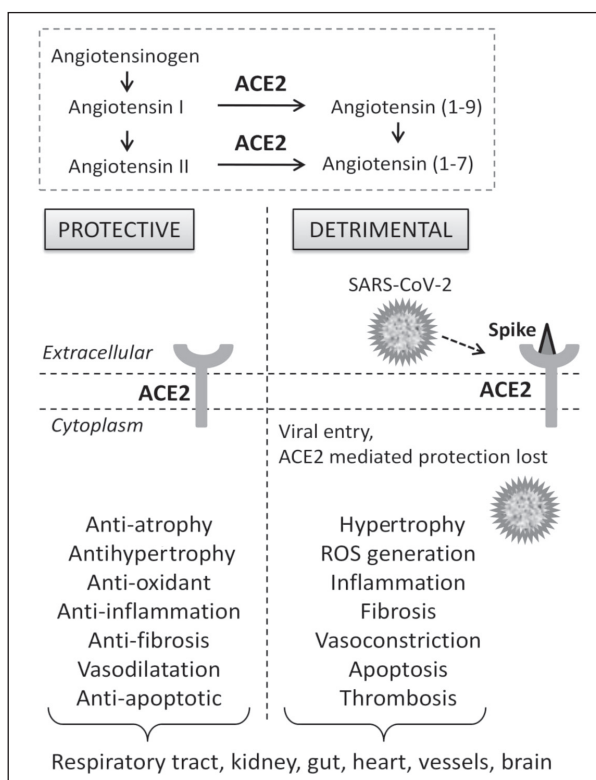


Fig. 1. Protective effects of angiotensin-converting enzyme 2 (ACE2) and detrimental consequences after SARS-CoV-2 infection. (Adapted according to ref. 13)

Since ACE2 was discovered, attention has been focused mainly on its function and possible roles in hypertension associated kidney and heart diseases and in pregnancy, as well as in patients with diabetes (13). However, the knowledge of ACE2 to date is still in-

sufficient to comprehend fully all aspects of the action of this enzyme, particularly regarding its role in the infection with SARS-CoV-2 and all the consequences of this infection, including the severity of COVID-19. It is located on the outer membrane of epithelial cells in the lungs (particularly in type 2 pneumocytes and macrophages) (16). The entry of SARS-CoV-2 into the cell takes place with the simultaneous activity of ACE2 and other receptors (co-receptors), such as *Mas* receptors and type II transmembrane serine protease receptor (TMPRSS2) (13, 14). SARS-CoV employs the TMPRSS2 for S protein priming. It is not yet known whether SARS-CoV-2 also employs both ACE2 and TMPRSS2 for host cell entry (17). ACE2 associated with the *Mas* receptor plays a beneficial role because it reduces inflammation and prevents development of fibrosis and pulmonary damage (13, 14). However, when SARS-CoV-2 enters cells *via* ACE2 as a receptor with consequent endocytosis, this beneficial effect will be absent and detrimental consequences will occur in the cells into which the virus has entered (Figure 1). According to the previous research on SARS-CoV infection, ACE2 has a dual function. It plays a critical role in the entry of the virus into cells, and may also be involved in post-infectious regulation (18). This post-infection regulation is supported by data that the expression of ACE2 increases 12 hours after infection, that it continues to increase significantly for 24 hours after infection, and that after 48 hours high expression still persists (19). Recently, bioinformatics methodology has enabled to identify not only ACE2 expression in the lung, but also the potential protein-protein interaction network, which regulates the network between ACE2 and inflammatory cytokines (19).

#### AGE-DEPENDENT EXPRESSION OF ANGIOTENSIN-CONVERTING ENZYME 2

Studies in rat lung tissues have shown that ACE2 expression in younger animals is significantly higher than in adult animals regardless of gender, and that in older animals there is a weak decrease in ACE2 expression in comparison with young and adult animals (20). These data would support the notion that ACE2 has a greater protective role, i.e. anti-atrophy, anti-oxidant, anti-inflammation, etc. in younger individuals, as presented in Figure 1. Besides, in the lungs, ACE2 expression levels and immune signature enrichment levels displayed positive correlation in older animals and negative correlation in younger animals (20). Research on ACE2 expression in lung tissue is currently limited, and is being conducted in animal tissues. To define the true role of ACE2 as a receptor for SARS-CoV-2 in children, adults and elderly patients, further research will be needed, presumably on cell cultures as well.

#### INNATE AND ADAPTIVE IMMUNE RESPONSE TO SARS-COV-2 VIRUS

SARS-CoV-2 first replicates rapidly in epithelial cells of respiratory and enteric system. Once the virus enters the host cells, both non-specific (cellular and humoral) and specific (cellular and humoral) (21, 22) immune mechanisms are activated, as well as the inflammatory cascade (3, 22). The first contact with the pathogen leads to the activation of the mechanisms of innate immunity, and the achievement of memory *via* memory T helper lymphocytes, in order to initiate specific immune response in re-contact with the same pathogen. This response of the adaptive immune system is particularly rapid (23).

Experience with SARS-CoV has shown that innate immunity is crucial for successful defense against the virus (24). It is not yet clear whether the immune/inflammatory response to SARS-CoV can be projected onto SARS-CoV-2, but it can be assumed that there is certain parallelism. The first reaction of the host after infection is to limit the spread of the virus in the host cells. Dendritic cells, macrophages, IFN- $\alpha$ , innate immune mediators, and the complement system are involved in this first phase of viral replication control (Figure 2). The proinflammatory reaction takes place simultaneously because proinflammatory cytokines are released from the infected cells, e.g., IL-6, TNF- $\alpha$  and IFN- $\beta$ , which induce direct antiviral response and modulate other mediators of innate and adaptive immunity (such as NK cells, CD8+ lymphocytes) and the complement system (24, 25). Dendritic cells also act as antigen presenting cells, followed by the activation of naïve T lymphocytes and subsequent activation of CD4+ and CD8+ lymphocytes. CD8+ lymphocytes stimulate the synthesis of IFN- $\gamma$ , which inhibits viral replication directly. CD4+ lymphocytes are aimed at stimulating the inflammatory response in the lungs (hyperinflammation). Immunohistochemical analysis of patients who died of COVID-19 revealed that deceased patients had atrophy and necrosis of the spleen and lymph node cells. In addition, lymphatic tissue macrophages contained SARS-CoV-2 nucleoprotein antigen and showed upregulation of IL-6, suggesting that macrophages may contribute to viral spread, severe inflammation, and activation-induced lymphocytic cell death during COVID-19 (26).

Upon activation, B lymphocytes are involved in the immune response by synthesizing specific immunoglobulins directed against the S and N antigens of CoV (27). Patients who manage to synthesize significant amounts of antibodies have better outcome of the infection (24).

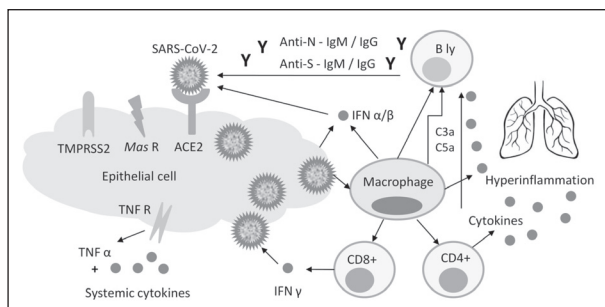


Fig. 2. Predicted immune response and inflammation during SARS-CoV-2 infection.

Anti-N-IgM/IgG – IgM/IgG antibodies against viral N-antigen; Anti-S-IgM/IgG – IgM/IgG antibodies against viral S-antigen; ACE2 – angiotensin converting enzyme 2; Bly – B lymphocytes; C3a – complement component 3a; C5a – complement component 5a; CD4+ – CD4+ T helper lymphocytes; CD8+ – CD8+ T helper lymphocytes; IFN – interferon; Mas R – Mas receptor; TMPRSS2 – type II transmembrane serine protease receptor; TNF  $\alpha$  – tumor necrosis factor  $\alpha$ ; TNF R – tumor necrosis factor receptor; Y – antibody; black circle – cytokine

## IMMUNITY FROM FETAL LIFE TO OLD AGE

It is generally known that the immune system develops over lifetime. At birth, the immune system is relatively immature. In general, neonatal immunity is weaker than that of adults because of tissue leukopenia, cell intrinsic hyporesponsiveness, and high values of adenosine in extracellular fluids, and inhibitory mechanisms (28). Innate immunity is considered to play a more dominant role in protecting against infection in childhood than in adulthood. The complement system represents the backbone of the innate immune system (25). In infant serum, the concentration of complement components does not exceed 80% of the value of adults, but some components may reach the value in adults already after the first month of life (28). In the first two decades, the immune system develops to a certain degree of maturity, which is maintained in adulthood, followed by a gradual decrease or weakening of physiological functions, including those of the immune system. Generally, in early adulthood, the immune system successfully maintains its balance against environmental antigens, suppresses inflammation, and heals visible and invisible damage to various tissues (Figure 3). As age advances, the immune system homeostasis becomes weaker, malignant and autoimmune diseases can occur due to environmental factors in people with genetic predisposition (28). Decline of the immune response is a consequence of impaired innate and adaptive immunity function and increasing immunosenescence, which is ultimately reflected in reduced phagocytic function, decreased number of macrophage precursors, neutrophil dysfunction, and impaired function of B and T lymphocytes (23, 28-30). In addition to immunosenescence, worsening of

the clinical status of the elderly with COVID-19 is also affected by systemic chronic inflammation, known as senoinflammation (31). Due to senoinflammation, the values of proinflammatory cytokines increase in the elderly. In addition, the ability to synthesize specific antibodies decreases.

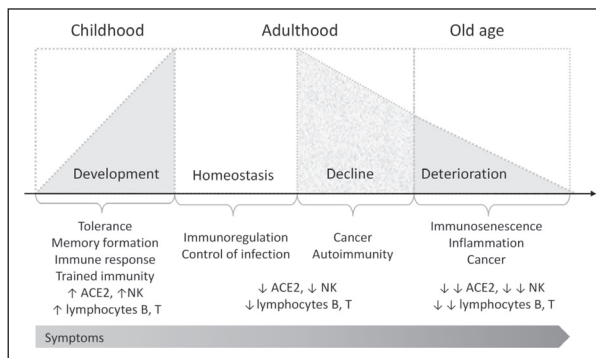


Fig. 3. Basic features of the immune response over lifetime.

After birth, the mechanisms of innate immunity play a major role. As the child encounters different antigens, the mechanisms of acquired immunity are increasingly emerging. In adulthood, a stable balance of the immune system and exposure to numerous antigens is established. The immune system is increasingly weakening with age, resulting in the onset of inflammation, malignant and autoimmune diseases. COVID-19 symptoms worsen with patient age. (Adapted according to ref. 22 and 28)

## OUTCOMES OF SARS-COV-2 INFECTION DEPENDING ON PATIENT AGE

Short-time experience with SARS-CoV-2 infection has shown that the initial infectious dose of virus is in correlation with more severe disease (32). Children and adolescents are the healthiest segment of the entire population and generally have mild symptoms of SARS-CoV-2 infection, mainly on upper respiratory airways. If a child with SARS-CoV-2 pneumonia does not have another associated disease, COVID-19 prognosis is good (33). However, in rare cases, children may have pneumonia or multisystem inflammatory syndrome (MIS). The disease has a more severe course in patients with associated chronic diseases (cardiovascular diseases, diabetes, chronic respiratory diseases, renal disease, coagulopathy, etc.). The most severe form of the disease, often fatal, occurs in the elderly, due to more pronounced immunosenescence (3). From these observations, it can be concluded that people of good general health have milder or moderate symptoms of COVID-19, and that older people have more severe symptoms than younger patients, which can be interpreted with the functional capacity of the immune system (Figure 3). In addition, children



have higher expression of ACE2 than adults have and are less susceptible to detrimental effects of virus than older persons are. Moreover, due to low expression of ACE2, elderly patients may have more severe COVID-19 outcomes, especially those with multiple comorbidities (34, 35). Within the kidneys, ACE2 is mostly localized in tubular epithelial cells and less in glomerular epithelial cells and in renal vessels (36), where it plays a key role in the RAS. Despite the higher levels of ACE2 observed in renal epithelial cells than in lung epithelial cells, the incidence of acute kidney injury in COVID-19 is relatively low (29%), in contrast to 71% incidence of severe lung injury. Renal damage could result from pre-existing renal diseases in some adult patients, and especially older patients (37).

Recent epidemiological studies involving more than 3,000 children have shown that the majority of patients with proven SARS-CoV-2 infection were asymptomatic or had mild and moderate symptoms of COVID-19, and a 14-year-old boy died (38-40). The initial symptoms in children are fever and dry cough, and after the disease begins to worsen, rhinitis, nasal congestion, fatigue, headache, diarrhea and dyspnea can occur (41). Several reasons could affect the diagnosis of illness in children. These are less exposure of children to the source of the infection, milder symptoms of the disease, sometimes the infection goes through even without significant symptoms, thus laboratory testing for the virus is less frequently performed in children (42). Mild COVID-19 presentation in children might be associated with higher expression of ACE2 and with innate immune memory, i.e. trained immunity (immunological memory in innate immune pathways) (35). It has also been hypothesized that SARS-CoV-2 infection is less common among children than adults because of the lower maturity and function of ACE2 (38), resulting in a reduced possibility that such less functional ACE2 can bind the virus and allow it enter host cell. Differences in the immune systems between children and adults may be another reason why children respond to SARS-CoV2 infection differently from adults. Furthermore, children are more up-to-date with vaccination, which potentially may protect them from other infections due to some non-specific benefits of childhood vaccine (43).

Changes in the functional capacity of the immune system over lifetime are reflected in the values of particular immune mediators, such as absolute cell counts of B and T lymphocytes, T lymphocyte subsets in peripheral blood, as well as serum cytokine concentration (44, 45).

The number of NK cells decreases from infancy to adulthood, but in the elderly, their number gradually increases. In the elderly, the capacity of the antiviral

cytokine IFN- $\alpha$  decreases. The percentage of T lymphocytes increases from childhood to adulthood, but decreases in the elderly. Regarding proinflammatory cytokines, the concentration of IL-1, IL-6, IL-8 and TNF- $\alpha$  has been shown to increase in old age in comparison to adults. At the same time, in the elderly, the concentration of Th1 cytokines (IL-2, IFN- $\gamma$ ) decreases, and the concentration of Th2 cytokines (IL-4, IL-10) increases (44, 45).

In the general population, about 80% of infected persons have mild signs and symptoms (tiredness, fever, cough, loss of taste and smell, headache). Other patients, i.e. those already suffering from a serious chronic illness (hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and chronic renal disease) and the elderly are at a high risk of developing a severe form of the disease (acute respiratory distress syndrome (ARDS), nausea, vomiting, diarrhea) with possible lethal outcome (1, 46, 47). In individuals with impaired immunity, SARS-CoV-2 will almost undisturbed cause massive destruction of target tissues, especially in the organs with ACE2 expression, such as the lungs, intestines, and kidney. Due to inflammation damaging, pneumonia is the main cause of life-threatening respiratory disorders in the severe stage of the disease.

Elderly patients with associated diseases, such as hypertension, cardiovascular (arrhythmia) and cerebrovascular disease, chronic obstructive pulmonary disease (COPD), are at a high risk of death, with dyspnea being a key symptom (48). The main predictors of death are complications that occur in these patients, such as acute cardiac injury and cardiac insufficiency, arrhythmia, acute renal injury, ARDS, and bacterial infection.

## LABORATORY FINDINGS

The aim of laboratory diagnosis in patients with SARS-CoV2 infection is to prove the presence of the virus in biological samples (nasopharyngeal and oropharyngeal swab or wash in outpatients and sputum and/or endotracheal aspirate or bronchoalveolar lavage (BAL) in inpatients), to assess the patient's general health status of target organs, immune status, and intensity of inflammation.

### A. DETECTION OF SARS-COV-2

The gold standard for the detection of SARS-CoV-2 is the nucleic acid amplification testing (NAAT) by real-time polymerase chain reaction (rtPCR) and fur-

ther confirmed by next-generation sequencing (49). A positive result establishes whether the individual is currently infected with SARS-CoV-2.

## B. MONITORING PATIENT HEALTH STATUS

Complete blood count (CBC), basic metabolic panel, panels for assessment of cardiac and renal function, coagulation tests, and indicators of inflammation are determined to assess the general health of the patient and screening for underlying diseases. Since children generally do not have associated diseases, changes in laboratory parameters are typical for viral infection. Children with MIS may have lymphopenia, neutrophilia, increased lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, fibrinogen, procalcitonin, D-dimer, IL-6 and decreased albumin values (50, 51). It could be assumed that otherwise healthy adults will have the same changes in laboratory findings, except for those findings that relate to changes caused by simultaneous damage to particular organs, e.g., cardiac and renal damage (Table 1) (41, 52).

Non-specific hematologic and biochemical findings depend on comorbidities and therefore on the severity of the disease (53). Accordingly, risk factors for severity of COVID-19 in adults/elderly are lymphopenia, neutrophilia, increased LDH, CRP and proinflammatory cytokines (54). It has also been established that older men who have heart damage and those with higher LDH may have an increased risk of death from COVID-19. In severe inflammatory state, inpatients may have a number of coagulation abnormalities (i.e. hypercoagulability) such as thrombocytosis, increased prothrombin time, fibrinogen, D-dimer, factor VIII (55).

Significant differences were found in laboratory findings between the dead and survivors. Longitudinal monitoring has shown that patients with worsening CBC (lymphopenia, thrombocytopenia, monocytopenia, neutrophilia), coagulation (partial thromboplastin time, D-dimer), increased biochemical parameters (aspartate aminotransferase, urea), myocardial injury markers (creatinine kinase-MB, high sensitive troponin), inflammatory markers (CRP, IL-6), cellular immunity marker (CD4+), and bacterial infection marker (procalcitonin) have an increased risk of death (48).

Table 1.  
 Changes in common laboratory tests and their clinical significance

| LABORATORY FINDING  | POTENTIAL CLINICAL SIGNIFICANCE   |
|---|---|
| <b>Detection of SARS-CoV-2</b>  |   |
| <b>Molecular diagnostics</b>  |   |
| SARS-CoV-2 (positive)   | Confirmed SARS-CoV-2 infection  |
| <b>Health assessment</b>  |   |
| <b>Hematology</b>   |   |
| Leukocytes, ↓ ↑ or ↓, <sup>S</sup><br>Lymphocytes, ↓, <sup>S, D</sup><br>Neutrophils, ↑, <sup>S, D</sup><br>Monocytes, ↓, <sup>S, D</sup><br>MDW, ↑<br>Platelets, ↓, <sup>S, D</sup><br>Hemoglobin, ↓   | Reduced immune response to the virus<br>Reduced immune response to the virus<br>Secondary bacterial infection<br><br>Severe viral infection/viral sepsis<br>Consumption (disseminated)/coagulopathy<br>Possible anemia during acute infection   |
| <b>Coagulation</b>  |   |
| Prothrombin time, ↑, <sup>S, D</sup><br>D-dimer, ↑, <sup>S</sup>  | Activation of coagulation and/or disseminated coagulopathy<br>Activation of coagulation and/or disseminated coagulopathy  |
| <b>Biochemistry</b>   |   |
| LDH, ↑, <sup>S, D</sup><br>AST, ↑, <sup>A</sup> ALT ↑, <sup>S, D</sup><br><br>Bilirubin, ↑;<br>Fibrinogen, ↓, <sup>A, S</sup><br>Albumin, ↓, <sup>S</sup><br><br>Urates, ↑, <sup>S</sup><br>Creatinine, urea, ↑, <sup>A, S, D</sup><br>CK-MB, hs-troponin, ↑, <sup>A, S, D</sup><br>pro-BNP, BNP, ↑, <sup>A</sup> | Pulmonary injury and/or multisystem damage<br>Hepatic failure and/or widespread organ damage<br>Hepatic failure<br>Hepatic failure<br>Impaired liver function, secondary bacterial infection, septic shock<br>Renal injury, oxidative stress<br>Renal injury<br>Cardiac injury; associated with higher mortality  |
| <b>Inflammation</b>   |   |
| Platelets, ↑, <sup>S</sup><br>Fibrinogen, ↑, <sup>S</sup><br>Acute phase proteins, ↑<br>C-reactive protein, ↑, <sup>S, D</sup><br>IL-6, IL-10, ↑, <sup>S, D</sup><br>Tumor necrosis factor-α, ↑<br>Procalcitonin, ↑, <sup>S, D</sup><br><br>Ferritin, ↑, <sup>S</sup>   | Inflammation, reactive thrombocytosis<br>Inflammation<br>Acute inflammation (<6 days)<br>Viral infection; secondary bacterial infection<br>Proportional to the severity of inflammation<br>Proportional to the severity of inflammation<br>Secondary bacterial infection and progression of the severity<br>Viral infection; secondary bacterial infection; |
| <b>Immunity status</b>  |   |
| Natural killer cells, ↓<br>T lymphocyte subsets, ↓, <sup>S, D</sup><br>B lymphocytes, ↓<br>Specific IgM antibodies, ↑<br>Specific IgG antibodies, ↑   | Innate immunity; possible impaired cellular immunity<br>Adaptive immunity; possible impaired cellular immunity<br>Adaptive immunity; possible impaired humoral immunity<br>Indicator of (acute) contact with SARS-CoV-2<br>Indicator of former contact with SARS-CoV-2  |

A – typical finding in adult/old patients; BNP – B-type natriuretic peptide; AST – aspartate aminotransferase; ALT – alanine aminotransferase; CK-MB – creatine kinase-myocardial band; hs – high sensitive; D – death risk; LDH – lactate dehydrogenase; MDW – monocyte volume distribution width; S – proportional to the severity of inflammation; SARS-CoV-2 – Severe Acute Respiratory Syndrome-CoronaVirus-2.

### C. DETECTION OF ANTIBODIES AGAINST SARS-COV-2 ANTIGENS

About 10 days after the onset of symptoms, specific IgM and IgG antibodies to N, E, M and S antigens of SARS-CoV-2 can be detected in patient serum (56). The maximum value of antibodies is reached in the middle of the third week from the onset of the disease. After this time, the antibody values gradually decrease. IgM antibodies reach the lowest values about five weeks after the onset of the disease and disappear from the circulation in the seventh week after the onset of the disease. The decrease in IgG antibodies is slower and begins about seven weeks after the onset of symptoms (57). Compared to the PCR method, determination of antibodies to N antigen has the highest diagnostic sensitivity and to S antigen the greatest diagnostic specificity (56, 58).

### FINAL REMARKS

At the time of writing this article, the scientific community has not reliably investigated all the characteristics of SARS-CoV-2 and the host immune and inflammatory response. Currently, there is very limited knowledge about the host immune response to SARS-CoV-2 infection. For now, conclusions on how the body copes with the virus are largely based on the knowledge about previous coronaviruses.

The virus has been shown to have the ability to infect the host, enter cells *via* ACE2, and actively reproduce in the respiratory tract and primarily cause pneumonia. Children constitute a small fraction of individuals with COVID-19, and have a milder form of the disease, probably due to higher ACE2 expression than adults, successful action of mediators of innate immunity (i.e. trained immunity) and higher number of decisive lymphocytes in the first years of life. Further research is needed to examine the true function of ACE2 in SARS-CoV-2 infection.

Most healthy adults have mild symptoms. In patients with comorbidities (hypertension, cardiovascular and cerebrovascular disease, COPD), the virus will cause more severe forms of the disease. Lymphopenia in patients with severe disease occurs mainly due to a decrease in the number of T lymphocytes. Elderly patients are at a risk of death, with worsening laboratory findings that indicate cardiac and renal damage, severe inflammation, and decreased immune function.

Explaining the mechanisms of immunosenescence and inflamm-aging may help better understand not only age-related disorders and diseases but also SARS-CoV-2 infection. Attention has been paid to determin-

ing diagnostic sensitivity, specificity and predictive value of certain biomarkers of inflammation, as well as the possible biomarkers of senescence and aging.

Determination of anti-SARS-CoV-2 antibodies (IgM and IgG classes) has no diagnostic value, but serves to assess the host's humoral response, to retrospectively assess the individual's exposure to the virus, and for epidemiological purposes. In order for the serologic test to precisely distinguish SARS-CoV-2 infection from infection with other coronaviruses, future research should examine cross-reactivity in antibody binding to specific antigens of different viruses.

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## SAŽETAK

### DOB I INFEKCIJA VIRUSOM SARS-COV-2

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RSARS-CoV-2 (engl. *Severe Acute Respiratory Syndrome Coronavirus 2*), novi virus iz skupine RNA betakoronavirusa, odgovoran je za zoonotsku bolest nazvanu COVID-19 (bolest uzrokovana koronavirusom iz 2019.). Glavni receptor pomoću kojega virus ulazi u stanicu domaćina je angiotenzin konvertirajući enzim 2 (ACE2), poznat kao multifunkcionalni protein. Receptor ACE2 prisutan je u oralnoj i nosnoj sluznici, plućima, masnom tkivu, srcu, mozgu, bubrezima, vaskularnom tkivu, želucu, jetri. Nakon ulaska virusa u ciljne stanice domaćina pokreću se dva procesa, imunosni odgovor domaćina i upalna kaskada. Budući da se imunosni (urođeni i stečeni) i upalni odgovori tijekom života mijenjaju u kvalitativnom i kvantitativnom smislu, oba procesa su odgovorna za različit stupanj ozbiljnosti bolesti, ovisno o pacijentovoj dobi. Kratkotrajno iskustvo s infekcijom uzrokovanom virusom SARS-CoV-2 pokazalo je da: (i) djeca i adolescenti razvijaju bolest s blagim simptomima, uglavnom na gornjim dišnim putevima; (ii) bolest ima teži tijek u odraslih bolesnika s pridruženim kroničnim bolestima kao što su kardiovaskularne i bubrežne bolesti, kronične respiratorne bolesti, dijabetes i sl.; (iii) najteži, često fatalni oblik pojavljuje se u starijih osoba zbog izraženijih procesa imunosenescencije i upale pri starenju.

*Ključne riječi:* starija dob, angiotenzin konvertirajući enzim2 (ACE2), koronavirusi, COVID-19, SARS-CoV-2