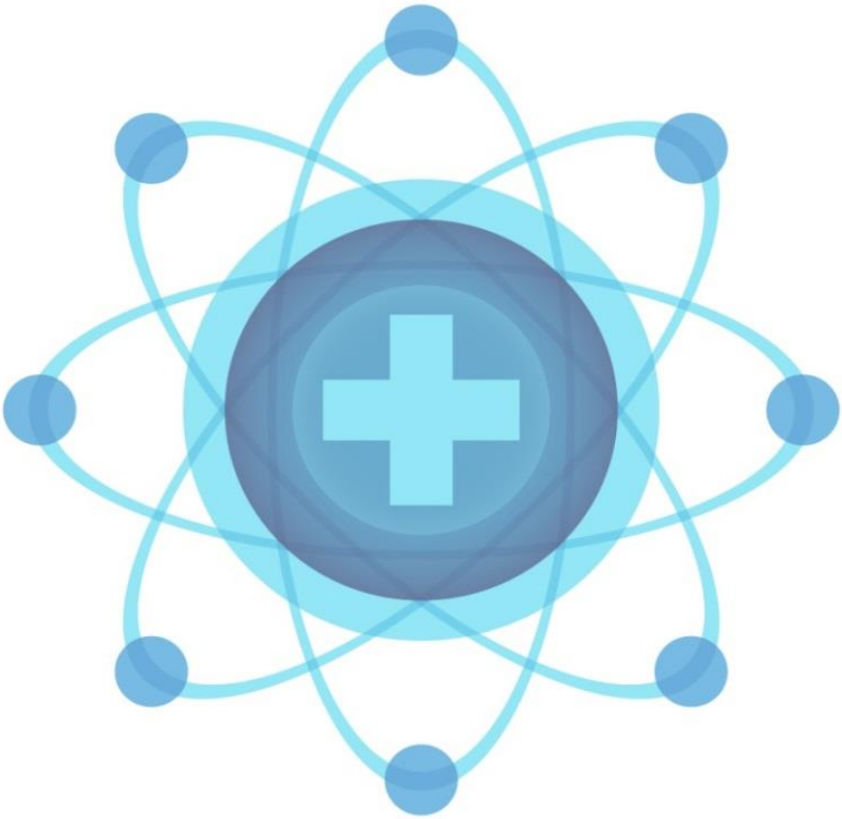

INTERNATIONAL MEDICAL SCIENTIFIC JOURNAL

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11931 Barlow Pl Philadelphia, PA 19116, USA +1 (929) 266-0862

Available at https://www.bookwire.com/
ISBN: 978-0-578-26510-0

PATHOGENETIC ASPECTS OF COVID-19

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Abstract: to study in detail the pathogenetic aspects of COVID-19, which will allow us to understand the genesis of the development of the disease, as well as their complications. This will improve the medical care provided to this category of patients. The relationship between triggering the release of pro-inflammatory cytokines with the development of infiltration in endothelial cells, microvascular dysfunction, and an increase in respiratory failure is presented. Based on the literature review data, the article describes the genesis of the trigger development of respiratory pathology, as well as multiple organ failure, which contribute to the progression of COVID-19.

Keywords: enzyme (ACE2), virus, infectious process, internal organs, ACE2, hypoxemia, hospitalization

INTRODUCTION

The SARS-CoV-2 virus, being highly contagious, leads to a large-scale and rapid spread of the disease throughout the world [1]. The peak of the spread of COVID-19 in the Republic of Uzbekistan for the second year falls on the summer-autumn period, at the height of the hottest days, when in other countries this disease was recorded to a greater extent during the cold season. It has been noted that against the background of the rapid spread of SARS-CoV-2, an intensive evolution of the virus occurs with the emergence of new strains [2]. SARS-CoV-2 has pantropism towards cells that have angiotensin-converting enzyme (ACE2) receptors present in the respiratory tract, kidneys, heart, CNS, and other organs [3,4]. This explains the damage by the virus to various target organs of the human body [5]. SARS-CoV-2

RNA was detected not only in bioassays from the respiratory tract and blood, but also in urine and feces [6]. This confirms the generalization of the infectious process. Already when observing the first patients with COVID-19, it was noted that the second organ affected by the virus after the lungs are the kidneys. Damage to the structure of the kidneys by the SARS-CoV-2 virus is confirmed by the detection of viral RNA in them along with the expression of ACE2 and dipeptidylpeptidase-4 receptors in the renal tubules of patients with COVID-19 [7]. It has been established that the physiological blood supply to the kidneys is 50 times more intense than the blood supply to other internal organs. Consequently, any substances that enter the body are found in the kidney at a concentration 50 times greater than in other organs. This indicates that the kidney with COVID-19 can pass through itself the largest number of viruses that have invaded the body, along with other organs [8]. Studies indicate that the highest expression of ACE2 receptors in the human body is observed in the cells of the small intestine (much more than in the lungs) [9]. This explains the presence, according to a number of authors, in 30-59% of patients with COVID-19 signs of gastrointestinal damage, with predominant registration in children [6]. Thus, the median duration of virus RNA detection from the intestine is approximately 11 (9.0-16.0) days, and from the respiratory tract - 9.5 (6.0-11.0) days [10]. At the same time, a number of authors argue that SARS-CoV-2 is deactivated in the colon, and therefore, active forms of the virus capable of being transmitted to another person are absent in the feces of patients. Currently, in order to confirm or exclude the fecal-oral route of infection, the study of the properties of the virus excreted with feces continues [9]. Li Y.C. et al., 2020, indicate that some human endothelial and intestinal cells that express ACE2 are not infected with SARS-CoV-2, while cells that do not contain ACE2, namely hepatocytes, can be infected with SARS-CoV [11]. This indicates that the introduction of the SARS-CoV-2 virus into the cells of the macroorganism occurs using other receptors as well [12]. Numerous data confirm the possibility of damage to the heart and brain by the coronavirus. Back in 2009, a direct damaging effect of coronavirus on cardiomyocytes was described, which was confirmed by the detection of SARS-CoV RNA in 35% of heart autopsy samples during the SARS outbreak in Toronto [13]. Baig A.M. et al, 2020 state that the penetration of the virus into the brain leads to damage to the endothelium of microvessels, glial cells and neurons [14].

MATERIALS AND METHODS

This is the reason for the presence in our studies conducted in 2021 in the clinic of the Research Institute of Epidemiology, Microbiology and Infectious Diseases at the Ministry of Health of the Republic of Uzbekistan in 1.1% of patients with coronavirus infection of such symptoms as sleep disturbance, a sense of fear of death, in 0.2% - hallucinations. Thus, the detection of SARS-CoV-2 RNA in patients with COVID-19 not only in bioassays from the respiratory tract and blood, but also in urine, feces, cardiomyocytes, and vessels explains the possibility of damage to various target organs and contributes to the deterioration of the patient's condition when associated somatic pathologies. Establishment of data on a receptor-dependent decrease in the severity of viral organ damage showed that, due to the reduced

expression of the ACE2 gene in the cells of the respiratory tract, in patients suffering from bronchial asthma of an allergic (atopic) nature, their susceptibility to COVID-19 decreases [15]. Since the beginning of the pandemic, scientists have assumed that ACE inhibitors (antihypertensive drugs) can facilitate the entry of SARS-CoV-2 into host cells [16]. However, more recent studies have shown that the use of ACE inhibitors for antihypertensive purposes in elderly patients, on the contrary, contributes to protection against COVID-19 and reduces the risk of their hospitalization by 40%. At the same time, in young patients, this protective effect was not found [17]. Having entered the body by airborne droplets, the virus multiplies in the epithelium of the upper and lower respiratory tract, causing damage to the epithelial and endothelial components of the air-blood barrier of the lungs [18]. After assembly of virions in the cells of the alveolar epithelium, SARS-CoV-2 passes into cytoplasmic vacuoles, followed by their migration to the cell membrane, where by exocytosis they enter the intercellular space and quickly spread through the tissue, or lead to the fusion of epitheliocytes and the formation of syncytium (receptacles for cells), which, according to a number of scientists, is the basis for the trigger development of the pathology of the respiratory tract [4]. SARS-CoV-2 causes an increase in the permeability of cell membranes and increased transport of fluid rich in albumin into the interstitial tissue of the lung and the lumen of the alveoli [7]. On the one hand, surfactant proteins and lipids are capable of inhibiting the synthesis of SARS-CoV-2, and on the other hand, the virus itself is capable of progressively damaging type 2 alveolocytes and, consequently, inhibiting the surfactant synthesis, the inactivation of which leads to a deterioration in lung tissue expansion. This contributes to the development of alveolar collapse and impaired gas exchange with the development of acute respiratory distress syndrome (ARDS), which additionally supports the development of hypoxemia with a decrease in oxygen content of less than 90-88%, vasoconstriction of blood vessels and hypoperfusion of the lungs [19]. It has been established that the inhibition of surfactant production occurs under the action of insulin, androgens, atropine, as well as damage to type 2 alveolocytes, chronic hypoxia, inhalation of tobacco smoke, pure oxygen, etc. In this case, the diffusion of gases is disturbed, atelectasis and pulmonary edema develop, and foam is formed. It has been established that thyroxine, catecholamines, estrogens, glucocorticoids enhance the production of surfactant. In addition, therefore, the use of glucocorticoids in patients with lung damage during coronavirus infection will enhance the production of surfactant with improved expansion of the lung tissue [19]. Direct damage by the SARS-CoV-2 virus to vascular and heart endothelial cells promotes the activation of macrophages through the CD13 and CD66a receptors with stimulation of apoptosis of epithelial cells. It has been established that in the period of convalescence, the affected areas of the lung tissue can be replaced by connective tissue (fibrotic changes), which suggested the initiation of apoptosis by the SARS-CoV-2 virus. Perhaps this is the reason for the deterioration in the condition of a number of patients soon after discharge from the hospital [20]. The introduction of SARS-CoV-2 into the vascular endothelial cell also occurs through platelets, which bind the virus with their HLA receptors and deliver it to macrophage cells to initiate

an immune response. In turn, platelets can be consumed by endothelial cells in a natural way, because they are their food product, and, consequently, there is a high probability of endothelial cells being "colonized" by the virus, bypassing the ACE1 and ACE2 receptors [3]. It is important to emphasize that damage to the vascular endothelium that regulates vascular tone and hemostasis occurs mainly in organs containing the so-called miraculous network (bone marrow, lungs, heart, kidneys, etc.), which contributes to the formation of lymphocytic endothelitis of the terminal vessels of vital organs. [3]. Damage to all layers of the walls of the blood vessels of the lungs with the development of systemic capillary-alveolitis is called panvasculitis, because of which the permeability of the alveolar-capillary membrane increases. This contributes to excessive perspiration of fluid and protein into the lung tissue, the release of the liquid part of the blood into the lumen of the alveoli themselves, massive destruction of the surfactant, and the development of pulmonary collapse [21]. This explains the registration of a rather high mortality rate in patients on mechanical ventilation (about 80%), in which there is insufficient humidification of the air mixture, damage to epithelial cells, pulmonary alveoli and capillaries, which enhances the inflammatory process [22]. Endothelial microvascular dysfunction with a tendency to vasoconstriction often leads to tissue edema, organ ischemia, and the development of a procoagulant state of the blood [3]. Violation of microcirculation in the capillaries of the lungs, the development of DIC with the formation of microthrombi is the main link in the development of severe forms of COVID-19, and its consequence is the development of functional lung failure with the development of acute respiratory failure (ARF) [23]. Hemostasiological disorders in COVID-19, referred to as covid-associated coagulopathy, are characterized by an extremely high incidence of thrombotic complications, which, despite pharmacoprophylaxis, are recorded in approximately 31-40% of patients in intensive care units, reaching a cumulative frequency of up to 48% [24,25]. Intraalveolar fibrin formation in COVID-19 is controlled by the urokinase-type plasminogen activator system uPA/uPAR. At the same time, the viral load directly correlates with the expression of pulmonary urokinase and the clinical course of COVID-19 [26]. It has been noted that pulmonary embolism in acute respiratory distress syndrome (ARDS) caused by COVID-19 occurs 3 times more often than in ARDS of other etiologies [27]. The frequency of detection at autopsy during pathoanatomical examination of thrombotic occlusion of small and medium-sized pulmonary vessels with subsequent infarction of the lung parenchyma ranges from 60 to 87% [28,29], and thrombosis of the veins of the lower extremities is recorded in 58% of cases [30]. The appearance of the "danger" signal and the recognition of pathogens that have entered the body, in this case the SARS-CoV-2 virus, contributes to the release of interferons and transmembrane and cytoplasmic proteins that have antigen-binding properties by resident cells. Upon activation of these proteins, tissue macrophages, stromal and mast cells begin to secrete inflammatory mediators such as pro-inflammatory cytokines/pyrogenic leukokines (tumor necrosis factor-alpha/TNF-α, interleukins/IL 1,6), prostaglandin, vasoactive amines, lipid mediators, histamine, etc. [31]. An avalanche-like increase in pro-inflammatory cytokines is referred to as a "cytokine

shock/storm", which can result in multiple organ failure [25]. It becomes obvious that COVID-19 is a systemic disease that affects not only the lungs, but also other organs. It can be assumed that the "cytokine storm" is a pathological variant of the immune response and, by analogy, is similar to some rheumatic diseases (macrophage activation syndrome or secondary hemophagocytic lymphohistiocytosis, when a systemic inflammatory response is activated, manifested by damage to many organs and systems [32]. Damaged epithelial cells also produce pro-inflammatory cytokines, which attract leukocytes, neutrophils, macrophages to the focus and activate neighboring endothelial cells, helping to stimulate infiltration [18,33,34,35]. At the same time, leukocytes induce the production of reactive oxygen species and nitric oxide, which also damage the alveolar-capillary barrier [18]. This explains the possibility of progression of COVID-19 to subtotal or total pneumonia, ARDS, respiratory failure and death in some patients by the end of the first week of the disease [33,34]. It has been established that the severity of the development of ARF directly depends on the severity of the increase in pro-inflammatory cytokines, namely IL-1,-6,-7,-8,-10, TNF-α, C-reactive protein [22,23]. Weber V.R. et al., 2018 argues that immunity and hemostasis are a single whole, and cytokines, such as TNF-α and IL-6, are the link between the cellular and humoral components, vascular-platelet hemostasis, and the blood coagulation process [36]. Damage caused by the virus "opens the way" for bacterial and fungal flora, which can result in viral-bacterial pneumonia [20]. Not only the SARS-CoV-2 virus itself, but also the associated bacterial infection, in addition to diffuse damage to alveocytes, causes an increase in the permeability of cell membranes and increased transport of fluid rich in albumin and fibrin into the interstitial tissue of the lung and the lumen of the alveoli, followed by the development of interstitial and alveolar edema. Along with this, there is a change in the properties of the surfactant, in particular elastic ones: it breaks down faster during cyclic stretching in the act of breathing and affects the surface tension forces inside the alveoli to a lesser extent [35]. Currently, the study of the dependence of the severity of the course and prognosis of COVID-19 on the genetic characteristics of the body, which determine the formation of a pronounced mediator response to SARS-CoV-2 and thrombosis, is ongoing. In many countries, the prevalence of men among the sick and dead is described. It was revealed that double X chromosomes in women are to some extent a kind of protection against SARS-CoV-2. It has been established that the genes of one of the receptors responsible for the entry of the virus into the cell (ACE2, but not TMPRSS2) are located just on the "female" chromosome [37]. In addition, it is on the X chromosomes that the genes responsible for the implementation of cellular and humoral immunity, as well as the development of inflammation, are located [9]. Scientists suggest that the relative protection against COVID-19 of people with O(I) blood type is associated with the absence of an increase in their Willebrand factor (VWF), which is directly involved in platelet adhesion [26]. To date, a relationship has been established between the severe course of COVID-19 and the development of ARF and the polymorphism of the glycosyltransferase gene associated with the blood groups of the ABO system [26], the genes of the angiotensin-converting pathway [38], and the leukocyte

formylpeptide receptor 1 (FPR1) [39]. A genetic hypothesis of the dependence of high thrombotic potential in COVID-19 on a homozygous mutation in the FII gene (plasma hemostasis), polymorphism in Gp1a and F13A1 (plasma and platelet hemostasis), and the absence of protective polymorphism in FVII (plasma hemostasis) has also been published [24]. Data from the Military Medical University in Xian (China) showed that SARS-CoV-2 is able to penetrate into the erythrocyte through CD147 receptors located on their membrane, destroying hemoglobin in the erythrocyte, releasing iron from it, which is involved in the formation of reactive oxygen species and is an inducer of oxidative stress [5,22].

Destroyed hemoglobin loses its ability to bind oxygen, which leads to transport (hemic) hypoxia in all tissues and organs. In turn, the iron released into the blood is so toxic that it causes oxidative damage. For this reason, not only oxygen starvation occurs, but also the processes of oxidative stress are triggered. In turn, not only activation of the inflammatory response, but also hypoxemia observed in patients with severe pneumonia and ARDS can potentiate the development of multiple organ failure, disseminated intravascular coagulation syndrome, and in some cases lead to death [35]. The conducted study suggested that viral pneumonia could actually be a chemical pneumonitis resulting from the deposition in the alveoli of oxidized iron that entered the blood from destroyed erythrocytes. If this hypothesis is correct, then the action of chloroquine (an antimalarial drug) becomes clear, which in patients with COVID-19 prevents the release of iron, as well as the penetration of the virus into the cell by inhibiting the binding of viral proteins to porphyrin in erythrocytes [40].

Thus, the main mechanism for the development of hypoxia in COVID-19, leading to oxygen starvation of the organs and tissues of the whole organism, is not only a violation of respiratory functions (the bronchoalveolar epithelium does not retain oxygen, the lungs lose the ability to transfer oxygen from air to blood, etc.), but and a decrease in the level of hemoglobin with an increase in the level of heme (loss of the ability of hemoglobin in red blood cells to carry oxygen to the organs and tissues of the body). Therefore, elderly patients, persons with diseases of the cardiovascular system (atherosclerosis, coronary heart disease, etc.), patients with concomitant diseases accompanied by hypoxia and oxidative stress are the most vulnerable to SARS-CoV-2 and are at risk of a severe course of the disease.

CONCLUSIONS

So, according to WHO statistics, mortality from COVID-19 is distributed as follows: from 0.2% for people under 39 years old to 17.8% for people over 80 years old. At the same time, the overall mortality of patients with confirmed cases of the disease was 1.44% (95% confidence interval 1.10-1.86), and the adjusted mortality of all patients was 3.06% (95% confidence interval 2.02-4 .59) [22].

1. The detection of SARS-CoV-2 RNA in patients with COVID-19 not only in bioassays from the respiratory tract and blood, but also in urine, feces, cardiomyocytes, and vessels explains the possibility of damage to various target organs and contributes to the deterioration of the patient's condition with concomitant somatic pathologies.

2. Damage by the SARS-CoV-2 virus to the epithelial and endothelial components of the air-blood barrier of the lungs, followed by its release into the intercellular space and spread into tissues or the formation of syncytium, contributes to the trigger development of respiratory pathology.

3. Activation of macrophages by the affected endothelial cells of the vessels and the heart stimulates apoptosis of epithelial cells, which explains the replacement of the affected areas of the lung tissue with connective tissue.

4. There is a relationship between the severity of COVID-19 and the tendency to thrombosis with the genetic characteristics of the organism in the formation of a pronounced mediator response to SARS-CoV-2 infection.

5. SARS-CoV-2 is able to penetrate into erythrocytes, destroy hemoglobin, inducing oxidative stress and cause chemical pneumonitis because of deposition of oxidized iron in the alveoli.

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