Инфекция и иммунитет
2021, Т. 11, № 6, с. 1020–1036

Russian Journal of Infection and Immunity = Infektsiya i immunitet
2021, vol. 11, no. 6, pp. 1020–1036

GENDER-RELATED RESPONSE OF BODY SYSTEMS IN COVID-19 AFFECTS OUTCOME

M. Khaksari[a], N. Sabet[a], Z. Soltani[a], H. Bashiri[a,b]

[a] *Kerman University of Medical Sciences, Kerman, Iran*
[b] *Sirjan University of Medical Sciences, Sirjan, Iran*

Abstract. Severe acute respiratory syndrome (SARS)-like coronavirus (SARS-CoV-2) is the seventh member of the coronaviruses (CoVs) family that infects humans and causes coronavirus disease 2019 (COVID-19), which is currently a global pandemic. Widespread secretion of cytokines has been shown to occur early in severe cases of the disease and can be an effective factor in the rapid progression of the disease. Systemic inflammation indicates an advanced stage of acute disease, which is characterized by multiple organ failure and elevated key inflammatory markers. Studies have shown a gender difference between the incidence and mortality of COVID-19. In this review, we investigated the gender difference in the systemic effects of COVID-19 and found that this gender difference exists especially in the respiratory, cardiovascular, liver, gastrointestinal and kidney systems. Due to the worse outcome of COVID in males, the role of female sex hormones in causing these gender differences is noticeable. There can be a systemic and local effect of female sex hormones, especially estrogen and possibly progesterone, on various cells. Among the effects of these hormones is the regulation of localized angiotensin-converting enzyme 2 (ACE2) levels. ACE2 is the route of entry for SARS-CoV-2 virus into the cell. It is hoped that this review would address gender differences for better management of COVID-19 treatment.

Key words: *COVID-19, gender difference, inflammation, angiotensin-converting enzyme 2, estrogen, progesterone.*

ПОЛ ПАЦИЕНТА ВЛИЯЕТ НА ОТВЕТ СИСТЕМ ОРГАНИЗМА И КЛИНИЧЕСКИЙ ИСХОД ПРИ COVID-19

Хаксари М.[1], Сабет Н.[1], Солтани З.[1], Башири Х.[1,2]

[1] *Керманский университет медицинских наук, г. Керман, Иран*
[2] *Сирджанский университет медицинских наук, г. Сирджан, Иран*

Резюме. Коронавирус тяжелого острого респираторного синдрома (SARS-CoV-2) является седьмым представителем семейства коронавирусов (CoV), патогенным для человека, и возбудителем коронавирусного инфекционного заболевания (COVID-19), достигшего к настоящему времени масштаба глобальной пандемии. Было показано, что на ранней стадии тяжелых случаев заболевания секретируется значительный объем цитокинов. Это может стать важным фактором быстрого прогрессирования заболевания. Системное воспаление указывает на запущенную стадию острого заболевания, которая характеризуется полиорганной недостаточностью и повышенным уровнем ключевых воспалительных маркеров. Ранее проведенные исследования продемонстрировали гендерные различия в уровне заболеваемости и смертности от COVID-19. В данном обзоре мы исследовали гендерные различия в системных эффектах COVID-19 и обнаружили, что подобные различия наиболее выражены в дыхательной, сердечно-сосудистой системах, желудочно-кишечном тракте, печени и почках. На основании регистрации худшего исхода COVID-19 у мужчин высказано предположение о возможном влиянии женских половых гормонов на течение болезни. Женские половые гормоны, особенно эстроген и, возможно, прогестерон, могут оказывать системное и местное действие на различные типы клеток, а также регулировать локальные уровни ангиотензинпревращающего фермента 2 (ACE2). Установлено, что вирус SARS-CoV-2 проникает в клетку через ACE2. Мы полагаем, что рассмотренные в настоящем обзоре гендерные различия позволят улучшить ведение пациентов с COVID-19.

Ключевые слова: *COVID-19, гендерные различия, воспаление, ангиотензинпревращающий фермент 2, эстроген, прогестерон.*

Адрес для переписки:
Захра Солтани
Иран, г. Керман, Керманский университет медицинских наук.
Тел./факс: +98 3433257581.
E-mail: z.soltani@kmu.ac.ir, soltaniy@yahoo.com

Contacts:
Zahra Soltani
Iran, Kerman, Kerman University of Medical Sciences.
Phone/fax: +98 3433257581.
E-mail: z.soltani@kmu.ac.ir, soltaniy@yahoo.com

Для цитирования:
Хаксари М., Сабет Н., Солтани З., Башири Х. Пол пациента влияет на ответ систем организма и клинический исход при COVID-19 // Инфекция и иммунитет. 2021. Т. 11, № 6. С. 1020–1036.
doi: 10.15789/2220-7619-GRR-1664

Citation:
Khaksari M., Sabet N., Soltani Z., Bashiri H. Gender-related response of body systems in COVID-19 affects outcome // Russian Journal of Infection and Immunity = Infektsiya i immunitet, 2021, vol. 11, no. 6, pp. 1020–1036.
doi: 10.15789/2220-7619-GRR-1664

DOI: http://dx.doi.org/10.15789/2220-7619-GRR-1664

Gender-related response of body systems in COVID-19 affects outcome

Coronavirus disease 2019 (COVID-19) is currently a global pandemic that has affected approximately 212 countries worldwide and has so far claimed the lives of more than 931 321 people in the world. Currently there are approximately 29 444 198 confirmed cases of COVID-19 in the world [28, 152]. The COVID-19 first originated in Wuhan, China in December 2019, and scientists around the world are working to understand this virus and its properties in order to design interventional strategies to combat the disease. COVID-19 is caused by a virus called severe acute respiratory syndrome (SARS)-like coronavirus (SARS-CoV-2), which is a single-stranded RNA (ssRNA) virus with genome size of 29 903 bp. The SARS-CoV-2 belongs to the same beta-coronavirus that were previously reported as SARS-CoV and middle east respiratory syndromecoronavirus (MERS-CoV). They are not only sequentially similar, but the point of entry to human for both is through the same receptor [3, 55]. SARS-CoV-2 is the seventh member of the coronaviruses (CoVs) family that infects humans and causes COVID-19 [153].

Human CoVs (HCoVs) have neuronal invasive capacities and may act through two main mechanisms [12, 30, 31]: virus replication within glial or neuronal cells of the brain, or an autoimmune reaction with the host's inadequate immune response [79]. In relation to COVID-19, data on central nervous system (CNS) involvement are unusual but growing, which indicate a high frequency of neurological symptoms [99, 112, 115]. Coronaviruses can cause nerve damage through direct infection pathways (circulatory and nerve pathways), hypoxia, immune damage, angiotensin-converting enzyme (ACE2) activity, and other mechanisms. In addition, they can enter the nervous system directly through the olfactory nerve, bloodstream or nerve pathways, resulting in neurological disorders. Also, coronaviruses have destructive effects on the lung tissue and cause a series of lung lesions such as hypoxia [154].

Extensive secretion of cytokines has been shown to occur prematurely in severe cases of COVID-19, and this can be a factor in the rapid progression of the disease. Multiple organ failure (Fig. 1) observed in many patients is caused by the storm of inflammatory cytokines, including interleukin (IL)-1β, IL-2, IL-7, IL-6, IL-8, IL-10, IL-17, and gamma interferon (IFNγ), which is possibly associated with diffuse macrophage activity [154]. Excessive systemic inflammation or induced cytokine cascade may be associated with lymphocytopenia, and is one of the characteristics of severe inflammatory disease [90]. Systemic inflammation indicates an advanced stage of acute disease which is characterized by multiple organ failure and elevated key inflammatory markers [125]. Based on clinical data, these inflammatory markers include IL-6, IL-2, IL-7, tumor necrosis factor-α (TNFα), IFNγ inducible protein (IP)-10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP) 1-α, granulocyte-colony stimulating factor (G-CSF), C-reactive protein (CRP), procalcitonin and ferritin [62, 90, 119, 125, 148]. Following a viral infection, these cytokines activate the pathways that lead to the differentiation of immune cells, the migration of leukocytes to the sites of infection, and the proliferation of hematopoietic stem cells [139].

Responses to viruses as well as compatible immune responses during viral infections differ between men and women [147]. Women have been shown to have higher inflammatory, antiviral, and humoral immune responses than men during viral infections [147], which help the better clearance of viruses, including SARS-CoV [18]. Enhanced immunity in women can lead to more immunopathology and tissue damage in the late stages of viral disease [145]. This review article intends to address the effects of COVID-19 on different systems of the body, the issue of gender differences in the outcomes of COVID-19, and separation of different body systems if we can find any research on that (Fig. 2). With this review, the research gap in this area will be identified and maybe better treatment management will be provided when the effects of gender difference are taken into consideration.

COVID-19 and gender differences

A published study of 168 patients with severe COVID-19 in Wuhan, China, reported that men were hospitalized and died more than women, and few of them were discharged during the study period [91]. A difference between men and women at the ages of 60 and older is evident. In this study, the ratio of neutrophils to lymphocytes and serum C-reactive protein concentration were twice as high in men with COVID-19 then in women with the same disease. These data suggest that inflammatory immune responses and cell counts may be higher in men, and also can be associated with worse COVID-19 outcomes in men than in women [91].

Studies conducted on mice have shown that, the males are more susceptible to coronavirus infection than females [27, 66, 131]. Another study reported that male patients with COVID-19 were 65% more likely to die than women with the same disease. The World Health Organization states that a smaller percentage of women infected with the virus die from it in comparison with the men [85]. Another study also reported that female patients were less in need of intensive care compared to male patients [44].

The potential factors influencing these gender differences need to be identified. Numerous factors, such as immune system, sex hormones, physiological factors, lifestyle and socio-cultural behaviors are likely to be responsible for these differences [9, 10, 14, 16, 27, 52].

Women's immune cells are more active than men, which is associated with the stimulation of Toll-like receptor 7 (TLR-7) and production of interferon [26]. In addition, after infection with viral agents, women produce lower levels of IL-6 than men, which are associated with longer life expectancy [26, 111]. In the face of viral infections, women's immune system functions differently from men's; this triggers a stronger immune response that leads to viral clearance. In general, antibody production in women is higher and lasts for longer than in men. Differences in women's immune responses may be related to sex hormones and factors related to X chromosome [59, 72]. Female sex steroids [121, 128] regulates inflammatory responses as well as immune system-regulating genes located on the X chromosome [80, 114, 132], so it can be assumed that cytokine cascades, which are associated with impaired regulation of immune system, occur less frequently in women than in men [80, 97].

Sex steroids are potential modulators of the immune system, and different concentrations of estrogens, progesterone, and androgens between men and women, in addition to genetics, are likely to affect immune responses to COVID-19 and inflammatory outcomes. This is especially important because acute illnesses, such as COVID-19, may alter the function of gonadal-hypothalamic-pituitary axis and reduce the endogenous production of estrogens and progesterone [88].

Among factors that cause gender differences in the outcome of COVID-19, the role of sex hormones that affect immune responses should not be ignored. Some studies suggest that estrogen therapy plays an important role in the creation of protective immune response against COVID-19 [134]. It has been reported that female sex hormones, especially estrogen, can lead to better outcomes and greater resistance to COVID-19 in women. This resistance is due to the systemic and local effect of female hormones on different cells. In particular, estrogens stimulate the immune system by modulating the function of B cells and improving the activity of T-helper 2 cells (Th2) [137]. Estrogen boosts immune respons-

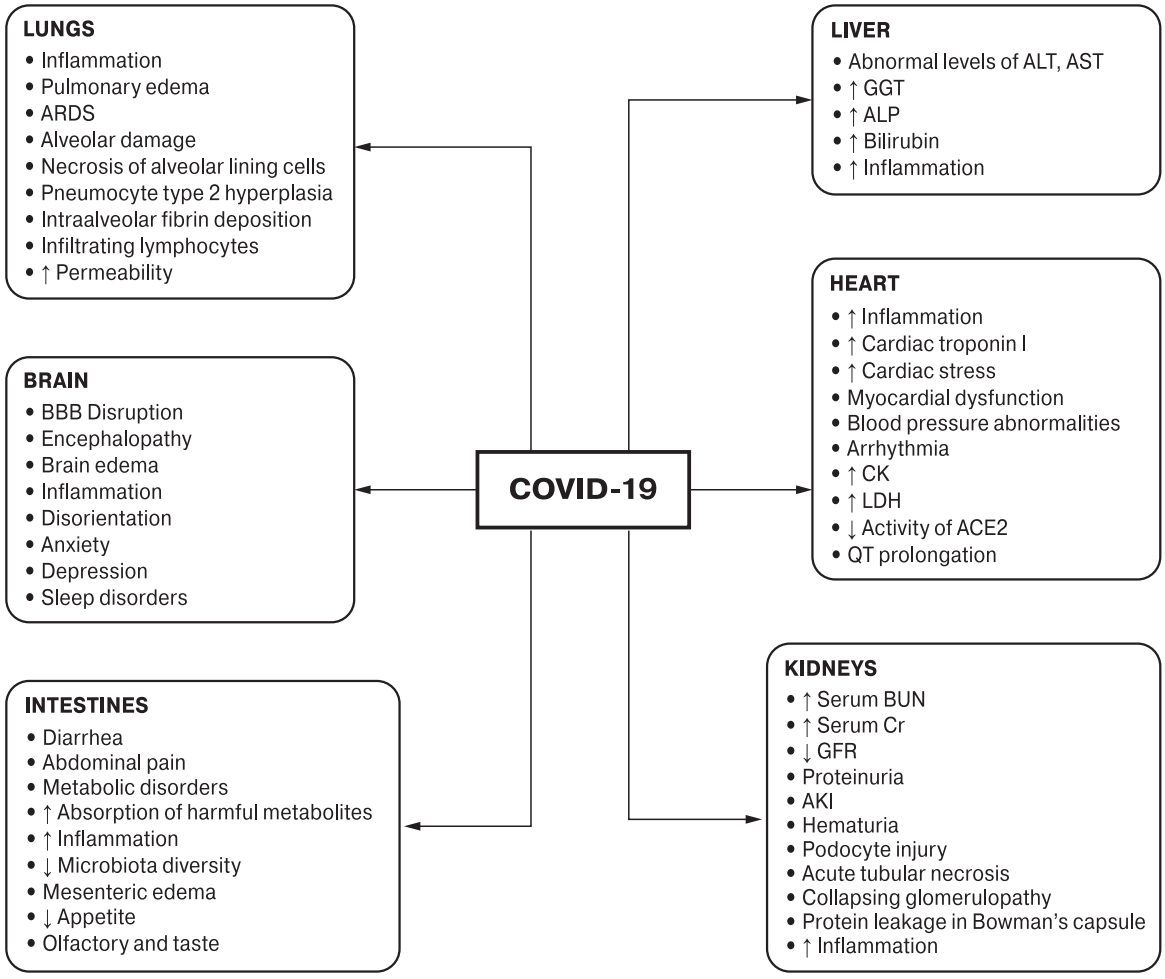

Figure 1. Systemic effects of COVID-19

Note. ↑ — increase; ↓ — decrease; ACE2 — angiotensin-converting enzyme 2; AKI — acute kidney injury; ALP — alkaline phosphatase; ALT — alanine transaminase; ARDS — acute respiratory distress syndrome; AST — aspartate transaminase; BBB — blood-brain barrier; BUN — blood urea nitrogen; CK — creatine kinase; COVID-19 — coronavirus disease; Cr — creatinine; GFR — glomerular filtration rate; GGT — gamma-glutamyltransferase; LDH — lactate dehydrogenase.

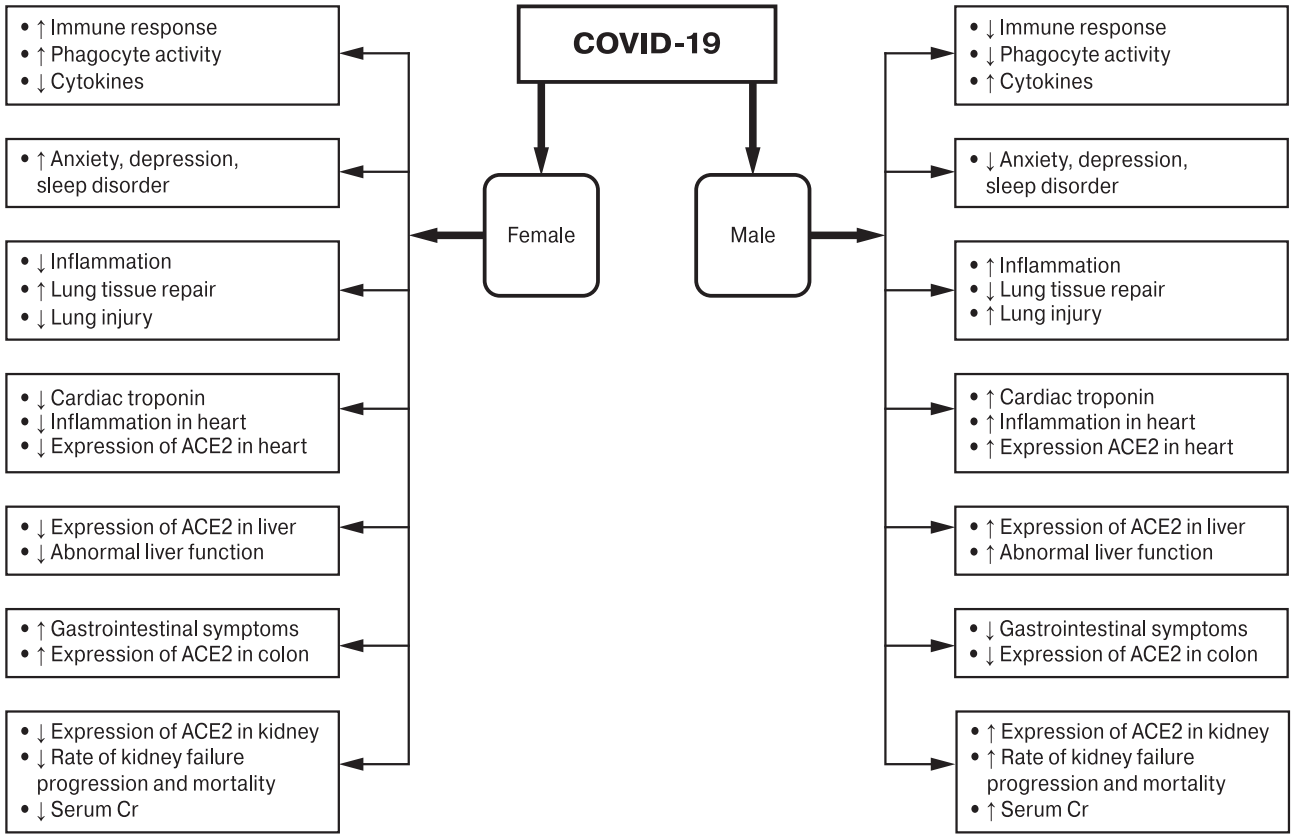

Figure 2. Gender difference in the effects of COVID-19 on body different systems

Note. ↑ — increase; ↓ — decrease; ACE2 — angiotensin-converting enzyme 2; COVID-19 — coronavirus disease; Cr — creatinine.

es, causing virus clearance to occur more quickly and vaccines to be more effective [4, 66]. In most human or rodent experimental models, the anti-inflammatory effects of estradiol (E2) on innate immunity include suppression of the production of inflammatory cytokines (such as IL-6, IL-1β and TNFα) by monocytes and macrophages (TNFα is a major factor in cytokine cascade of COVID-19), strong inhibition of chemokine (C-C motif) ligand 2 (CCL2), and prevention of innate immune cell migration to inflamed areas, especially neutrophils and monocytes [88]. E2 produces helper T cells ($CD4^+$) and anti-inflammatory cytokines, such as IL-4, IL-10, and IFNγ [2].

Estrogen receptors (ERs) are expressed in all immune cells, and act as transcriptional regulators of cellular function. In human peripheral blood mononuclear cells (PBMCs), $CD4^+$ T lymphocytes express higher levels of ERα-related mRNA than ERβ, while B cells show higher levels of ERβ-related mRNA than ERα [107]. Peripheral blood $CD8^+$ T cells and monocytes express low levels of both receptors [107]. In female mice with COVID-19, the highest sex-specific protection was observed during their reproductive period with strong ER signaling. Therefore, in adult women, stronger ER signaling may play an important role in health protection against COVID-19 infection compared to men [18].

Progesterone (P4) is another important hormone that modulates the immune and anti-inflammatory system, which is produced at high levels by the placenta during pregnancy. Progesterone receptors (PRs) are expressed in most immune cells, including epithelial cells, macrophages, lymphocytes, mast cells, and eosinophils [72]. P4 inhibits the production of pro-inflammatory cytokines of IL-1β and IL-12 by human and rodents' macrophages and dendritic cells [72, 108, 135]. Also, P4 treatment fastens recovery by increasing Transforming growth factor (TGF-β), IL-6, IL-22, and number of Th17 cells [54].

Plasma testosterone levels decreases with age, and studies in older men with COVID-19 [7] show that low testosterone level is associated with high inflammatory conditions [83]. In addition, testosterone therapy has been shown to reduce IL-6, IL-1β and TNFα [96]. However, unlike estrogen, testosterone has been shown to play an inhibitory role in the body's immune processes, which is a further possible explanation for men's susceptibility to infections [4]. High and low testosterone concentrations appear to increase the risk of infection and possible complications of COVID-19 [129].

Due to the age-related decrease in sex hormones in the elderly, these hormones can be suggested as a treatment option and may help reduce inflammation in elderly patients with COVID-19 [69, 105].

COVID-19 and the nervous system

Outcomes of severe COVID-19 in patients include destruction of blood-brain barrier (BBB) and secondary intracranial infection, which may cause headache, vomiting, loss of vision, and seizures [109]. Viral encephalitis, infectious toxic encephalopathy, and acute cerebrovascular disease are some of the neurological diseases associated with COVID-19 [154].

Encephalitis is known as one of the symptoms of COVID-19. Encephalitis refers to inflammatory lesions in the brain parenchyma, including neuronal damage and nerve tissue damage caused by pathogens. This disease is characterized by an acute onset and its common symptoms include headache, fever, vomiting, seizure, and disturbances of consciousness [36]. Early detection of viral encephalitis is very important [156].

Infectious toxic encephalopathy, also known as acute toxic encephalopathy, refers to a syndrome of reversible brain dysfunction caused by factors such as systemic toxemia, metabolic disorders, and hypoxia during the acute infection process [95, 138, 161]. Major pathological changes in this disease include cerebral edema for which there is no evidence of inflammation in cerebrospinal fluid analysis. Patients with a mild course of the disease may experience headache, delirium, mental disorders, and anxiety. Patients with high severity of the disease may experience loss of consciousness, disorientation, coma, and paralysis [33, 95]. Acute viral infection is one of the major causes of this disease, which is exemplified by CoV-induced respiratory infection. Patients with COVID-19 often have severe hypoxia and viremia [50], which can lead to toxic encephalopathy. In addition, approximately 40% of patients with COVID-19 develop headache, loss of consciousness, and other symptoms of brain dysfunction [87]. One study reported that edema was diagnosed in the brain tissue of patients with COVID-19. In general, these findings provide evidence that COVID-19 can cause infectious toxic encephalopathy [159].

In the case of acute cerebrovascular disease, there is considerable evidence that respiratory-related infection is an independent risk factor for it [35, 150]. Data from laboratory models show that the influenza (flu) virus can exacerbate ischemic brain damage by stimulating a cytokine cascade, and increase the risk of cerebral hemorrhage following a treatment with tissue-type plasminogen activator [101]. The CoV infection, particularly SARS-CoV-2, has been widely reported to cause a cascade of cytokines, which may be one of the factors, by which CoV causes acute brain disease [20, 90].

In fact, although severe respiratory complication is the most common symptom in patients with COVID-19 that leads to hospitalization in intensive care units, some patients have also shown neurological symptoms, which are classified in three categories; symptoms of CNS disease (headache, dizziness, impaired consciousness, ataxia, acute cardiovascular disease and epilepsy), symptoms of peripheral nervous system (PNS) (hypogeusia, hyposmia, neuralgia) and symptoms of musculoskeletal [78, 87].

According to reports, hACE2 (human angiotensin-converting enzyme-2 receptor), like other organs in the brain, is expressed primarily in the brainstem and in areas involved in cardiovascular function and blood pressure regulation [45, 155]. It is also considered the entry point of SARS-CoV-2 viruse in human, which is why the brain is not immune to viral infection. It has been reported that ACE2 levels are different in men and women, and women have lower levels of ACE2 than men [85].

Although SARS-CoV-2 has not yet been detected in cerebrospinal fluid, SARS-CoV has been identified in cerebrospinal fluid of patients with similar structural and functional characteristics, indicating the virus's ability to cause extremely severe BBB damage [78]. If previous studies with other CoVs are considered, SARS-CoV-2, like other members of its family, first infects peripheral nerve terminals and then slowly travels to CNS through the synaptic pathway [140]. Reported involuntary respiration, hyposmia, and ageusia in patients with COVID-19 have speculated that SARS-CoV-2 not only infects the lungs but also significantly affects neurons, especially in the medulla oblongata, which regulates pulmonary and cardiac function, and any damage to it can lead to chronic respiratory distress, which has been reported in COVID-10 patients [78]. Recently, more serious complications including acute hemorrhagic necrotizing encephalopathy (ANE) have been reported in studies [112]. ANE is a rare complication of viral infections such as flu, and is associated with a significant increase in intracranial cytokines, leading to the failure of BBB [118].

One study found that more than a quarter of people with COVID-19 suffered from mental illness, anxiety and depression, and about a third had sleep disorders. In addition, the prevalence of anxiety and depression in COVID-19 pandemic was higher than the 2003 acute respiratory syndrome (SARS) epidemic. Endocrine system function often plays a role in the biological explanation of gender differences in psychological outcomes, so that the prevalence of anxiety, depression and sleep disorders in women with COVID-19 is much higher than men. Decreased estrogen may increase the risk of anxiety in women [92]. Effective treatment for anxiety in women should eliminate mental illness and also should include comprehensive interventions such as hormone regulation Approximately 30.6% of patients showed sleep problems [42]. Regarding the effect of COVID-19 on the nervous system, not much study was found to examine the effect of sex differences in this regard.

COVID-19 and the respiratory system

There is a crosstalk between the brain and lungs during COVID-19 infection. SARS-CoV-2 uses ACE2 as a receptor for viral cell entry, and induces lung damage by increasing cytokines in the immune system, which can reduce the expression of central ACE2 protein. Inhibition of ACE2 activity reduces the sensitivity of baroreceptor reflex that controls heart rate and also increases sympathetic tone, which ultimately leads to increased blood pressure and impaired heart function. In addition, in the case of neuroprotective property of ACE2, its inhibition may upset the neurotoxicity/neuroprotection balance within the brain. Elevated inflammatory cytokines during lung injury, hypoxemia, and increased sympathetic tone through inhibition of central ACE2 lead to overactive CNS, which may play a critical role in the etiopathogenesis of neurogenic pulmonary edema and possibly COVID-19 pulmonary complications in patients [57]. It has been reported that 3% to 20% of patients with COVID-19 are associated with acute respiratory distress syndrome (ARDS) [21, 48, 148]. Recent studies have shown that renin angiotensin system (RAS) activation plays an important role in acute lung injury [164]. Animals with ARDS have reduced ACE2 activity, and a lack of ACE2 can lead to excessive neutrophil accumulation, increased vascular permeability, exacerbated pulmonary edema and eventually ARDS. Exogenous ACE2 exogenous supplement can reduce the inflammatory response and increase oxygen delivery in various ARDS animal models [164].

Progressive respiratory failure is the leading cause of death in COVID-19 disease. One study showed that all lung samples from the COVID-19 group had diffuse alveolar damage with alveolar epithelial cell necrosis, pneumocyte type-2 hyperplasia, intra-alveolar fibrin deposition, and infiltration of perivascular lymphocytes. But in some people, the changes were local and they only had mild interstitial edema [86].

The lungs of patients with COVID-19 have three characteristics. First, severe endothelial damage associated with the intracellular SARS-CoV-2 virus, and destruction of endothelial cell membranes. Second, the lungs of patients with COVID-19 have extensive vascular thrombosis with microangiopathy and alveolar capillary occlusion [84, 89]. Third, the lungs of patients with COVID-19 show significant vascular growth through the intussusceptive mechanism of angiogenesis [86]. Tissue hypoxia is also observed in these patients and a large number of ACE2 positive cells are observed in the lungs of these patients [144].

Impaired intercellular connections, cell swelling, and loss of contact with the basal pulmonary membrane are shown in COVID-19 patients [144]. Another study showed that in the lungs of patients with COVID-19, there was obvious destruction of pulmonary parenchyma, including interstitial inflammation and extensive consolidation [38]. In a study of several different patients with COVID-19, a significant increase was found in pulmonary edema in the lungs with a slight increase in consistency of the lower lobe of the lung. No local changes were observed on the incised surfaces of the lung. Histologically, in addition to detected pulmonary edema, capillary florid endotheliitis was shown in lower lobs with increased neutrophils and formation of microthrombus in alveolar capillaries and small pulmonary vessels including septal veins, and also cytokines such as IL-1β and IL-6 were increased in the lung tissue [13].

The cytokine cascade is the cause of lung tissue damage and the immunopathogenesis of COVID-19 infection. It has been shown that, the level of IL-6 (one of the important components of cytokine cascade and the driving force behind cytokine cascade) is higher in men than women [151]. High levels of IL-6 in men may be associated with worse outcomes than in women, which may indicate a higher risk of cytokine cascade in male patients. It has also been shown that antibody levels are higher in women with COVID-19 than in men [132].

COVID-19 has been shown to be transmitted through the upper respiratory tract, mucosal contact and eye conjunctiva, and droplets in the air or on surfaces contaminated by coughing or sneezing [137]. Estrogen has a beneficial effect on the upper and lower airways [137]. First, women's noses respond to changes in estrogen levels by improving the local immune response. This hormone stimulates the nasal mucosa and hypertrophy of the nasal turbines, and increases the production of nasal mucosa, which contains mucin, electrolytes, immunoglobulin A (IgA), IgG, lysozyme, lactoferrin and oligosaccharides. These substances have antiviral and antibacterial properties that are essential against upper respiratory tract infections [51, 141]. In addition, estrogen stimulates the production of hyaluronic acid, which maintains a warm and moist environment in the nasal mucosa and cilia [51, 141]. Finally, estrogen acts directly on the nasal immune system by increasing the activity of phagocytes, dendritic cells, and natural killers [51]. Estrogen is also involved in the oral mucosa making it well hydrated by stimulating the production of hyaluronic acid, and also improves the function of lower respiratory tract by acting directly on bronchial epithelial cells, which increase the production of mucus rich in antiviral substances [136]. Estrogens, especially E2, can protect premenopausal women from the most serious side effects of COVID-19, given the higher levels of serum estrogen [46].

The positive effect of estrogen is supported by the action of progesterone, which regulates epidermal growth factor of amphiregulin by inducing lung structure repair in the event of a viral infection. Progesterone administration during menopause in women improves the outcome of lung disease [54, 136]. In a study in mice, progesterone treatment reduced the inflammatory environment of the lungs,

improved pulmonary function, and promoted cell proliferation and pulmonary repair, resulting in earlier recovery without affecting viral load [54].

COVID-19 and the cardiovascular system

Heart damage seems to be one of the prominent features of COVID-19 disease, which occurs in 20 to 30% of hospitalized patients and contributes to 40% of deaths [62, 119, 124]. Although the clinical manifestations of COVID-19 are related to the respiratory system, some patients have severe cardiovascular damage. In addition, some patients with cardiovascular disease (CVDs) may have an increased risk of death [62]. Patients with COVID-19 who do not have cardiovascular disease have better outcomes than patients with cardiovascular disease and hypertension [168].

In patients with COVID-19, studies have shown that 51% of patients with heart disease died, while only 4.5% of patients without heart disease died from COVID-19 [62]. The mortality rate in COVID-19 patients without Cardiovascular disease (CVD) with a normal cardiac troponin (cTn) level was 7.6%. In patients with CVD and a normal cTn level, it was 13.3%. In patients without CVD and a high cTn level, it was 37.5%. In patients with CVD and a high cTn level, it was 69.4% [62]. Huang et al., reported that 12% of patients with COVID-19 were diagnosed with acute myocardial injury, which was mainly manifested by an increase in troponin I [5], and had blood pressure disorders [62, 119]. In another study, it was shown that among 138 patients with COVID-19, 17.6% had arrhythmia and 7.2% had acute heart damage [148]. There is a significant relationship between plasma troponin T levels of patients with COVID-19 and their plasma C-reactive protein and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels [62]. Like SARS, patients with COVID-19 also showed potential heart damage. Chen et al. reported that out of 99 confirmed COVID-19 patients admitted to Wuhan Jinyintan Hospital, 13 (13%) showed elevated creatine kinase and 75 (76%) showed elevated lactate dehydrogenase [21].

As seen in the reports, abnormal electrocardiogram (ECG) changes have also been recorded in critical situations [58]. One study found that a high percentage of patients had prolonged QT and rare arrhythmias [63]. There are several possible mechanisms for that. First, ACE2 was first identified as a functional receptor for coronavirus that is highly expressed in the heart and lungs [143]. Therefore, ACE2-related signaling pathways may play a role in heart damage. Second, COVID-19-induced hypoxemia may damage myocardial cells. Third, systemic inflammatory responses and immune system disorders may be important factors in that [99]. However, it is also possible that the disorder may be due to decreased ACE2 activity in the heart, just like SARS [49]. Oudit et al. observed the presence of SARS-CoV and reduced expression of ACE2 in the hearts of SARS-CoV-infected mice. They also reported that SARS-CoV was isolated from 7 autopsied human hearts among 20 patients, and the myocardial damage was associated with decreased expression of myocardial ACE2 protein [104].

In general, ACE1 converts angiotensin 1 to 2, and angiotensin 2 induces vasoconstriction, inflammation, fibrosis, and proliferation through its receptor, which ultimately increases blood pressure, cardiac fibrosis, thrombosis, and ARDS [49, 120]. On the other hand, angiotensin 2 is converted to angiotensin 1–7 by ACE2, which is a peptide without biological functions and has vasodilatory, anti-fibrotic, anti-apoptotic and anti-proliferative effects, and finally reduces blood pressure, heart fibrosis, thrombosis and ARDS [73]. COVID-19 inhibits this conversion and these effects in the heart [49].

A higher percentage of men (65.4%) had higher cardiac troponin (cTn) than women (42.2%) with COVID-19 [62]. Estrogen levels are inversely related to the expression of cTn, which is released from cardiomyocytes exposed to ischemia or hypoxia [94]. The action of estrogen may explain these findings, as estrogen has been shown to decrease the concentration of low-density lipoprotein (LDL) and increase the concentration of high-density lipoprotein (HDL) [93]. The 17β-Estradiol specifically mediates the activity of nitric oxide synthase (NOS) through interaction with estrogen receptors. Functional estrogen receptors are also present in cardiomyocytes, which regulate NOS expression to protect against cardiovascular damage by inhibiting platelet activity, thrombus formation, and leukocyte-endothelial cell adhesion [74].

There is growing evidence that sex and sex hormones affect many circulatory and tissue-based components of RAS such as ACE2 [41, 81]. The 17β-Estradiol regulates the expression of ACE2 in the heart, kidneys and uterus [65, 68]. For example, 17β-estradiol increases local ACE2 activity in the heart and weakens the RAS system by isolating a residue angiotensin II to enhance angiotensin 1–7 production, which protects the heart, and has anti-inflammatory and anti-oxidative effects [15, 40, 123]. Reducing the regulation of angiotensin II receptor type 1 (AT1R) by estrogens and regulating renin activity by estrogens have been shown [113, 122]. Recently, estrogen has been shown to modulate localized RAS in the atrial myocardium by down-regulating ACE1 and simultaneously regulating ACE2, AT2R, and MAS expression levels [15]. The ACE2/Ang1-7/Mas receptor axis appears to be more closely related to each other in women than in men [19].

COVID-19 infection causes harmful hypercoagulability by exacerbating patients' endothelial dysfunction [6]. Activation of endothelial estrogen receptors has been shown to increase nitric oxide

(NO) and decrease Reactive oxygen species (ROS), and also protects the vascular system against angiotensin 2-mediated vasoconstriction, inflammation, and ROS production [77, 98, 130]. Higher mortality in men seems to be partly related to the prevalence of underlying diseases. One of the most common complications of high-intensity COVID-19 is cardiovascular disease, and testosterone activates the main pathway of myocardial inflammation, while estrogen has a protective effect against cardiovascular disease [70, 74, 102]. It has been reported that, in clinical trials in which testosterone level was high, there was an increased susceptibility to cardiovascular inflammation, and these men were more vulnerable to COVID-19 [26].

COVID-19 and liver

More than one-third of patients hospitalized with SARS-CoV-2 infection have abnormal liver function, which is associated with longer hospital stays [37]. Liver failure in 60% of patients with SARS3 and in patients infected with MERS-CoV, have been reported. Patients with severe COVID-19 appear to have higher liver dysfunction. Liver damage in severe cases of COVID-19 is more common than in mild cases [153]. One study found that 2–11% of patients with COVID-19 had liver obstruction and 14.8–53.1% had abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) during disease progression [153]. The prevalence of chronic liver disease has been shown to be relatively low in patients with COVID-19. However, individuals with severe forms of COVID-19 show significant changes in liver enzymes as well as coagulation and fibrinolytic pathways due to the innate immune response to the virus [86].

An increase in the prevalence of liver injury in patients with COVID-19 was reported from 39.6% to 43.4%, which was mainly associated with increased ALT and AST as well as hypoalbuminemia [21, 149]. In one study, 132 patients with liver damage were found to have slight increase in total bilirubin (TBIL), of whom 72 were male (54.5%) and 60 were female (45.5%), [149]. Another study found that among COVID-19 patients admitted to an American academic medical center, 69% had abnormal liver biochemical factors at the time of admission and 93% had higher-than-normal hepatic biochemical factors during hospitalization. Approximately one in five hospitalized patients was at risk for grade 3 or 4 liver injury [11].

It has also been shown that the level of gamma glutamyl transferase (GGT), a biological diagnostic marker for cholangiocyte damage, increases in COVID-19 patients. Increased alkaline phosphatase (ALP) levels have also been observed in several COVID-19 patients during hospitalization [162]. Another study showed that ACE2 receptor expression in infinite cholangiocytes increases and this suggests that SARS-CoV-2 may bind directly to ACE2-positive cholangiocytes to impair liver function [17].

Liver damage in patients with COVID-19 infection may be directly due to viral infection of the liver cells. Approximately 2–10% of patients with COVID-19 have diarrhea, and SARS-CoV-2 RNA has been detected in fecal and blood samples [160]. This evidence suggests that, the virus may be present in the liver. Both SARS-CoV-2 and SARS-CoV bind to ACE2 receptor in order to enter the target cell (148), where the virus multiplies and subsequently infects other cells in the upper respiratory tract and lung tissue. Patients then begin to show clinical signs and symptoms [162].

Immune-mediated inflammation, such as cytokine influx and pneumonia-induced hypoxia, may also contribute to liver damage or even liver failure in patients with COVID-19, who are in critical stages of the disease [162]. In these patients, the mild acute hepatic congestion and activation of non-inflamed Kupffer cells have been shown [13]. A recent study reported that moderate microvascular steatosis and mild lobular and portal activity occur in liver biopsy specimens, indicating that liver damage can be caused by SARS-CoV-2 infection [159].

After SARS-CoV-2 infection, pathogenic T cells are rapidly activated, producing granulocyte-macrophage (GM-CSF), IL-6, and other inflammatory factors, and also activate inflammatory monocytes $CD14^+$ and $CD16^+$, resulting in higher levels of IL-6 and other inflammatory factors, which lead to an inflammatory storm and immune damage to the liver. IL-6 and GM-CSF are two important inflammatory factors that cause inflammatory storm in patients with COVID-19 [39]. One study found that, the prevalence of liver damage in male patients was higher than female ones [47]. Abnormal liver function has been shown to be more common in men with COVID-19 than in women, who have higher inflammatory markers such as C-reactive protein and procalcitonin [37]. ACE2 expression in the liver of women is very low compared to men [110].

COVID-19 and gastrointestinal tract

COVID-19 infection may be present in the intestine, leading to gastrointestinal symptoms such as diarrhea and abdominal pain. Intestinal metabolic disorders caused by this disease increase the absorption of harmful metabolites, which affects the function of central nervous system through the intestinal axis and brain, and then leads to dizziness and fatigue. These metabolites are also harmful to liver tissue [170]. Although patients usually have fever and respiratory symptoms, some have gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain [47]. In the small intestine, mesenteric edema and peritoneal fluid have also been observed [8].

Studies have shown that RNA of SARS-CoV-2 is present in anal/rectal swabs and fecal samples of COVID-19 patients, even after virus clearance from the upper respiratory tract [158, 166]. In addition, ACE2 expression has been observed in gastrointestinal epithelial cells [55, 157]. Zhang et al., reported that ACE2 is expressed in esophageal epithelial cells and enterocytes in ileum and colon [163]. Intestinal epithelial cells, especially small intestinal enterocytes, also express ACE2 receptors. In the intestine, ACE2 regulates the absorption of amino acids and the balance of intestinal bacteria to reduce intestinal inflammation [56], and because ACE2 is the entry point of virus, the presence of ACE2 predisposes the intestine to viral infection [76].

The role of intestinal microbiota in lung diseases is well confirmed. Respiratory viral infections have also been shown to disrupt the intestinal microbiota. Diet, environmental factors and genetics play an important role in the formation of intestinal microbiota that can affect immunity [29, 34, 53, 146]. The diversity of intestinal microbiota is decreased in old age and COVID-19 has been mainly fatal for elderly patients, pointing again to the role that intestinal microbiota play in this disease [32, 82, 100].

Odor and taste disorders are common in patients with mild to moderate COVID-19. One study reported that in women infected with COVID-19, the rate of gastrointestinal symptoms, including diarrhea, loss of appetite, and olfactory and taste disturbances, was almost twice as high as in infected men [126], which were accompanied by higher levels of inflammation and poorer liver function [170].

Levels of ACE2 expression in adipose and subcutaneous tissue of the large intestine are significantly higher in women than in men [142]. Another study found that, the proportion of gastrointestinal symptoms in female patients was significantly higher than in male patients. Clinical manifestations such as sore throat, dizziness, and fatigue were also more common in patients with gastrointestinal symptoms [170].

COVID-19 and kidney

Although COVID-19 infection is primarily a respiratory disease, other organs, including the kidneys, are often affected by it [60]. Acute kidney injury (AKI) is one of the major complications of COVID-19, which occurs in 0.5–7% of cases and in 2.9–23% of ICU patients [48, 62]. In a cohort study, 43.9% of hospitalized patients had proteinuria and 26.7% had hematuria. The prevalence of high serum creatinine, hyperuricemia and estimated glomerular filtration rate below 60 ml/min/1.73 m^2 were 14.4, 13.1 and 1.13%, respectively. During the study period, AKI occurred in 5.1 patients [23].

Podocytes and proximal direct tubule cells, as kidney cells, host the virus. According to the findings, the effects of SARS-CoV-2 cytopathy on podocytes and proximal direct tubule may cause AKI in patients with COVID-19. Podocytes and proximal direct tubule cells play an important role in urine purification, reabsorption and excretion. It should be noted that podocytes are particularly vulnerable to viral and bacterial attacks, and podocyte damage easily induces heavy proteinuria [64]. As the data from one study showed, 43.9% of patients infected with SARS-CoV-2, especially patients with AKI, had proteinuria [24].

In the case of renal histopathology in COVID-19 patients, in one study, significant ATI and occlusion of microvascular lumens were observed mainly by red blood cells with endothelial damage as well as glomerular and vascular changes [132]. These findings suggest that, the COVID-19 infection causes direct infection of renal parenchyma and possibly secondary endothelial damage. Acute tubular injury is associated with loss of edging brushes and non-isometric vacuolation, which may in part be due to the direct effect of SARS-CoV-2, as demonstrated by ultrastructural evaluation [133]. A study showed an important relationship between AKI and respiratory failure for the following reasons [60]:

First, severe AKI usually occurs during intubation and mechanical ventilation. Second, the AKI rate in patients under mechanical ventilation was 89.7%, while in other patients it was 21.7%. Third, severe AKI (stages 2 and 3) occurred in 65.5% of patients using mechanical ventilation compared with 6.7% of patients who were not using mechanical ventilation [60].

The most obvious risk factors for the development of AKI in COVID-19 patients have been the need for ventilator support or treatment with vasopressor. Reported risk factors for poor COVID-19 outcomes, include aging, male gender, and high Body mass index (BMI) [22, 67, 127, 165, 169].

This virus has also been shown to cause interstitial inflammation, acute tubular necrosis, podocytopathy, microangiopathy, and collapsing glomerulopathy [71, 75, 103, 106]. Another study found that in patients with COVID-19, endothelium in the kidney, which is responsible for proteinuria, is affected by the disease [117]. In addition, virus particles are present in renal endothelial cells. The viraemia is considered as a possible cause of endothelial damage in the kidney and a possible cause of AKI. Also, SARS-CoV-2 can directly infect renal tubular epithelium and podocytes via ACE2-dependent pathway, causing mitochondrial dysfunction, acute tubular necrosis, formation of protein reabsorption vacuoles, collapsing glomerulopathy, and protein leaks into Bowman capsules [75, 133].

Another potential mechanism for the development of AKI is impaired regulation of immune response to COVID-19 virus [116, 169]. Other factors that may contribute to AKI include rhabdomyolysis, macrophage activation syndrome, and the development

of micro-embolism and micro-thrombosis in the context of hypercoagulability and endotheliitis [144, 167].

Although the incidence of chronic kidney disease is more common in women, the progression of kidney failure and mortality is higher in men [25]. There is a significant interaction between sex hormones and ACE2 expression. Removal of ovaries increased ACE2 expression in the kidney and adipose tissue of women, and estradiol replacement decreased ACE2 expression [41]. Also, testosterone appears to increase ACE2 levels in the kidneys, while estrogen decreases ACE2 expression in the kidneys [41, 43]. Compared to men, women showed lower levels of serum monocytes and creatinine [61].

Conclusion

Sex differences have been reported in the effects of COVID-19 on the respiratory system, cardiovascular system, liver and kidneys. This sex difference appears to be attributable to levels of ACE2, a high expression of which has been reported in males. Estrogen, and perhaps progesterone, may regulate localized ACE2 levels, thereby reducing inflammation and oxidative stress, leading to protection against the virus. Further studies are needed to investigate the impact of sex differences on the nervous and gastrointestinal systems to better manage COVID-19 treatment.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Funding

Not applicable.

References

1. Ackermann M., Verleden S.E., Kuehnel M., Haverich A., Welte T., Laenger F., Vanstapel A., Werlein C., Stark H., Tzankov A., Li W.W., Li V.W., Mentzer S.J., Jonigk D. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N. Engl. J. Med., 2020, vol. 383, no. 1, pp. 20–128. doi: 10.1056/NEJMoa2015432*
2. Amadori A., Zamarchi R., De Silvestro G., Forza G., Cavatton G., Danieli G.A., Clementi M., Chieco-Bianchi L. Genetic control of the CD4/CD8 T-cell ratio in humans. *Nat. Med., 1995, vol. 11, no. 2, pp. 1279–1283. doi: 10.1038/nm1295-1279*
3. Baig A.M., Khaleeq A., Ali U., Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. *ACS Chem. Neurosci., 2020, vol. 11, no. 7, pp. 995–998. doi: 10.1021/acschemneuro.0c00122*
4. Bartz D., Chitnis T., Kaiser U.B., Rich-Edwards J.W., Rexrode K.M., Pennell P.B., Goldstein J.M., O'Neal M.A., LeBoff M., Behn M., Seely E.W., Joffe H., Manson J.E. Clinical advances in sex-and gender-informed medicine to improve the health of all: a review. *JAMA Intern. Med., 2020, vol. 1804, no. 5, pp. 74–83. doi: 10.1001/jamainternmed.2019.7194*
5. Bernheim A., Mei X., Huang M., Yang Y., Fayad Z.A., Zhang N., Diao K., Lin B., Zhu X., Li K., Li S., Shan H., Jacobi A., Chung M. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. *Radiology, 2020: 200463. doi: 10.1148/radiol.2020200463*
6. Berthelot J.-M, Drouet L., Lioté F. Kawasaki-like diseases and thrombotic coagulopathy in COVID-19: delayed over-activation of the STING pathway? *Emerg. Microbes Infect., 2020, vol. 9, no. 1, pp. 1514–1522. doi: 10.1080/22221751.2020.1785336*
7. Bhasin S., Brito J.P., Cunningham G.R., Hayes F.J., Hodis H.N., Matsumoto A.M., Snyder P.J., Swerdloff R.S., Wu F.C., Yialamas M.A. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J. Clin. Endocrin. Metabol., 2018, vol. 103, no. 5, pp. 1715–1744. doi: 10.1210/jc.2018-00229*
8. Bianco F., Ranieri A., Paterniti G., Pata F., Gallo G. Acute intestinal ischemia in a patient with COVID-19. *Tech. Coloproctology, 2020, vol. 24: 1217–1218. doi: 10.1007/s10151-020-02255-0*
9. Binder E., Künzel H., Nickel T., Kern N., Pfennig A., Majer M., Uhr M., Ising M., Holsboer F. HPA-axis regulation at in-patient admission is associated with antidepressant therapy outcome in male but not in female depressed patients. *Psychoneuroendocrinology, 2009, vol. 34, no. 1, pp. 99–109. doi: 10.1016/j.psyneuen.2008.08.018*
10. Blau F.D., Kahn L.M. Gender differences in pay. *J. Econ. Perspect., 2000, vol. 14, no. 4, pp. 75–99. doi: 10.1257/jep.14.4.75*
11. Bloom P.P., Meyerowitz E.A., Reinus Z., Daidone M., Gustafson J., Kim A.Y., Schaefer E., Chung R.T. Liver biochemistries in hospitalized patients with COVID-19. *Hepatology, 2021, vol. 73, no. 3, pp. 890–900. doi: 10.1002/hep.31326*
12. Bohmwald K., Galvez N., Ríos M., Kalergis A.M. Neurologic alterations due to respiratory virus infections. *Front. Cell Neurosci., 2018, vol. 12: 386. doi: 10.3389/fncel.2018.00386*
13. Bösmüller H., Traxler S., Bitzer M., Häberle H., Raiser W., Nann D., Frauenfeld L., Vogelsberg A., Klingel K., Fend F. The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. *Virchows Archiv., 2020, vol. 477, no. 3, pp. 349–357. doi: 10.1007/s00428-020-02881-x*
14. Brown R.P., Josephs R.A. A burden of proof: Stereotype relevance and gender differences in math performance. *J. Pers. Soc. Psychol., 1999, vol. 762, no. 2: 46. doi: 10.1037/0022-3514.76.2.246*
15. Bukowska A., Spiller L., Wolke C., Lendeckel U., Weinert S., Hoffmann J., Bornfleth P., Kutschka I., Gardemann A., Isermann B., Goette A. Protective regulation of the ACE2/ACE gene expression by estrogen in human atrial tissue from elderly men. *Exp. Biol. Med. (Maywood), 2017, vol. 2421, no. 4, pp. 1412–1423. doi: 10.1177/1535370217718808*
16. Byrnes J.P., Miller D.C., Schafer W.D. Gender differences in risk taking: a meta-analysis. *Psychol. Bull., 1999, vol. 125, no. 3, pp. 367–383.*
17. Chai X., Hu L., Zhang Y., Han W., Lu Z., Ke A., Zhou J., Shi G., Fang N., Fan J., Cai J., Fan J., Lan F. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *Biorxiv, 2020. doi: 10.1101/2020.02.03.931766*

18. Channappanavar R., Fett C., Mack M., Ten Eyck P.P., Meyerholz D.K., Perlman S. Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. *J. Immunol., 2017, vol. 198, no. 10, pp. 4046–4053. doi: 10.4049/jimmunol.1601896*
19. Chappell M.C., Marshall A.C., Alzayadneh E.M., Shaltout H.A., Diz D.I. Update on the angiotensin converting enzyme 2-angiotensin (1–7)-Mas receptor axis: fetal programing, sex differences, and intracellular pathways. *Front. Endocrinol., 2014, vol. 4: 201. doi: 10.3389/fendo.2013.00201*
20. Chen C., Zhang X., Ju Z., He W. Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies. *Zhonghua Shao Shang Za Zhi, 2020, vol. 36, no. 6, pp. 471–475. doi: 10.3760/cma.j.cn501120-20200224-00088*
21. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., Qiu Y., Wang J., Liu Y., Wei Y., Xia J., Yu T., Zhang X., Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet, 2020, vol. 39510223, no. 5, pp. 507–513. doi: 10.1016/S0140-6736(20)30211-7*
22. Chen R., Liang W., Jiang M., Guan W., Zhan C., Wang T., Tang C., Sang L., Liu J., Ni Z., Hu Y., Liu L., Shan H., Lei C., Peng Y., Wei L., Liu Y., Hu Y., Peng P., Wang J., Liu J., Chen Z., Li G., Zheng Z., Qiu S., Luo J., Ye C., Zhu S., Liu X., Cheng L., Ye F., Zheng J., Zhang N., Li Y., He J., Li S., Zhong N; Medical Treatment Expert Group for COVID-19. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. *Chest. 2020, vol. 158, no. 1, pp. 97–105. doi: 10.1016/j.chest.2020.04.010*
23. Cheng Y., Luo R., Wang K., Zhang M., Wang Z., Dong L., Li J., Yao Y., Ge S., Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int., 2020, vol. 975, no. 8, pp. 829–838. doi: 10.1016/j.kint.2020.03.005*
24. Cheng Y., Luo R., Wang K., Zhang M., Wang Z., Dong L., Li J., Yao Y., Ge S., Xu G. Kidney impairment is associated with in-hospital death of COVID-19 patients. *MedRxiv, 2020. doi: 10.1101/2020.02.18.20023242.*
25. Cobo G., Hecking M., Port F.K., Exner I., Lindholm B., Stenvinkel P., Carrero J.J. Sex and gender differences in chronic kidney disease: progression to end-stage renal disease and haemodialysis. *Clin. Sci. (Lond.)., 2016, vol. 13014, no. 1, pp. 1147–1463. doi: 10.1042/CS20160047*
26. Conti P., Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. *J. Biol. Regul. Homeost. Agents, 2020, vol. 342, no. 3, pp. 339–343. doi: 10.23812/Editorial-Conti-3*
27. Darnall B.D., Suarez E.C. Sex and gender in psychoneuroimmunology research: past, present and future. *Brain Behav. Immun., 2009, vol. 235, no. 5, pp. 595–604. doi: 10.1016/j.bbi.2009.02.019*
28. Das G., Mukherjee N., Ghosh S. Neurological insights of COVID-19 pandemic. A*CS Chem. Neurosci., 2020, vol. 119, no. 1, pp. 1206–1209. doi: 10.1021/acschemneuro.0c00201*
29. De Filippis F., Pellegrini N., Vannini L., Jeffery I.B., La Storia A., Laghi L., Serrazanetti D.I., Di Cagno R., Ferrocino I., Lazzi C., Turroni S., Cocolin L., Brigidi P., Neviani E., Gobbetti M., O'Toole P.W., Ercolini D. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut. 2016, vol. 651, no. 11, pp. 1812–1821. doi: 10.1136/gutjnl-2015-309957*
30. Desforges M., Le Coupanec A., Dubeau P., Bourgouin A., Lajoie L., Dubé M., Talbot P.J. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses. 2020, vol. 12, no. 1: 14. doi: 10.3390/v12010014*
31. Desforges M., Le Coupanec A., Stodola J.K., Meessen-Pinard M., Talbot P.J. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res., 2014, vol. 194, pp. 145–158. doi: 10.1016/j.virusres.2014.09.011*
32. Dhar D., Mohanty A. Gut microbiota and COVID-19-possible link and implications. *Virus Res., 2020, vol. 285: 198018. doi: 10.1016/j.virusres.2020.198018*
33. Dobbs M.R. Toxic encephalopathy. *Semin. Neurol., 2011, vol. 31, no. 2, pp. 184–193. doi: 10.1055/s-0031-1277989*
34. Earley Z.M., Akhtar S., Green S.J., Naqib A., Khan O., Cannon A.R., Hammer A.M., Morris N.L., Li X., Eberhardt J.M., Gamelli R.L., Kennedy R.H., Choudhry M.A. Burn injury alters the intestinal microbiome and increases gut permeability and bacterial translocation. *PLoS One, 2015, vol. 10, no. 7: e0129996. doi: 10.1371/journal.pone.0129996*
35. Elkind M.S. Why now? Moving from stroke risk factors to stroke triggers. *Curr. Opin. Neurol., 2007, vol. 20, no. 1, pp. 51–57. doi: 10.1097/WCO.0b013e328012da75*
36. Ellul M., Solomon T. Acute encephalitis — diagnosis and management. *Clin. Med. (Lond)., 2018, vol. 18, no. 2, pp. 155–159. doi: 10.7861/clinmedicine.18-2-155*
37. Fan Z., Chen L., Li J., Cheng X., Yang J., Tian C., Zhang Y., Huang S., Liu Z., Cheng J. Clinical features of COVID-19-related liver damage. *Clin. Gastroenterol. Hepatol., 2020, vol. 18, no. 7, pp. 1561–1566. doi: 10.1016/j.cgh.2020.04.002*
38. Fang Y., Zhang H., Xie J., Lin M., Ying L., Pang P., Ji W. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology, 2020, vol. 296, no. 2, pp. 115–117. doi: 10.1148/radiol.2020200432*
39. Feng G., Zheng K.I., Yan Q.Q., Rios R.S., Targher G., Byrne C.D., Poucke S.V., Liu W.Y., Zheng M.H. COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies. *J. Clin. Transl. Hepatol., 2020, vol. 8, no. 1, pp. 18–24. doi: 10.14218/JCTH.2020.00018*
40. Ferreira A.J., Murça T.M., Fraga-Silva R.A., Castro C.H., Raizada M.K., Santos R.A. New cardiovascular and pulmonary therapeutic strategies based on the Angiotensin-converting enzyme 2/angiotensin-(1–7)/mas receptor axis. *Int. J. Hypertens., 2012: 147825. doi: 10.1155/2012/147825*
41. Fischer M., Baessler A., Schunkert H. Renin angiotensin system and gender differences in the cardiovascular system. *Cardiovasc. Res., 2002, vol. 53, no. 3, pp. 672–677. doi: 10.1155/2012/147825*
42. Fu W., Wang C., Zou L., Guo Y., Lu Z., Yan S., Mao J. Psychological health, sleep quality, and coping styles to stress facing the COVID-19 in Wuhan, China. *Transl. Psychiatry, 2020, vol. 10: 225. doi: 10.1038/s41398-020-00913-3*
43. Gebhard C., Regitz-Zagrosek V., Neuhauser H.K., Morgan R., Klein S.L. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol. Sex Differ., 2020, vol. 11: 29. doi: 10.1186/s13293-020-00304-9*

44. Gemmati D., Bramanti B., Serino M.L., Secchiero P., Zauli G., Tisato V. COVID-19 and individual genetic susceptibility/receptivity: role of ACE1/ACE2 genes, immunity, inflammation and coagulation. Might the double X-chromosome in females be protective against SARS-CoV-2 compared to the single X-chromosome in males? *Int. J. Mol. Sci., 2020, vol. 21, no. 10: 3474. doi: 10.3390/ijms21103474*
45. Gowrisankar Y.V., Clark M.A. Angiotensin II regulation of angiotensin-converting enzymes in spontaneously hypertensive rat primary astrocyte cultures. *J. Neurochem., 2016, vol. 138, no. 1, pp. 74–85. doi: 10.1111/jnc.13641*
46. Grandi G., Facchinetti F., Bitzer J. The gendered impact of coronavirus disease (COVID-19): do estrogens play a role? *Eur. J. Contracept. Reprod. Health Care, 2020, vol. 25, no. 3, pp. 233–234. doi: 10.1080/13625187.2020.1766017*
47. Gu J., Han B., Wang J. COVID-19: gastrointestinal manifestations and potential fecal–oral transmission. *Gastroenterology, 2020, vol. 158, no. 6, pp. 1518–1519. doi: 10.1053/j.gastro.2020.02.054*
48. Guan W.J., Ni Z.Y., Hu Y., Liang W.H., Ou C.Q., He J.X., Liu L., Shan H., Lei C.L., Hui D.S.C., Du B., Li L.J., Zeng G., Yuen K.Y., Chen R.C., Tang C.L., Wang T., Chen P.Y., Xiang J., Li S.Y., Wang J.L., Liang Z.J., Peng Y.X., Wei L., Liu Y., Hu Y.H., Peng P., Wang J.M., Liu J.Y., Chen Z., Li G., Zheng Z.J., Qiu S.Q., Luo J., Ye C.J., Zhu S.Y., Zhong NS; China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med., 2020, vol. 382, pp. 1708–1720. doi: 10.1056/NEJMoa2002032*
49. Guo J., Huang Z., Lin L., Lv J. Coronavirus disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. *J. Am. Heart Assoc., 2020, vol. 9, no. 7: e016219. doi: 10.1161/JAHA.120.016219*
50. Guo Y.R., Cao Q.D., Hong Z.S., Tan Y.Y., Chen S.D., Jin H.J., Tan K.S., Wang D.Y., Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. *Mil. Med. Res., 2020, vol. 7: 11. doi: 10.1186/s40779-020-00240-0*
51. Haeggström A., Östberg B., Stjerna P., Graf P., Hallén H. Nasal mucosal swelling and reactivity during a menstrual cycle. *ORL J. Otorhinolaryngol. Relat. Spec., 2000, vol. 62, no. 1, pp. 39–42. doi: 10.1159/000027713*
52. Haist S.A., Wilson J.F., Elam C.L., Blue A.V., Fosson S.E. The effect of gender and age on medical school performance: an important interaction. *Adv. Health Sci. Educ. Theory Pract., 2000, vol. 5, no. 3, pp. 197–205. doi: 10.1023/A:1009829611335*
53. Hall A.B., Tolonen A.C., Xavier R.J. Human genetic variation and the gut microbiome in disease. *Nat. Rev. Genet., 2017, vol. 181, no. 1, pp. 690–699. doi: 10.1038/nrg.2017.63*
54. Hall O.J., Limjunyawong N., Vermillion M.S., Robinson D.P., Wohlgemuth N., Pekosz A., Mitzner W., Klein S.L. Progesterone-based therapy protects against influenza by promoting lung repair and recovery in females. *PLoS Pathog., 2016, vol. 12, no. 9: e1005840. doi: 10.1371/journal.ppat.1005840*
55. Harmer D., Gilbert M., Borman R., Clark K.L. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS Lett., 2002, vol. 532, no. 1–2, pp. 107–110. doi: 10.1016/s0014-5793(02)03640-2*
56. Hashimoto T., Perlot T., Rehman A., Trichereau J., Ishiguro H., Paolino M., Sigl V., Hanada T., Hanada R., Lipinski S., Wild B., Camargo S.M., Singer D., Richter A., Kuba K., Fukamizu A., Schreiber S., Clevers H., Verrey F., Rosenstiel P., Penninger J.M. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature, 2012, vol. 487, no. 7408, pp. 77–81. doi: 10.1038/nature11228*
57. Hassanzadeh K., Perez Pena H., Dragotto J., Buccarello L., Iorio F., Pieraccini S., Sancini G., Feligioni M.Considerations around the SARS-CoV-2 Spike Protein with particular attention to COVID-19 brain infection and neurological symptoms. *ACS Chem. Neurosci., 2020, vol. 11, no. 15, pp. 2361–2369. doi: 10.1021/acschemneuro.0c00373*
58. He J., Wu B., Chen Y., Tang J., Liu Q., Zhou S., Chen C., Qin Q., Huang K., Lv J., Chen Y., Peng D. Characteristic ECG manifestations in patients with COVID-19. *Can. J. Cardiol., 2020, vol. 36, no. 6, pp. 966.e1–966.e4. doi: 10.1016/j.cjca.2020.03.028*
59. Hill-Burns E.M., Clark A.G. X-linked variation in immune response in Drosophila melanogaster. *Genetics, 2009, vol. 183, no. 4, pp. 1477–1491. doi: 10.1534/genetics.108.093971*
60. Hirsch J.S., Ng J.H., Ross D.W., Sharma P., Shah H.H., Barnett R.L., Hazzan A.D., Fishbane S., Jhaveri KD; Northwell COVID-19 Research Consortium; Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int., 2020, vol. 98, no. 1, pp. 209–218. doi: 10.1016/j.kint.2020.05.006*
61. Hu X., Pan X., Zhou W., Gu X., Shen F., Yang B., Hu Zh. Clinical epidemiological analyses of overweight/obesity and abnormal liver function contributing to prolonged hospitalization in patients infected with COVID-19. *Int. J. Obes., 2020, vol. 44, pp. 1784–1789. doi: 10.1038/s41366-020-0634-3*
62. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., Zhang L., Fan G., Xu J., Gu X., Cheng Z., Yu T., Xia J., Wei Y., Wu W., Xie X., Yin W., Li H., Liu M., Xiao Y., Gao H., Guo L., Xie J., Wang G., Jiang R., Gao Z., Jin Q., Wang J., Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet, 2020, vol. 395, no. 10223, pp. 497–506. doi: 10.1016/S0140-6736(20)30183-5*
63. Jain S., Workman V., Ganeshan R., Obasare E.R., Burr A., DeBiasi R.M., Freeman J.V., Akar J., Lampert R., Rosenfeld L.E. Enhanced electrocardiographic monitoring of patients with coronavirus disease 2019. *Heart Rhythm., 2020, vol. 17, no. 9, pp. 1417–1422. doi: 10.1016/j.hrthm.2020.04.047*
64. Jefferson J.A., Nelson P.J., Najafian B., Shankland S.J. Podocyte disorders: core curriculum 2011. *Am. J. Kidney Dis., 2011, vol. 58, no. 4, pp. 666–677. doi: 10.1053/j.ajkd.2011.05.032*
65. Ji H., Menini S., Zheng W., Pesce C., Wu X., Sandberg K. Role of angiotensin-converting enzyme 2 and angiotensin (1–7) in 17β-oestradiol regulation of renal pathology in renal wrap hypertension in rats. *Exp. Physiol., 2008, vol. 93, no. 5, pp. 648–657. doi: 10.1113/expphysiol.2007.041392*
66. Jin J.M., Bai P., He W., Wu F., Liu X.F., Han D.M., Liu S., Yang J.K. Gender differences in patients with COVID-19: Focus on severity and mortality. *Front. Public Health., 2020, vol. 8: 152. doi: 10.3389/fpubh.2020.00152*
67. Jordan R.E., Adab P., Cheng K. COVID-19: risk factors for severe disease and death. *BMJ, 2020, vol. 368: m1198. doi: 10.1136/bmj.m1198*

68. Joyner J., Neves L.A., Granger J.P., Alexander B.T., Merrill D.C., Chappell M.C., Ferrario C.M., Davis W.P., Brosnihan K.B. Temporal-spatial expression of ANG-(1-7) and angiotensin-converting enzyme 2 in the kidney of normal and hypertensive pregnant rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol., 2007, vol. 293, no. 1, pp. 169–177. doi: 10.1152/ajpregu.00387.2006*
69. Karaahmet F., Karaahmet O.Z. Potential effect of natural and anabolizan steroids in elderly patient with COVID-19. *Med. Hypotheses. 2020, vol. 140: 109772. doi: 10.1016/j.mehy.2020.109772*
70. Kelly D.M., Jones T.H. Testosterone: a vascular hormone in health and disease. *J. Endocrinol., 2013, vol. 217, no. 3, pp. 47–71. doi: 10.1530/JOE-12-0582*
71. Kissling S., Rotman S., Gerber C., Halfon M., Lamoth F., Comte D., Lhopitallier L., Sadallah S., Fakhouri F. Collapsing glomerulopathy in a COVID-19 patient. *Kidney Int., 2020, vol. 98, no. 1, pp. 228–231. doi: 10.1016/j.kint.2020.04.006*
72. Klein S.L., Dhakal S., Ursin R.L., Deshpande S., Sandberg K., Mauvais-Jarvis F. Biological sex impacts COVID-19 outcomes. *PLoS Pathog., 2020, vol. 16, no. 6: e1008570. doi: 10.1371/journal.ppat.1008570*
73. Kuba K., Imai Y., Rao S., Gao H., Guo F., Guan B., Huan Y., Yang P., Zhang Y., Deng W., Bao L., Zhang B., Liu G., Wang Z., Chappell M., Liu Y., Zheng D., Leibbrandt A., Wada T., Slutsky A.S., Liu D., Qin C., Jiang C., Penninger J.M. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat. Med., 2005, vol. 11, no. 8, pp. 875–879. doi: 10.1038/nm1267*
74. Kypreos K.E., Zafirovic S., Petropoulou P.I., Bjelogrlic P., Resanovic I., Traish A., Isenovic E.R. Regulation of endothelial nitric oxide synthase and high-density lipoprotein quality by estradiol in cardiovascular pathology. *J. Cardiovasc. Pharmacol. Ther., 2014, vol. 19, no. 3, pp. 256–268. doi: 10.1177/1074248413513499*
75. Larsen C., Bourne T., Wilson J., Saqqa O., Sharshir M. Collapsing glomerulopathy in a patient with coronavirus disease 2019 (COVID-19). *Kidney Int. Rep., 2020, vol. 5, no. 6, pp. 935–939. doi: 10.1016/j.ekir.2020.04.002*
76. Leung W.K., To K.F., Chan P.K., Chan H.L., Wu A.K., Lee N., Yuen K.Y., Sung J.J. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. *Gastroenterology, 2003, vol. 125, no. 4, pp. 1011–1017. doi: 10.1016/s0016-5085(03)01215-0*
77. Li H., Liu Z., Gou Y., Yu H., Siminelakis S., Wang S., Kong D., Zhou Y., Liu Z., Ding Y., Yao D. Estradiol mediates vasculoprotection via ERRα-dependent regulation of lipid and ROS metabolism in the endothelium. *J. Mol. Cell Cardiol., 2015, vol. 87, pp. 92–101. doi: 10.1016/j.yjmcc.2015.08.008*
78. Li Y.C., Bai W.Z., Hashikawa T. The neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients. *J. Med. Virol., 2020, vol. 92, no. 6, pp. 552–555. doi: 10.1002/jmv.25728*
79. Li Y., Li H., Fan R., Wen B., Zhang J., Cao X., Wang C., Song Z., Li S., Li X., Lv X., Qu X., Huang R., Liu W. Coronavirus infections in the central nervous system and respiratory tract show distinct features in hospitalized children. *Intervirology, 2016, vol. 59, no. 3, pp. 163–169. doi: 10.1159/000453066*
80. Libert C., Dejager L., Pinheiro I. The X chromosome in immune functions: when a chromosome makes the difference. *Nat. Rev. Immunol., 2010, vol. 10, no. 8, pp. 594–604. doi: 10.1038/nri2815*
81. Liu J., Ji H., Zheng W., Wu X., Zhu J.J., Arnold A.P., Sandberg K. Sex differences in renal angiotensin converting enzyme 2 (ACE2) activity are 17β-oestradiol-dependent and sex chromosome-independent. *Biol. Sex Differ., 2010, vol. 1: 6. doi: 10.1186/2042-6410-1-6*
82. Looft T., Allen H.K. Collateral effects of antibiotics on mammalian gut microbiomes. *Gut Microbes., 2012, vol. 3, no. 5, pp. 463–467. doi: 10.4161/gmic.21288*
83. Maggio M., Basaria S., Ceda G.P., Ble A., Ling S.M., Bandinelli S., Valenti G., Ferrucci L. The relationship between testosterone and molecular markers of inflammation in older men. *J. Endocrinol. Invest., 2005, vol. 28, no. 11, pp. 116–119.*
84. Magro C., Mulvey J.J., Berlin D., Nuovo G., Salvatore S., Harp J., Baxter-Stoltzfus A., Laurence J.Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl. Res., 2020, vol. 220, pp. 1–13. doi: 10.1016/j.trsl.2020.04.007*
85. Maleki Dana P., Sadoughi F., Hallajzadeh J., Asemi Z., Mansournia M.A., Yousefi B., Momen-Heravi M. An insight into the sex differences in COVID-19 patients: what are the possible causes? *Prehosp. Disaster Med., 2020, pp. 1–4. doi: 10.1017/S1049023X20000837*
86. Mantovani A., Beatrice G., Dalbeni A. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. *Liver Intern., 2020, vol. 40, no. 6, pp. 1316–1320. doi: 10.1111/liv.14465*
87. Mao L., Jin H., Wang M., Hu Y., Chen S., He Q., Chang J., Hong C., Zhou Y., Wang D., Miao X., Li Y., Hu B. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *JAMA Neurol., 2020, vol. 77, no. 6, pp. 683–690. doi: 10.1001/jamaneurol.2020.1127*
88. Mauvais-Jarvis F., Klein S.L., Levin E.R. Estradiol, progesterone, immunomodulation, and COVID-19 outcomes. *Endocrinol., 2020, vol. 161, no. 9: bqaa127. doi: 10.1210/endocr/bqaa127*
89. McGonagle D., O'Donnell J.S., Sharif K., Emery P., Bridgewod C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol., 2020, vol. 2, no. 7, pp. 437–445. doi: 10.1016/S2665-9913(20)30121-1*
90. Mehta P., McAuley D.F., Brown M., Sanchez E., Tattersall R.S., Manson J.J.; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (Lond.), 2020, vol. 395 no. 10229, pp. 1033–1034. doi: 10.1016/S0140-6736(20)30628-0*
91. Meng Y., Wu P., Lu W., Liu K., Ma K., Huang L., Cai J., Zhang H., Qin Y., Sun H., Ding W., Gui L., Wu P. Sex-specific clinical characteristics and prognosis of coronavirus disease-19 infection in Wuhan, China: a retrospective study of 168 severe patients. *PLoS Pathog., 2020, vol. 16, no. 4: e1008520. doi: 10.1371/journal.ppat.1008520*
92. Mikkelsen K., Stojanovska L., Polenakovic M., Bosevski M., Apostolopoulos V. Exercise and mental health. *Maturitas. 2017, vol. 106, pp. 48–56. doi: 10.1016/j.maturitas.2017.09.003*
93. Miller V., Larosa J., Barnabei V., Kessler C., Levin G., Smith-Roth A., Griffin M., Stoy D.B., Bush T., Zacur H., Foster D., Anderson J., McKenzie A., Miller S.C., Wood P., Stefanick M., Marcus R., Akana A., Heinrichs W., Kirchner C., O'Hanlan K., Ruyle M., Sheehan M., Judd H., Greendale G., Bayalos R., Lozano K., Kawakami K., Barrett-Connor E., Langer R., Kritz-

Silverstein D., Carrion-Petersen M., Cavero C., Schrott H., Johnson S.R., Feddersen D., Krutzfeldt D.L., Benda J., Pauerstein C., Trabal J., Schenken R., Stern M., Rodriguez-Sifuentes M., Easton C., Hb W., Espeland M., Howard G., Byington R., Legault C., Shumaker S., Hogan P., Hire D., Wasilauskas C., James M.K., Lane K., Terrell T., Reece S., Pierce J., Snow M., Anthony S., Mebane-Sims I., Einhorn P., Hunsberger S., Waclawiw M., Lippel K., Lucas D.L., Verter J., Jackson S., Kelaghan J., Perlman J., Wolf P., McGowan J., Gordon S., Heyse S., Fradkin J., Sherman S., Page L., Sorenson A., Hulka B., Brody B., Burkman R., Heaney R., Krauss R., Roberts H., Wittes J., Riggs L., Moss R., Albers J., Marcovina S., Fineberg S., Tracy R., Merino M., Scully R., Livolsi V., Kessler G. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA, 1995, vol. 273, no. 3, pp. 199–208. doi: 10.1001/jama.1995.03520270033028*

94. Mingels A.M.A., Kimenai D.M. Sex-related aspects of biomarkers in cardiac disease. *Adv. Exp. Med. Biol., 2018, vol. 1065, pp. 545–564. doi: 10.1007/978-3-319-77932-4_33*
95. Mizuguchi M., Yamanouchi H., Ichiyama T., Shiomi M. Acute encephalopathy associated with influenza and other viral infections. *Acta Neurol. Scand. Suppl., 2007, vol. 115, pp. 45–56.*
96. Mohamad N.V., Wong S.K., Wan Hasan W.N., Jolly J.J., Nur-Farhana M.F., Ima-Nirwana S., Chin K.Y. The relationship between circulating testosterone and inflammatory cytokines in men. *Aging Male, 2019, vol. 22, no. 2, pp. 129–140. doi: 10.1080/13685538.2018.1482487*
97. Moieni M., Muscatell K.A., Jevtic I., Breen E.C., Irwin M.R., Eisenberger N.I. Sex differences in the effect of inflammation on subjective social status: a randomized controlled trial of endotoxin in healthy young adults. *Front. Psychol., 2019: 02167. doi: 10.3389/fpsyg.2019.02167*
98. Moreau K.L. Intersection between gonadal function and vascular aging in women. *J. Appl. Physiol. (1985), 2018, vol. 125, no. 12, pp. 1881–1887. doi: 10.1152/japplphysiol.00117.2018*
99. Moriguchi T., Harii N., Goto J., Harada D., Sugawara H., Takamino J., Ueno M., Sakata H., Kondo K., Myose N., Nakao A., Takeda M., Haro H., Inoue O., Suzuki-Inoue K., Kubokawa K., Ogihara S., Sasaki T., Kinouchi H., Kojin H., Ito M., Onishi H., Shimizu T., Sasaki Y., Enomoto N., Ishihara H., Furuya S., Yamamoto T., Shimada S. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int. J. Infect. Dis., 2020, vol. 94, pp. 55–58. doi: 10.1016/j.ijid.2020.03.062*
100. Mosca A., Leclerc M., Hugot J.P. Gut microbiota diversity and human diseases: should we reintroduce key predators in our ecosystem? *Front. Microbiol., 2016, vol. 7: 455. doi: 10.3389/fmicb.2016.00455*
101. Muhammad S., Haasbach E., Kotchourko M., Strigli A., Krenz A., Ridder D.A., Vogel A.B., Marti H.H., Al-Abed Y., Planz O., Schwaninger M. Influenza virus infection aggravates stroke outcome. *Stroke, 2011, vol. 42, no. 3, pp. 783–791. doi: 10.1161/STROKEAHA.110.596783*
102. Nettleship J., Jones R., Channer K., Jones T. Testosterone and coronary artery disease. Advances in the management of testosterone deficiency. *Front. Horm. Res. Basel, Karger, 2009, vol. 37, pp. 91–107. doi: 10.1159/000176047*
103. Nichols B., Jog P., Lee J.H., Blackler D., Wilmot M., D'Agati V., Markowitz G., Kopp J.B., Alper S.L., Pollak M.R., Friedman D.J. Innate immunity pathways regulate the nephropathy gene apolipoprotein L1. *Kidney Int., 2015, vol. 87, no. 2, pp. 332–342. doi: 10.1038/ki.2014.270*
104. Oudit G.Y., Kassiri Z., Jiang C., Liu P.P., Poutanen S.M., Penninger J.M., Butany J. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur. J. Clin. Invest., 2009, vol. 39, no. 7, pp. 618–625. doi: 10.1111/j.1365-2362.2009.02153.x*
105. Papadopoulos V., Li L., Samplaski M. Why does COVID-19 kill more elderly men than women? Is there a role for testosterone? *Andrology, 2021, vol. 9, no. 1, pp. 65–72. doi: 10.1111/andr.12868*
106. Peleg Y., Kudose S., D'Agati V, Siddall E., Ahmad S., Nickolas T., Kisselev S., Gharavi A., Canetta P. Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. *Kidney Int. Rep., 2020, vol. 5, no. 6, pp. 940–945. doi: 10.1016/j.ekir.2020.04.017*
107. Phiel K.L., Henderson R.A., Adelman S.J., Elloso M.M. Differential estrogen receptor gene expression in human peripheral blood mononuclear cell populations. *Immunol. Lett., 2005, vol. 97, no. 1, pp. 107–113. doi: 10.1016/j.imlet.2004.10.007*
108. Piccinni M.P., Giudizi M.G., Biagiotti R., Beloni L., Giannarini L., Sampognaro S., Parronchi P., Manetti R., Annunziato F., Livi C. Progesterone favors the development of human T helper cells producing Th2-type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones. *J. Immunol., 1995, vol. 155, no. 1, pp. 128–133.*
109. Pinzon R.T., Wijaya V.O., Buana R.B., Al Jody A., Nunsio P.N. Neurologic characteristics in coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Front. Neurol., 2020, vol. 11: 565. doi: 10.3389/fneur.2020.00565*
110. Pirola C.J., Sookoian S.C. COVID-19 and ACE2 in the liver and gastrointestinal tract: Putative biological explanations of sexual dimorphism. *Gastroenterology, 2020, vol. 159, no. 4, pp. 1620–1621. doi: 10.1053/j.gastro.2020.04.050*
111. Pisitkun P., Deane J.A., Difilippantonio M.J., Tarasenko T., Satterthwaite A.B., Bolland S. Autoreactive B cell responses to RNA-related antigens due to TLR7 gene duplication. *Science, 2006, vol. 312, no. 5780, pp. 1669–1672. doi: 10.1126/science.1124978*
112. Poyiadji N., Shahin G., Noujaim D., Stone M., Patel S., Griffith B. COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology, 2020, vol. 296, no. 2, pp. E119–E120. doi: 10.1148/radiol.2020201187*
113. Regitz-Zagrosek V., Oertelt-Prigione S., Seeland U., Hetzer R. Sex and gender differences in myocardial hypertrophy and heart failure. *Circ. J., 2010, vol. 74, no. 7, pp. 1265–1273. doi: 10.1253/circj.cj-10-0196*
114. Rettew J.A., Huet-Hudson Y.M., Marriott I. Testosterone reduces macrophage expression in the mouse of toll-like receptor 4, a trigger for inflammation and innate immunity. *Biol. Reprod., 2008, vol. 78, no. 3, pp. 432–437. doi: 10.1095/biolreprod.107.06354*
115. Romero-Sánchez C.M., Díaz-Maroto I., Fernández-Díaz E., Sánchez-Larsen Á., Layos-Romero A., García-García J., González E., Redondo-Peñas I., Perona-Moratalla A.B., Del Valle-Pérez J.A., Gracia-Gil J., Rojas-Bartolomé L., Feria-Vilar I., Monteagudo M., Palao M., Palazón-García E., Alcahut-Rodríguez C., Sopelana-Garay D., Moreno Y., Ahmad J., Segura T. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology, 2020, vol. 95, no. 8, pp. 1060–1070. doi: 10.1212/WNL.0000000000009937*

116. Ronco C., Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat. Rev. Nephrol., 2020, vol. 16, pp. 308–310. doi: 10.1038/s41581-020-0284-7*
117. Ronco C., Reis T., Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir. Med., 2020, vol. 8, no. 7, pp. 738–742. doi: 10.1016/S2213-2600(20)30229-0*
118. Rossi A. Imaging of acute disseminated encephalomyelitis. *Neuroimaging Clin. N. Am., 2008, vol. 18, no. 1, pp. 149–161. doi: 10.1016/j.nic.2007.12.007*
119. Ruan Q., Yang K., Wang W., Jiang L., Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med., 2020, vol. 46, no. 5, pp. 846–848. doi: 10.1007/s00134-020-05991-x*
120. Santos R.A.S., Sampaio W.O., Alzamora A.C., Motta-Santos D., Alenina N., Bader M., Campagnole-Santos M.J. The ACE2/angiotensin-(1–7)/MAS axis of the renin-angiotensin system: focus on angiotensin-(1–7). *Physiol. Rev., 2018, vol. 98, no. 1, pp. 505–553. doi: 10.1152/physrev.00023.2016*
121. Sarkaki A.R., Khaksari H.M., Soltani Z., Shahrokhi N., Mahmoodi M. Time-and dose-dependent neuroprotective effects of sex steroid hormones on inflammatory cytokines after a traumatic brain injury. *J. Neurotrauma., 2013, vol. 30, no. 1, pp. 47–54. doi: 10.1089/neu.2010.1686*
122. Seeland U., Regitz-Zagrosek V. Sex and gender differences in pharmacology. *Handb. Exp. Pharmacol., 2012, vol. 214, pp. 13–22. doi: 10.1007/978-3-642-30726-3_1*
123. Shenoy V., Grobe J.L., Qi Y., Ferreira A.J., Fraga-Silva R.A., Collamat G., Bruce E., Katovich M.J. 17β-Estradiol modulates local cardiac renin-angiotensin system to prevent cardiac remodeling in the DOCA-salt model of hypertension in rats. *Peptides, 2009, vol. 30, no. 12, pp. 2309–2315. doi: 10.1016/j.peptides.2009.09.005*
124. Shi S., Qin M., Shen B., Cai Y., Liu T., Yang F., Gong W., Liu X., Liang J., Zhao Q., Huang H., Yang B., Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiology, 2020, vol. 5, no. 7, pp. 802–810. doi: 10.1001/jamacardio.2020.0950*
125. Siddiqi H.K., Mehra M.R. COVID-19 illness in native and immunosuppressed states: a clinical–therapeutic staging proposal. *J. Heart Lung Transplant., 2020, vol. 39, no. 5, pp. 405–407. doi: 10.1016/j.healun.2020.03.012*
126. Sierpiński R., Pinkas J., Jankowski M., Zgliczyński W.S., Wierzba W., Gujski M., Szumowski Ł. Gender differences in the frequency of gastrointestinal symptoms and olfactory or taste disorders among 1942 non-hospitalized patients with COVID-19. *Pol. Arch. Intern. Med., 2020, vol. 130, no. 6, pp. 501–505. doi: 10.20452/pamw.15414*
127. Simonnet A., Chetboun M., Poissy J., Raverdy V., Noulette J., Duhamel A., Labreuche J., Mathieu D., Pattou F., Jourdain M; LICORN and the Lille COVID-19 and Obesity study group. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity, 2020, vol. 28, no. 7, pp. 1195–1199. doi: 10.1002/oby.22831*
128. Soltani Z., Shahrokhi N., Karamouzian S., Khaksari M., Mofid B., Nakhaee N., Reihani H. Does progesterone improve outcome in diffuse axonal injury? *Brain Inj., 2017, vol. 31, no. 1, pp. 16–23. doi: 10.1080/02699052.2016.1213421*
129. Spagnolo P.A., Manson J.E., Joffe H. Sex and gender differences in health: What the COVID-19 pandemic can teach us. *Ann. Intern. Med., 2020, vol. 173, no. 5, pp. 385–386. doi: 10.7326/M20-1941*
130. Stanhewicz A.E., Wenner M.M., Stachenfeld N.S. Sex differences in endothelial function important to vascular health and overall cardiovascular disease risk across the lifespan. *Am. J. Physiol. Heart Circ. Physiol., 2018, vol. 315, no. 6, pp. 1569–1588. doi: 10.1152/ajpheart.00396.2018*
131. Stelzig K.E., Canepa-Escaro F., Schiliro M., Berdnikovs S., Prakash Y., Chiarella S.E. Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. *Am. J. Physiol. Lung Cell Mol. Physiol., 2020, vol. 318, no. 6, pp. 1280–1281. doi: 10.1152/ajplung.00153.2020*
132. Straub R.H. The complex role of estrogens in inflammation. *Endocrine Rev., 2007, vol. 28, no. 5, pp. 521–574. doi: 10.1210/er.2007-0001*
133. Su H., Yang M., Wan C., Yi L.X., Tang F., Zhu H.Y., Yi F., Yang H.C., Fogo A.B., Nie X., Zhang C. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int., 2020, vol. 98, no. 1, pp. 219–227. doi: 10.1016/j.kint.2020.04.003*
134. Suba Z. Prevention and therapy of COVID-19 via exogenous estrogen treatment for both male and female patients. *J. Pharm. Pharm. Sci., 2020, vol. 23, no. 1, pp. 75–85. doi: 10.18433/jpps31069*
135. Szekeres-Bartho J., Wegmann T. A progesterone-dependent immunomodulatory protein alters the Th1Th2 balance. *J. Reprod. Immunol., 1996, vol. 31, no. 1–2, pp. 81–95. doi: 10.1016/0165-0378(96)00964-3*
136. Tam A., Wadsworth S., Dorscheid D., Man S.-F.P., Sin D.D. Estradiol increases mucus synthesis in bronchial epithelial cells. *PloS One, 2014, vol. 9, no. 6: e100633. doi: 10.1371/journal.pone.0100633*
137. Taneja V. Sex hormones determine immune response. *Front. Immunol., 2018, vol. 9: 1931. doi: 10.3389/fimmu.2018.01931*
138. Tauber S.C., Eiffert H., Brück W., Nau R. Septic encephalopathy and septic encephalitis. *Expert Rev. Anti Infect. Ther., 2017, vol. 15, no. 2, pp. 121–132. doi: 10.1080/14787210.2017.1265448*
139. Tisoncik J.R., Korth M.J., Simmons C.P., Farrar J., Martin T.R., Katze M.G. Into the eye of the cytokine storm. *Microbiol. Mol. Biol. Rev., 2012, vol. 76, no. 1, pp. 26–32. doi: 10.1128/MMBR.05015-11*
140. Toljan K. Letter to the editor regarding the viewpoint "Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanism". *ACS Chem. Neurosci., 2020, vol. 11, no. 8, pp. 1192–1194. doi: 10.1021/acschemneuro.0c00174*
141. Toppozada H., Toppozada M., El-Ghazzawi I., Elwany S. The human respiratory nasal mucosa in females using contraceptive pills: an ultramicroscopic and histochemical study. *J. Laryngol. Otol., 1984, vol. 98, no. 1, pp. 43–51. doi: 10.1017/s002221510014616x*
142. Tukiainen T., Villani A.C., Yen A., Rivas M.A., Marshall J.L., Satija R., Aguirre M., Gauthier L., Fleharty M., Kirby A., Cummings B.B., Castel S.E., Karczewski K.J., Aguet F., Byrnes A; GTEx Consortium; Laboratory, Data Analysis &Coordinating Center (LDACC)—Analysis Working Group; Statistical Methods groups—Analysis Working Group; Enhancing GTEx (eGTEx) groups; NIH Common Fund; NIH/NCI; NIH/NHGRI; NIH/NIMH; NIH/NIDA; Biospecimen Collection Source Site—

NDRI; Biospecimen Collection Source Site—RPCI; Biospecimen Core Resource—VARI; Brain Bank Repository—University of Miami Brain Endowment Bank; Leidos Biomedical—Project Management; ELSI Study; Genome Browser Data Integration &Visualization—EBI; Genome Browser Data Integration & Visualization—UCSC Genomics Institute, University of California Santa Cruz, Lappalainen T., Regev A., Ardlie K.G., Hacohen N., MacArthur D.G. Landscape of X chromosome inactivation across human tissues. *Nature, 2017, vol. 550, no. 7675, pp. 244–248. doi: 10.1038/nature24265*

143. Turner A.J., Hiscox J.A., Hooper N.M. ACE2: from vasopeptidase to SARS virus receptor. *Trends Pharmacol. Sci., 2004, vol. 25, no. 6, pp. 291–294. doi: 10.1016/j.tips.2004.04.001*
144. Varga Z., Flammer A.J., Steiger P., Haberecker M., Andermatt R., Zinkernagel A.S., Mehra M.R., Schuepbach R.A., Ruschitzka F., Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet, 2020, vol. 395, no. 10234, pp. 1417–1418. doi: 10.1016/S0140-6736(20)30937-5*
145. Vermillion M.S., Ursin R.L., Kuok D.I.T., Vom Steeg L.G., Wohlgemuth N., Hall O.J., Fink A.L., Sasse E., Nelson A., Ndeh R., McGrath-Morrow S., Mitzner W., Chan M.C.W., Pekosz A., Klein S.L. Production of amphiregulin and recovery from influenza is greater in males than females. *Biol. Sex Differ., 2018, vol. 9: 24. doi: 10.1186/s13293-018-0184-8*
146. Voigt R.M., Forsyth C.B., Green S.J., Mutlu E., Engen P., Vitaterna M.H., Turek F.W., Keshavarzian A. Circadian disorganization alters intestinal microbiota. *PLoS One, 2014, vol. 9, no. 5: e97500. doi: 10.1371/journal.pone.0097500*
147. Vom Steeg L.G., Klein S.L. SeXX matters in infectious disease pathogenesis. *PLoS Pathog., 2016, vol. 12, no. 2: e1005374. doi: 10.1371/journal.ppat.1005374*
148. Wang D., Hu B., Hu C., Zhu F., Liu X., Zhang J., Wang B., Xiang H., Cheng Z., Xiong Y., Zhao Y., Li Y., Wang X., Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA, 2020, vol. 323, no. 11, pp. 1061–1069. doi: 10.1001/jama.2020.1585*
149. Wang S., Han P., Xiao F. Manifestations of liver injury in 333 hospitalized patients with coronavirus disease 2019. *Chinese J. Digest., 2020, vol. 40, no. 00: E008. doi: 10.3760/cma.j.issn.0254-1432.2020.0008*
150. Warren-Gash C., Blackburn R., Whitaker H., McMenamin J, Hayward A.C. Laboratory-confirmed respiratory infections as triggers for acute myocardial infarction and stroke: a self-controlled case series analysis of national linked datasets from Scotland. *Eur. Respir. J., 2018, vol. 513, no. 1: 701794. doi: 10.1183/13993003.01794-2017*
151. Lv D., Qin C., Gu D., Zhang B., Chen W., Hou J., Song N., Zeng G., Ren S. Sex differences in severity and mortality among patients with COVID-19: evidence from pooled literature analysis and insights from integrated bioinformatic analysis. *ArXiv, 2020. doi: 2003.13547*
152. WHO. WHO Coronavirus Disease (COVID-19) Dashboard. *URL: https://covid19.who.int/*
153. Wong S.H., Lui R.N., Sung J.J. COVID19 and the digestive system. *J. Gastroenterol. Hepatol., 2020, vol. 35, no. 5, pp. 744–748. doi: 10.1111/jgh.15047*
154. Wu Y., Xu X., Chen Z., Duan J., Hashimoto K., Yang L., Liu C., Yang C. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav. Immun., 2020, vol. 87, pp. 18–22. doi: 10.1016/j.bbi.2020.03.031*
155. Xia H., Lazartigues E. Angiotensin-converting enzyme 2: central regulator for cardiovascular function. *Curr. Hypertens. Rep., 2010, vol. 12, no. 3, pp. 170–175. doi: 10.1007/s11906-010-0105-7*
156. Xiang P., Xu X.M., Gao L.L., Wang H.Z., Xiong H.F., Li R.H. First case of 2019 novel coronavirus disease with Encephalitis. *ChinaXiv, 2020, vol. 202003: 00015.*
157. Xiao F., Tang M., Zheng X., Liu Y., Li X., Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology, 2020, vol. 158, no. 6, pp. 1831–1833. doi: 10.1053/j.gastro.2020.02.055*
158. Xu Y., Li X., Zhu B., Liang H., Fang C., Gong Y., Guo Q., Sun X., Zhao D., Shen J., Zhang H., Liu H., Xia H., Tang J., Zhang K., Gong S. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat. Med., 2020, vol. 26, no. 4, pp. 502–505. doi: 10.1038/s41591-020-0817-4*
159. Xu Z., Shi L., Wang Y., Zhang J., Huang L., Zhang C., Liu S., Zhao P., Liu H., Zhu L., Tai Y., Bai C., Gao T., Song J., Xia P., Dong J., Zhao J., Wang F.S. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir. Med., 2020, vol. 8, no. 4, pp. 420–422. doi: 10.1016/S2213-2600(20)30076-X*
160. Zhang W.C., Kaushal S., Yeo D. Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol. Hepatol., 2020, vol. 5, no. 4, pp. 335–337. doi: 10.1016/S2468-1253(20)30048-0*
161. Young G.B. Encephalopathy of infection and systemic inflammation. *J. Clin. Neurophysiol., 2013, vol. 305, no. 4, pp. 454–461. doi: 10.1097/WNP.0b013e3182a73d83*
162. Zhang C., Shi L., Wang F.-S. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol. Hepatol., 2020, vol. 5, no. 5, pp. 428–430. doi: 10.1016/S2468-1253(20)30057-1*
163. Zhang H., Kang Z., Gong H., Xu D., Wang J., Li Z., Cui X., Xiao J., Meng T., Zhou W., Liu J., Xu H. The digestive system is a potential route of 2019-nCoV infection: a bioinformatics analysis based on single-cell transcriptomes. *BioRxiv, 2020. doi: 10.1101/2020.01.30.927806*
164. Zhang H., Baker A. Recombinant human ACE2: acing out angiotensin II in ARDS therapy. *Crit. Care, 2017, vol. 21, no. 1: 305. doi: 10.1186/s13054-017-1882-z*
165. Zhang J., Wang X., Jia X., Li J., Hu K., Chen G., Wei J., Gong Z., Zhou C., Yu H., Yu M., Lei H., Cheng F., Zhang B., Xu Y., Wang G., Dong W. Risk factors for disease severity, unimprovement, and mortality of COVID-19 patients in Wuhan, China. *Clin. Microbiol. Infect., 2020, vol. 26, no. 6, pp. 767–772. doi: 10.1016/j.cmi.2020.04.012*
166. Zhang W., Du R.H., Li B., Zheng X.S., Yang X.L., Hu B., Wang Y.Y., Xiao G.F., Yan B., Shi Z.L., Zhou P. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg. Microbes Infect., 2020, vol. 9, no. 1, pp. 386–389. doi: 10.1080/22221751.2020.1729071*
167. Zhang Y., Xiao M., Zhang S., Xia P., Cao W., Jiang W., Chen H., Ding X., Zhao H., Zhang H., Wang C., Zhao J., Sun X., Tian R., Wu W., Wu D., Ma J., Chen Y., Zhang D., Xie J., Yan X., Zhou X., Liu Z., Wang J., Du B., Qin Y., Gao P., Qin X., Xu Y., Zhang W., Li T., Zhang F., Zhao Y., Li Y., Zhang S. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. *N. Engl. J. Med., 2020, vol. 382: e38. doi: 10.1056/NEJMc2007575*

168. Zheng Y.-Y., Ma Y.-T., Zhang J.-Y., Xie X. COVID-19 and the cardiovascular system. *Nat. Rev. Cardiol., 2020, vol. 17, no. 5, pp. 259–260. doi: 10.1038/s41569-020-0360-5*
169. Zhou F., Yu T., Du R., Fan G., Liu Y., Liu Z., Xiang J., Wang Y., Song B., Gu X., Guan L., Wei Y., Li H., Wu X., Xu J., Tu S., Zhang Y., Chen H., Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet, 2020, vol. 395, no. 10229, pp. 1054–1062. doi: 10.1016/S0140-6736(20)30566-3*
170. Zhou Z., Zhao N., Shu Y., Han S., Chen B., Shu X. Effect of gastrointestinal symptoms in patients with COVID-19. *Gastroenterology, 2020, vol. 158, no. 8, pp. 2294–2297. doi: 10.1053/j.gastro.2020.03.020*

Авторы:

Хаксари М., д.н., профессор физиологии, Исследовательский центр нейронаук, Институт нейрофармакологии, Керманский университет медицинских наук, г. г. Керман, Иран; Исследовательский центр эндокринологии и метаболизма, Институт фундаментальных и клинических физиологических наук, медицинский факультет, Керманский университет медицинских наук, г. Керман, Иран;
Сабет Н., к.н. (физиология), Исследовательский центр тропических и инфекционных заболеваний, Керманский университет медицинских наук, г. Керман, Иран; Исследовательский центр эндокринологии и метаболизма, Институт фундаментальных и клинических физиологических наук, медицинский факультет, Керманский университет медицинских наук, г. Керман, Иран; старший ассистент, кафедра физиологии и фармакологии медицинского факультета им. А. Афзалипюра, Керманский университет медицинских наук, г. Керман, Иран;
Солтани З., д.н., профессор физиологии, Исследовательский центр эндокринологии и метаболизма, Институт фундаментальных и клинических физиологических наук, медицинский факультет, Керманский университет медицинских наук, г. Керман, Иран; Исследовательский центр тропических и инфекционных заболеваний, Керманский университет медицинских наук, г. Керман, Иран; кафедра физиологии и фармакологии, медицинский факультет им. А. Афзалипюра, Керманский университет медицинских наук, г. Керман, Иран;
Башири Х., д.н., профессор фармакологии, Научно-исследовательский центр нейронаук, Институт нейрофармакологии, Керманский университет медицинских наук, г. Керман, Иран; медицинский факультет Сирджанского университета медицинских наук, Сирджан, Иран.

Authors:

Khaksari M., MD, PhD, Professor of Physiology, Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran; Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran;
Sabet N., PhD (Physiology), Senior Assistant, Research Center of Tropical and Infectious Diseases, Kerman University of Medical Sciences, Kerman, Iran; Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran; Department of Physiology and Pharmacology, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran;
Soltani Z., MD, PhD, Professor of Physiology, Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran; Research Center of Tropical and Infectious Diseases, Kerman University of Medical Sciences, Kerman, Iran;Department of Physiology and Pharmacology, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran;
Bashiri H., MD, PhD, Professor of Pharmacology, Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran; Sirjan Faculty of Medicine, Sirjan University of Medical Sciences,Sirjan, Iran.

Поступила в редакцию 09.01.2021
Принята к печати 10.04.2021

Received 09.01.2021
Accepted 10.04.2021