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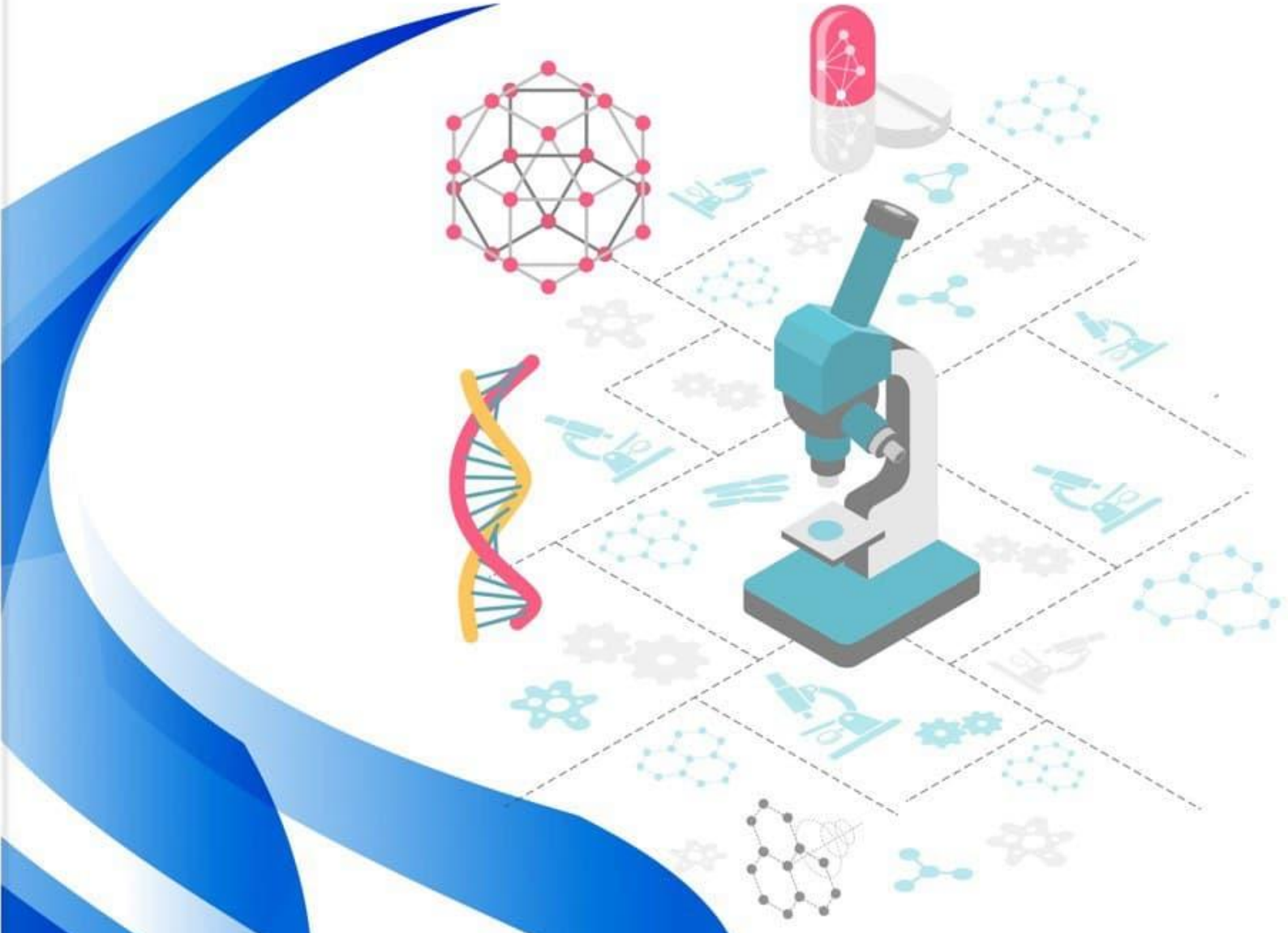

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Editorial board

Institute of Nuclear Medicine and Allied Sciences (INMAS), India
Brig SK Mazumdar Marg, Timarpur, New Delhi, Delhi 110054 India

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SARS-COV-2 AND KIDNEY DAMAGE

Akhmedova N.Sh., Rakhimova D.S., Amonov M.K.,
Bukhara State Medical Institute, Bukhara, Uzbekistan

Abstract: The COVID-19 pandemic has been ongoing on the planet for more than 3 years, but scientists have not yet reached the complete identification of the SARS-CoV-2 virus itself and its effect on the body. Therefore, it is vital not only a detailed and careful study by virologists of SARS-CoV-2 and its variations, but also an understanding of the fundamental physiological and immunological processes underlying the clinical manifestations of COVID-19. The purpose of the study is to analyze the available scientific publications to identify the features of the influence of the SARS-CoV-2 virus on the nephrological system.

Keywords: SARS-CoV-2, kidney pathology, pandemic

Relevance. At present, the world community is faced with a new infectious disease that has not only medical, but also enormous socio-economic significance - the COVID-19 pandemic. As you know, a new strain of coronavirus causes a dangerous infectious disease in humans, most often manifested by interstitial pneumonia. But more and more published data indicate that SARS-CoV-2 also penetrates into other parts of the body, such as the heart, blood vessels, liver, intestines, kidneys, and causes multisystem effects, the consequences of which are devastating [2].

With the application of evidence-based therapies and new treatments, the short-term survival of these patients is changing in a positive direction. But more recently, clinicians and scientists have argued that the number of people at risk of adverse long-term outcomes from COVID-19 will continue to rise.

Clinicians from different countries began to note that among the infected, the number of people with renal insufficiency has sharply increased. Also, in a study published in April 2020, Chinese experts noted that 27% of hospitalized patients with COVID-19 had kidney damage, 59% had changes in urine tests [3-6].

According to the Ministry of Health of Russia, in addition to patients with chronic kidney disease (CKD), 20-30% of patients hospitalized with COVID-19 develop acute renal failure (ARF), which increases the need for dialysis. However, the appearance of clinical signs of acute renal failure against the background of

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COVID-19 is considered an unfavorable prognosis for the survival of patients, because about 50% of them die [1,2].

The purpose of the study is to analyze the available scientific publications to identify the features of the influence of the SARS-CoV-2 virus on the nephrological system.

Materials and methods. A search was made for modern foreign and local scientific literature sources on the Internet electronic network using the databases: Elibrary, Medscape, PubMed, on the impact of coronavirus infection on the kidneys and the risks of severe disease in people with an advanced state of health.

The work was guided by the results of research by scientists from China, Great Britain, Italy, Australia, USA, Germany and Russia [6,9].

The results of the study and their discussion The COVID-19 pandemic has been ongoing on the planet for more than 3 years, but scientists have not yet reached the complete identification of the SARS-CoV-2 virus itself and its effect on the body. Therefore, it is vital not only a detailed and careful study by virologists of SARS-CoV-2 and its variations, but also an understanding of the fundamental physiological and immunological processes underlying the clinical manifestations of COVID-19 [1,11,15].

As the pandemic progressed, it became clear that the pathology inherent in COVID-19 is not limited to the respiratory tract, but can also involve other organs and systems. As experience has accumulated, evidence has emerged in the literature that kidney disease is an important risk factor for severe COVID‑19 and its fatal outcome [3,4,7]. Moreover, this does not depend on whether there was a kidney disease before infection or arose already during a coronavirus infection.

According to the 2020 report of the Italian Health Institute, chronic renal failure (CRF) is among the main comorbidities in those who died from COVID-19, accounting for 23.1% and being in 4th place in frequency after arterial hypertension (66%), type 2 diabetes mellitus (29%) and coronary heart disease (27.9%) [4,12,13].

At the moment, it is not known whether the virus affects the nephrological system directly or is it a side effect of infection. However, it has been confirmed that people with chronic diseases are more difficult to carry the infection than people without concomitant diseases [6,14].

Literature data confirm the assumption of an increased prevalence of COVID 19 among patients on hemodialysis compared to the general population, although

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their number in publications of different authors varies in a wide range (from 2.5% to 36% and even 49%). An analysis of these data suggests that the high variability of this indicator depends on a number of factors, including the geographic region where a particular dialysis center operates, its size, the composition of patients, in particular, the ratio of the number of hospital and outpatient patients, as well as the organization their surveys [5,10,12].

The multiorgan and, in particular, renal tropism of SARS‑Cov‑2 has been considered by many authors as a factor underlying kidney damage in COVID‑19. When examining kidney biopsies of patients who died from COVID‑19, in 60% of cases, the presence of SARS‑CoV‑2 RNA was found in them. In AKI, viral RNA was detected more frequently than in cases without AKI [5,11]. The data obtained allow us to conclude that there is a correlation between extra-respiratory and, in particular, renal tropism of SARS-CoV-2 and the severity of COVID-19 [3].

It is already known that COVID-19 uses the angiotensin-converting enzyme type 2 (ACE2) receptor to enter the cell. The kidneys are organs more susceptible to damage in COVID-19 due to the expression of angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase-4. Due to the fact that the pathogenesis of kidney damage in coronavirus infection is multifactorial, there are several hypotheses of damage: direct cytopathic damage, immunogenic damage, iatrogenic damage, rhabdomyolysis, impaired microcirculation of the kidneys and impaired coagulation inside the renal vessels [4,7,9].

Cytopathic damage is confirmed by the detection of coronavirus fragments in the urine of patients with COVID-19 by the polymerase chain reaction method. According to L. Peng et al. SARS-CoV-2 RNA was present in all types of samples studied (scrapings from the upper respiratory tract, blood, urine, anal scrapings), although not all types of samples were positive at the same time. According to the results of light microscopy, Su H. etal also noted in patients with COVID-19 diffuse damage to the proximal nephron tubules with signs of vacuolar degeneration of epitheliocytes, and even areas of necrosis.

It is preferred that there are two main mechanisms of direct damage to kidney cells. The first hit of the virus with blood in the urine occurs when the kidney tubules are damaged due to the "cytokine storm". Or the virus is excreted into the urine directly from the urothelium due to the high number of ACE-2 receptors in the proximal convoluted tubules of the kidneys, in the renal corpuscle (podocytes, mesangial cells), in the endothelium of the capillaries of the vascular vascular [2].

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The immunogenic mechanism of kidney damage develops as a result of the fact that the COVID-19 viral infection causes a massive release of cytokines, macrophages are activated and lymphocytes infiltrate the kidney parenchyma.

In patients, at the height of inflammation and the "cytokine storm", there is a decrease in filtration pressure and glomerular filtration rate, with a parallel decrease in the intensity of the renal blood flow, which can lead to type 1 cardiorenal syndrome and the development of acute renal failure with the subsequent development of chronic kidney disease (CKD) [5-9].

People who have recovered from covid-19 have a greater risk of kidney disease, even if they only experienced mild to moderate covid-19 symptoms and were not admitted to hospital, shows a study published in the *Journal of the American Society of Nephrology*. Damage to organ systems such as the kidneys is a recognised complication of the post-acute phase for patients who were severely ill during the acute phase of covid-19, but the risks for patients who experienced milder covid-19 is less clear [9].

Iatrogen or drug damage due to the use of nephrotoxic drugs (hydroxychloroquine, cyclosporine, aminoglycosides, cephalosporins) in the treatment of coronavirus infection [7]. Kidney damage in patients with COVID-19 may manifest as hematuria or proteinuria, primary pyelonephritis, glomeluronephritis, acute renal failure, acute kidney injury (AKI) with a transition to CKD, which predict a greater risk.

Chinese scientists have published the results of the first prospective cohort study that reported on the relationship between kidney disease and mortality in hospitalized patients with COVID-19. At the same time, about 13% of patients who died had disorders in the nephrological system [6,9].

The authors also noted that AKI was diagnosed in such patients more often than heart disease (23%) and liver disease (23%). 25% of patients with acute renal failure on the background of coronavirus infection needed continuous hemodialysis, and 80% of patients died in the first week of admission to the hospital [7].

Independent risk factors for the development of AKI in patients with COVID-19 are the need for mechanical ventilation or vasopressor drug therapy, as well as advanced age, arterial hypertension, diabetes mellitus, and cardiovascular disease. In a study by Jamie S. et al. it was found that 37% of covid-infected patients were diagnosed with AKI, and there was a strong association with respiratory failure.

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AKI occurred in 90% of patients on mechanical ventilation, while among other patients, only in 21.7% of cases. AKI in patients with coronavirus disease was accompanied by a worse prognosis: 35% of patients died at the time of publication of the results (May 2020) [4]. According to a study by Kissling S., more than 40% of covid patients had signs of impaired renal function and 5.1% developed AKI during their stay in the hospital. Moreover, between the stages of AKI and death, there was a relationship with an increased risk of death by 4 times among patients with stage 3 AKI. However, according to the results of a retrospective meta-analysis, a trend towards an increase in the mortality of patients with AKI by 13 times was revealed [3].

An analysis of the causes of deaths in coronavirus infection showed that these are mainly patients over 60 years of age with concomitant diseases that contribute to the development of critical conditions with a sad ending. And patients with CKD are a group with a particularly high risk of contracting COVID-19 and high mortality in the development of the disease due to immunosuppression and a tendency to severe infectious diseases [5,6]. This is due to the fact that the cause of CKD is the main population diseases (diabetes, hypertension, obesity, atherosclerosis), as well as old age. These groups of patients are different. According to Shahid Z. et al. the mortality rate of patients with COVID-19 without concomitant diseases was 1.4%, while against the background of CKD it was 13.2%, which was comparable with the group of patients with cardiovascular diseases.

What is the mechanism of chronic kidney injury in SARS-CoV-19? What are the long-term effects of COVID-19 on the kidneys?

The scientific literature discusses 3 mechanisms of chronic kidney injury in SARS-CoV-19:

First, COVID-19 can affect the kidneys in different ways, and the contribution of acting factors may change over time. The conclusion of the study, published in the Journal of the American Society of Nephrology, shows that patients who have recovered from Covid-19 with mild to moderate symptoms of the disease have a higher risk of developing chronic kidney disease. Many of the direct and indirect effects of the SARS-CoV-2 virus may persist during recovery and may lead to recurrent episodes of inflammation, relapses of AKI, and an increased risk of CKD [8].

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Second, there seems to be a bidirectional relationship between COVID-19 and CKD. Mild CKD (often late diagnosed) may increase the risk of developing AKI, with persistent renal dysfunction, delayed recovery progressing to CKD.

Thirdly, chronic kidney damage under the influence of complications of COVID-19 (hypercoagulation-ischemia of the kidneys, increased blood glucose, pathology of the brain and heart, increased risk of fibrosis, impaired water and electrolyte metabolism) and the action of nephrotoxic drugs (NSAIDs, antibiotics, glucocorticoids) [8,11].

Kidney damage in COVID 19 can be considered as a consequence of a complex of mechanisms induced by the SARS CoV 2 virus directly or indirectly. Currently, two main pathophysiological mechanisms can be distinguished. The first includes the direct cytopathic effect of SARS CoV 2 on the renal epithelium with the development of acute tubulonecrosis and immune-mediated damage to the renal interstitium. The second is a cytokine storm syndrome that occurs as a result of hyperactivation of the immune system with the development of acute renal and multiorgan inflammatory damage, accompanied by hypoxia, persistent hypotension, rhabdomyolysis, hyperactivation of the coagulation cascade, and microcirculation disorders [3,6,9,12].

Over the course of the pandemic, as experience has accumulated, evidence has emerged in the literature that kidney pathology is an important risk factor for severe COVID-19 and its death. Moreover, this does not depend on whether there was a kidney disease before infection or arose already during a coronavirus infection [7,13].

A number of observations demonstrated a high frequency (40 to 75%) of detection of urinary syndrome in the form of different levels of proteinuria and/or hematuria against the background of SARS-CoV-2 infection, including in patients who had no previous signs of CKD. In 5–7% of cases, these changes were accompanied by the development of acute kidney injury.

Conclusions. Clinical manifestations of COVID-19 are mainly represented by symptoms of damage to the respiratory system, but special attention should be paid to urogenital manifestations and complications.

The question of the nature of kidney pathology in COVID-19 remains open. In a number of risk factors for the development of chronic kidney disease, another global factor has been added - infection with a virus. SARS‑ Cov‑ 2

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Monitoring of the functions of the nephrological system, in patients with symptoms of varying severity of COVID-19, is of great importance. And emergency measures to protect kidney function and stop the "cytokine storm" can be crucial for improving the condition and a favorable outcome of the disease.

The COVID-19 pandemic provides a unique opportunity to develop and deepen our knowledge of the development of infection-associated AKI and CKD, requiring the development of new treatments to slow the progression of kidney disease.

Multi-organ and, in particular, renal tropism of SARS-Cov-2 is considered by many authors as a factor underlying chronic kidney damage. This indicates the need for timely monitoring, prevention and, if necessary, specialized treatment of kidney damage in people carrying COVID-19.

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