



# Epidemiological, clinical and morphological aspects of kidney damage in COVID-19

Batir Daminov<sup>ID</sup>, Sherzod Abdullaev<sup>\*</sup><sup>ID</sup>, Olimkhon Sharapov<sup>ID</sup>, Ranokhon Igamberdieva<sup>ID</sup>

Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

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## ABSTRACT

The mini-review presents modern data on the epidemiology, clinical and morphological aspects of kidney damage in COVID-19. Potential mechanisms of kidney involvement in the clinical picture of the disease may include cytokine damage, cross-organ damage, and systemic effects that determine the treatment strategy. These mechanisms are closely interrelated and are especially important for individuals undergoing extracorporeal therapy and kidney transplants. Autopsy data provide evidence of SARS-CoV-2 virus invasion into kidney tissue with damage to tubular epithelial cells and podocytes, and erythrocyte aggregation in persons with severe COVID-19. By including people with chronic kidney disease in planned COVID-19 research protocols, an evidence base for effective and safe treatments can be generated.

### Implication for health policy/practice/research/medical education:

In this mini review we tried to clarify epidemiological, clinical and morphological aspects of kidney damage in COVID-19. Kidney diseases are one of the main common complications of COVID-19 and a significant risk factor for death. Therefore, monitoring of kidney function should begin in patients with mild respiratory symptoms of COVID-19.

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## Introduction

Novel coronavirus disease (COVID-19) is a recently identified infectious disease caused by the severe acute respiratory syndrome virus (SARS)-coronavirus (CoV) type 2, initially manifesting as an acute respiratory disease with interstitial and alveolar pneumonia, with further possible damage to various organs and systems: kidneys, heart, digestive tract, circulatory and nervous systems. The rapidly spreading outbreak, which first occurred in December 2019 in Wuhan, Hubei province, China, is of high concern over the emergence of a global pandemic.

In March 2020, the World Health Organization (WHO) announced the state of a global pandemic associated with the very rapid spread of the SARS-CoV-2 virus. The virus causes a wide range of clinical manifestations, from mild symptoms to acute respiratory distress syndrome

(ARDS) in adults. The available evidence suggests that the potentially severe acute respiratory infection COVID-19 caused by SARS-CoV-2 poses a real threat to patients with concomitant diseases such as diabetes mellitus, hypertension, cardiovascular, renal or hepatic impairment (1).

Clinical manifestations of the disease can vary widely from asymptomatic carriage or minor symptoms of SARS to severe respiratory failure, often requiring ventilation support (2). The main links of pathogenesis are considered to be direct viral damage to the upper respiratory tract and lungs, which in some cases is accompanied by an inadequate immune response with the release of a large number of cytokines and chemokines, the development of a "cytokine storm" pattern and subsequent involvement of the coagulation system (3).

\*Corresponding author: Sherzod Abdullaev, Email: sh.abdullaev@tashpmi.uz, Sherzod.abdullaev83@gmail.com

The factors associated with a severe course of infection and a high risk of death are old age, overweight, and the presence of comorbid pathologies, including diabetes mellitus, arterial hypertension, cancer, chronic cardiovascular and pulmonary diseases as well as kidney disease, especially requiring renal replacement therapy (RRT) (4). All immunocompromised patients, including organ transplant recipients and cancer patients receiving chemotherapy, are also at high risk (5).

Seven different coronaviruses are known to have the ability to infect human cells (6). Some of these viruses cause mild upper respiratory symptoms, while others are potentially fatal (7). According to the WHO, in 2020 SARS-CoV-2 (COVID-19) infection spread rapidly in many countries and reached pandemic proportions (8). SARS-CoV-2 is a line B beta coronavirus that causes severe respiratory illness (9). It has several transmembrane glycoproteins that facilitate molecular interaction with human cells (10). S-glycoproteins SARS-CoV-2 contain two functional subunits: S1-ensures the binding of the receptor to the angiotensin converting enzyme 2 (ACE2), and S2-is responsible for the fusion of viral and cell membranes (11).

To date, there is no specific vaccine against the SARS-CoV-2 virus, and there is also no effective drug for the treatment of COVID-19. Therefore, to reduce the overall level of morbidity and mortality, it is necessary to identify risk factors.

The main clinical manifestations of COVID-19 in humans are known; fever, unproductive cough, shortness of breath, myalgia, fatigue, normal or low leukocyte count, typical changes in the lungs on computed tomography in the form of “ground glass” darkening (9). Until now, it has been reported that the main risk factors for COVID-19, contributing to severe clinical course and death, include old age, immune deficiencies, and comorbid diseases (12). Some researchers indicate that over 70% of patients who died from COVID-19 had diabetes or cardiovascular disease (13).

The prevalence of CKD in the UK in patients with COVID-19 has reached 16% (14). Wang et al believe that CKD is directly correlated with the severity of the clinical course of COVID-19 (odds ratio 2.22; 95% CI: 1.14, 4.31), with moderate heterogeneity ( $I^2 = 38.1\%$ ) (15). In a meta-analysis that included 1389 patients with COVID-19, the prevalence of CKD was significantly higher among patients with severe COVID-19 versus mild; 3.3% versus 0.4% (odds ratio 3.03, 95% CI: 1.09–8.47) (16). The results of the study by Oyelade et al demonstrate that in patients with a severe clinical picture of COVID-19, CKD is present in 47 (83.93%) of 56 people (16). Pei et al note that CKD is a risk factor for coronavirus infection. For example, 251 (75.4%) of 333 patients with COVID-19 had kidney disease (17).

Additionally, researchers began to note an increase in

kidney disease against the background of coronavirus infection in the form of acute renal failure (ARF) (18). Chinese doctors were the first to note the development of ARF against the background of COVID-19 (5). However, the authors show different statistics. According to studies from Italy (19) and the USA (20), cases of ARF were registered in more than 20% of patients who were in critical condition. Rabb in his observations noted the development of ARF in 5% of hospitalized patients in the general cohort, and in 50% of patients who underwent intensive therapy in the intensive care unit (21).

The most common symptom in CKD in patients with coronavirus infection was proteinuria, which results from direct damage to podocytes as a result of ACE2 expression (22). The results of a study by Martinez-Rojas et al demonstrate the presence of hematuria in 20% of COVID-19 infected patients (23). The authors explain the pathogenesis of hematuria against the background of COVID-19 as a consequence of endotheliitis, leading to coagulopathy, and destruction of the filtration barrier in the renal corpuscles (23). Some authors believe that the emerging proteinuria and hematuria in a COVID-19 patient are independent predictors of the development of the critical stage of the disease (24). Moreover, the relief of proteinuria and hematuria in coronavirus infection is possible, subject to intensive therapy, but not earlier than 3 weeks after the onset of the disease (25).

The results of observation of 116 patients who were admitted to a hospital with a confirmed diagnosis of COVID-19 showed that only 10.8% of people had short-term azotemia (an increase in urea levels up to 26  $\mu\text{mol/L}$ ), and 7.2% of patients had albuminuria (26). The authors did not record ARF in any of the patients. Moreover, all patients gradually returned to normal without specific renal treatment. Wang et al consider temporary impairment of renal function as secondary trauma caused by hypoxia (27). The authors also evaluated the filtration function of the kidneys in patients with and without chronic kidney disease (CKD) against the background of coronavirus infection. Thus, the glomerular filtration rate (GFR) averaged  $15.96 \pm 8.72$  mL/min and  $127.96 \pm 9.65$  mL/min (normal >90 mL/min), respectively (30). Remarkably, in this study, scientists did not record a significant change in the dynamics of the GFR throughout the entire period of treatment of viral pneumonia in patients of both groups ( $P = 0.152$ ) (30). Guan et al also presented the results of treatment of 1590 patients with confirmed COVID-19 (22). The study of renal function in patients of this cohort ( $n = 752$ ) showed that the level of creatinine above 133.0  $\mu\text{mol/L}$  was only in 12 (1.6%) people (22).

According to the study by Stolyarevich et al morphological signs of kidney damage in patients who died from COVID-19 are diverse (28).

In patients with a high frequency, chronic changes caused by old age and concomitant pathology; arterial

hypertension, diabetes mellitus and metabolic syndrome were detected. Thus, glomerulosclerosis of varying severity was detected in approximately 46% of all patients, in 26% of them it was accompanied by interstitial fibrosis and tubular atrophy. Signs of hypertensive nephroangiosclerosis were detected in 29% of cases, in nine patients with morbid obesity secondary focal segmental glomerulosclerosis was observed against the background of severe glomerulomegaly, in four more cases there were signs of diabetic nephropathy. In two cases, the morphological picture corresponded to chronic interstitial nephritis. One patient had a cholesterol crystal embolism with the development of ischemic nephropathy. Generally, according to morphological studies, preexisting pathology was found in 43% of patients, which, nevertheless, in most cases was not manifested by a decrease in the GFR. In contrast, not all patients who had a decrease in GFR at the time of admission had morphological changes characteristic of CKD.

Thus, morphological signs of preexisting renal pathology were observed in 62% of patients who had a decrease in GFR at the time of hospitalization, and in 24% of patients with normal renal function on admission ( $P < 0.01$ ).

The morphological substrate of acute kidney injury (AKI) in patients who died from COVID-19, in the overwhelming majority of cases, turned out to be acute damage to the tubular epithelium, which was observed to some extent in almost all patients with AKI. Despite the fact that more than 3/4 of patients with normal renal function also showed signs of acute tubular damage, in most cases they were limited to only complete or partial loss of the brush border, and the damage was generally less pronounced than in patients without AKI. Thus, severe acute tubular necrosis with symptoms of karyolysis and detachment of tubulocytes from the tubular basement membrane was observed in 60% of cases of AKI and 31% of cases of normal renal function. A more rare variant of damage was tubular epithelium dystrophy by the type of nonisometric vacuolization.

In addition, approximately half of the patients, regardless of the clinical picture, had pronounced venous plethora with blood stasis in the peritubular capillaries and venules. In some cases, these changes were combined with pronounced plethora of glomeruli and the formation of erythrocyte sludge and blood stasis in them without thrombosis and fibrinoid necrosis.

Thus, it seems that kidney damage in COVID-19 is in most cases determined by acute tubular injury, associated mainly with the severity of the lung damage and prolonged mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

According to Italian researchers from Lombardy, potential mechanisms of kidney involvement in the clinical picture of the disease may include cytokine damage, cross-organ damage and systemic effects that

determine the treatment strategy (29). These mechanisms are closely interrelated and are especially important for individuals on extracorporeal therapy and with a kidney transplant.

In patients with cytokine storm syndrome, AKI can develop as a result of increased vascular permeability, intrarenal inflammation, as part of the cardiorenal syndrome type 1. The latter includes systemic endothelial dysfunction manifested by pleural effusion, edema, intra-abdominal hypertension, fluid loss in “the third space” and hypotension. ECMO, invasive mechanical ventilation, and continuous RRT can also promote cytokine production.

Cross-organ damage also affects the heart-kidney axis (cattle type 1) in patients with COVID-19. Cardiomyopathy and acute viral myocarditis, contributing to the overload of the renal veins, hypotension, renal hypoperfusion, lead to a decrease in the GFR. Rhabdomyolysis, metabolic acidosis, and hyperkalemia are also common in COVID-19 patients and are associated with hemodynamic instability.

Patients receiving programmed hemodialysis are a particularly vulnerable category in a pandemic. One of the first reports from Wuhan concerned one of 61 dialysis centers, where 37 of 230 patients and 33 employees developed COVID-19 within a month. The cause of death of 6 out of 7 deaths was determined to be cardiovascular and not directly related to viral infection. Patients with COVID-19 on hemodialysis showed more pronounced lymphopenia, low levels of proinflammatory cytokines in the blood serum, and relatively mild clinical manifestations compared to other patients with this infection (30).

The recommendations cover the issues of minimizing the spread of infection in dialysis centers (assessing the health of staff and patients before entering the center, identifying patients with suspected COVID-19, observing social distancing whenever possible, personal protective equipment for staff, familiarizing with symptoms of the disease, using masks, training in social isolation and hand washing, screening for a new coronavirus infection in case of need for surgery, the use of telemedicine for monitoring), issues of transportation, disinfection of devices. Dialysis patients whose family members or caregivers are in “general quarantine” are scheduled for routine RRT treatment for 14 days. In the case of a confirmed diagnosis of infection in a family member or caregiver, the patient is identified as a “contact” and is treated according to the appropriate guidelines. For infected patients, it is not recommended to change the place of dialysis, shift and staff (in order to avoid further spread of infection), as well as use public transport. Protection measures for personnel, other patients, family members, immediate disinfection of devices should be strengthened, distance standards should be observed; dialysis and waiting rooms should be well air-conditioned and ventilated. The problem of reducing the number and/or duration of sessions for patients on chronic dialysis in conditions of an increased demand

for RRT, including due to the temporary limitation of the kidney transplant program, cannot be ruled out. It is very important that, like all patients with renal disease,

Kidney disease is a risk factor for coronavirus infection due to high expression of ACE2 in various parts of the nephron. In the context of the SARS-CoV-2 pandemic, CKD is the most common comorbid disease competing with hypertension and cardiovascular disease.

In turn, kidney disease is a common complication of COVID-19 and a significant risk factor for death. Therefore, monitoring of kidney function should begin in patients with mild respiratory symptoms of COVID-19. Early detection, correction of renal filtration and excretory function, including adequate hemodynamic support and restriction of nephrotoxic drugs, can improve the prognosis of a COVID-19 patient.

### Conclusion

Thus, in the absence of specific treatment and vaccination, the COVID-19 pandemic caused by the new coronavirus remains a global threat to humanity. The involvement of the kidneys in the clinical picture seems to be more and more significant, and AKI acts as an independent predictor of mortality. In such a situation, people with CKD represent a group of particular risk and attention. Only by including them in the planned research protocols for COVID-19 can the evidence base for effective and safe treatments be obtained.

### Authors' contribution

BT, SA, OS and RI contributed equally to prepare the study and paper. BT and SA were included in preparing the concept and design. OS and RI revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy of any part of the work.

### Conflicts of interest

The authors declare that they have no conflict of interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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