Acute kidney injury in patients with COVID-19: Epidemiology, pathogenesis and treatment

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Abstract

Acute kidney injury occurs in about 30% of patients hospitalized with coronavirus disease 2019 (COVID-19) and is one of the most common extrapulmonary complications of this disease. The highest risk of acute kidney injury is found in hospitalized patients who require mechanical ventilation. The pathogenesis of acute kidney injury in COVID-19 is multifactorial and seems to not be fully understood. Both direct and indirect mechanisms of kidney injury caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be considered. The histological picture of kidney specimens obtained from patients with acute kidney injury in the course of COVID-19 is dominated by acute tubular necrosis. Some patients also have acute interstitial nephritis, blood clots in the kidney vessels and focal segmental glomerulosclerosis (the variant with collapsing vascular loops). Acute kidney injury in COVID-19 is primarily caused not by direct viral effect, but by indirect pathophysiological mechanisms. The histopathological findings in these patients does not differ from the majority of the other patients with acute kidney injury. The main pathophysiological mechanisms underlying acute kidney injury in COVID-19 are: hemodynamic abnormalities, hypoxia and cytokine storm. The methods of treating the underlying disease, i.e., COVID-19 in patients with acute kidney injury and those without acute kidney injury are similar. However, it should be stressed that in the treatment of COVID-19 accompanied by acute kidney injury, the contraindication to remdesivir is estimated using glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. The general principles of management in patients with both, COVID-19 and acute kidney injury do not differ from the principles of management in patients with acute kidney injury due to the other causes.

Key words: acute kidney injury, COVID-19, SARS-CoV-2

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, China. This coronavirus belongs to the zoonotic viruses, and its genetic material is single-stranded ribonucleic acid (RNA). The SARS-CoV-2 causes coronavirus disease 2019 (COVID-19), which is an acute infectious disease of the respiratory system. The disease was declared a global pandemic by the World Health Organization (WHO) on 11 March, 2020. Coronavirus disease 2019 is characterized by a mortality of about 3% and an usual transmission rate (the number of newly infected persons per previously infected person) of about 2.5–3.0.[1]

Objectives

The purpose of this article was to present data on the effects of COVID-19 on the kidneys based on a review of the current literature. The review specifically considers the effect of COVID-19 on the risk of developing acute kidney injury and the risk of renal replacement therapy.

Pathogenesis and clinical manifestations of COVID-19

From the pathophysiological point of view, it is important to note that SARS-CoV-2 has a lipophilic envelope that determines its way of spreading inside the infected organism and the spike (S) protein, which is involved in the penetration of virus inside the cell.[1] The SARS-CoV-2 mainly infects bronchial epithelial cells and type II pneumocytes, where it binds to the surface receptor, angiotensin-converting enzyme type 2 (ACE2).[1] The SARS-CoV-2 spreads in the human body due to its lipophilic properties, mainly through continuity, but not through blood. This is confirmed by the analyses completed by the Chinese Center for Disease Control and Prevention. The greatest amount of SARS-CoV-2 RNA has been detected in the lavage from the bronchial tree, then in the sputum, nasal discharge, pharyngeal discharge and feces. In this study, using the reverse transcription polymerase chain reaction (RT-PCR), viremia in the blood was detected only in trace amounts and no SARS-CoV-2 RNA was found in the urine (i.e., viruria).[2] Similar results were obtained by Wu et al. in a study involving 132 patients with COVID-19, where viremia was found only in 4 patients (3%).[3] The analysis by Peng et al. of urine and blood samples in 9 patients with COVID-19 and moderately severe symptoms showed that SARS-CoV-2 RNA was present in only 2 blood samples and in only 1 urine sample.[4] The SARS-CoV-2 RNA was not found in urine samples collected from 10 patients with COVID-19 (almost half of whom required oxygen therapy during hospitalization).[5] Similarly, in the study by Wölfel et al. involving 9 patients with moderately severe COVID-19, no SARS-CoV-2 RNA was found in the blood or urine during the entire hospitalization period.[6] Wang et al. analyzed the occurrence of SARS-CoV-2 RNA in 307 blood samples and 72 urine samples taken from 205 patients with COVID-19 (nearly 20% of them were characterized by a severe course of the disease). The SARS-CoV-2 RNA in the blood was found in only 1% of the samples, while it was not found in the urine.[7] In another study, viremia was found in approx. 15% of patients with severe COVID-19.[8]

The SARS-CoV-2 viremia seems to be a factor that worsens the prognosis in patients with COVID-19. In the study by Tan et al. involving 33 patients with COVID-19, viremia was found in 4 of them. The clinical status of patients with viremia deteriorated rapidly due to septic shock.[9] In the study by Fajnzylber et al., which included 88 hospitalized patients with COVID-19, in 27% of them SARS-CoV-2 RNA was found in the blood. Patients with viremia were characterized by a greater severity of respiratory disease symptoms, a lower number of lymphocytes in the blood, and a higher concentration of both, C-reactive protein (CRP) and interleukin 6 (IL-6) in the plasma. Moreover, among these patients, the mortality was higher than in patients without viremia (32% compared to 8%, respectively; odds ratio (OR) = 5.5; p = 0.02).[10]

In the course of COVID-19, there are 3 phases of varying severity of disease, covering the time from the onset of disease to a recovery or death (Fig. 1).[11]

The 1st phase covers the onset of the disease and is characterized by mild to moderate flu-like symptoms. The dominant symptoms in the 2nd phase are associated with the development of pneumonia (connected to hypoxemia and dyspnea). Patients in the 3rd phase suffer from severe, generalized inflammation and symptoms of sepsis. These patients require hospitalization in the intensive care unit (ICU). High mortality is observed in patients in the 3rd phase of the disease.[11] The severity of the course, the type of clinical symptoms, and the mortality in the course of COVID-19 depend on age (greater severity over the age of 65) and comorbidities (mainly diabetes, cardiovascular diseases including hypertension, chronic lung diseases and chronic kidney diseases).[11]

Epidemiology and clinical characteristics of acute kidney injury in patients with COVID-19

Acute kidney injury is one of the most common beyond pulmonary complications of COVID-19.[12] Patients with acute kidney injury in the course of COVID-19 are characterized by high mortality. According to the epidemiological studies, the incidence of acute kidney injury in COVID-19 varies greatly depending on the population

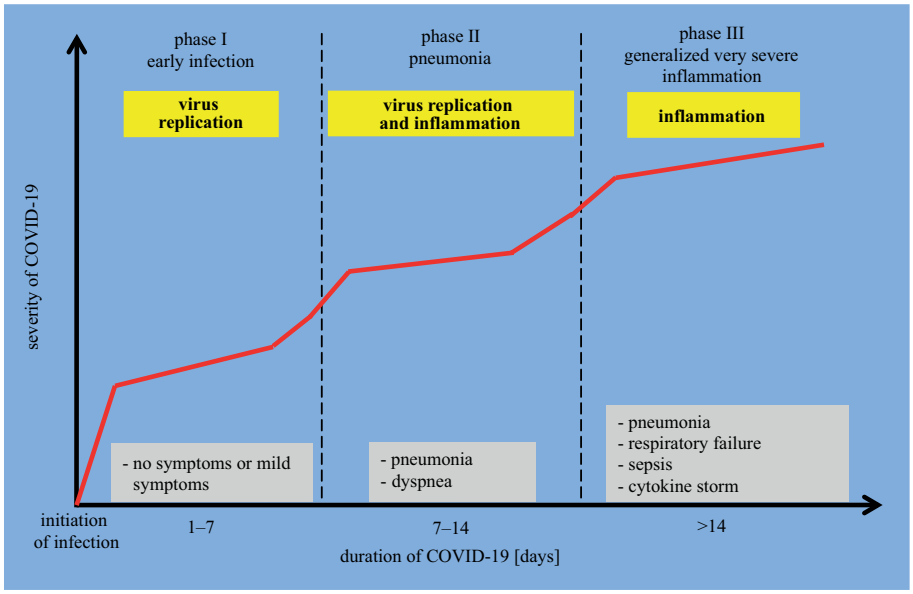

Fig. 1. Course of coronavirus disease 2019 (COVID-19) in severe cases

studied and the region of the world from which the published data is derived (Table 1).

A study by Fisher et al. comparing the incidence of acute kidney injury in hospitalized patients with and without COVID-19 showed a higher incidence of acute kidney injury in patients with COVID-19, when compared to the control group (56.9% compared to 25.1%, respectively).[17] A literature review by Hassanein et al. showed that acute kidney injury occurred in 0.5–56.9% of hospitalized COVID-19 patients.[23] The differences in the incidence of acute kidney injury in COVID-19 depending on the location of the study and the timing of the observation (i.e., early studies from Asia, later studies from Europe and the United States) were shown in a meta-analysis by Fu et al. They found that in China (a meta-analysis of 62 studies), the incidence of acute kidney injury in hospitalized COVID-19 patients was 5.6%. In contrast, a meta-analysis of 20 studies conducted in Europe and the United States showed that the incidence of acute kidney injury in hospitalized COVID-19 patients was 28.6%.[24] Similar results were presented by Lin et al. in a meta-analysis of 79 studies, showing that the incidence of acute kidney injury in patients with COVID-19 was 4.3%, 11.6% and 22.6% in Asia, Europe, and the United States, respectively.[25] A meta-analysis of 39 clinical trials (n = 25,566) by Fabrizi et al. showed that the incidence of acute kidney injury in hospitalized patients with COVID-19 was 15.4% (95% confidence interval (95% CI): 10.7–20.1%; $p < 0.0001$).[26] Another meta-analysis of 26 studies (n = 5,497) by Hansrivijit et al. showed that the incidence of acute kidney injury in hospitalized patients with COVID-19 was 8.4% (95% CI: 6.0–11.7%).[27]

Acute kidney injury in the course of COVID-19 can occur at any stage of the disease, but it is most often found in the 3rd phase (Table 2). Predominantly, it develops in patients at the onset of artificial ventilation.[16,20] In a study by Hirsch et al. including 5,449 patients with COVID-19 hospitalized in 13 hospitals in New York (USA), it was shown that acute kidney damage occurred in as many as 90% of patients who required artificial ventilation. However, in those who did not require it, this

Table 1. Epidemiology of acute kidney injury in the course of coronavirus disease 2019 (COVID-19) in hospitalized patients[13–22]

Authors	Number of hospitalized patients with COVID-19	Country of origin	Analyzed period	Prevalence of acute kidney injury in hospitalized patients	Necessity of kidney replacement therapy in hospitalized patients
Shi et al.	416	China	I–II 2020	1.9%	0.4%
Cheng et al.	1392	China	I–II 2020	7.1%	1.1%
Portoles et al.	1603	Spain	II–IV 2020	20.8%	1.1%
Chan et al.	3235	USA	II–IV 2020	43.4%	8.7%
Fisher et al.	3345	USA	III 2020	56.9%	4.9%
Argenziano et al.	1000	USA	III–IV 2020	33.9%	13.8%
Richardson et al.	5700	USA	III–IV 2020	24.0%	3.2%
Hirsch et al.	5449	USA	III–IV 2020	36.6%	5.2%
Zahid et al.	469	USA	III–IV 2020	27.3%	4.7%
Kolhe et al.	1161	UK	III–V 2020	26.2%	7.6%

Table 2. Epidemiology of acute kidney injury in the course of coronavirus disease 2019 (COVID-19) in hospitalised patients in the intensive care unit (ICU)[16,18,20,28–32]

Authors	Number of patients with COVID-19	Country of origin	Analyzed period	Prevalence of acute kidney injury in hospitalized patients in ICU	Necessity of kidney replacement therapy in hospitalized patients in ICU
Xu et al.	239	China	I–II 2020	49.8%	5.0%
Yu et al.	226	China	II 2020	25.2%	10.6%
Chan et al.	976	USA	II–IV 2020	56.6%	19.2%
Mohamed et al.	173	USA	III 2020	60.7%	44.5%
Suleyman et al.	141	USA	III 2020	69.5%	17.0%
Argenziano et al.	236	USA	III–IV 2020	78.0%	35.2%
Hirsch et al.	1395	USA	III–IV 2020	76.0%	not given
Doher et al.	201	Brazil	III–V 2020	50.2%	17.0%

percentage was 22%.[20] A meta-analysis by Fabrizi et al. showed that in patients with severe COVID-19, the incidence of acute kidney injury was 53% (95% CI: 42.7–63.3%).[26] Similar results were found in the meta-analysis by Hansrivijit et al., which showed that the incidence of acute kidney injury was higher in critically ill patients, when compared to other COVID-19 hospitalized patients (19.9% compared to 7.3%).[27]

In another study, Chan et al. found that acute kidney injury occurred in 76% of patients with COVID-19 hospitalized in the ICU.[16] In the recently published meta-analysis by Silver et al., including 54 studies in 30,657 patients suffering from COVID-19, the incidence of acute kidney injury was assessed at 28%, while among patients hospitalized in the ICU it was 46%.[33]

Thus, it has been unequivocally shown in all publications that the highest incidence of acute kidney injury in breakthrough COVID-19 occurs in patients hospitalized in ICUs.

The results of the abovementioned epidemiological studies indicate that patients with COVID-19 are at high risk of acute kidney injury. This risk increases with the severity of clinical symptoms of COVID-19. The significant discrepancies in the incidence of acute kidney injury in hospitalized COVID-19 patients between studies conducted in Asia (low frequency) and in Europe and the United States (high frequency) may result primarily from the differences in indications for hospitalization, and thus, the differences in the general status of hospitalized patients.[24,25]

The risk of acute kidney injury from COVID-19 depends mainly on the severity of the disease. The general clinical status in the course of COVID-19 and the incidence of acute kidney injury are influenced by similar factors, such as: demographic features (age over 60, male gender, and African descent), comorbidities (chronic kidney disease, diabetes mellitus, cardiovascular diseases, arterial hypertension, obesity and chronic obstructive pulmonary disease).[31] In the previously cited meta-analyses by Fu et al., Lin et al., in a meta-analysis by Tian et al. including 11 studies, and in a study by Chan et al., the influence of various factors in patients with COVID-19 on the risk of acute kidney injury was assessed. Numerous demographic and clinical features that significantly increased the risk of acute kidney injury in patients with COVID-19 were described (Table 3).[16,24,25,34] Factors with the most important impact on the risk of acute kidney injury in the course of COVID-19 were those related to the severity of a patient's condition, i.e., the need to use catecholamines infusion (in the course of septic shock), and the need to use artificial ventilation (due to respiratory failure).[23,24,31]

Pathogenesis of acute kidney injury in COVID-19 patients

The pathogenesis of acute kidney injury in COVID-19 is multifactorial and not yet fully understood. In patients with COVID-19, acute kidney injury may be prerenal or renal. Both direct and indirect mechanisms of kidney injury induced by SARS-CoV-2 should be taken into account (Fig. 2).[35]

Table 3. Risk factors of acute kidney injury in patients with coronavirus disease 2019 (COVID-19)[24,25,34]

Coexisting factor	Risk of acute kiney injury	Reference
Age over 60 years	OR = 3.5, 95% CI: [2.9; 4.3]	25
Male sex	OR = 1.4, 95% CI: [1.1; 1.7]	24
Severe COVID-19 course	OR = 6.0, 95% CI: [2.5; 14.6]	25
Artificial ventilation required	OR = 9.4, 95% CI: [5.2; 17.3]	34
Need to use catecholamines	OR = 19.4, 95% CI: [16.8; 22.3]	34
CKD	OR = 1.6, 95% CI: [1.4; 1.9]	24
Diabetes	OR = 1.5, 95% CI: [1.2; 1.8]	24
Cardiovascular disease	OR = 1.5, 95% CI: [1.1; 2.0]	24
Arterial hypertension	OR = 1.5, 95% CI: [1.3; 1.7]	24
Obesity	OR = 1.8, 95% CI: [1.6; 2.0]	34
COPD	OR = 1.7, 95% CI: [1.4; 2.1]	34

CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; OR – odds ratio; 95% CI – 95% confidence interval.

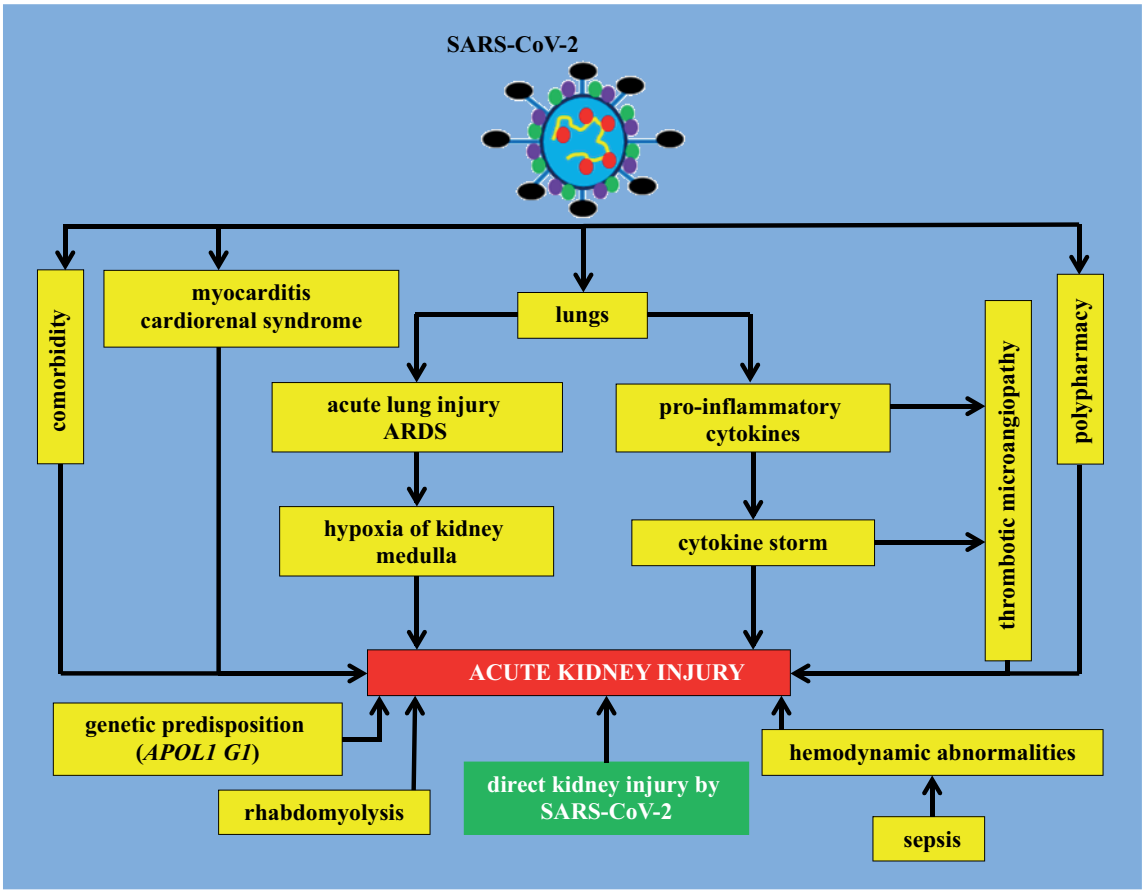

Fig. 2. Mechanisms of acute kidney injury in coronavirus disease 2019 (COVID-19)

ARDS – acute respiratory distress syndrome; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2; *APOL1 G1* – apolipoprotein L1 polymorphisms.

Indirect mechanisms

Dehydration and hypotension (prerenal acute kidney injury)

Important pathophysiological mechanisms of prerenal acute kidney injury in patients with COVID-19 include: dehydration due to fever (temperature >38.5°C), nausea, vomiting or diarrhea, which often accompanies COVID-19 (11% of COVID-19 patients have gastrointestinal symptoms). The cause of dehydration may also be the displacement of fluid into the so-called third space (fluid escapes into the pleural cavities; accumulation of fluid in skeletal muscles occurs in the course of rhabdomyolysis). Moreover, hypotension due to either dehydration, sepsis or heart failure (in the course of myocarditis or cardiomyopathy) also plays a role in the pathogenesis of prerenal acute kidney injury in COVID-19 patients.[36,37] A study by Hirsch et al. showed that in 66% of patients with COVID-19 and acute kidney injury, urine sodium concentration was below 35 mmol/L, which suggests a prerenal mechanism of acute kidney injury.[20] This observation indicates that the factors mentioned above, leading to prerenal acute kidney injury, play a key role in the pathogenesis of acute kidney injury in patients with COVID-19.

Acute tubular necrosis

In the few studies conducted so far in patients with acute kidney injury, in whom histopathological analyses have been completed, acute tubular necrosis was found in a significant proportion of patients (in biopsy studies, in 60% of patients with acute kidney injury).[19,38] The histological image was dominated by widening of the lumen of the renal tubules and the remaining cell debris within them. In addition, damage to the brush border and vacuolar degeneration in the proximal tubular epithelium cells were observed.[39]

Several possible mechanisms may be involved in the pathogenesis of acute renal tubular necrosis in COVID-19. Prolonged dehydration and hypotension might lead to acute tubular necrosis. The so-called cytokine storm induced by SARS-CoV-2 infection, causing hemodynamic changes that interfere with renal perfusion (reduction in blood pressure), may also promote acute tubular necrosis.[38] Moreover, it has been shown that interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) are characterized by direct nephrotoxic properties. The expression and release of these cytokines are particularly increased in the cytokine storm accompanying COVID-19. The SARS-CoV-2 has been shown to increase the production of metalloproteinase ADAM17 in cells, which in turn increases the release of TNF-α and IL-6.[40,41]

Passive renal congestion due to heart failure also promotes acute tubular necrosis. Lung injury caused by COVID-19 may lead to hypoxia of the renal medulla and, consequently, acute tubular necrosis.[37,42] Other risk factors for acute renal tubular necrosis in patients with COVID-19 are: increased pressure in the chest (e.g., when using ventilation with positive end-expiratory pressure), sepsis, rhabdomyolysis (in 19% of hospitalized COVID-19 patients), and the use of iodinated contrast agents and other nephrotoxic drugs (including nonsteroidal anti-inflammatory drugs).[23,37] In addition, the deposition of complement components C5b-C9, which form a membrane attack complex (MAC), has been found in tubular cells. The stimulation of the complement system in COVID-19 and the production of MAC may lead to direct destruction of the proximal tubular cells.[3,39,43–45]

Acute interstitial nephritis

In some patients with acute kidney injury in the course of COVID-19, infiltration of mononuclear cells within the renal interstitium has been found.[37] The pathophysiological mechanisms involved in the pathogenesis of acute interstitial nephritis include increased expression of signal transducer and activator of transcription 1 (STAT1) and of interferon regulatory factor 3 (IRF3) by interferon γ (INF-γ) and TNF-α, and increased secretion of pro-inflammatory cytokines by macrophages.[46–49] In the pathogenesis of acute interstitial nephritis in COVID-19 patients, allergic reactions to drugs, especially to frequently used antibiotics, may also play a role.[50]

Prothrombotic state in kidneys

In COVID-19, coagulation is increased.[51,52] Radiological examinations in some COVID-19 patients may show kidney infarctions.[53] Moreover, the histopathological examination in these patients may show micro clots in the vessels of the glomeruli.[52,54] The pathophysiological mechanisms of thrombotic changes include: an increase in serum angiotensin II concentration, the so-called cytokine storm, the increased secretion of von Willebrand factor by damaged vascular endothelium, the occurrence of antibodies similar to cardiolipin, antiphospholipid and anti-2-glycoprotein antibodies, as well as damage to endothelial cells, caused directly by MAC.[49–58]

Direct mechanisms

There is no clear evidence whether SARS-CoV-2 directly contributes to acute renal tubular damage and glomerulopathy.

As previously mentioned, viremia is rare in patients with COVID-19, which makes a direct damage mechanism unlikely in most of the patients.[59] Hypothetically, SARS-CoV-2 could pass into the kidneys through continuity by infecting vascular endothelial cells. However, it seems that there is insufficient evidence to support this hypothesis.

The issue of infection of vascular endothelial cells by the SARS-CoV-2 virus has been a subject of in vitro studies on organoids and cell cultures. The study by Monteil et al. assessed the possibility of direct infection of human vascular endothelial cells using the capillary organoid formed from induced pluripotent stem cells. The organoid was incubated with SARS-CoV-2 and the occurrence of SARS-CoV-2 RNA inside the vascular endothelial cells was analyzed by RT-PCR after 3 and 6 days. The SARS-CoV-2 RNA was found inside these cells, and SARS-CoV-2 replication was observed in vascular endothelial cells. Moreover, the supernatant taken from the organoid culture on day 6 of the experiment was found to infect Vero E6 cells (renal epithelial cells isolated from primates), indicating that the cells of the capillary organoid were multiplying and releasing new SARS-CoV-2 virions.[60] However, the results of the studies on organoids were not confirmed by Ahmetaj-Shala et al. in a study with cell culture. In this study, vascular endothelial cells were incubated for 1 h with SARS-CoV-2, and then 24 and 72 h later they were analyzed by indirect immunofluorescence microscopy for the occurrence of virus inside the cells (staining for the occurrence of nucleocapsid (N) protein and S protein). Using this method, SARS-CoV-2 has not been found to occur inside vascular endothelial cells.[61]

The endocytosis of SARS-CoV-2 requires the coexistence of the proteins ACE2 and TMPRSS2 on the cell surface. The ACE2 protein is present on the endothelial cells of arteries and veins.[62] The TMPRSS2, in turn, is present on vascular endothelial cells, but its expression is variable.[63]

To sum up, the results of the presented in vitro studies are inconsistent and do not allow for unequivocal confirmation of the hypothesis that SARS-CoV-2 spreads through continuity by infecting vascular endothelial cells. Moreover, to date, this issue has not been analyzed in vivo.

The results of histopathological examinations do not clearly confirm the occurrence of SARS-CoV-2 in kidney cells. In a study by Su et al. using autopsy material from 26 patients with COVID-19 and acute damage to the renal tubules, particles similar to the virus were found in 6 of them by electron microscopy.[54] However, the results of an electron microscopy examination are not specific. The occurrence of similar structures in the cytoplasm of endothelial cells, which in fact were organelles involved in intracellular transport with clathrin-coated vesicles, was demonstrated in kidney biopsy material obtained before 2020, i.e., before the COVID-19 pandemic.[64]

In the previously mentioned study, the identification of SARS-CoV-2 proteins was carried out using immunofluorescence staining. Nevertheless, this study used antibodies against SARS-CoV and not SARS-CoV-2, reducing the reliability of the obtained results, in which the presence of the SARS-CoV-2 protein was found in 3 out of 26 samples.[54] In the autopsy study completed by Diao et al., which included material from 6 patients with COVID-19, in situ hybridization with the use of rabbit monoclonal antibody

against SARS-CoV-2 RNA demonstrated the occurrence of virus RNA within the kidney tissue in all patients.[45] However, there are significant doubts related to the specificity of the hybridization technique used in this study.[65,66] In 32 samples of homogenized kidneys obtained from patients with COVID-19 and acute kidney injury, Braun et al. found the occurrence of SARS-CoV-2 RNA in 23 of them.[67] A significant limitation of this study seems to be the fact that it is not possible to determine in which kidney structures SARS-CoV-2 RNA was detected. In the study by Puelles et al., which included autopsies of those who died due to COVID-19, the presence of SARS-CoV-2 RNA in the kidneys was demonstrated by RT-PCR. Moreover, in this study using laser microdissection, SARS-CoV-2 was found to occur in the renal medulla, cortex, glomerulus and renal interstitium in 50% (3 out of 6) of samples. The SARS-CoV-2 titer was highest in the glomeruli.[68]

The occurrence of SARS-CoV-2 RNA in kidney autopsy material does not conclusively prove the pathogenicity of the virus. In order to allow the SARS-CoV-2 virus to enter the cell, it is necessary that ACE2 (the virus receptor) and TMPRSS2 (a serine protease that cleaves the S protein) should coexist on its surface. The ACE2 is expressed in the proximal tubular nephron (about 100 times bigger than in the lung), while TMPRSS2 is expressed in the urinary tract epithelium.[69–71] Thus, SARS-CoV-2 is unable to enter podocytes and proximal tubular cells of the nephron using the ACE2 and TMPRSS2 mechanism.

The protein CD147 is located in the podocytes and cells of the proximal tubules of the nephron, which is also suspected to be involved in the process of SARS-CoV-2 virus penetration into the cell. The effectiveness of this alternative route for virus entry into the cell is unknown. Perhaps, in some patients, the SARS-CoV-2 virus causes the direct damage to the podocytes and proximal tubular cells through this mechanism (i.e., with the participation of the CD147 protein). In such patients, the histopathological changes described in some of the subjects with acute kidney injury in the course of COVID-19 can be found: acute tubular necrosis and focal segmental glomerulosclerosis (the variant with collapsing vascular loops). In kidneys with focal segmental glomerulosclerosis (the variant with collapsing vascular loops), the confluence of the foot processes of podocytes, the detachment of podocytes from the glomerular basement membrane and the formation of pseudo-crescents have been observed.[72,73] It is worth mentioning that a similar focal segmental glomerulosclerosis (the variant with collapsing vascular loops) is also found in other virus infections, such as human immunodeficiency virus 1 (HIV-1), human T-cell leukemia-lymphoma virus 1 (HTLV1), cytomegalovirus, parvovirus B19, and Epstein–Barr virus.[72]

The occurrence of the abovementioned podocytopathy in the course of COVID-19 is favored by the APOL1 G1 polymorphism (apolipoprotein L1) and an increase in CD147 expression in damaged podocytes, which may allow SARS-CoV-2 to penetrate the cells. It seems that patients with coexisting diabetes and/or obesity are particularly at risk of developing focal segmental glomerulosclerosis (the variant with collapsing vascular loops) in the course of COVID-19, as they have an increased expression of CD147 in podocytes.[73,74] The penetration of SARS-CoV-2 through CD147 into the podocyte may result in disturbances in the structure and function of the cytoskeleton, stimulation of the mitogen-activated protein kinase (MAPK) pathway, and increased production of pro-inflammatory cytokines.[37] In patients with focal segmental glomerulosclerosis (the variant with collapsing vascular loops), significant proteinuria is found.[38]

Thus, the presented data indicate that acute kidney damage in COVID-19 is primarily caused by indirect pathophysiological mechanisms, and does not differ in the histopathological picture, in the vast majority of patients, from acute kidney damage of a different etiology. The main pathophysiological mechanisms underlying acute kidney injury in COVID-19 include hemodynamic disorders, hypoxia, and the so-called cytokine storm.

Prognosis of patients with acute kidney injury in COVID-19

Acute kidney injury in COVID-19 patients is often irreversible. Gupta et al. showed that there was a need for dialysis on the day of discharge from hospital in 34% of patients. On the other hand, 18% of patients needed dialysis on day 60 of observation after the discharge from hospital.[75]

The occurrence of acute kidney injury in a patient with COVID-19 is unfavorable in terms of prognosis. A study by Chan et al. found that in-hospital mortality in patients with COVID-19 was 50% in patients with acute kidney injury, compared to 8% in patients without acute kidney injury (OR = 9.2; 95% CI: 7.5–11.3).[16] The meta-analysis by Fabrizi et al. showed that the OR for the incidence of acute kidney injury in deceased COVID-19 positive patients was greater than among the survivors (OR = 15.4; 95% CI: 11.4–20.99; $p < 0.001$).[26] The meta-analysis by Lin et al. showed that the occurrence of acute kidney injury in hospitalized patients with COVID-19 was associated with a significant increase in the risk of death (OR = 11.05; 95% CI: 9.13–13.36).[25] Similar results were obtained by Fisher et al. in a study involving 3,345 patients with COVID-19. They found that mortality in patients with COVID-19 and acute kidney injury was significantly higher than in hospitalized patients with COVID-19 but without acute kidney injury (33.7% compared to 9.3%, respectively).[17] A meta-analysis of 142 studies by Fu et al., including 49,048 patients hospitalized with COVID-19, showed a significant increase in the risk of death in patients with coexisting acute kidney injury (relative risk (RR): 4.6; 95% CI: 3.3–6.5).[24] In the meta-analysis by Hansrivijit et al., it was shown that the estimated OR for mortality from acute kidney injury was 13.33 (95% CI: 4.05–43.91).[27]

Treatment of acute kidney injury in COVID-19

The general principles of management in patients with COVID-19 and acute kidney injury, developed by the Acute Disease Quality Initiative (ADQI) Working Group, do not differ from the principles of management in patients with acute kidney injury due to other causes. The methods of therapy in COVID-19 patients are summarized in Table 4.[50]

Methods of therapy of the underlying disease, i.e., COVID-19, in patients with acute kidney injury and in patients without acute kidney injury, are similar. However, it should be stressed that in the treatment of COVID-19 accompanied by acute kidney injury, the contraindication to remdesivir is estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.[50] The abovementioned recommendation for the use of remdesivir is due to the possible accumulation of the solvent substance, i.e., cyclodextrin derivative (sulfobutylether-β-cyclodextrin (SBECD)).[76] Animal studies have shown that SBECD has nephrotoxic and hepatotoxic properties.[77] Observational studies in patients with COVID-19 and impaired kidney function treated with remdesivir by Thakare et al. (including 46 patients) and Estiverne et al. (including 18 patients), and case reports of patients with COVID-19 and impaired kidney function, did not confirm significant toxicity of such treatment.[78–81] Nevertheless, in the study by Estiverne et al., 2 out of 18 observed patients showed a significant increase in the activity of serum transaminases.[79] It is necessary to conduct clinical trials to answer the question of whether the benefits of remdesivir in patients with acute kidney injury in the course of COVID-19 might outweigh the potential risks caused by the toxicity of such treatment.[76]

In the treatment of acute kidney injury in a patient with COVID-19, kidney replacement therapy is often necessary (Table 1,2). A review of the literature by Hassanein et al. showed a large variation in the frequency of the need for kidney replacement therapy in patients with acute kidney injury due to COVID-19, ranging from 0.8% to 31%.[23] The meta-analysis by Fabrizi et al. showed that the frequency of the need for renal replacement therapy in patients with COVID-19 was 4.3% (95% CI: 3.1–5.5%; $p < 0.0001$).[26] The meta-analysis by Hansrivijit et al. found that the incidence of renal replacement therapy was 3.6% (95% CI: 1.8–7.1%).[27]

The method of kidney replacement therapy in patients with COVID-19 is similar to the treatment of patients with acute kidney injury with another etiology. So far, no benefit has been found of an earlier initiation of renal replacement therapy. Continuous techniques should be preferred (nevertheless, the type of treatment depends mainly on a center's experience and the availability of the treatment method). The best location to place a hemodialysis catheter is in the right jugular vein. Heparin should also be used in some patients in between hemodialysis treatments. For continuous techniques, local use of citrate should be preferred. Peritoneal dialysis can also be used.[50,82,83]

In order to reduce the risk of infection of medical personnel, the video transmission from the dialysis room has been used in some dialysis centers, allowing for remote patient supervision. Moreover, some of the centers have used longer than usual drains for hemodialysis, which allowed for the positioning of the hemodialysis machine outside the room in which the patient was staying.[23]

Table 4. Principles of management in a patient with coronavirus disease 2019 (COVID-19) and acute kidney injury

Patients at increased risk of acute kidney injury (AKI) and patients with AKI
Applying standard principles of care for prevention and treatment of multiple organ failure
Individualization of fluid therapy
Consideration of vigorous hemodynamic monitoring
Monitoring serum creatinine concentration and urine volume
Maintaining normal blood glucose concentration
If possible, considering using alternative diagnostic methods for testing with iodine-based contrast agents, but without delaying the radiological examination
If possible, avoidance of nephrotoxic drugs
Risk of AKI when choosing a strategy for artificial ventilation
Additionally, patients with stage II/III AKI
Kidney replacement therapy consideration
Avoidance of vascular access for hemodialysis using a subclavian vein puncture

Limitations of the study

The main limitation of this review paper is that we analysed results from the studies published before November 2021, i.e., during the still ongoing COVID-19 pandemic. The studies discussed in paper covered the period before the introduction of vaccination against COVID-19. Therefore we were not able to anticipate the influence of both vaccination and new variants SARS-CoV-2 virus on the acute kidney injury epidemiology and pathogenesis. Mechanisms by which SARC-CoV-2 affects kidney function presented in this review paper are not well understood and undoubtedly require further research.

Conclusions

Acute kidney injury in the course of COVID-19 occurs in approx. 30% of patients requiring hospitalization. In COVID-19, acute kidney injury is most often caused by prerenal causes. In the histological picture of acute kidney injury in the course of COVID-19, acute tubular necrosis was found to be dominating. The principles of prevention and treatment of acute kidney injury in the course of COVID-19 are similar to those of acute kidney injury in the course

of other infections. The contraindication to the use of remdesivir is eGFR < 30 mL/min/1.73 m^2. It must be emphasized that acute kidney injury in the course of COVID-19 is an unfavorable prognostic factor.

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