The nature of kidney damage causing the development of acute renal failure in patients with COVID-19 (according to morphological studies)

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

The literature review presents data on the study of the nature of kidney damage in patients with COVID-19 with acute renal insufficiency according to histo-morphological lifetime and postmortem studies of the kidneys during the peak of the epidemic of infection in 2020-2022. In the analysis, the role of direct viral damage to tissues and organ cells is questioned. The frequency of diagnosis of glomerular, tubular, interstitial and vascular lesions is specified, the significance of the presence of variants of the apolipoprotein-1 (APOL1) gene in patients with severe respiratory complications of acute viral infection is assessed.

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Keywords: COVID-19, acute kidney injury, histo-morphological diagnosis, apolipoprotein-1 (APOL1) genotype.

A close relationship between the severity of COVID-19 and the frequency of acute renal injury (AKI) has been noted by most researchers of the problem. So, in a literary review of the staff of a specialized nephrological hospital in New Jersey (USA). the authors presented their own and literature data on the high incidence of acute kidney injury (ACI) among patients with COVID-19 hospitalized in the hospital - from 10 to 43% and the intensive care unit (43-75%). In general,

according to their data, patients with AKI have a much higher need for artificial lung ventilation, the use of vasopressors and intensive care. In addition, the proportion of patients with acute renal failure who require renal replacement therapy is significantly increasing [1].

Rarely, when analyzing the incidence of AKI, researchers compare it with the level of development in the pre-covid-19 period, as was done in a retrospective observational study conducted by employees of the Department of Nephrology of the Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center (Bronx, New York, USA). The authors assessed the incidence of AKI, risk factors and outcomes in 3,345 adults with COVID-19 and 1,265 without COVID-19 who were hospitalized in the New York City health Care system and compared them with a historical cohort of 9859 people hospitalized a year earlier in the same health care structure. As a result, there was a higher incidence of AKI among patients with COVID-19 compared to the historical cohort (56.9% vs. 25.1%, respectively). The authors concluded that patients with acute renal failure (ARF) and COVID-19 more often than patients without COVID-19 needed renal replacement therapy (RRT), they were less likely to recover kidney function at the end of the inpatient period [2].

In separate studies on this problem, the authors estimate separately the frequency of AKI developed at the pre-hospital stage, diagnosed at the patient's admission and separately occurred in the hospital. Thus, in a Canadian retrospective cohort study from the registry of patients with COVID-19 (Department of Internal Medicine of McMaster University, Hamilton, Ontario, Canada and 10 other Canadian institutions), the frequency of AKI in a cohort of patients with COVID-19 hospitalized in the Department of Medicine and Intensive care (ICU) was determined and its relationship with hospital mortality and severity of the disease. A total of 815 patients admitted to the hospital with COVID-19 in the period from March 4, 2020 to April 23, 2021 were examined. AKI was diagnosed by comparing the highest and lowest registered serum creatinine in the hospital and setting AKI based on the system "Kidney disease: Improving global outcomes" (KDIGO). Of the 815 registered patients, 439 (53.9%) developed AKI, including 186 (42.4%) developed it in the hospital. The probability of hospitalization in the intensive care unit, artificial ventilation and death increased as the stage of AKI increased. The likelihood of hospitalization in the intensive care unit, mechanical ventilation and death increased as the stage of AKI increased. Acute stage 3 injury that occurred during hospitalization was associated with an increased probability of death (odds ratio = 7.87), and stage 3 AKI that occurred before hospitalization was associated with increased risks of death (relative risk = 5.28). The authors concluded that acute kidney injury, regardless of whether it developed before or after hospitalization, was associated with a high risk of adverse outcomes in patients with COVID-19 [3].

The study of the incidence of AKI in patients who did not suffer from CKD and had not previously received renal replacement therapy was performed in a multicenter study by nephrologists from the USA (Tufts Medical Center, Tufts University, Boston, Mass.). They analyzed data on 4,221 adult patients with COVID-19 who had not previously received renal replacement therapy. 2,361 (56%) of them developed AKI, including 876 (21%), with the need for RRT. More severe AKI was associated with higher mortality. Among the survivors, more severe OCI was associated with an increased frequency of kidney failure and lower kidney function at discharge. Of 876 patients with AKI–RRT, 588 (67%) died, and 95 (11%) had non-recovery of nitrogen-releasing kidney function, and 193 (22%) had kidney recovery by the time of discharge. The probability of non-recovery of renal function was higher for lower baseline GFR, with odds ratios of 2.09,

4.27 and 8.69 for baseline GFR levels of 31-60, 16-30, ≤15 ml/min/1.73 m2, respectively, compared with GFR > 60 ml/min/1.73 m2. Oliguria at the start of RRT was also associated with a lack of normalization of GFR – the relative risk was 2.10 and 4.02 for patients with 50-499 and <50 ml/day of urine, respectively, compared with ≥500 ml/day of urine), [4].

According to the literature data that appeared at the beginning of the intensive study of this problem, compactly presented in analytical reviews, coronaviruses have high contagiousness and high tropicity to kidney tissue. The new coronavirus infection is capable of causing a wide range of pathological changes in the kidneys, due to the content of angiotensin converting enzyme type 2, transmembrane serine protease 2 and cathepsin L in the organs, which are considered targets for SARS-CoV-2. Clinical manifestations can vary from mild forms of acute respiratory viral infection to severe multiple organ lesions. It is assumed that various clinical forms of kidney damage in COVID-19 are caused by numerous pathogenetic mechanisms, such as the direct cytopathic effect of the virus on kidney structures, endothelial dysfunction, cytokine storm, hemodynamic and water metabolism disorders, damage to the renin-angiotensin-aldosterone system. SARS-CoV-2 interacts with APF2 receptors located on the endothelium of blood vessels, having an adverse effect on the microvascular bed. In addition, damage to renal tissue can be caused by the synthesis of pro-inflammatory interleukins, as well as hypovolemia and the accumulation of angiotensin II and bradykinin. Kidney damage in patients with COVID-19 may include such clinical and morphological forms as collapsing nephropathy, minimal changes disease, membranous glomerulopathy, anti-GBM nephritis, acute tubular necrosis, exacerbation of autoimmune glomerulonephritis, allograft rejection [5].

Patients infected with the new SARS-CoV-2 coronavirus may have an increased incidence of acute kidney injury (AKI), which is more often diagnosed with collapsing glomerulopathy and severe tubulo-interstitial damage. This type of kidney pathology is a special variant of proteinuric kidney disease - focal segmental glomerulosclerosis (FSGS). The histologically destructive form of FSGS (cFSGS) is characterized by segmental or global condensation and obliteration of glomerular capillaries, the appearance of hyperplastic and hypertrophied podocytes and severe tubulointerstitial damage. Clinically, patients with cFSGS have acute kidney damage, nephrotic proteinuria and a high risk of rapid progression to irreversible renal failure. CFSGS can be attributed to a lesion associated with numerous causes, namely viral infections such as HIV, cytomegalovirus, Epstein-Barr virus and parvovirus B19, as well as medications and severe multiple organ ischemia. Theoretically, it has been suggested that variants of the apolipoprotein-1 (APOL1) gene, found mainly in people of African descent, may increase the risk of developing cFSGS. Patients infected with the new SARS-CoV-2 coronavirus have an increased incidence of acute kidney injury (AKI) more often in severe cases of COVID-19 infection. In addition to hemodynamic instability, cytokine-mediated damage, direct virus penetration and infection of kidney epithelial cells contributing to AKI, there are reports of cFSGS associated with SARS-CoV-2 infection in patients of predominantly African ethnicity. The staff of the Faculty of Medicine of the University Medical Center Hamburg-Eppendorf (Hamburg, Germany) suggest that the pathogenesis of cFSGS is associated with direct viral infection of podocytes, as described for HIV-associated glomerulopathy. Nevertheless, there is increasing evidence that the systemic inflammatory cascade activated in acute viral infections, such as COVID-19, may be the main factor of damage to renal podocytes [6].

The studies carried out to date on this issue, including the most informative ones: using methods of in vivo kidney biopsy,

postmortem morphological examination, light and electron microscopy, genetic analysis, etc. in patients with COVID-19, there are still few and their results are ambiguous. We present the data of the most informative, completed to date, works of this orientation.

Genetic, histopathological and molecular features of kidney damage were studied in a Chinese-American study by employees of the Department of Pathology, School of Fundamental Medical Sciences, Fudan University (Shanghai, China), Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center (Nashville, Tennessee) and the Arkan Laboratory (Little Rock, Arkansas, USA). The study was conducted in six black patients with COVID-19 who were diagnosed with acute renal injury (AKI) and de novo nephrotic proteinuria. The kidney biopsies showed signs of collapsing glomerulopathy, extensive erasure of podocytes in the glomeruli, and focal/diffuse acute tubular injury. Endothelial reticular aggregates were found in three patients. No viral particles or SARS-CoV-2 RNA were found in kidney biopsies. Kidney tissue biopsies were examined by in situ hybridization to detect viruses and using NanoString to identify genes associated with COVID-19 and acute tubule damage. Peripheral blood samples for APOL1 genotyping were also examined in black patients. The average age of the patients was 55 years. This series of cases included six black patients with COVID-19 (four men, two women), on the day of the biopsy, the average serum creatinine was 6.5 mg/dl, and the average ratio of urine protein to creatinine was 11.5 g. The kidney biopsies showed signs of collapsing glomerulopathy, extensive erasure of podocytes in the glomeruli and focal/diffuse acute tubular damage. Endothelial reticular aggregates were detected in three patients. No viral particles or SARS-CoV-2 RNA were found in kidney biopsies. The NanoString genetic study method showed an increased expression of the chemokine gene and changes in the expression of genes associated with acute damage to the tubules, compared with the control group. All six patients had a high-risk APOL1 genotype. Five patients needed dialysis (two of them died); one was discharged without the need for dialysis. Collapsing glomerulopathy in black patients with COVID-19 was associated with high-risk APOL1 variants. The researchers found no signs of viral infection in the kidney biopsies. They suggested a possible alternative mechanism for the development of AKI: a "two-stroke" combination of genetic predisposition and a cytokine-mediated reaction of the host organism to SARS-CoV-2 infection. Given the similarity of this entity with HIV-associated nephropathy, the authors proposed the term COVID-19-associated nephropathy to describe it [7].

A lifetime kidney biopsy in a study by nephrologists from the USA (Department of Nephrology and Hypertension, Feinberg School of Medicine, Northwestern University, Chicago, Illinois) was performed in patients with AKI with signs of total proteinuria who were hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). [8]. In some of them, a biopsy revealed collapsing glomerulopathy, a form of glomerular damage that is also described in kidney damage by other viruses, including HIV. COVID-19 was diagnosed with a positive smear from the nasopharynx RT-PCR for SARS-CoV-2 infection. Biopsy samples from one transplanted kidney and five native kidneys were examined. Three of the six patients underwent genetic analysis of APOL1, the gene encoding the APOL1 protein, from DNA extracted from peripheral blood. In addition, genomic DNA was isolated from paraffin embedded tissue and the APOL1 genotype of one of the native biopsies and a donor kidney transplant was analyzed.Six patients of recent African descent developed COVID-19-associated AKI with podocytopathy, collapsing glomerulopathy, or a combination of both. The patients had mild respiratory disorders, none of them needed artificial lung ventilation (ventilator). Genetic testing conducted in three

patients confirmed the presence of high-risk apolipoprotein-1 (APOL1) genotypes. One high-risk APOL1 patient developed collapsing glomerulopathy in a kidney that was transplanted from a donor who had a low-risk APOL1 genotype. The authors concluded that glomerular damage, manifested both by proteinuria with and without AKI, is an important manifestation of COVID-19 infection and may be associated with the high-risk APOL1 genotype [8].

In the report of the staff of the Department of Nephrology of Paris (private hospital Peupliers, Ramsay General de Santé (Paris, France, Department of Pathology, Sorbonne University, Assistance Publique-Hôpitaux de Paris, Groupement Hospitalier Pitié-Salpêtrière, Paris, France), evidence was presented in favor of the presence of a causal relationship between SARS-CoV infection-2 and the occurrence of collapsing glomerulopathy (KG) in patients homozygous for the high-risk APOL1 genotype. The authors evaluated the data of a lifetime kidney biopsy in two cases of collapsing glomerulopathy associated with acute tubular necrosis during COVID-19. In two cases, as in 14 others previously reported, the patients were of African descent. 14 examined patients had a high-risk APOL1 genotype. At the end of the reporting period, two patients had died and five patients still required dialysis. The 16 cases described in detail in this report strongly support a causal relationship between SARS-CoV-2 infection and the occurrence of HCG in patients homozygous for the high-risk APOL1 genotype, for which the term COVID-associated nephropathy (COVIDAN) has been proposed [9].

A possible association of non-collapsing FSGS with secondary acute interstitial nephritis and AKI with the low-risk APOL1 genotype was suggested by the staff of the Department of Nephrology, Hypertension and Kidney Transplantation of the Medical University of Lodz (Poland), who described a clinical case with the results of a lifetime kidney biopsy in a young white man who had COVID-19 pneumonia and had a history of arterial hypertension, taking anabolic steroids and a long-term diet with a high protein content. He fully recovered from type 1 respiratory failure and AKI after transfusion of COVID-19 convalescent plasma and intravenous treatment with dexamethasone administered for 16 days at a dose reduced from 16 to 2 mg / day. Due to progressive severe nephrotic proteinuria (22.6 g / 24 h), he was injected with intravenous methylprednisolone (1500 mg divided into 3 pulses for 3 days), which was immediately followed by oral prednisolone (0.6 mg / kg body weight), after 19 weeks the dose was reduced and switched to cyclosporine A (4 mg / kg of body weight). Repeated kidney biopsy at that time showed a decrease in the proportion of glomeruli affected by podocytopathy, but progression of interstitial lesions. After 23 weeks of therapy, partial remission of FSGS was achieved and proteinuria decreased to 3.6 g / 24 h. After 43 weeks, proteinuria decreased to 0.4 g / 24 h, and serum creatinine concentration remained stable. The researchers concluded that high-dose glucocorticoid therapy was effective in the initial treatment of non-collapsing FSGS associated with COVID-19, but did not affect interstitial changes in the kidneys. The additional introduction of cytostatic cyclosporine A into therapy contributed to the remission of the disease[10].

In a study of American employees from the Department of Nephrology, Duke Institute of Molecular Physiology, Duke University School of Medicine (Durham, North Carolina, USA), using a lifetime kidney biopsy in 9 patients with severe kidney disease, called COVID-19-associated nephropathy (COVAN) by the authors, experts demonstrated that the APOL1 b protein was expressed in podocytes and glomerular endothelial cells (GEC) of the kidneys in COVAN, but not in the kidneys of patients in control. Most COVAN patients carried 2 APOL1 risk alleles. From these data, it follows that recombinant cytokines induced by SARS-CoV-2 acted synergistically, stimulating the expression of APOL1 via the

JAK/STAT pathway in primary human podocytes, GECs and kidney microorganoids obtained from the carrier of 2 APOL1 risk alleles, but expression was blocked by the JAK1/2 inhibitor. These studies confirm the conclusion that cytokines induced by COVID-19 infection are sufficient to cause COVAN-associated podocytopathy in diseased patients through JAK/STAT/APOL1 signaling, and that JAK inhibitors can block this pathogenic process [11].

Comparison of morphological changes in the kidney with collapsing glomerulopathy associated with COVID-19 in African Americans with risk alleles of the apolipoprotein L1 (APOL1) gene and HIV-associated nephropathy was performed by employees of the Department of Nephrology of the Faculty of Medicine of the Icahn School of Medicine at Mount Sinai (New York, USA) and the Department of Nephrology of Shanghai Ninth Hospital, Jiao University Medical School Tong (Shanghai, China) [12]. According to a lifetime kidney biopsy and RNA sequencing analysis of a kidney tissue sample of a patient with collapsing glomerulopathy associated with COVID-19 and APOL1 (G1/G1) risk alleles revealed similar levels of APOL1 and angiotensin converting enzyme 2 (ACE2 messenger RNA transcripts compared with 12 control kidney samples uploaded from the GTEx Genotype portal-Tissue Expression). Genome-wide sequencing of a kidney sample with collapsing glomerulopathy associated with COVID-19 revealed 4 variants of the indel gene, 3 of which have unknown significance for chronic kidney disease and/or focal segmental glomerulosclerosis. Molecular profiling of the kidney has demonstrated activation of cell damage pathways associated with COVID-19, such as inflammation and coagulation. There was no evidence of direct infection of kidney cells with coronavirus 2 with severe acute respiratory syndrome in the work. Immuno-staining of kidney biopsy sections performed in the study revealed increased expression of phosphostat3 (signal converter and transcription activator 3) in both COVID-19-associated collapsing glomerulopathy and HIV-associated nephropathy compared to the control kidney tissue. The researchers concluded that STAT3 activation induced by interleukin 6 may be a targeted mechanism leading to acute kidney injury associated with COVID-19 [12].

The development of collapsing glomerulopathy, in many cases of COVID-19 infection, is more often noted by researchers in patients with a permorbid background and glomerular lesions of various genesis that existed before the onset of viral infection. In their report, the staff of the Department of Pathology and Cell Biology, Columbia University Irving Medical Center (New York, USA), after evaluating biopsy samples of native and allografted kidneys in patients with COVID-19 concluded that collapsing glomerulopathy developed more often in patients with glomerular and podocyte lesions of various types as a premorbid background origin. The researchers evaluated native and allografted kidney biopsy samples from COVID-19 patients at a center in New York City between March and June 2020. Among 14 patients with native kidney biopsy, 5 were diagnosed with collapsing glomerulopathy, 1 was diagnosed with glomerulonephritis with minimal changes, 2 were diagnosed with membranous glomerulopathy, 1 was diagnosed with sickle-shaped transformation of lupus nephritis, 1 was diagnosed with anti-GBM nephritis and 4 were diagnosed with isolated acute damage to the tubules. Three allotransplantations were complicated by acute grade 2a T-cell-mediated rejection or acute damage to the tubules. Immunohistochemistry, in situ hybridization and electron microscopy were used to examine this tissue for the presence of coronavirus. (SARS-CoV-2). The authors included 17 COVID-19 patients with severe acute respiratory syndrome in the study group (12 men, 12 blacks; average age 54 years). Sixteen patients had concomitant diseases, including hypertension, obesity, diabetes, malignant neoplasms or kidney or heart allograft. Nine patients developed pneumonia caused by COVID-19. Fifteen patients (88%) had AKI; nine had nephrotic range proteinuria. Genotyping of

three patients with collapsing glomerulopathy and a patient with nephritis with minimal changes showed that all four patients had high-risk APOL1 gene variants. The authors found no evidence of SARS-CoV-2 in kidney cells. According to the results of the study, it was concluded that patients with COVID-19 develop a wide range of lesions of the glomeruli and tubules. The data of this study indicate against direct viral kidney damage as the main pathomechanism of kidney damage associated with COVID-19 and the authors suggest that the damaging effects mediated by cytokines and hyperergic adaptive immune responses [13].

A variety of glomerular lesions preceding covid-19 nephropathy were identified in a study with a lifetime kidney biopsy performed by employees of the Department of Kidney Diseases and Hypertension of the Faculty of Medicine of the Donald and Barbara Zucker School of Medicine at Hofstra / Northwell, Great Neck (New York, USA) in ten hospitalized patients who had COVID-19 and clinical signs of AKI, including proteinuria with or without hematuria. The analysis included ten patients who had a kidney biopsy (average age: 65 years); five patients were black, three were Hispanic and two were white. All patients had proteinuria. Eight patients had severe AKI that required RRT. All biopsy samples showed signs of acute tubular necrosis, and one patient had associated multiple myoglobin casts. In addition, two patients showed signs of thrombotic microangiopathy, one had weakly immune sickle cell glomerulonephritis, and the other had global as well as segmental glomerulosclerosis with signs of cured collapsing glomerulopathy. Infection caused by coronavirus 2 with severe acute respiratory syndrome (SARS-CoV-2) was confirmed in patients using RT-PCR, but immunohistochemical staining of kidney biopsy samples for SARS-CoV-2 was negative in all ten patients. There were no signs of SARS-CoV-2 in the kidney tissue biopsies. Ultrastructural examination using electron microscopy revealed no signs of viral particles in the biopsy samples. The authors concluded that acute tubular necrosis was the most common injury in kidney biopsy samples in ten hospitalized patients with AKI and COVID-19 [14].

Severe damage to the glomeruli and signs of tubular necrosis in a lifetime kidney biopsy in a patient with covid-19 and acute renal failure was described by nephrologists from Switzerland (Service of Nephrology and Hypertension, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland.Service of Clinical Pathology, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland et.al.). The paper describes a clinical case of covid-19 infection complicated by the development of AKI. A kidney biopsy was performed on day 8. Light microscopy revealed 2 main signs: severe collapsing focal segmental glomerulosclerosis (FSGS) and acute tubular necrosis without any significant interstitial inflammation. The immunofluorescence study did not reveal significant immune deposits (including anti-C5b-9 staining). The reverse transcriptase-polymerase chain reaction for SARS-CoV-2 in RNA extracted from a frozen biopsy tissue sample was negative (reverse transcriptase-polymerase chain reaction was similarly negative in blood). Further work showed that the patient was homozygous for the apolipoprotein A (APOL1) G1 variant (A342G and I348M). No specific treatment was carried out. The patient maintained spontaneous urine discharge and did not need dialysis. Kidney function subsequently improved and proteinuria decreased. The patient was discharged on day 17 with serum creatinine 5.5 mg/dl and persistent proteinuria (1.8 g/l). Electron microscopy revealed vacuoles containing numerous spherical particles in the cytoplasm of podocytes. The authors concluded that they may correspond to the viral inclusion bodies reported in patients with SARS-CoV-2 in early studies [15].

The researchers of the issue suggest that acute hypoxia with the development of respiratory distress syndrome and damage mediated by cytokines and hyperergic adaptive immune reactions in covid-19 may be the main causes of combined glomerular damage and tubular necrosis. In favor of this hypothesis, we can cite data from the work of Spanish specialists of the Department of Nephrology of the University Hospital of Alorkona (Servicio de Nephrología. Hospital Universitario Fundación Alcorcón, Madrid, España). The authors described a clinical case of a 52-year-old woman, a native of the Dominican Republic, with severe respiratory distress syndrome, with acute renal failure associated with COVID-19, who did not have a burdened nephrological history and did not take medications or nephrotoxic substances. A kidney biopsy was performed on her, segmental and focal glomerulosclerosis was detected (a variant of the NOSE according to the Columbia classification) in combination with signs of acute tubular necrosis in the regenerative phase. Immunohistochemical examination of kidney biopsies for CoV-2 was negative. Electron microscopy showed diffuse fusion of podocytes affecting more than 80% of the capillary surface, along with visualization of microvilli, but podocyte transformation and viral inclusions were not detected. Subsequently, during the therapy, in parallel with the improvement of respiration and inflammation, the patient experienced a gradual remission of proteinuria up to 0.4 g / 24 h with complete remission of nephrotic syndrome at discharge [16]. The researchers concluded that the main causes of acute renal injury could be acute hypoxia with the development of respiratory distress syndrome and damage to glomerular podocytes mediated by cytokines and hyperergic adaptive immune reactions [16].

The issue of the main causes of AKI development in patients with covid-19 is discussed in the thematic literature, among which not only direct viral damage to kidney structures is considered, but also acute hypoxia with the development of respiratory distress syndrome, including in combination with drug-induced lesions. Researchers from the clinic of North American Columbia University (Department of Pathology, Division of Renal Pathology, Columbia University Irving Medical Center, New York, New York, USA) described a clinical case of nephropathy in a patient with COVID-19 and clinical signs of AKI taking the NSAID drug ibuprofen. He was a 46-year-old West African man who was admitted to the emergency department on March 15, 2020 with severe acute kidney injury. He reported that 2-3 weeks before his hospital presentation, he had a subjective fever, myalgia, sore throat and cough, which he treated with several doses of ibuprofen. These complaints were resolved 1 week before this hospital admission, but subsequently he developed a deterioration: abdominal pain, nausea and anorexia, which persisted for the next week, which led to his placement in the hospital department. Upon admission, the patient complained of difficulties in lifting the body from a supine position, decreased diuresis, but denied visible hematuria, foamy urine, lower back pain, swelling of the lower extremities or orthopnea, vomiting, diarrhea, changes in mental behavior, persistent respiratory infectious symptoms, recent trips or hospital contacts. Apart from his recent use of ibuprofen, he denied any other medications, vitamin supplements or herbal remedies. The patient underwent a kidney biopsy. The preparation contained 2 nuclei of the renal cortex, it had 20 glomeruli, none of which was globally sclerotic. In fourteen glomeruli there were signs of segmental-global collapse of glomerular capillaries, accompanied by violent hypertrophy and hyperplasia of overlying glomerular epithelial cells, some of which contained individual protein droplets positive for periodic Schiff acid. The other 6 uninvolved glomeruli turned out to be normal in size and cellularity. No inflammatory crescents, Bowman capsule ruptures, or fibrinoid necrosis were detected. There were diffuse and severe tubular degenerative and regenerative changes in the renal cortex, characterized

by flattening of the epithelium, loss of the brush border, an increase in nuclei with protruding nucleoli and focal mitotic figures. Some proximal tubular cells contained abundant intracytoplasmic protein droplets positive for periodic Schiff acid. Scattered tubular microquists were seen. The interstitium was enlarged with edema and mild to moderate interstitial inflammation, consisting mainly of mononuclear leukocytes and random plasma cells, without tubulitis. Moderate focal tubular atrophy and interstitial fibrosis with approximately 10% of the cortical parenchyma were observed. Signs of minimal severity of atherosclerosis and moderate arteriosclerosis were noted in the renal vessels [17]. The patient had no respiratory symptoms in the clinical picture, but a positive result for SARS-CoV-2 was repeated on the 17th day of hospitalization. Despite the fact that lactate dehydrogenase activity decreased in his blood serum and albumin increased by the end of hospitalization, he remained dependent on dialysis. On the 23rd day of hospitalization, tocilizumab therapy became possible for him and a dose of 400 mg was administered. He also started taking prednisone at a dose of 80 mg per day with a 1-month therapy plan with a further dose reduction to be determined based on changes in residual kidney function. On the 26th day of hospitalization), he remained dependent on dialysis with serum creatinine before dialysis of 16.6 mg/dl. The authors concluded that segmental-global collapse of a part of the glomerular capillaries of the kidneys, mild focal tubular atrophy and interstitial fibrosis could have a combined infectious and drug origin and had no connection with respiratory symptoms [17].

In a relatively small number of studies to date, the nature of kidney damage has been studied in patients who died from COVID-19 complications according to morphobiopsy data, during autopsies of patients, including those who died in China. Morphological studies most often revealed signs of acute tubular necrosis in the kidneys, and collapsing glomerulopathy was described in several reports [18].

The predominant pathological finding, according to pathomorphological studies of patients who died from COVID-19 complications in the study of employees of the Department of Nephrology from the hospital of the Beijing Medical College (Chinese Academy of Medical Sciences) was acute tubular injury. The number of patients with AKI in this study was 41 (50.6%). Tests for nucleic acids and immunohistochemistry failed to detect the virus in renal tissues. Older age and higher serum IL-6 levels were risk factors for acute renal failure, and stage 3 CDIGO was an independent prognostic factor of death. The authors concluded that AKI was a common and multifactorial complication in critically ill COVID-19 at a late stage of the disease [18].

In another pathomorphological study of Chinese pathologists from the Institute of Immunology in Wuhan (Institute of Immunology, PLA, Third Military Medical University, Chongqing, P. R. China.Department of Medical Laboratory Center, General Hospital of Central Theater Command, Wuhan, Hubei Province, P. R. China), it was found that the SARS-CoV virus-2 can directly affect the tubules of the human kidneys, thus causing acute damage to the tubules (ORL) and probably also cause transmission of infection with urine. Kidney tissues of six other patients were stained with hematoxylin and eosin (H&E) during pathoanatomic examination, and the expression of viral nucleocaspid protein (NP) antigen in situ was evaluated using immunohistochemistry. The authors of the study conducted a retrospective analysis of the estimated glomerular filtration rate (eGFR), plasma creatinine concentration and urea concentration, along with other clinical parameters, in 85 patients with laboratory-confirmed COVID-19 admitted to the hospital in Wuhan from January 17, 2020 to March 3., 2020. Of 85 patients with COVID-19, 27.06% (23/85) of patients with COVID-19 developed acute renal failure

(ARF). Concomitant diseases, such as hypertension and heart failure, were more common in patients who developed ARL (69.57% vs. 11.29%, p<0.001). The evaluation of eGFR in dynamics showed that in deceased patients there is a rapid decrease in eGFR, a rapid increase in the level of creatinine and urea in plasma. Hematoxylin-eosin staining showed that there were signs of severe acute tubular necrosis in the renal tissues in 6 pathoanatomic cases, but without signs of glomerular pathology. During immunohistochemistry, it was noted that the NP SARS-CoV-2 antigen accumulated in the renal tubules. The researchers concluded that the development of ARL is an important negative prognostic indicator of survival in COVID-19. The SARS-CoV-2 virus directly affects the tubules of the human kidneys, thus causing acute damage to the ORL tubules and probably also leading to the transmission of infection with urine [19].

The predominant lesion of the renal tubules was also revealed during the autopsy of 26 patients with COVID-19, when assessing changes in renal biopsies by light microscopy, ultrastructural observation and immune staining by employees of the Department of Nephrology of Huazhong University of Science (Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China). The average age of the patients was 69 years (19 men and 7 women), all suffered from respiratory failure associated with multiple organ dysfunction syndrome as a cause of death. Nine of the 26 had clinical signs of kidney damage, which included elevated serum creatinine levels and/or newly developed proteinuria. With light microscopy, diffuse lesion of the proximal tubules with loss of the brush border, non-isometric vacuolar dystrophy and even pronounced necrosis were observed. Single hemosiderin granules and pigmented cylinders were found. There were noticeable accumulations of erythrocytes blocking the lumen of the capillaries, without platelet or fibrinoid material. There were no signs of vasculitis, interstitial inflammation or hemorrhage. Electron microscopic examination showed clusters of coronavirus-like particles with characteristic spikes in the tubular epithelium and podocytes. In addition, it was found that the SARS-CoV-2 receptor, ACE2, is activated in patients with COVID-19, and immuno-staining with antibodies to the SARS-CoV nucleoprotein was positive in the tubules. According to the authors, in addition to the direct virulence of SARS-CoV-2, factors contributing to acute kidney injury include systemic hypoxia, abnormal coagulation, and possible drug-related or hyperventilation-related rhabdomyolysis [20].

The morphological substrate of AKI in patients who died from COVID-19, according to a Russian study conducted by the staff of the Moscow City Nephrological Center (Moscow State Medical and Dental University named after A.I. Evdokimov), in the vast majority of cases was acute damage to the tubular epithelium. The study included 220 patients who died in the period from April 20 to May 20, 2020 in GKB No. 52 from COVID-19, confirmed by PCR. The average age of patients was 71.4±14 years, the ratio of men and women was 1:1. 35 (15%) patients had signs of chronic kidney disease (CKD) at the time of hospitalization. Acute kidney injury (AKI) developed in 135 patients (61%), including 33 patients with previous renal pathology. The frequency of AKI did not significantly differ depending on the initial renal function, amounting to 66% and 61% in CKD and initially normal function. The only significant predictor of AKI development was the duration of the ventilator (6.1 vs 1.7 days). The number of patients receiving ventilator or ECMO for 5 or more days was 43% vs 10% in AKI and normal renal function, respectively.In a morphological study performed in 178 patients, pre-existing renal pathology was detected in 76 (43%), including 34 out of 55 (62%) patients who had a decrease in glomerular filtration rate (GFR) at the time of hospitalization, and in 40 out of 165 (24%) patients, who had normal kidney function at admission (P<0.01).According to histo-morphological examination of the kidneys, almost half of the patients had pronounced venous

fullness with blood stasis in peritubular capillaries and venules, in some cases in combination with pronounced fullness of the glomeruli and erythrocyte sludge. A more rare variant of the damage was the dystrophy of the tubular epithelium by the type of isometric vacuolization. 6 patients with AKI (5%) had morphological signs of thrombotic microangiopathy, accompanied by clinical manifestations (anemia, thrombocytopenia, increased LDH). The authors concluded that acute kidney injury is a frequent complication of severe forms of coronavirus infection, a significant predictor of which is the duration of ventilation. Thrombotic microangiopathy may be one of the rare causes of kidney damage in COVID-19 [21].

The most frequent type of renal injury according to the pathomorphological study of Spanish nephrologists from the clinic of the University of Madrid (Servicio de Nephrología, Universitario Puerta de Hierro, Majadahonda, Madrid) was also acute damage to the tubules. The authors analyzed the data of 41 patients with AKI and severe COVID-19, average age 66.8 years (SD 2.1), of which 90.2% were men and with a history of chronic kidney disease in 36.6%. The etiology of AKI was prerenal in 61%. Of the 9 deceased patients, according to the pathomorphological examination of the kidneys, 24.4% had acute tubular necrosis, 7.3% had glomerular damage and signs of tubular dystrophy in 7.3% of cases. The researchers concluded that hypovolemia and dehydration are a common cause of AKI among patients with COVID-19. Those patients who developed acute renal failure during hospitalization had the worst prognosis in terms of lung damage, kidney damage and analytical results [22].

Frequent damage to the tubules in patients with AKI and severe COVID-19 was revealed in a clinical and morphological study of Australian nephrologists from the Department of Nephrology of the University of Brisbane (Department of Nephrology, Ochsner Health System, New Orleans, Louisiana.2Ochsner Clinical School, The University of Queensland, Brisbane, Queensland, Australia). The researchers analyzed 575 hospitalizations (70% of blacks) with COVID-19 [173 (30%)] to the intensive care unit (ICU). In 161 (28%) cases, signs of acute renal failure (ACI) were detected, including 61% of those hospitalized in the intensive care unit (ICU) and 14% of general hospitalizations to the ward. The patients were mainly men (62%) and hypertensive patients (83%). The median body mass index (BMI) was higher among patients with OCI (34 vs. 31 kg/m2, p<0.0001). OKI compared to pre-existing CKD was observed in 35%. The median follow-up was 25 (1-45) days. The hospital mortality rate for the OKI cohort was 50%. Vasopressors and/or mechanical ventilation were required in 105 (65%) patients with OIC. Renal replacement therapy (RRT) was necessary in 89 (55%) patients. Those who required replacement therapy (AKI-RRT) during the development of AKI had a higher median BMI (35 vs. 33 kg/m).2, p=0.05) and younger (61 vs. 68, p=0.0003). The initial values of ferritin, C-reactive protein, procalcitonin and lactate dehydrogenase were higher in patients with OCI and among them the values were higher for those who had artificial lung ventilation (AKI-RRT). Ischemic acute tubular injury (ATI) and rhabdomyolysis accounted for 66% and 7% of causes, respectively. 13% did not have an obvious cause of OCI, except for the diagnosis of COVID-19. The researchers concluded that covid-19-induced OCI (CoV-AKI) is associated with high rates of RRT and mortality. Higher levels of BMI and inflammatory markers are associated with OCI, as well as with OCI-PPT. Hemodynamic instability leading to ischemic ATI was the predominant cause of AKI in these conditions [23].

Combined kidney damage of the type of focal segmental glomerulosclerosis (FSGS) and acute tubular necrosis (ATN) were the most common histological variants of kidney damage and acute renal failure in patients with COVID-19 in an

Iranian study conducted by employees of the Center for Clinical Research Development, Imam Hossein Educational Hospital (Shahid Beheshti University of Medical Sciences, Tehran, Iran). The authors provide data on 499 patients with COVID-19 (60.9% of men) who were diagnosed with AKI in 168 (33.7%) cases, and the mortality rate was 92 (18.4%) cases. 12 of the 44 patients included in the analysis, with the data of a pathomorphological examination of the kidneys, had a history of chronic kidney disease (CKD). Focal segmental glomerulosclerosis (FSGS) and acute tubular necrosis (ATN) were the most common histological variants of kidney damage. Hyponatremia (adjusted odds ratio (AOR) = 2.34, hypernatremia (AOR = 8.52) and hyperkalemia (AOR = 4.63), upon admission were associated with a poor prognosis. In addition, hyponatremia (AOR = 3.02) and hyperphosphatemia (AOR = 5.12) at admission were associated with a later occurrence of AKI. The authors conclude that the results of the study indicate the role of electrolyte disorders such as hyponatremia, hypernatremia, hyperkalemia and hyperphosphatemia in the poor prognosis of patients with COVID-19 complicated by AKI. To improve the results of treatment, the authors recommend monitoring and correction of electrolyte disturbances in patients with COVID-19 and AKI when signs of AKI are detected during hospitalization [24].

The condition of transplanted organs, including kidneys, in a patient who died from complications of COVID-19, was evaluated in a pathomorphological study by employees of the Swiss University Hospital (Department of Pathology and Molecular Pathology, University Hospital Zurich, CH-8091 Zurich, Switzerland.2Department of Cardiology, University Heart Center, University Hospital Zurich, CH-8091 Zurich, Switzerland). The nature of the damage to the transplanted kidney was assessed according to electron microscopy data in a patient who died from complications of COVID-19, including acute renal failure. A male patient aged 71 with coronary heart disease and arterial hypertension was a recipient of a kidney transplant. His condition worsened immediately after the verification of the COVID-19 diagnosis. In the hospital, he developed acute respiratory failure and needed artificial lung ventilation. With the development of polysystemic organ failure, the patient died on day 8. Pathoanatomic examination of the transplanted kidney tissues by electron microscopy revealed the structures of viral inclusion in endothelial cells. Histological analyses revealed an accumulation of inflammatory cells associated with the endothelium, as well as apoptotic bodies, in the heart, small intestine and lungs. A cluster of mononuclear cells was found in the lungs, and most of the small pulmonary vessels were overloaded. The researchers concluded that the intracellular introduction of the pathogen into endothelial cells with their apoptosis and the development of multiple organ failure was important in the development of multiple organ failure in a patient with a transplanted kidney[25].

In meta-analyses performed on this problem, the most frequent and significant morphological changes in the kidneys in the development of AKI, according to postmortem biopsies in COVID-19 patients were: collapsing focal segmental glomerulosclerosis (c-FSGS) in 54% and thrombotic microangiopathy (TMA) in 9% of patients. The analysis was performed by Dutch authors from the Intensive Care Unit of Groningen (Department of Critical Care, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands). They conducted a meta-analysis of studies that reported histopathological results of diagnostic and postmortem kidney biopsies in patients with COVID-19, published in the period from January 1, 2020 to January 31, 2021. In total, the results of 89 diagnostic and 194 postmortem kidney biopsies from individual patients in 39 published studies that were included in the analysis were evaluated. According to the combined data, in the diagnostic biopsy group, the average age was 56 years, and the

frequency of AKI exceeded 96%. In the postmortem biopsy group, the average age of the deceased was 69 years, and the frequency of AKI reached 80%. In this group, the prevalence of acute glomerular diseases was 74%. The most frequent glomerular lesions were collapsing focal segmental glomerulosclerosis and thrombotic microangiopathy (TMA). Kidney damage of the TMA type was also found in 10% of patients in the postmortem biopsy group. Acute tubular necrosis (OCN), which was present in 87% of patients in the diagnostic and in 77% of patients in the postmortem biopsy group. In addition, the authors observed a high prevalence of previously developed chronic lesions in both groups, such as atherosclerosis and glomerulosclerosis. Histopathological changes in kidney biopsies of patients with COVID-19 showed a heterogeneous picture with acute lesions of the glomeruli, mainly c-FSGS and TMA, and acute lesions of the tubules, mainly OCN. The authors concluded that in many patients these lesions developed against the background of previous chronic kidney damage [26].

In a meta-analysis of Indian morphologists from the Department of Pathology and Laboratory Medicine of the Jodhpur Hospital (Jodhpur, Rajasthan, India), the nature of kidney damage was assessed according to morphological studies in COVID-19 patients. The authors summarized the results of renal histopathological studies in COVID-19 from published reports on individual cases and series. The authors conducted a systematic search in databases such as MEDLINE, EMBASE and the Cochrane Library for published reports on COVID-19 patients with renal histopathological changes from autopsy studies and biopsies for indications "for a reason". The analysis included case reports and case series with extractable quantitative data on patient demographics, such as age, gender, ethnicity, as well as data on kidney function tests, their concomitant diseases and biopsies to study histopathological changes. The analyzed studies included a total of 139 cases where details of individual cases, including clinical and histopathological results, were available. The average age of the patients was 62 years, and the ratio of men and women was 2.5:1. Concomitant diseases were noted in 78.4% of cases. Most patients with AKI had renal dysfunction with proteinuria, which was recorded in more than two thirds of cases. In morphological preparations, frequent tubular kidney damage was observed, and glomerular pathology was most often collapsing glomerulopathy, which was noted in 46.8% of histological studies. Only a small part of cases (4.3%) of kidney damage had the character of thrombotic microangiopathy. The authors concluded that tubular kidney damage was associated with several factors, including organ ischemia, sepsis, and other causes. In their opinion, the presence of viral particles in renal tissue in patients with renal injury and AKI remains controversial and requires further study [27].

Thus, acute tubular injury, collapsing focal segmental glomerulosclerosis (FSGS), myoglobin toxicity associated with sepsis and fibrin glomerular thrombi are the most significant causes and part of the mechanism of AKI development in patients with COVID-19 proven in original studies. Patients with 2 high-risk APOL1 alleles appear to be at increased risk of COVAN, similar to other forms of collapsing glomerulopathy, such as HIV-associated nephropathy. Thrombotic microangiopathy (TMA) is a poorly understood, rare cause of collapsing glomerulopathy. Histological signs of TMA were most often associated with hypertensive nephropathy, genetic complement abnormalities and the use of medications [28]. Acute interstitial nephritis (AIN) is less common in patients with COVID-19, and the reported cases were mild. Reports of the AIN subtype, granulomatous interstitial nephritis (GIN), among patients with COVID-19 are extremely rare and have not been reported in connection with COVAN [29]. The previous hypothesis that the pathophysiology of AKI associated

with COVID-19 may be associated with non-specific mechanisms, as well as with COVID-specific mechanisms, such as direct cell damage as a result of virus penetration through the receptor (ACE2), which is highly expressed in the kidneys, unbalanced activity of the renin-angotensin-aldosterone system, increased levels of proinflammatory cytokines caused by viral infection and thrombotic events [6][30] have not been confirmed in studies of in vivo and posthumously taken kidney biopsies of patients, including during electron microscopy. Only in isolated studies it has been demonstrated that SARS-CoV-2 can infect podocytes and tubular epithelial cells, which contributes to the development of the aforementioned renal lesions and AKI [31] (Martínez-Rojas MÁ, Sánchez-Navarro A, 2022. Department of Molecular Physiology, Institute of Biomedical Research, National Autonomous University of Mexico, Ciudad de Mexico). Therefore, the relationship between the presence of viral particles in renal tissue and kidney damage has not been fully proven. The frequency of drug-induced causes of AKI in COVID-19, according to preliminary data, exceeds 12%, but has not yet been precisely determined, since the effect of nephrotoxic drugs is difficult to isolate from the total effect of a complex of drugs used to treat this type of pathology according to available therapy standards [32].

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Conflict of interest: not stated. "The authors declare that there is no conflict of interest."

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