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RENAL PATHOLOGY IN PATIENTS WITH COVID-19

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Abstract:

SARS-CoV-2 virus (COVID-19) is highly contagious, virulent and shows tropism to many human organ cells. To enter the cell, SARS-CoV-2 virus utilizes the angiotensin-converting enzyme type 2 (ACE2) receptor, which is highly expressed in the kidney. Through the ACE2-dependent signaling pathway, SARS-CoV-2 can directly infect renal tubule epithelium and podocytes.

Keywords: SARS-CoV2, kidneys, endotheliitis, endocapillary proliferation.

INTRODUCTION COVID-19 predisposing factors of kidney damage include chronic kidney disease (CKD), cardiovascular pathology, congestive heart failure and, as a consequence, the development of cardiorenal syndrome, the presence of immunodeficiency states, including those associated with the use of immunosuppressants and/or radiation therapy, hypovolemia, intake of nephrotoxic drugs, etc. [1]. As is known, the most common causes of CKD development are diabetes mellitus, hypertension, obesity, atherosclerosis, advanced age, which are also the main risk factors for SARS-CoV-2 infection, besides, their presence complicates the clinical course and worsens the disease outcomes [1,3,5,7].)

Coronaviruses are highly infectious and highly tropic to renal tissue. Novel coronavirus infection is capable of causing a wide range of pathologic renal abnormalities due to the RNA 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 range from mild forms of acute respiratory viral infection to severe multi-organ lesions. The different clinical forms of renal damage in COVID-19 are due to multiple pathogenetic mechanisms, such as direct cytopathic action of the virus on renal structures, endothelial dysfunction, cytokine storm, disturbances in hemodynamics and water metabolism, and damage to the renin-angiotensin-aldosterone system [5,7,28,29].

. SARS-CoV-2 interacts with ACE2 receptors located on the endothelium of blood vessels, exerting adverse effects on the microvascular bed. In addition, renal tissue damage is caused by the synthesis of proinflammatory interleukins, as well as hypovolemia and accumulation of angiotensin II and bradykinin. Renal damage in COVID-19 patients includes such nosologic forms as collapsing nephropathy, minimal change disease, membranous glomerulopathy, anti-GBM nephritis, acute tubular necrosis, exacerbation of autoimmune glomerulonephritis, and allograft rejection. [2,4,6,22,23]. T cell necrosis or apoptosis promotes the release of cytokine storm leading to T cell shrinkage (C. Huang, et al., 2020), especially in cases with severe disease, lower circulating CD4+ and CD8+ T cells and higher circulating CD4+ and CD8+ T cells, IL-10 and tumour necrosis factor-α (TNFα) [9,11,13,15,15,24]. Consequently, systemic inflammation is detrimental to viral clearance, contributing to T-cell depletion [8,10,12,14].

Almost all patients with SARS-CoV-2 developed lymphopenia as an important marker of immune dysfunction [17,19,21]. Renal macrophages play a key role in immune defence as they are the predominant cells interacting with virus targets and can activate phagocyte and chemokine signalling [16,18,20,25]. In addition, the cytopathic effect of SARS-CoV-2 virus can directly damage renal tubular cells during infection and replication stages, propagating a complex immune response. In addition, the chemokine network, activation of complement cascades and coagulation play a potential role in the development of PP in SARS-CoV-2 patients [3,4,7,8,26,27].

During clinical observations, scientists from different countries have established an association between confirmed COVID-19 and the following laboratory findings: hematuria, proteinuria, elevated blood urea nitrogen, serum creatinine, uric acid, and D-dimer. Recent studies have demonstrated that patients with COVID-19 often suffer from renal failure, which is closely associated with higher mortality and morbidity and is an indicator of survival in coronavirus infection[2,7,18]. In addition, the presence of risk factors such as chronic kidney disease, cardiovascular pathology, presence of immunodeficiency states, intake of nephrotoxic drugs, diabetes mellitus, hypertension, obesity, atherosclerosis, and advanced age complicates the course of infection and worsens the prognosis of the patient. Thus, the pathologic effect of coronavirus on the body in general and on the kidneys in particular, as

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well as the high mortality rate among patients with renal pathology determine the relevance of studying this problem and searching for ways to solve it. [14,15,30].Cell death and tissue damage can occur due to the presence of high levels of circulating cytokines. In addition, there is haemolysis of red blood cells and anaemia as cytokines can activate macrophages; together (impaired vascular haemostasis, anaemia and cytokine-induced injury), lead to multi-organ failure, including the kidneys in the list. It is erythrocyte haemolysis that develops as a result of cytokine storm and causes renal dysfunction

MATERIAL AND METHODS OF THE STUDY: the data concerning the complex examination and treatment of 62 patients with kidney damage who underwent SARS-CoV-2 are presented in the paper. The distribution of patients was based on a prospective targeted open randomised study.

The study period and clinical collection period started from the second quarter of 2020 and ended December 2023. Meanwhile, for the period from April to August 2020, the clinic was still functioning as a specialist covid centre, with specialists from all disciplines according to quarantine requirements. All patients were combined into one main group.

Criteria for inclusion of patients in the main group were: age of patients not younger than 20 and not older than 75 years; presence in the history of coronavirus infection disease, with severe course, with signs of kidney damage during the treatment period; persistence of signs of kidney disease (proteinuria, albuminuria, micro- or macrohaematuria, decreased rate of glomerular filtration, high values of creatinine and urea in blood, etc.); presence of negative results of PCR in the blood; presence of negative results of PCR in the clinic.); negative PCR test for SARS-CoV-2 on admission to our clinic; voluntary informed consent of the patient to participate in the clinical trial.

Due to the fact that the patients of the main group came to the clinic with different duration of the anamnestic period of the disease development and terms of SARS-CoV-2 before us, there was a necessity to randomise the main group itself. Based on the principles of evidence-based medicine the main group of patients was subdivided by us into two subgroups:

The first subgroup - 34 (54.8%) patients who were transferred from a specialised covid infectious disease clinic after achieving a negative PCR test result for SARS-CoV-2 with signs of renal damage and the need for renal replacement therapy.

The second subgroup - 28 (45.2%) patients who were transferred from other therapeutic clinics or hospitalised as in the primary treatment for the underlying disease. All of them had a history of SARS-CoV-2 and were treated as inpatients in a specialised covid infectious disease clinic. During treatment, they were diagnosed with acute kidney injury, but remission of complications was achieved by the time of hospital discharge. However, later, after 1 to 3 months, the patients came to our clinic with the need for renal replacement therapy.

The chronology of hospitalisation of patients with kidney damage after SARS-CoV-2 showed that patients of the first subgroup were predominantly (70.6%) admitted to our clinic during the peak of the first and second waves of the COVID-19 pandemic, whereas patients of the second subgroup sought specialised care predominantly after the passage of the COVID-19 pandemic waves in the period 2021-2023 (92.9%).

The diagnosis of kidney damage was established according to the recommendations of the Global Foundation for the Improvement of Kidney Diseases (KDIGO) in the presence of one of three signs of pathological process manifestation in the form of: increase in serum creatinine level at 26.5 μmol/l or higher within 48 hours; increase in serum creatinine above 1.5 times compared to baseline during the previous 7 days; decrease in urine output less than 0.5 ml/kg/hour within 6 hours.

All patients in the main group were subdivided according to the stages of kidney damage after SARS-CoV-2, which were also recommended by KDIGO.

As our data showed, among the patients of the main group the third stage of kidney damage prevailed (62,9%), when the level of creatinine in blood of patients increased 3 times from the initial level or the beginning of renal replacement therapy. In the remaining 37.1% of cases, patients had stage 1 and 2 kidney damage after SARS-CoV-2. From 17,7% of cases the first stage of kidney damage was diagnosed, when creatinine level in blood increased 1,5-1,9 times from the initial level, and in 19,4% of cases - 2 - 2,9 times under the same conditions.

Distribution of patients by age showed predominance of patients in the age category of 51 and older (67.8%). At the same time between the patients of the age category from 51 to 60 years and from 61 to 75 years the distribution of the number of patients was the same (21 patients or 33,9% each). The second place was occupied by patients aged 41-50 years (24.2%). Patients at younger age were only in 8.1 per cent of cases. It should be noted that among the patients of the first subgroup prevailed in the age category from 51 to 60 years, and in the second subgroup - from 61-75 years.

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Club filtration rate (ml/hour/kg) = [Urine volume (ml) x urine creatinine (mg/ml)] / [time (hour) x serum creatinine (mg/ml) x patient weight (kg)].

All patients underwent ultrasound examination of the kidneys in a functional diagnostics room. To determine morphostructural changes in the kidneys all patients of the main group underwent percutaneous puncture biopsy of kidneys in the surgical department under aseptic conditions. Biopsy material was examined by standardised histological technique with staining under light in conditions of the central research laboratory.

Factor analysis was used to study the reciprocal relationship of various studied features, which determined the variance of specific factors in the form of a variance cloud. Statistically significant linear combinations of a number of factors allowed the dimensionality of the trait graphical cloud to be reduced, which can be analysed.

Linearising the data allowed us to compare specific factors against each other. This in turn was the key to examining the actions on the final outcome of the factors analysed in each variance data cloud. Using this method of statistical analysis allowed us to quantify the observed signs of change.

The factors under study and their constituent immunological data were represented in quantitative form; the observable attributes influenced by the factors under study were the outcome attributes.

RESULTS AND THEIR DISCUSSION. Before analysing the clinical and laboratory manifestations of renal damage in SARS-CoV2 patients, we considered it fair to present the background status of the patients, i.e. the presence of comorbidities. In total 232 names of concomitant diseases were diagnosed among the patients of the main group. At the same time, there were 3.7 nosological forms of disease concomitant to kidney injury for each patient on average. To a greater extent the correlation was expressed among the patients of the second subgroup - 4.3 pathologies, than among the patients of the first subgroup - 3.3 nosological diseases. Among the patients of the first subgroup an even half of concomitant diseases (50%) were pathologies of the cardiovascular system. At the same time among the patients of the second subgroup the share of pathologies from the side of cardiovascular system was also the largest, but equalled only 34,2% within the subgroup. Associated diseases on the side of cardiovascular system were represented by ischaemic heart disease (29,9%), hypertension (44,3%), varicose veins of lower limbs (11,3%) and atherosclerotic lesions of vessels (14,4%).

The second and third places by frequency were occupied by concomitant respiratory (25.4%) and digestive (19.8%) diseases. They were in the same proportion among the patients of the first subgroup (18.8% each), whereas among the patients of the main group the patients with concomitant diseases of the respiratory organs prevailed (31.7%).

Associated diseases on the part of gastrointestinal tract among the patients of the second subgroup made up 20.8%. Associated diseases on the side of the respiratory system were represented by the presence of exudative pleurisy (50.8%), which were noted to a greater extent among patients of the second subgroup (55.3%), chronic obstructive lung diseases (28.8%), which were noted predominantly among patients of the first subgroup, and chronic nonspecific lung diseases (20.3%). Associated diseases of the gastrointestinal tract were represented by the presence of chronic colitis (43.5%), pathologies of the pancreato-hepatobiliary system (chronic hepatitis and chronic calculous cholecystitis - 19.6% each), peptic ulcer disease (6.5%) and chronic gastritis (10.9%).

Associated diseases of the musculoskeletal system were diagnosed in 8 (3.4%) patients, with their prevalence among the patients of the second subgroup (4.2%) over the number of patients of the first subgroup (2.7%). In 62.5% of cases they were represented by gout.

Diseases of the nervous system were noted in 2.2% of cases (1.8% in the first subgroup of patients and 2.5% in the second subgroup of patients). Another 17 (7.3%) patients had diabetes mellitus as a concomitant pathology (8.0% among patients of the first subgroup and 6.7% among patients of the second subgroup).

Clinical examination of patients with renal injury, following SARS-CoV2, revealed 241 complaints. Although predominantly (55,2%) they were noted among the patients of the first subgroup, nevertheless for each patient of both subgroups they were in the same proportion of 3,9 complaints per 1 patient. The main complaints of patients were general weakness (96.8%). Among the patients of the first subgroup it was noted in 94.1% of patients, and among the patients of the second subgroup - in all cases.

Arterial hypertension was the second most frequent (69.4%) and prevailed among patients of the second subgroup (75%) over the number of patients of the first subgroup (64.7%). Local edema, puffiness of the face bothered 22 (64.7%) patients of the first subgroup and 16 (57.1%) patients of the second subgroup. In total such complaints were noted in 38 (61.3%) patients.

The next most frequently registered complaint was urine colour change (50%), which was noted in

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38.2% of patients of the first subgroup and in 64.3% of patients of the second subgroup. Massive oedema was noted in 23 (37.1%) patients, which was prevalent among the second subgroup patients (39.3%).

Hyperthermia was noted in 24 (38.7%) patients. At that, in 19 (30.6%) patients hyperthermia was subfebrile, and in 5 (8.1%) patients - febrile. This clinical sign of renal damage after SARS-CoV2 was predominantly observed among the patients of the first subgroup.

Dysuric phenomena were noted in 13 (21%) patients, and polyarthralgia - in 9 (14,5%) patients. Dysuric phenomena prevailed among the patients of the first subgroup (26.5%), and polyarthralgia - among the patients of the second subgroup (17.9%).

Biopsy material of kidneys was obtained in all patients of the main one in order to reveal the peculiarities of morphological changes at the stage of pathological process development.

In puncture biopsy material there was an increase in neutrophils cellularity. Increased exudation of capillary endothelial cells was revealed, and in some cases it was with signs of transition to proliferation. Infiltration of renal tissue with neutrophils and monocytes was noted. There were biopsy specimens with haemorrhagic character of the lesion. Such character of changes in kidneys correlated to exudative proliferation of endocapillaries.

In other cases the lumen of capillaries was narrowed with predominantly proliferative changes in capillaries. The narrowing of the lumen was due to both increased proliferation and deposition of immune complexes, predominantly on the epithelial side of the basal membrane of the tubular capillaries.

The dispersion of the distribution of these leading morphological values among patients of different subgroups was not unambiguous. Thus, among the patients of the first subgroup, diffuse endocapillary proliferation was noted in only 7 (20.59%) patients, whereas diffuse endocapillary exudation was the predominant renal lesion and characteristic of 27 (79.41% of patients. In patients of the second subgroup, changes on the side of renal tissue were more prone to proliferative processes. The predominant type of lesion (26 patients, 92.86%) was diffuse endocapillary proliferation of renal vessels. Only in 2 (7,14%) patients we revealed the presence of diffuse endocapillary exudation. Thus, the character and analysis of clinical and morphological manifestations of renal damage in patients who underwent SARS-CoV2 showed that pathological process in kidneys predominantly proceeds by acute inflammatory type, characterised by predominance of diffuse endocapillary exudation (79,41%). In patients with distant consequences of kidney damage after SARS-CoV2, diffuse endocapillary proliferation becomes predominant (92.86%), which after coronavirus endotheliitis can inevitably lead to the development of chronic renal failure.

CONCLUSIONS:

1. analysis of the results of patients who underwent SARS-CoV2, showed that the pathological process in the kidneys is predominantly of acute inflammatory type, characterised by predominance of diffuse endocapillary exudation (79.41%).
2. In patients with distant consequences of kidney damage after SARS-CoV2, diffuse endocapillary proliferation prevails (92,86%), which after coronavirus endotheliitis can inevitably lead to the development of chronic renal failure.

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