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Pathomorphological features of the kidneys in patients with chronic kidney disease on dialysis with COVID-19 infection

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ABSTRACT: **The current study aimed to investigate the pathomorphology of the kidneys in patients with chronic kidney disease (CKD) on dialysis infected with COVID-19, focusing on structural changes and their correlation with the severity of the infection. The study included autopsy data from patients infected with COVID-19 who had been undergoing renal replacement therapy for 6 months to 1 year and died at the Zangiota Republican Specialized Center in 2022. The study was conducted using kidney biopsy samples. Morphological analysis included macroscopic examination, histological, and microscopic methods to identify signs of inflammation, fibrosis, and thrombosis. The results showed that kidneys of patients with COVID-19 were enlarged, with a granular surface and subcapsular hemorrhages. Histological examination revealed necrotic nephrosis, tubulointerstitial fibrosis, significant vascular involvement, and vacuolar degeneration of the tubules. Thrombosis of vessels and ischemic infarctions were frequently observed, correlating with the severity of COVID-19. The formation of focal segmental glomerulosclerosis, associated with chronic inflammation, was a notable feature. COVID-19 induces significant pathological changes in the kidneys of patients with CKD on dialysis, aggravating the course of chronic kidney failure. It is concluded that there is a need for early detection and prevention of renal complications in patient with COVID-19.**

KEYWORDS: **Chronic kidney disease, COVID-19, Pathomorphology, Glomerulosclerosis, Dialysis.**

INTRODUCTION

COVID-19 has significantly altered approaches to treating patients with chronic diseases, especially among those on hemodialysis. Studies show that patients receiving renal replacement therapy (RRT) have a significantly higher incidence of COVID-19 compared to the general population, with rates ranging from 2.5% to 49%, depending on data sources. The SARS-CoV-2 virus uses the angiotensin-converting enzyme 2 (ACE2) as a receptor to enter target cells, which explains its ability to affect kidney tissues, particularly in patients with renal failure [1, 2]. ACE2 is actively expressed in tubular epithelial cells and podocytes, making the kidneys one of the targets for COVID-19 [3].

Kidney involvement in the pathological process of COVID-19 ranges from mild abnormalities, such as proteinuria, to severe acute kidney injury (AKI), which may require renal replacement therapy [4]. Mechanisms of kidney damage include not only the direct viral impact on renal tissue but also systemic inflammatory responses and thrombosis, as confirmed by autopsy studies [5].

Studies of kidney biopsies from patients who died from COVID-19 have shown the presence of viral RNA in renal tissues in 60% of cases, especially in AKI [6]. This indicates a specific tropism of SARS-CoV-2 for the kidneys and a correlation between the degree of renal involvement and the severity of COVID-19 [7]. Furthermore, data show that viral antigens accumulate in renal tubules, supporting the hypothesis of direct viral impact on the kidneys [4]. Thus, patients with chronic kidney disease (CKD) on dialysis are a high-risk group for COVID-19 and require special attention during the pandemic.

The present study aimed to investigate the pathomorphological changes in the kidneys of these patients to identify risk factors and possible mechanisms of kidney damage during COVID-19 infection.

MATERIALS AND METHODS

The study utilized data from patients with chronic kidney disease (CKD) undergoing dialysis therapy and infected with COVID-19, who were admitted to the Republican Specialized Center "Zangiota" from January to December 2022. The study included patients with a confirmed COVID-19 diagnosis through PCR testing and who had been receiving renal replacement therapy for 6 months to 1 year prior to hospitalization.

Ethical approval

The review board and ethics committee of Republican Specialized Hospital Zangiota-1 approved the study protocol and informed consents were taken from all the participants.

Inclusion and exclusion criteria

Patients over 18 years old with diagnosed end-stage CKD who were on continuous hemodialysis therapy were selected for participation. Patients with acute infectious diseases unrelated to COVID-19, as well as those with chronic conditions requiring other types of replacement therapy, were excluded.

Clinical data

The study focused on the clinical manifestations of COVID-19, including the frequency and severity of dyspnea, hyperthermia, myalgia, arthralgia, nausea, and vomiting, as well as general biochemical parameters. All clinical data were collected based on medical history reviews, clinical examinations, and data from ultrasound, biochemical, and laboratory studies. Key parameters included creatinine levels, blood urea nitrogen, the presence of proteinuria, and hematuria.

Pathomorphological analysis

Pathological studies were conducted based on autopsy material from patients diagnosed with coronavirus infection. The macroscopic appearance of the kidneys was examined through visual inspection, documenting tissue structure changes, including kidney size, surface characteristics, and the presence of subcapsular hemorrhages. Histological analysis was performed using high-resolution microscopy to assess the condition of the proximal and distal tubules, blood vessels, and glomeruli. Particular attention was given to the presence of necrotic and dystrophic changes in the tubular epithelium, as well as signs of fibrosis and inflammatory processes in renal tissues.

Pathology and light microscopy

The tissue samples taken for histological evaluation were fixed in 10% neutral buffered formalin and dehydrated by ethanol gradient, then embedded in paraffin blocks following routine tissue procedures, sectioned into 5-µm thick slices and stained by hematoxylin and eosin (H&E) for light microscopy (Olympus BX51) performing to observation. The samples were photographed in different directions in 20 mm near the optic disc. Tissue samples were carefully examined by the expert pathologist in a blind and unbiased manner.

RESULTS

The study of pathomorphological changes in the kidneys of patients with CKD on dialysis and infected with COVID-19 revealed a number of characteristic macroscopic and histological changes, confirming the virus's impact on kidney condition.

Macroscopic changes

In most patients with COVID-19, the kidneys were significantly enlarged. The kidney surface was often granular, in some cases finely granular, with visible subcapsular hemorrhages. The kidney tissue had a flaccid consistency, and in some instances, small cysts filled with clear serous fluid were observed on the surface. These changes indicated pronounced pathological processes in the kidney tissue associated with COVID-19. Upon cross-section of

the kidneys, areas of redness, necrotic nephrosis, and hyperemia of the corticomedullary junction were noted, further confirming the presence of significant damage.

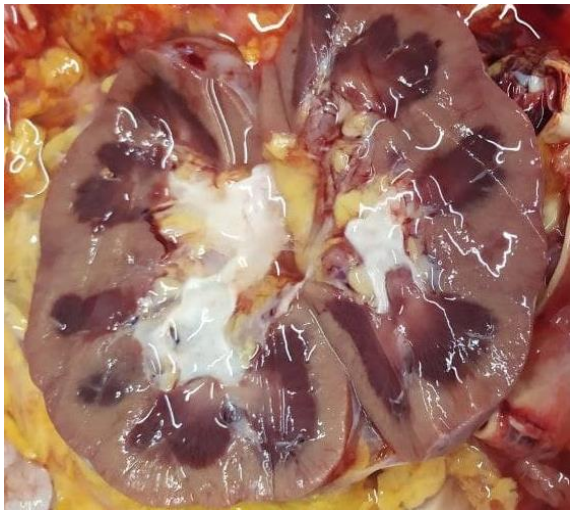

Figure 1. Macroscopic section of the kidney of patient with chronic glomerulonephritis without coronavirus infection. The cortical layer is thickened, pale in color, and well demarcated from the dark red medullary tissue.

Histological changes

Histological examination revealed significant tubulointerstitial changes in patients with COVID-19 in the interstitial tissue of the kidneys so that edema and infiltration by inflammatory cells, including lymphocytes, macrophages, and plasma cells, were observed. Dystrophic changes of varying severity were seen in the epithelium of both proximal and distal tubules, indicating acute tubular necrosis. Thrombosis in the renal vessels was frequently noted, leading to glomerulosclerosis and fibrosis of the interstitial tissue. These findings indicated severe kidney damage in patients with COVID-19 (Figures 2 and 3).

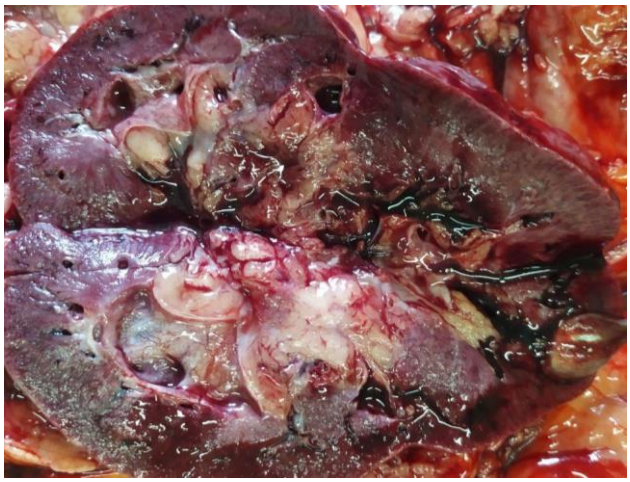

Figure 2. Macroscopic specimen of a patient with chronic kidney disease combined with coronavirus infection. The kidney is enlarged, with no clear differentiation between the cortical and medullary layers. The calyceal-pelvic system is dilated.

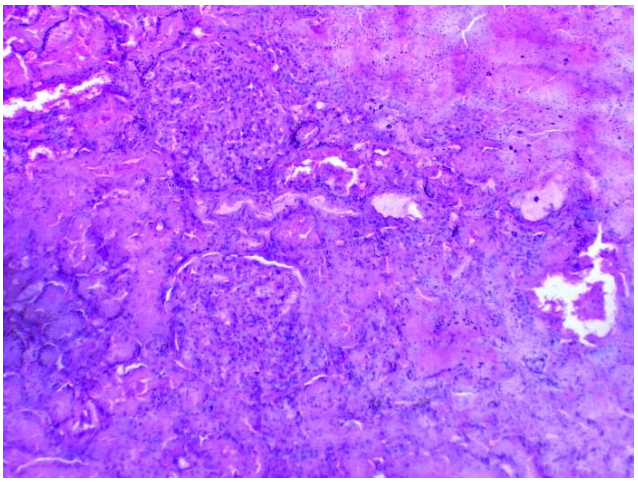

Figure 3. Infiltration and fibrotic changes in the interstitial tissue of kidney in patient with chronic kidney disease (CKD). H&E stain, magnification 20 µm

Comparison of kidney damage in patients with and without COVID-19

In patients without COVID-19 who suffered from chronic glomerulonephritis, renal changes were less pronounced (Figure 4). The cortical layer of the kidneys was broader, light yellow in color, and clearly demarcated from the dark red medullary substance. There was no significant thrombosis or fibrotic changes observed. In

contrast, patients with COVID-19 exhibited more severe alterations: infiltration of the interstitial tissue, edema, as well as tubular dystrophy and necrosis. These changes in COVID-19 patients indicated systemic inflammation and significant kidney damage, which considerably worsened their condition.

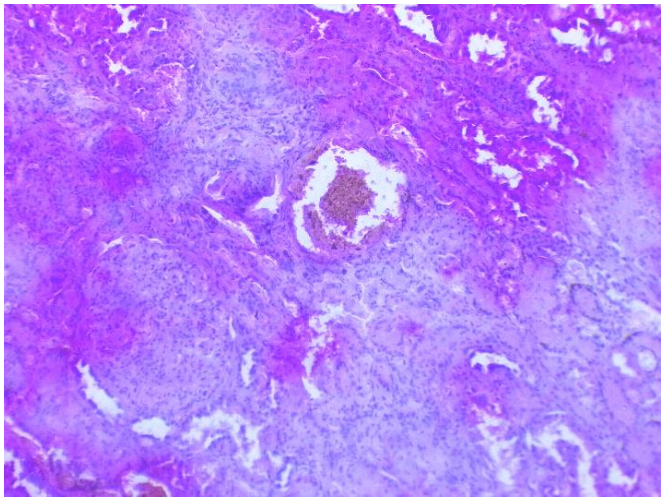

Figure 4. Edema of the interstitial tissue, polymorphous cellular infiltration, dystrophic changes in the tubules, and sclerotic alterations in patients without COVID-19. H&E stain, magnification 20 μm

Complications

One of the most severe complications in patients with CKD on dialysis and COVID-19 was ischemic renal infarction, which occurred due to thrombosis of the renal vessels (Figure 5). These infarctions were associated with significant damage to the kidney tissue, worsening renal failure and leading to the development of acute kidney injury. Histological analysis revealed extensive areas of necrosis, tubular dystrophy, and microangiopathy (Figure 6). Patients with COVID-19 also more frequently exhibited signs of microangiopathy and the formation of focal segmental glomerulosclerosis, confirming severe kidney damage.

These results confirm the significant impact of COVID-19 on renal tissue, especially in patients with chronic kidney disease on dialysis. The high frequency of thrombosis, necrosis, and fibrotic changes highlights the need for enhanced monitoring of these patients and the development of individualized therapeutic approaches to prevent the progression of renal failure.

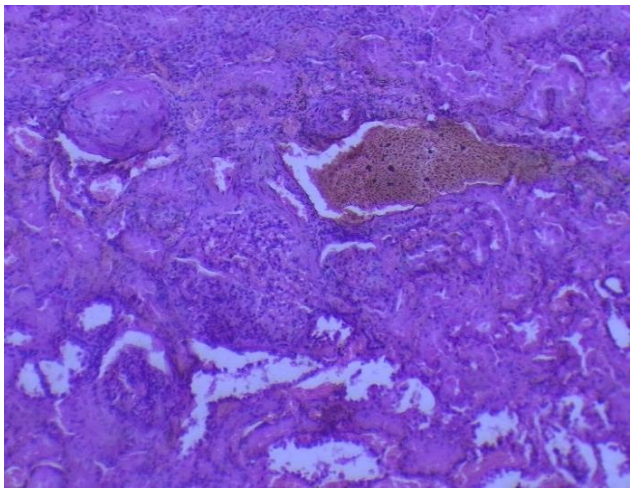

Figure 5. Tubular necrosis, vacuolar dystrophy of varying degrees, thrombosis, and glomerulosclerosis in patients with chronic kidney disease (CKD). on dialysis and COVID-19. H&E stain, magnification 20 μm

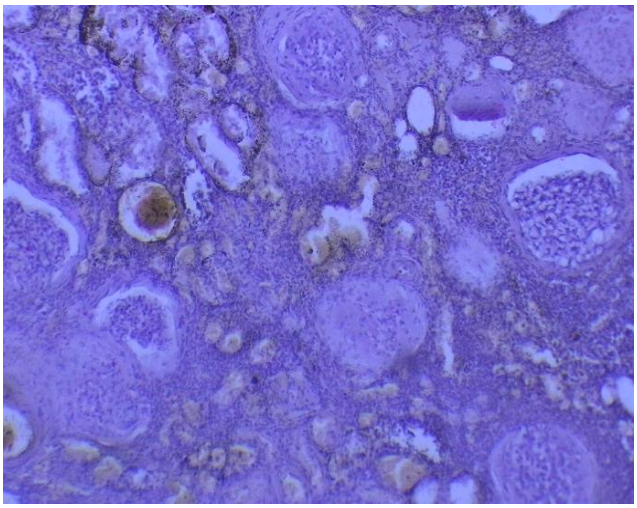

Figure 6. Epithelium of the proximal and distal tubules with marked vacuolar dystrophy in patients with chronic kidney disease (CKD) on dialysis and COVID-19. Some tubules showed signs of atrophy and cystic dilatation plus arterial and venous vessels with thickened walls due to fibrosis. H&E stain, magnification x20.

DISCUSSION

The study conducted by Gambella et al. [8] revealed severe kidney damage associated with COVID-19 and identified various histopathological findings in nine patients. The primary diagnoses included minimal change disease, acute tubular necrosis, collapsing glomerulopathy, and C3 glomerulopathy, with no viral particles found in the biopsies. This absence complicates the direct link between SARS-CoV-2 and kidney damage, highlighting the need for comprehensive clinical and pathological evaluation. The findings underscore the importance of monitoring kidney function in COVID-19 patients to prevent chronic kidney disease and suggest further investigation into the mechanisms connecting viral infections and kidney pathology [8].

The study by Amann et al. [9] stated severe kidney complications caused by COVID-19, particularly AKI, which is common among critically ill patients. The authors emphasize that SARS-CoV-2 can be detected in kidney tissue, indicating its direct impact on kidney health. Patients with chronic kidney disease (CKD) and those on dialysis are especially vulnerable. The findings highlight the need for further research into the pathophysiology of kidney damage and challenges in diagnosing kidney injury in COVID-19 patients, as traditional methods do not always detect the virus in kidney tissues [9].

The article by Amann et al. [10] reported the significant impact of COVID-19 on kidney health, particularly emphasizing that acute kidney injury (AKI) is a common complication in severe cases. The authors stated that SARS-CoV-2 has been found in kidney tissue, raising concerns for patients with pre-existing CKD and those on dialysis, who are particularly vulnerable. Their study highlighted the need for further research to understand the direct and indirect effects of the virus on kidney function, as Amman et al. [10] data suggest a multifactorial pathogenesis of AKI in COVID-19 patients [10].

The study by Teixeira Júnior et al. [11] in Brazil highlighted severe kidney complications associated with COVID-19. It emphasizes the need for comprehensive analysis of kidney morphology in virus-affected patients, using advanced methods such as immunohistochemistry and electron microscopy. The study aims to explore the link between SARS-CoV-2 and kidney damage, particularly in a diverse population with a high prevalence of high-risk APOL1 genotypes. This multicenter study [11], conducted in 17 federal university hospitals, to provide insights into the immediate and long-term effects of COVID-19 on kidney health.

Our results was in consistent with the results of Kamyshnikova et al. [12] which examined the long-term effects of COVID-19 on the kidneys, focusing on the involved pathogenic mechanisms. The study, conducted in Russia, showed that kidney damage can manifest as a decrease in glomerular filtration rate, increased creatinine levels, and proteinuria. The authors emphasize the role of ACE-2 receptors in viral entry and subsequent kidney damage, as well as inflammatory responses. Notably, the Dickkopf-3 protein is proposed as a potential biomarker of kidney damage. This study [12] highlighted the importance of monitoring kidney health in patients recovering from COVID-19 for effective treatment of emerging complications. Our results was in consistent with the results of Kamyshnikova et al. [12].

Zhu et al. [13] in China focused on the clinical and pathological features of kidney damage associated with the SARS-CoV-2 variant caused by the Omicron virus. They reported that AKI, CKD, and nephrotic syndrome (NS) are common among patients. Also IgA nephropathy (IgAN) was the most common observed pathological type. Notably, kidney damage was less pronounced in Asian patients, and their prognosis was more favorable compared to other demographic groups. They underscored the need for ongoing monitoring and individualized treatment strategies for COVID-19 patients to mitigate kidney complications [13].

Rai [14] in a comprehensive review discussed significant kidney damage in COVID-19 patients across various countries, and stated that AKI and CKD are common complications. , The author highlighted that those patients with pre-existing kidney failure face more severe outcomes. The multifactorial nature of kidney damage during SARS-CoV-2 infection includes inflammation and hypercoagulation. Monitoring and long-term screening of patients recovering from COVID-19 is important to prevent the progression of CKD and improve treatment strategies for patients with pre-existing kidney diseases [14].

CONCLUSION AND RECOMMENDATION

The current study demonstrated significant morphological changes in the kidneys of patients with CKD on dialysis and infected with COVID-19. Enlarged kidney sizes, granular surface texture, the presence of subcapsular hemorrhages, and necrotic nephrosis indicate severe tissue damage. Histological examination revealed tubulointerstitial fibrosis, tubular dystrophy, vascular thrombosis, and glomerulosclerosis, confirming systemic inflammation and kidney damage associated with COVID-19. Patients with COVID-19 exhibited more pronounced

changes, including microangiopathy and necrotic processes, which also reflected their severe clinical condition. Kidney transplant recipients showed signs of acute rejection, large vessel thrombosis, and hemorrhages, indicating a high risk of complications when infected. These findings underscore the need for enhanced monitoring and treatment of CKD patients in the context of COVID-19, especially those on dialysis.

DECLARATIONS

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Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Authors' contributions

All authors contributed equally to this work.

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None.

Competing interests

All authors declare that they have no conflict of interest.

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