PREVENTION OF THE DEVELOPMENT AND PROGRESSION OF CKD IN PATIENTS WITH COVID-19

Nilufar Sh. Akhmedova - D.M.Sc., professor
Bukhara State Medical Institute (Bukhara, Uzbekistan)
Muzaffar Kh. Khattabov - head of department
Bukhara Regional Multidisciplinary Medical Center (Bukhara, Uzbekistan)
muzaffar.hattabov@yandex.ru

Abstract. *The article is devoted to the study of diagnostic, preventive, and rehabilitation features of nephropathies in patients who have recovered from COVID-19. The study included 249 patients who underwent inpatient treatment for COVID-19 at the Bukhara Regional Multidisciplinary Medical Center. Renal function parameters (creatinine, urea, cystatin C, microalbuminuria) were analyzed dynamically at 6, 12, 18, and 24 months after infection. It was found that 55.4% of patients developed albuminuria, which was most pronounced in individuals with comorbidities such as arterial hypertension, type 2 diabetes mellitus, and obesity. Key risk factors for post-COVID nephropathy were identified, and an individualized prevention system was proposed, including laboratory screening, a nephroprotective diet, physical activity, and staged monitoring. The findings confirm the importance of early diagnosis and rehabilitation to prevent the progression of chronic kidney disease after COVID-19.*

Keywords: *CKD, COVID-19, nephropathy, arterial hypertension, risk factors.*

Introduction.

COVID-19 affects not only the respiratory system but also has a significant impact on renal function. A number of studies have demonstrated that SARS-CoV-2 can directly invade nephrocytes and, through mechanisms such as cytokine storm, hypoxia, and thrombosis, lead to the development of acute kidney injury (AKI) and subsequently chronic kidney disease (CKD) [9]. Moreover, a decline in glomerular filtration rate (GFR), including cystatin C-based GFR, has been observed in patients even 6 and 12 months after COVID-19 infection [1,9].

A substantial proportion of patients who recovered from COVID-19 had concomitant comorbidities, including arterial hypertension, type 2 diabetes mellitus, metabolic syndrome, obesity, ischemic heart disease, and others. These conditions themselves increase the risk of nephropathy; however, the post-viral inflammatory background, hypercoagulability, and autoimmune reactions further potentiate their deleterious effects. The pathogenesis of post-COVID nephropathy is therefore complicated by this multifactorial interplay [4,5].

The impact of rehabilitation on nephropathy remains an insufficiently studied area. Post-COVID-19 rehabilitation has primarily focused on restoring respiratory function, psycho-emotional well-being, and general physical condition. However, there are virtually no specific rehabilitation protocols aimed at preventing or delaying the progression of nephrological disorders. Therefore, this issue highlights the need to develop an individualized, multifactorial rehabilitation system for patients who have had COVID-19 and are at high risk of developing nephropathy. Although the COVID-19 pandemic has officially ended, post-COVID syndrome continues to be widely observed among populations worldwide [2,3].

Post-COVID syndrome is a newly recognized nosological entity associated with a wide range of symptoms and dysfunction of multiple organ systems. The seriousness of this pathology is determined by the large number of patients affected by it. According to available data, up to 30–40% of individuals who have recovered from COVID-19 suffer from post-COVID syndrome. For

example, it is currently estimated that approximately 15 million people in the United States are experiencing the consequences of coronavirus disease [8,9].

Many countries are allocating substantial financial resources to the study and treatment of post-COVID syndrome. Over the past few years, the United Kingdom's healthcare system has invested significant funding in supporting individuals with long COVID. This has included the establishment of specialized post-COVID services and medical facilities. In addition, clinical guidelines for the management of post-COVID syndrome have been developed in this country [7].

Unfortunately, comprehensive recommendations for the early diagnosis and effective treatment of post-COVID syndrome are still lacking.

In recent years, the global community has faced not only a medical challenge but also a global socio-economic problem of major importance for all countries: the pandemic-like rise in chronic non-communicable diseases and the annual increase in mortality and disability caused by their complications [11,13]. The results of kidney function assessments and urinalysis obtained through screening programs conducted among tens of thousands of individuals in different countries have shown that approximately one in ten people worldwide has some degree of chronic kidney damage. If not identified and treated in a timely manner, kidney damage of varying severity may progressively worsen over the years, ultimately forcing patients to undergo dialysis or kidney transplantation [12].

The widespread implementation of the CKD concept in clinical practice contributes to the identification of risk factors and causes of disease progression and encourages patients to consult nephrologists and cardiologists at the early stages of the disease [16,18].

The world continues to combat COVID-19, largely due to the emergence of new viral variants. At the same time, a proportion of recovered individuals continue to experience persistent and long-term consequences referred to as long COVID. Clinical, autopsy, animal, and in vitro studies have demonstrated endothelial injury in both acute COVID-19 and in patients during recovery. Endothelial dysfunction is now recognized as a central factor in the progression of COVID-19 and in the development of long COVID. Post-COVID-19 rehabilitation has mainly focused on restoring respiratory function, psycho-emotional well-being, and general physical condition. However, there are virtually no specific rehabilitation protocols aimed at preventing or delaying nephrological disorders. Therefore, this issue underscores the need to develop an individualized, multifactorial rehabilitation system for patients who have recovered from COVID-19 and are at high risk of developing nephropathy [15,17].

Materials and methods.

The study included 249 patients aged 18–74 years who were hospitalized with COVID-19 infection and received inpatient treatment at the Bukhara Regional Multidisciplinary Medical Center, which functioned as a COVID-19 center from March 16, 2020, to May 2021. COVID-19 infection was diagnosed in accordance with versions 6 and 7 of the National Clinical Guidelines.

Of the enrolled patients, 132 were men and 117 were women; the mean age was 48.1 ± 3.7 years. In accordance with the aims and objectives of the study, the patients were divided into two groups:

- Main group: patients who experienced COVID-19 infection on the background of comorbid conditions (n = 196);

- Comparison group: patients with COVID-19 infection in whom no comorbid conditions were identified (n = 53).

All patients underwent comprehensive history taking and physical examination, as well as standard laboratory and instrumental investigations, including complete blood count, biochemical blood tests, urinalysis, coagulation profile, electrocardiography, ultrasound examination of the abdominal cavity and kidneys, and chest radiography. To assess renal function, serum and urinary creatinine and urea levels were measured.

Results.

• Analysis of the study findings demonstrated that microalbuminuria (MAU) was detected in 55.4% of patients (n = 138) during the course of infection. This indicator was 63.4% in the main group and 22.6% in the comparison group.

• To assess renal dysfunction based on the level of albuminuria, a comparative analysis of albuminuria categories was performed between the groups (Figure 1).

• According to the presented data, significant differences in albuminuria levels were observed between the two groups. In the main group, albuminuria was distributed across different stages, whereas in the comparison group, most patients were concentrated within a single category.

• **A0 category (normal):** The proportion of patients corresponding to the A0 category was 77.4% in the comparison group, whereas in the main group this figure was 35.7%. This finding indicates that preserved renal function was more common in the comparison group.

• **A1 category (mild albuminuria):** In the main group, 32.7% of patients were classified in this category, while in the comparison group this proportion was only 7.5%. This suggests that signs of microalbuminuria were more frequently observed in the main group.

• **A2 category (moderate albuminuria):** The proportion was 15.8% in the main group and 7.5% in the comparison group. This may indicate that increased urinary albumin excretion and more advanced renal involvement were more common in the main group.

• **A3 category (severe albuminuria):** This category was observed in 11.7% of patients in the main group and 5.7% in the comparison group. These findings reflect a higher frequency of glomerular damage in the main group.

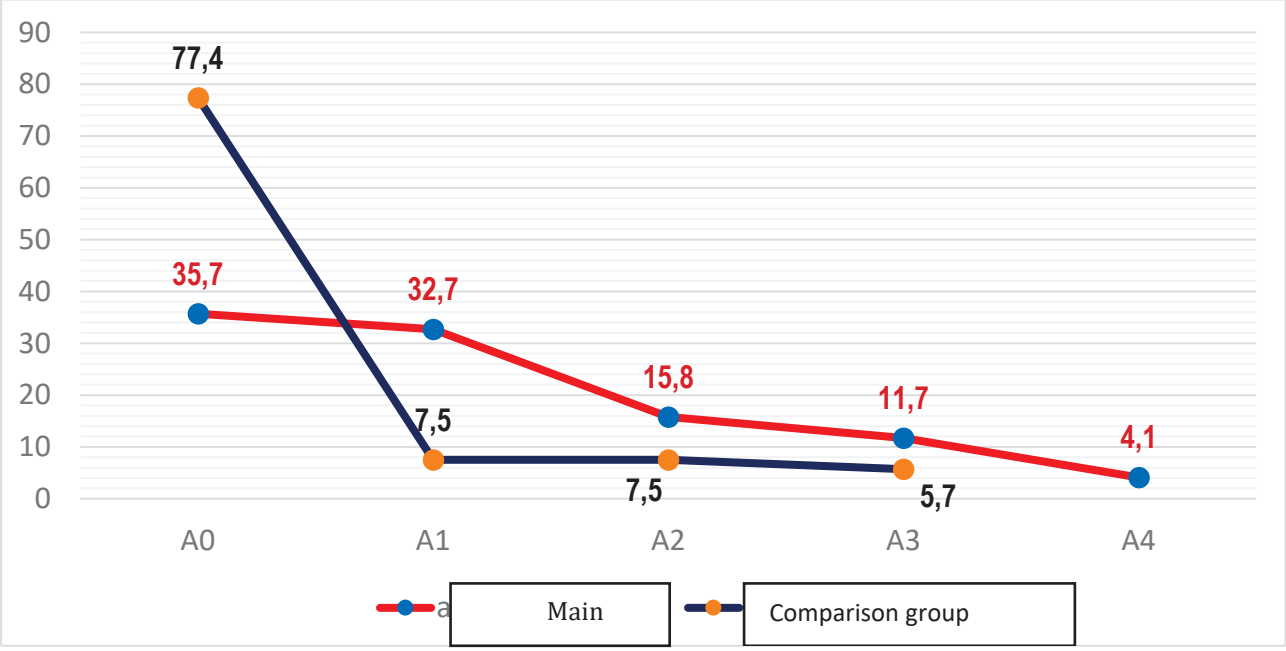


Figure 1. Comparative analysis of the frequency of albuminuria levels in the study groups (%)

• A4 category (very severe albuminuria): In the main group, this severe degree of renal involvement was still identified in 4.1% of patients, whereas no cases of albuminuria of this severity were observed in the comparison group (0%).

Albuminuria levels in the main group were distributed across a wide range, indicating varying degrees of renal dysfunction in this group. In particular, the relatively high proportions of patients in the A1–A3 categories (32.7%, 15.8%, and 11.7%, respectively) suggest that albuminuria in the main group could be detected at early and intermediate stages and reflect the clinical progression of renal

involvement. At the same time, the presence of patients even in the A4 category (4.1%) indicates the existence of severe nephropathic damage in this group.

In contrast, in the comparison group, albuminuria was not detected in nearly three-quarters of patients (A0 – 77.4%), while the remaining patients showed only mild degrees of albuminuria (A1–A3). This suggests that the risk of nephropathy was considerably lower in the comparison group.

To evaluate the pathogenetic features of nephropathy development in patients after COVID-19, an analysis was performed of the association between the prevalence of microalbuminuria (MAU) and comorbid conditions (Figure 2).

The analysis showed that the prevalence of MAU was highest among patients with type 2 diabetes mellitus, reaching 71.5%, which confirms the increased likelihood of nephropathy developing on the background of diabetes. High rates were also recorded in patients with arterial hypertension and coronary artery disease (68.2% and 63.9%, respectively). In patients with obesity and viral hepatitis, the prevalence of MAU was also statistically significantly elevated, indicating that these conditions should likewise be considered risk factors contributing to nephropathy.

To assess renal dysfunction in the post-COVID period among the patients included in the study, changes in microalbuminuria (MAU) and glomerular filtration rate (GFR) based on cystatin C were evaluated at 6, 12, 18, and 24 months after the infection.

The results showed that in the main group, MAU developed at 6 and 12 months in nearly 63.2% of patients who had no MAU during the acute phase of infection. Among these patients, A1 albuminuria was observed in 34.2% of cases, A2 in 20.5%, and A3 in 8.5%. In patients in whom MAU had already been detected, analysis of albuminuria dynamics showed that a decrease in MAU level was observed in only 39.8% of cases.

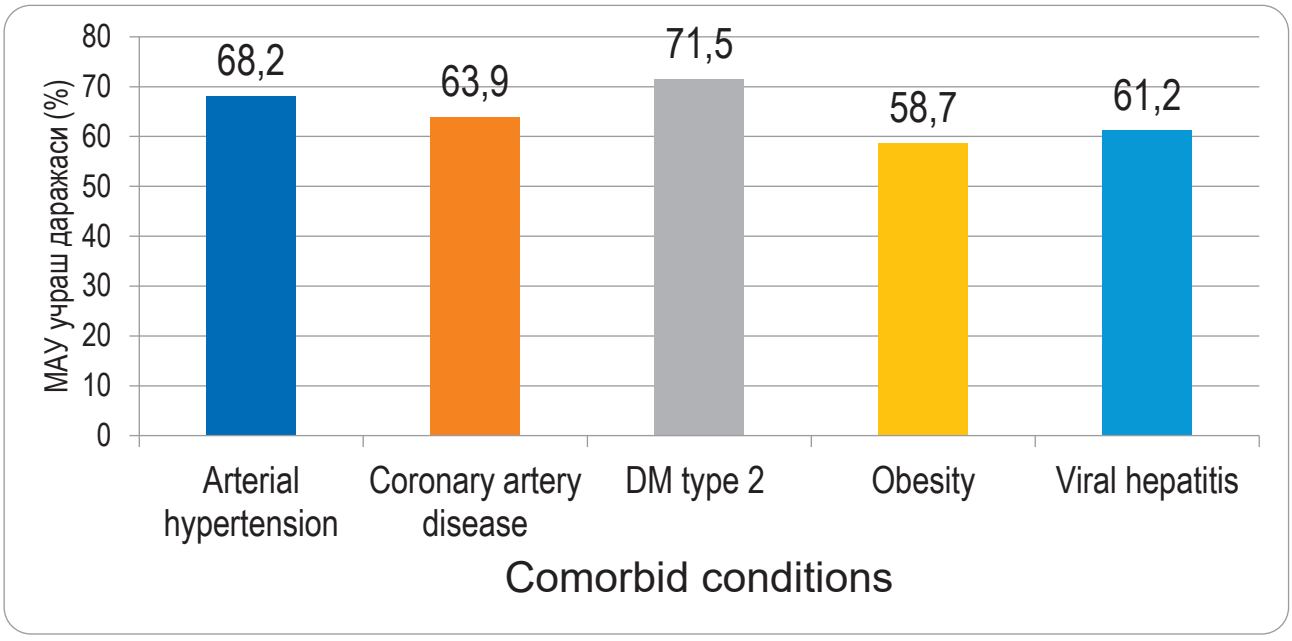


Figure 2. Analysis of the association between nephropathy development and comorbid conditions in patients after COVID-19 (%)

- In the comparison group, the proportion of patients with newly detected MAU increased to 32.7% at 6 months and to 38.1% at 12 months after infection. The main factors associated with increased cystatin C and MAU levels were as follows:
- the presence of more than two comorbid conditions — 68.5%;
- pulmonary fibrosis of stages F3–F4 — 59.3%;

- incomplete pathogenetic treatment in the comparison group — 44.7%.
- Based on the above findings, a rehabilitation roadmap aimed at restoring renal function in the early and late post-COVID periods was developed and recommended for implementation in clinical practice.
- The roadmap included six main components:
- **Identification of high-risk groups:**
- more than two comorbid conditions;
- pulmonary fibrosis of stages F3–F4;
- severe course of COVID-19.
- **Early screening:**
- MAU, cystatin C, IL-6, TGF-α.
- **Individualized follow-up:**

• **Monitoring parameters:** blood pressure, blood glucose, and GFR assessment.

4. **Nephroprotective diet:**
- restriction of sodium and protein intake;
- maintenance of electrolyte balance.

5. **Active rehabilitation:**
- aerobic exercise;
- breathing exercises.

6. **Educational programs:**
- improvement of patient awareness and self-monitoring skills.

The roadmap was developed within the framework of **prevention** and **rehabilitation**, and each block was structured according to the system: **cause → intervention → expected effect**.

Step 1. RISK STRATIFICATIONRationale: severe course of COVID-19 and the presence of ≥2 comorbid conditions.Intervention: screening for MAU, cystatin C, IL-6, and TGF-α within 0–3 months.Expected effect: identification of the high-risk group and initiation of early follow-up.

Step 2. PREVENTIVE STRATEGY (3–6 months)Rationale: the need to control blood pressure and glycemia.

• Risk: arterial hypertension and type 2 diabetes mellitus accelerate the progression of nephropathy.

• Intervention: target blood pressure <130/80 mmHg and HbA1c <7%.

• Expected effect: normalization of intraglomerular filtration pressure.

Dietary intervention: sodium and protein restriction

• Protein intake: 0.6–0.8 g/kg/day;

• Salt intake: <5 g/day;

• electrolyte and fluid balance should also be taken into account.

REHABILITATION STRATEGY (6–18 months)

Step 3. PHYSICAL ACTIVITY

• aerobic exercise (150 min/week);

• breathing exercises and supervised walking.Expected effect: improvement of endothelial function.

Step 4. PHARMACOLOGICAL APPROACH

• angiotensin receptor antagonists (ARAs) and SGLT2 inhibitors, if indicated.

Step 5. EDUCATIONAL SESSIONS

• improving patient awareness regarding MAU, GFR, clinical signs, and risk factors;

• information booklets and training sessions.

CONSOLIDATION AND MONITORING (18–24 months)

Step 6. PERIODIC FOLLOW-UP EXAMINATIONS

• MAU and cystatin C assessment every 6 months;

• hemodynamic assessment, ultrasound examination, GFR, and electrolyte monitoring;
• recommendation: nephrologist consultation at least once a year.

FINAL OUTCOME:

• Delay in CKD progression by up to 40–60%;
• Reduction in cystatin C levels by 30–50% at 18 months after rehabilitation;
• Supportive monitoring significantly reduces risk.

4. Conclusion. Assessment of post-COVID nephropathy risk based on comorbidity burden and inflammatory markers represents an effective approach.

• **MAU and cystatin C** are key markers for evaluating nephrological damage.
• Attention should be paid to the degree of pulmonary fibrosis and the completeness of treatment.
• Individualized rehabilitation and monitoring programs should be implemented, particularly for high-risk groups.

Conclusion.

The results of our study indicate that prevention of nephropathy after COVID-19 infection should be regarded not merely as an additional measure, but as an intervention whose importance may exceed that of many pathogenetic treatment approaches. In this field, identification of high-risk groups, early laboratory screening, rehabilitation programs, and educational strategies together constitute an integrated preventive model.

REFERENCES

1. Akhmedova, N. Sh. Laboratory markers for assessing renal function in nephropathy of different etiologies. *Tibbiyotda yangi kun*. 2022;(3(41)):56–59.

2. Bobkova, I. N., Shestakova, M. V., & Shchukina, A. A. Podocyte injury in diabetes mellitus. *Sakharnyy diabet*. 2014;17(3):39–50. doi:10.14341/DM2014339-50.

3. Kobalava, Zh. D., Villevalde, S. V., Borovkova, N. Yu., Shutov, A. M., Nichik, T. E., & Safuanova, G. Sh. Prevalence of chronic kidney disease markers in patients with arterial hypertension: results of the epidemiological study CHRONOGRAPH. *Kardiologiia*. 2017;57 (10):39–44.

4. Caramori, M. L., Fioretto, P., & Mauer, M. The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient? *Diabetes*. 2000;49(9):1399–1408. doi:10.2337/diabetes.49.9.1399.

5. Cederholm, J., Eliasson, B., et al. Microalbuminuria and risk factors in type 1 and type 2 diabetic patients. *Diabetes Research and Clinical Practice*. 2005; 67:258–266.

6. Dalla Vestra, M., Masiero, A., Roiter, A. M., Saller, A., Crepaldi, G., & Fioretto, P. Is podocyte injury relevant in diabetic nephropathy? Studies in patients with type 2 diabetes. *Diabetes*. 2003;52(4):1031–1035. doi:10.2337/diabetes.52.4.1031.

7. Forouzanfar, M. H., Liu, P., Roth, G. A., Ng, M., Biryukov, S., Marczak, L., Alexander, L., Estep, K., Hassen Abate, K., Akinyemiju, T. F., et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. *JAMA*. 2017;317(2):165–182.

8. Granier, C., Makni, K., Molina, L., Jardin-Watelet, B., Ayadi, H., & Jarraya, F. Gene and protein markers of diabetic nephropathy. *Nephrology Dialysis Transplantation*. 2008;23(3):792–799. doi:10.1093/ndt/gfm834.

9. Gupta, A., & Nadim, M. K. COVID-19 and the kidney: mechanism of injury and management. *Kidney International Reports*. 2020;5(12):2265–2273. doi:10.1016/j.ekir.2020.09.013.

10. Jim, B., Ghanta, M., Qipo, A., Fan, Y., Chuang, P. Y., Cohen, H. W., et al. Dysregulated nephrin in diabetic nephropathy of type 2 diabetes: a cross-sectional study. *PLoS One*. 2012;7(5):e36041. doi:10.1371/journal.pone.0036041.

11. Kopp, J. B., Anders, H. J., Susztak, K., Podestà, M. A., Remuzzi, G., Hildebrandt, F., & Romagnani, P. Podocytopathies. *Nature Reviews Disease Primers*. 2020;6(1):68. doi:10.1038/s41572-020-0196-7.

12. Lastra, G., Syed, S., Kurukulasuriya, L. R., Manrique, C., & Sowers, J. R. Type 2 diabetes mellitus and hypertension: an update. *Endocrinology and Metabolism Clinics of North America*. 2014;43(1):103–122. doi: 10.1016/j.ecl.2013.09.005.

13. Mills, K. T., Stefanescu, A., & He, J. The global epidemiology of hypertension. *Nature Reviews Nephrology*. 2020;16(4):223–237.

14. Nakatsue, T., Koike, H., Han, G. D., Suzuki, K., Miyauchi, N., Yuan, H., et al. Nephrin and podocin dissociate at the onset of proteinuria in experimental membranous nephropathy. *Kidney International*. 2005;67(6):2239–2253. doi:10.1111/j.1523-1755.2005.00328. x.

15. Ng, D. P., Tai, B. C., Tan, E., Leong, H., Nurbaya, S., Lim, X. L., et al. Nephrinuria associates with multiple renal traits in type 2 diabetes. *Nephrology Dialysis Transplantation*. 2011;26(8):2508–2514. doi:10.1093/ndt/gfq738.

16. Petrie, J. R., Guzik, T. J., & Touyz, R. M. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. *Canadian Journal of Cardiology*. 2018;34(5):575–584. doi: 10.1016/j.cjca.2017.12.005.

17. Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*. 2019; 157:107843.

18. Volpe, M., Battistoni, A., Savoia, C., & Tocci, G. Understanding and treating hypertension in diabetic populations. *Cardiovascular Diagnosis and Therapy*. 2015;5(5):353–363. doi: 10.3978/j.issn.2223-3652.2015.06.02.