

The Effect of COVID-19 Pandemic on Distribution of Biopsy-Proven Glomerular Disease: A Single Center Experience

El efecto de la pandemia de COVID-19 en la distribución de la enfermedad glomerular comprobada por biopsia: Experiencia de un solo centro

Zeki Toprak¹, Ezgi Ersoy Yesil¹, Hasan Kayabasi¹, Dede Sit¹, Fatima GURSOY²

RESUMEN

Introducción: El objetivo de este estudio es examinar a los pacientes sometidos a biopsia renal por anomalías urinarias y/o insuficiencia renal en nuestra unidad y, examinar si hubo un cambio en la distribución de las enfermedades glomerulares antes y después de la pandemia por coronavirus-2019. **Material y métodos:** Los pacientes se dividieron en dos grupos: prepandémicos (grupo 1) y postpandémicos (grupo 2). Se comparó la frecuencia de los resultados de la patología renal y el síndrome clínico representativo entre los grupos. **Resultados:** Se incluyeron en el estudio 452 pacientes [mediana de edad: 48 años (IQR: 36,25- 58), 54,8% varones], (grupo-1, n:215; 47,57%), (grupo-2, n:237; 52,43%). La proteinuria no nefrótica fue la indicación más frecuente en ambos grupos. La frecuencia de síndrome nefrótico fue significativamente mayor en el grupo-1 (19,5%, p:0,007). La frecuencia de insuficiencia renal aguda o rápidamente progresiva fue significativamente mayor en el grupo-2 (p:0,021). La mediana del nivel de proteínas en orina de 24 horas fue de 1354 (IQR:521-3000)

mg/día y fue significativamente menor en el grupo-2 (p:0,001). La enfermedad glomerular primaria fue la categoría más frecuente (42,19%), seguida de las enfermedades glomerulares secundarias (35,02%) y las nefropatías tubulointersticiales (6,32%) en el grupo-2. La frecuencia de enfermedad glomerular primaria fue significativamente mayor en el grupo-1 (p:0,022). La nefroesclerosis hipertensiva (6,80%) fue más frecuente en el grupo-2 (p:0,026). **Conclusiones:** No se detectó un aumento de la prevalencia de la enfermedad glomerular primaria, al contrario, hubo una disminución de la prevalencia de la enfermedad glomerular primaria en el período pospandémico. La frecuencia de insuficiencia renal aguda o rápidamente progresiva fue significativamente mayor en el periodo postpandémico. Se necesitan más estudios multicéntricos para determinar el efecto de la pandemia de COVID-19 en las enfermedades glomerulares.

Palabras clave: COVID-19, enfermedades glomerulares, biopsia renal

Correspondencia:
Zeki Toprak
ORCID:
0000-0002-7411-3628
zktprk@gmail.com

Financiamiento:
Ninguno.

Conflicto de intereses:
Ninguno que declarar

Recibido: 09-5-2023
Corregido: 23-5-2023
Aceptado: 19-7-2023

1) University of Health Sciences Umraniye Education and Research Hospital, Department of Nephrology, Istanbul, Turkiye

2) University of Health Sciences Umraniye Education and Research Hospital, Department of Pathology, Istanbul, Turkiye

ABSTRACT

Introduction: This study aims to examine the patients who underwent kidney biopsies due to urinary abnormalities and/or kidney failure in our unit and whether there was a change in the distribution of glomerular diseases before and after the coronavirus disease-2019 pandemic. **Materials and Methods:** The patients were divided into pre-pandemic (group-1) and post-pandemic (group-2). The frequency of renal pathology results and the representative clinical syndrome were compared between groups. **Results:** 452 patients [median age: 48 years (IQR: 36.25- 58), 54.8% male], (group-1, n:215; 47.57%), (group-2, n:237; 52,43%) were included in the study. Non-nephrotic proteinuria was the most common indication in both two groups. The frequency of nephrotic syndrome was significantly higher in group-1 (19.5%, p:0.007). The acute or rapidly progressive renal failure frequency was significantly higher in group-2 (p:0.021). The median 24-hour urine protein level was 1354 (IQR:521-3000) mg/day, significantly lower in group-2 (p: 0,001). Primary glomerular disease was the most common category (42.19%), followed by secondary glomerular diseases (35.02%) and tubulointerstitial nephropathies (6.32%) in group-2. The frequency of primary glomerular disease was significantly higher in group-1 (p:0.022). Hypertensive nephrosclerosis (6.80%) was common in group-2 compared to group-1 (p:0,026). **Conclusion:** We did not detect an increase in the prevalence of primary glomerular disease; on the contrary, there was a decrease in the prevalence of primary glomerular disease in the post-pandemic period. The acute or rapidly progressive renal failure frequency was significantly higher in the post-pandemic period. Further multicenter studies are needed to determine the effect of the COVID-19 pandemic on glomerular diseases.

Keywords: COVID-19, glomerular diseases, kidney biopsy

INTRODUCTION

A cluster of pneumonia cases was found to be caused by a novel coronavirus, which eventually spread worldwide and caused a global pandemic in Wuhan, a city in China, in 2019. It rapidly spread worldwide, resulting in

a global pandemic ⁽¹⁾. More than 762 million cases have been reported worldwide, and many vaccines have been put into clinical use to protect against coronavirus disease 2019 (COVID-19) ⁽²⁾. Furthermore, almost 12 billion doses of the different types of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been administered worldwide ⁽³⁾.

SARS-CoV-2 is a beta-coronavirus that displays spike protein through which the viral RNA enters the host cell by binding to the Angiotensin-converting enzyme-2 (ACE-2). ACE-2 is highly expressed in several organs ⁽⁴⁾. In the kidney, ACE-2 is expressed in several cell types, including podocytes, mesangial cells, the parietal epithelium of Bowman's capsule, and collecting ducts ^(5,6).

The mechanisms of renal involvement in COVID-19 infections and vaccines are still unclear. However, acute tubular necrosis has been reported to be the most common damage in infected patients, probably due to impaired renal perfusion ^(7,8). On the other hand, different complex pathophysiological processes may be involved due to direct viral infection to effects on the renin-angiotensin-aldosterone system, the activation of coagulopathy, the cytokine storm, and the activation of the immune system. A variety of glomerular, tubular, and vascular lesions are seen in the kidney tissue of infected and vaccinated people ⁽⁹⁻¹¹⁾. The development of de novo glomerular injuries after COVID-19 vaccines and infections has been suggested like Anca-associated vasculitis, Membranous glomerulonephritis (MGN), IgA nephropathy (IgAN), Anti-glomerular basement membrane glomerulonephritis and Minimal change disease (MCD) ^(10, 12-19).

In this study, we aimed to examine the patients who underwent kidney biopsy due to urinary abnormalities (UA) and/or kidney failure in our unit and whether there was a change in the distribution of glomerular diseases before and after the COVID-19 pandemic.

MATERIAL AND METHODS

Study design, participants, and data collection

This retrospective study included all the patients who underwent a native renal biopsy at the University of Health Sciences Umraniye Education and Research Hospital between June 2017 and April 2022.

The first diagnosed and confirmed COVID-19 case was in March 2020 in Türkiye. Since there is a 2-3 week waiting period for kidney biopsy in our center, except for emergencies, we have determined the date of April 2020 as a milestone. We divided the patients who underwent kidney biopsy into two groups: before and after April 2020. Exclusion criteria were: (a) transplant biopsy and (b) less than ten glomeruli in the biopsy sample. Inadequate biopsies (less than ten glomeruli in the specimen for light microscopy (LM) or absence of a glomerulus in immunofluorescence staining) were excluded. The Medical Ethics Committee of our hospital approved this study.

Age, sex, clinical presentation, laboratory data at the biopsy (serum creatinine, serum albumin, 24-hour urine protein), and histopathological diagnosis of each patient were collected from electronic medical records.

UA was defined as proteinuria ≥ 0.5 g/day and/or dysmorphic erythrocytes ≥ 10 RBC/HPMF. The definition of rapidly progressive glomerulonephritis was based on the clinical ground (Acute Kidney Injury) and the presence of the crescents on kidney biopsy. Renal function was assessed following The National Kidney Foundation recommendation using the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2021) to calculate eGFR. Urinary sediment and proteinuria were obtained by 24-h urine collection.

Clinical syndromes at presentation were categorized as the following: nephrotic syndrome (NS) (proteinuria of ≥ 3.5 g/day and serum albumin of ≤ 3.0 g/dL, usually accompanied by edema and hyperlipidemia), acute nephritic syndrome (hematuria and proteinuria, sometimes accompanied by hypertension, edema, or a reduced glomerular filtration rate (GFR)), and acute or rapidly progressive renal failure (A/RPRF) (rapid or slowly progressive decrease in GFR, often accompanied by oliguria or by glomerular proteinuria/hematuria).

A trained nephrologist or interventional radiologist obtained all tissue samples percutaneously with ultrasound guidance. Biopsy specimens were examined in the pathology laboratory of the University of Health Sciences Umraniye Education and Research Hospital by the same nephropathologist. Samples were

analyzed with a light and immunofluorescence (IF) microscope. For LM, paraffin sections were routinely stained with periodic acid-Schiff, hematoxylin & eosin, periodic acid-silver methenamine, and Congo red. IF microscopy panel included staining for IgG, IgM, IgA, C3, C1q, κ , and λ light chains. An electron microscopy facility was not available at our center.

Renal histopathology was classified into four categories:

- Primary glomerular disease (PGD): focal segmental glomerulosclerosis (FSGS), MGN, MCD, membranoproliferative glomerulonephritis (MPGN), IgAN, immunoglobulin M nephropathy (IgMN), pauci-immune glomerulonephritis.
- Secondary glomerular disease (SGD): lupus nephritis (LN), diabetic nephropathy (DN), hypertensive nephrosclerosis (HN), and amyloidosis (AA = amyloid A; AL = amyloid)
- Tubulo-interstitial nephropathies: tubulointerstitial nephritis (TIN), either acute or chronic, and acute tubular necrosis (ATN)
- Unclassified (hemolytic uremic syndrome, oxalate nephropathy, phosphate nephropathy, cast nephropathy)

The patients were divided into two groups pre-pandemic (before April 2020) and post-pandemic (after April 2020). COVID-19 PCR test was performed before the procedure in patients who underwent kidney biopsy in the post-pandemic period. Biopsy of patients with active infection (positive Covid test) was performed after the PCR result turned negative unless the patients have A/RPRF. The frequency of renal pathology results and the representative clinical syndrome were compared between groups.

Statistical analysis

Statistical Package for Social Science (IBM SPSS Statistics New York, USA) version 20.0 was used for statistical analyses. Continuous variables were expressed as the median with an interquartile range, presenting the categorical variables as percentages. The data showed abnormal distribution according to Kolmogorov Smirnov and Shapiro-Wilk test. The significance of differences for non-normally distributed variables was determined using the Mann-Whitney U test. The statistical level of significance was set at $p < 0.05$.

RESULTS

Five hundred forty-one native renal biopsies were performed on patients over 17 years of age between June 2017 and April 2022. Eighty-nine patients were excluded from the analysis due to inadequate sampling, which included less than ten glomeruli in the biopsy sample.

Four hundred fifty-two patients [median age:

48 years (IQR: 36.25- 58), 54.8% male] were included in the study. The patients were divided into two groups as before (group-1, n:215, 47.57%) and after (group-2, n:237; 52.43%) the onset of the COVID-19 pandemic in Türkiye (i.e., April 2020). The characteristics of the participants based on the timeline are presented in **Table 1**.

Table 1: The characteristics of the patients based on the timeline

| Characteristics | Pre-Pandemic (n=215) | Post-Pandemic (n=237) | p-value |
|--|----------------------|-----------------------|------------------|
| Age(years), median, IQR (25-75) | 48 (36-57) | 49 (38,5-59) | NS |
| Gender | | | |
| Female (n, %) | 96 (44.65) | 108 (45.56) | NS |
| Male (n, %) | 119 (55.34) | 129 (54.43) | |
| Comorbidities | | | |
| DM (n, %) | 57 (26.51) | 80 (33.75) | NS |
| HT (n, %) | 101 (43.72) | 119 (50.21) | NS |
| Hematuria (n, %) | 94 (4.72) | 102 (43.03) | NS |
| Urea (mg/dL), median, IQR (25-75) | 40 (25-58) | 40 (28-63,75) | NS |
| Creatinine (mg/dL), median, IQR (25-75) | 1,2 (0,78-1,74) | 1.24 (0,77-1,86) | NS |
| Hemoglobine (gr/dL), median, IQR (25-75) | 12.6 (10,9-13,8) | 12.7(10,8-14,35) | NS |
| Thrombocyte (cell/ml) median, IQR (25-75) | 250 (206-299) | 268 (226-316,5) | 0,015* |
| eGFR (mL/min/1.73m²), median, IQR (25-75) | 65 (41-101) | 62 (37,5-100,5) | NS |
| Albumin (gr/dL), median, IQR (25-75) | 38 (28-41) | 40 (34-43) | <0.05* |
| Proteinuria (mg/day), median, IQR (25-75) | 2086 (776-5378,25) | 1354 (521-3000) | 0,001* |

Abbreviations: *: indicates statistical significance. **A:** Mann Whitney U Test, **DM:** Diabetes Mellitus, **eGFR:** Estimated glomerular filtration rate **HT:** Hypertension, **NS:** non significant

In group-1, 96 patients were female, and the median age was 48 (IQR: 36-57) years. In group-2, 108 patients were female, and the median age was 49 (IQR: 38,5-59) years.

In 2020, there was a decrease in the number of performed kidney biopsies compared to the previous and following years (2017: 6 biopsies per month; 2018: 10.25 biopsies per month;

2019: 6 biopsies per month; 2020: 5 biopsies per month; 2021: 10.25 biopsies per month; 2022: 10.5 biopsies per month, respectively). The renal biopsy rate per month was lower in 2020 compared to the previous and following years. During the first year of the COVID-19 pandemic, we observed a reduction in total renal biopsies performed per month.

The median serum creatinine levels at the time of renal biopsy in group-1 and group-2 were 1.20 (IQR: 0,78-1,74) mg/dL and 1.24 (IQR:0,77-1,86) mg/dL, respectively (p > 0.05). There were no significant differences in age, gender, comorbidities, hemoglobin levels, serum urea levels, serum creatinine levels, hematuria frequencies, and eGFR levels between groups.

The median serum albumin level was 40.0 (IQR: 34-43) g/dL and was significantly higher in group-2 (p<0.05). The median 24-hour urine protein level was 1354 (IQR:521-3000) mg/day, significantly lower in group-2 (p: 0,001).

Table 2 shows the comparison of clinical syndromes at presentations between two groups.

Non-nephrotic proteinuria is the most common indication in the two groups. NS (19.5%) was more prevalent in group-1 than in group-2. The frequency of NS was significantly higher in group-1 (p:0.007). However, the frequency of A/RPRF was significantly higher in group-2 (p:0.021). However, the frequency of nephritic syndrome was similar between the two groups.

Table 2: The distribution of indications before and after the pandemic

| Indications | Pre-Pandemic (n=215) | Post-Pandemic (n=237) | p-value |
|---------------------------------|----------------------|-----------------------|---------------------------|
| Non-Nephrotic Proteinuria (n,%) | 91(42.30) | 104(43.90) | NS |
| Nephrotic Proteinuria (n,%) | 22(10.20) | 15(6.30) | NS |
| Microscopic Hematuria (n,%) | 4(1.90) | 3(1.30) | NS |
| Nephritic Syndrome (n,%) | 7(3.30) | 8(3.40) | NS |
| Nephrotic Syndrome (n,%) | 42(19.50) | 25(10.50) | 0.007^{*a} |
| Macroscopic Hematuria (n,%) | 0(0.00) | 2(0.80) | NS |
| Chronic Renal Failure (n,%) | 30(14) | 42(17.7) | NS |
| Acute Renal Failure (n,%) | 19(8.80) | 38(16) | 0.021^{*a} |

Abbreviations: * indicates statistical significance, a: Mann-Whitney U test, NS: non significant

In Table 3, the spectrum of renal pathologies is compared between group-1 and group-2.

Primary glomerular diseases were the most common category, accounting for 42.19% (n = 100), followed by secondary glomerular diseases (n=83, 35.02%) and tubulointerstitial nephropathies (n=15, 6.32%). The most frequent histopathological patterns of PGD in group-2 were IgAN, FSGS, and MGN in that order, whereas in group-1, they were FSGS, IgAN, and

MGN in decreasing order.

PGD was more common in group-1. The frequency of PGD was also significantly higher in the group-1 (p:0.022).

FSGS and IgMN were more prevalent in group-1. The frequency of FSGS and IgMN were significantly higher in group-1 (p:0.047 and p:0.006, respectively).

Among the patients with SGD, the most frequent diagnosis was DN in pre and post-

pandemic patients (14.90% and 20.70%, respectively). Amyloidosis (n=13, 5.5%) and LN (n:1, 0.40%) were uncommon histological

patterns in group-2. HN (n = 16, 6.80%) was more prevalent in group-2 (p:0.026).

Table 3: Distribution of kidney biopsy-based renal disease before and after the pandemic

| PATHOLOGICAL DIAGNOSIS | Pre-Pandemic (n=215) | Post-Pandemic (n=237) | p-value |
|--|-----------------------------|------------------------------|----------------|
| Primary Glomerular Disease (n,%) | 122 (56.74) | 100 (42.19) | 0.022* |
| FSGS | 43 (20.00) | 31 (13.10) | 0.047* |
| MGN | 22 (10.20) | 18 (7.60) | NS |
| MCD | 6 (2.80) | 4 (1.70) | NS |
| MPGN | 1 (0.50) | 2 (0.80) | NS |
| IgAN | 32 (14.90) | 31 (13.10) | NS |
| IgMN | 13 (6.00) | 2 (0.80) | 0.002* |
| PAUCI-IMMUNE GN | 5 (2.30) | 10 (4.20) | NS |
| C3G | 0 (0.00) | 1 (0.40) | NS |
| DDD | 0 (0.00) | 1 (0.4) | NS |
| Secondary Glomerular Disease (n,%) | 53 (24.65) | 83 (35.02) | NS |
| DN | 32 (14.90) | 49 (20.70) | NS |
| AMYLOIDOSIS | 12 (5.60) | 13 (5.50) | NS |
| LN | 2 (0.90) | 1 (0.40) | NS |
| HT NEPHROSCLEROSIS | 5 (2.30) | 16 (6.80) | 0.026* |
| APSGN | 1 (0.50) | 0 (0.00) | NS |
| CRYO GN | 1 (0.50) | 2 (0.80) | NS |
| HIVAN | 0 (0.00) | 2 (0.80) | NS |
| Tubulo-interstitial nephropathies (n,%) | 13 (6.04) | 15 (6.32) | NS |
| TIN | 11 (5.10) | 11 (4.60) | NS |
| ATN | 2 (0.90) | 4 (1.70) | NS |
| Unclassified (n,%) | 4 (1.86) | 5 (2.10) | NS |
| PHOSPHATE NEPHROPATHY | 0 (0.00) | 1 (0.40) | NS |
| OXALATE NEPHROPATHY | 2 (0.90) | 1 (0.40) | NS |
| MYELOMA-CAST NEPHROPATHY | 0 (0.00) | 1 (0.40) | NS |
| TMA | 2 (0.90) | 1 (0.40) | NS |
| ALPORT SYNDROME | 0 (0.00) | 1 (0.40) | NS |
| Non-diagnostic | 23 (6.97) | 34 (11.81) | NS |

Abbreviations: *: indicates statistical significance, **a:** Mann-Whitney U test. **APSGN:** acute poststreptococcal glomerulonephritis, **ATN:** acute tubular necrosis, **Cryo GN:** cryoglobulinemic glomerulonephritis, **C3G:** C3 glomerulopathy, **DDD:** dense deposit disease, **DN:** diabetic nephropathy, **FSGS:** focal segmental glomerulosclerosis, **HIVAN:** HIV-associated nephropathy, **HT-Nephrosclerosis:** hypertensive nephrosclerosis, **IgAN:** immunoglobulin A nephropathy, **IgMN:** Immunoglobulin M nephropathy, **LN:** Lupus nephritis, **MCD:** minimal change disease, **MGN:** membranous glomerulonephritis, **MPGN:** membranoproliferative glomerulonephritis, **NS:** non significant, **Pauci-immune GN:** Pauci-immune glomerulonephritis, **TIN:** tubulointerstitial nephritis, **TMA:** thrombotic microangiopathy.

DISCUSSION

We investigated whether the distribution of glomerular diseases changed in patients who underwent kidney biopsies for UA and/or kidney failure in our unit before and after the COVID-19 pandemic. This retrospective single-center study included 452 patients with native kidney biopsies in a tertiary hospital aged 17 to 91.

Healthcare systems around the world faced a significant challenge as a result of the COVID-19 pandemic. Many nephrology departments in Türkiye had to switch to urgent care for patients with COVID-19 from March to May and November to December 2020, reducing the number of biopsies that otherwise could have been

performed. In addition, patients with stable kidney disease and mild symptoms due to concern about the coronavirus avoided hospital visits. That is why our center's renal biopsy rate was lower in 2020 compared to the previous and following years. During the COVID-19 pandemic, we observed a reduction in total renal biopsies performed per month, and we saw a compensatory increased rate of renal biopsies in 2021 and 2022 in our study. Samy Hakroush, et al.'s study supported this finding⁽²⁰⁾. Adel Molnar et al. found that in 2020, there was a decrease in the number of kidney biopsies compared to the average of the previous three years (2020): 161 biopsies, 43.4 per one million person-years, versus 242.3 biopsies per year, 64.2 per one million person-years between 2017 and 2019⁽²¹⁾.

Samy Hakroush et al. found that in 2021 there was no significant difference in diagnoses of kidney diseases based on renal biopsies in their studies, indicating that the COVID-19 pandemic does not affect the overall distribution of kidney disease⁽²⁰⁾. Shane A. Bobart et al. compared the changes in kidney biopsy numbers and diagnoses before and during the COVID-19 pandemic in their study in 2022. The difference in the biopsy performed in the 12 months before COVID-19 (March 2019 to February 2020) and the first 12 months during COVID-19 (March 2020 to February 2021) was significant (696, 53% versus 624, 47%, $P=0.05$). This finding was similar to our study. They also found no change in the disease spectrum before and during the COVID-19 pandemic⁽²²⁾. However, our study did not detect an increase in the prevalence of PGD. On the contrary, there was a decrease in the prevalence of PGD in the post-pandemic period. (56.74% vs 42.19%, $p:0.022$) and the frequency of A/RPRF was significantly higher in the post-pandemic patient group ($p:0.021$). There was no significant difference in the prevalence of PGD.

Non-nephrotic proteinuria is the most common indication in the two groups in our study. Kim Ling Goh et al. found a similar result for indicating native kidney biopsy in their studies between 2007 and 2020⁽²³⁾. On the other hand, Ruimin Hu et al. conducted a study and found that NS was the most frequent indication for biopsy among cases of native kidney biopsy between 2009 and 2018⁽²⁴⁾. Since NS (19.5%) was detected less frequently in the post-pandemic group, the median serum

albumin level was 40.0 (IQR: 34-43) g/L and was significantly higher in the post-pandemic group ($p<0.05$). The median 24-hour urine protein level was 1354 (IQR:521-3000) mg/day and was significantly lower in the post-pandemic group ($p<0.05$). Unless cases of nephrotic syndrome are severe or complicated, peripheral centers may have treated patients during the pandemic with diuretics and other supportive treatments until performing a biopsy. Patients with such cases likely avoided tertiary care centers during the pandemic lockdown, which could explain the lower incidence of biopsy indications in the post-pandemic patient group.

The frequency of A/RPRF was significantly higher in the post-pandemic patient group: 8.80% in the pre-pandemic and 18% in the post-pandemic patient group, compared to that reported from other centers, ranging from 10 % to 20 % ($p:0.021$)^(25, 26). This scenario may have been caused by patients with stable kidney disease and mild symptoms avoiding hospital visits due to coronavirus concerns. The rate of pauci-immune GN increased in the post-pandemic period, although not statistically significant ($n:5$, 2.30 % in the pre-pandemic and $n:10$, 4.20% in the post-pandemic patient group). We can speculate that this increase contributes to the increase in the frequency of A/RPRF. More studies are needed in this regard.

The most frequent histopathological patterns of PGD in the post-pandemic group were IgAN, FSGS, and MGN, respectively. In contrast, the pre-pandemic patients were FSGS, IgAN, and MGN, respectively. IgAN was identified as the most common form of primary glomerulonephritis, which is similar to what has been reported by Abhilash Chandra⁽²⁷⁾. On the other hand, Bhalla et al. and Muthu et al. reported MCD and FSGS as the most common primary glomerulonephritis, respectively, in their studies^(26, 28). Although our database did not have large case numbers, we found that the rate of FSGS decreased significantly. The significant increase in the proportion of DN cases and pauci-immune GN cases may have reduced the frequency of FSGS. The frequency of IgAN before and after the pandemic did not differ between the groups, although we expected an increased incidence of the disease after viral infections.

In the secondary glomerular diseases group, the frequency of HN was significantly higher

in the post-pandemic patient group (p: 0.026): 2.30% in the pre-pandemic and 6.80% in the post-pandemic patient group.

Persistent symptoms and delayed or long-term complications beyond four weeks from the onset of COVID-19 symptoms have been classified as Post-acute COVID-19 or Long COVID syndrome^(29, 30). Research has demonstrated that hypertension development is influenced by both innate immune cells (e.g., macrophages, microglia, monocytes, dendritic cells, and myeloid-derived suppressor cells) and adaptive immune cells (e.g., CD8+ T cells, CD4+ T cells, and B cells)⁽³¹⁾. During hospitalization, COVID-19 patients with respiratory failure may experience elevated blood pressure or even develop spontaneous hypertension⁽³²⁻³⁴⁾. A recent prospective case-control study in hospitalized patients also shows that COVID-19 pneumonia individuals have a higher probability of a persistent elevated BP⁽³⁵⁾. The higher probability of persistent high blood pressure in patients with Post-Acute COVID-19 or Long-COVID syndrome may be a contributing factor to the increased incidence of HN.

The rate of diabetic nephropathy increased in the post-pandemic period, although not statistically significant (14.90% in the pre-pandemic and 20.70% in the post-pandemic patient group). This rate of diabetic nephropathy is high compared to some studies, but Shane A. Bobart et al. found DN rates of 15% in their studies in 2022⁽²²⁾. This finding was similar to our study and may be due to differences in biopsy preference between clinicians.

There are some limitations of our study. The primary limitations are the limited number of patients included as it was designed as a single-center study, and it is unknown whether the post-pandemic patient group was infected with COVID-19 at the time of the kidney biopsy or their vaccination rate. Our study may be biased due to excluding patients who died rapidly in the intensive care unit without a kidney biopsy.

CONCLUSION

Healthcare systems around the world faced a significant challenge as a result of the COVID-19 pandemic. During the COVID-19 pandemic, we observed a reduction in total renal biopsies performed per month, and there was no increase in the prevalence of PGD. The frequency of A/RPRF was significantly higher in the post-pandemic

patient group. Further multicenter studies are needed to determine the effect of the COVID-19 pandemic on glomerular kidney diseases.

BIBLIOGRAPHY

- 1) Who.int [Internet]. Organization WH. *World Health Organization*. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Available from: <http://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020>
- 2) *OurWorldInData.org* [Internet]. Ritchie H, Mathieu E, Rodés-Guirao L, Appel C, Giattino C, Ortiz-Ospina E, et al. *Coronavirus pandemic (COVID-19)*. 2020. Available from: <https://ourworldindata.org/coronavirus>
- 3) *OurWorldInData.org* [Internet]. Ritchie H, Ortiz-Ospina E, Beltekian DJS, Research. Coronavirus (COVID-19) vaccinations—statistics and research. *Our World in Data*. 2021. Available from: <https://ourworldindata.org/coronavirus>
- 4) Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: A peptidase in the renin–angiotensin system, a SARS receptor, and a partner for amino acid transporters. *Pharmacol Ther*. 2010;128(1):119-128.
- 5) Soler MJ, Wysocki J, Batlle D. ACE2 alterations in kidney disease. *Nephrol Dial Transplant*. 2013;28(11):2687-2697.
- 6) Lely A, Hamming I, H van Goor, Navis GJ. Renal ACE2 expression in human kidney disease. *J Pathol*. 2004;204(5):587-593.
- 7) Ahmadian E, Hosseiniyan Khatibi SM, Razi Soofiyani S, Abediazar S, Shoja MM, Ardalan M, et al. Covid-19 and kidney injury: Pathophysiology and molecular mechanisms. *Rev Med Virol*. 2021;31(3):e2176.
- 8) Su H, Yang M, Wan C, Yi L-X, Tang F, Zhu H-Y, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020;98(1):219-227.
- 9) Alwafi H, Ashoor D, Dairi M, Mokhtar G, Dairi K. Adult-Onset IgA Vasculitis Associated with Pulmonary-Renal Syndrome Following COVID-19 Infection: A Case Report and Literature Review. *Cureus*. 2023;15(2).
- 10) Waldman M, Sinaii N, Lerma EV, Kurien AA, Jhaveri KD, Uppal NN, et al. COVID-19 Vaccination and new onset glomerular disease: Results from the IRocGN2 International registry. *Kidney360*. 2023;4(3):349-362.
- 11) Grassi S, Arena V, Zedda M, Cazzato F, Cianci R, Gambassi G, et al. What can autopsy say about

- COVID-19? A case series of 60 autopsies. *Leg Med (Tokyo)*. 2023;62:102241.
- 12) Eun JK, Park MJ, Kim MS, Han MH, Kim Y-J, Baek HS, et al. De Novo Crescentic Glomerulonephritis Following COVID-19 Infection: A Pediatric Case Report. *J Korean Med Sci*. 2023;38(12): e89.
 - 13) Chandok T, Nasr R, Uday KA. A Case of Antineutrophil Cytoplasmic Antibody Vasculitis-Associated Acute Kidney Injury in a Patient With Asymptomatic COVID-19 Infection. *Cureus*. 2023;15(2):e35006.
 - 14) Gulumsek E, Ozturk DD, Ozturk HA, Saler T, Erdogan KE, Bashir AM, et al. Minimal Change Nephrotic Syndrome with Acute Kidney Injury after the Administration of Pfizer-BioNTech COVID-19 Vaccine. *Case Rep Infect Dis*. 2023; 2023:1-4.
 - 15) De las Mercedes Noriega M, Husain-Syed F, Wulf S, Csala B, Krebs CF, Jabs WJ, et al. Kidney Biopsy Findings in Patients with SARS-CoV-2 Infection or After COVID-19 Vaccination. *Clin J Am Soc Nephrol*. 2023;15(5):612-625.
 - 16) Mateus C, Manso RT, Martins AR, Branco PQ. Membranous nephropathy after a recent SARS-CoV-2 infection. *BMJ Case Rep*. 2023;16(1): e252468.
 - 17) Chen Y-S, Yang C-W, Tsai C-C, Ang M-D, Chou S-F, Chiang W-C, et al. Newly-diagnosed immunoglobulin A nephropathy with increased plasma galactose-deficient-IgA1 antibody associated with mRNA COVID-19 vaccination: a case report. *J Int Med Res*. 2022;50(10):03000605221129674.
 - 18) Tan MSH, Choo JCJ, Tan PH, Kwek JL, Lim CC, Mok IY, et al. Anti-glomerular basement membrane glomerulonephritis following COVID-19 infection without clinically evident pneumonia. *Int Urol Nephrol*. 2023;55(7):1-3.
 - 19) Özkan G, Bayrakçı N, Karabağ S, Güzel EÇ, Ulusoy S, Nephrology. Relapse of minimal change disease after inactivated SARS-CoV-2 vaccination: case report. *Int Urol Nephrol*. 2021;54(4):971-972.
 - 20) Hakroush S, Tampe D, Korsten P, Tampe B. Impact of the COVID-19 pandemic on kidney diseases requiring renal biopsy: a single center observational study. *Front Physiol*. 2021;12:649336.
 - 21) Molnár A, Thomas MJ, Fintha A, Kardos M, Dobi D, Tislér A, et al. Kidney biopsy-based epidemiologic analysis shows a growing biopsy rate among the elderly. *Sci Rep*. 2021;11(1):24479.
 - 22) Bobart SA, Portalatin G, Sawaf H, Shettigar S, Carrion-Rodriguez A, Liang H, et al. The Cleveland Clinic Kidney Biopsy Epidemiological Project. *Kidney360*. 2022 Oct 18;3(12):2077-2085.
 - 23) Goh KL, Abeyaratne A, Ullah S, Rissel C, Priyadarshana K. Histopathology pattern and survival analysis of patients with kidney biopsy in the top end of Northern Australia from 2007 to 2020. *BMC Nephrol*. 2022;23(1):385.
 - 24) Hu R, Quan S, Wang Y, Zhou Y, Zhang Y, Liu L, et al. The spectrum of biopsy-proven renal diseases in Central China: a 10-year retrospective study based on 34,630 cases. *Sci Rep*. 2020;10(1):1-12.
 - 25) Yim T, Kim S-U, Park S, Lim J-H, Jung H-Y, Cho J-H, et al. Patterns in renal diseases diagnosed by kidney biopsy: a single-center experience. *Kidney Res Clin Pract*. 2020;39(1):60.
 - 26) Muthu V, Ramachandran R, Nada R, Kumar V, Rathi M, Kohli H, et al. Clinicopathological spectrum of glomerular diseases in adolescents: A single-center experience over 4 Years. *Indian J Nephrol*. 2018;28(1):15.
 - 27) Chandra A, Rao N, Malhotra KP, Srivastava D, Nephrology. Impact of COVID-19 pandemic on patients requiring renal biopsy. *Int Urol Nephrol*. 2022;54(10):2617-2623.
 - 28) Bhalla S, Ahmad M, Raghuvanshi S, Agarwal P. Clinicopathologic spectrum of glomerular diseases in a tertiary care hospital. *Indian Journal of Health Sciences and Biomedical Research (KLEU)*. 2021;14(1):113-118.
 - 29) Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594(7862):259-264.
 - 30) Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601-615.
 - 31) Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. *J Exp Med*. 2018;215(1):21-33.
 - 32) Vicenzi M, Di Cosola R, Ruscica M, Ratti A, Rota I, Rota F, et al. The liaison between respiratory failure and high blood pressure: evidence from COVID-19 patients. *Eur Respir J*. 2020;56(1):2001157.
 - 33) Chen G, Li X, Gong Z, Xia H, Wang Y, Wang X, et al. Hypertension as a sequela in patients of SARS-CoV-2 infection. *PLoS One*. 2021;16(4):e0250815.
 - 34) Akpek M. Does COVID-19 cause hypertension? *Angiology*. 2022;73(7):682-687.
 - 35) Angeli F, Zappa M, Oliva FM, Spanevello A, Verdecchia P. Blood pressure increase during hospitalization for COVID-19. *Eur J Intern Med*. 2022;104:110-112.